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

Prof. Yashwant D. Vankar
Department of Chemistry
Indian Institute of Technology-Kanpur

Lecture - 43

C-C Bond Formations Using Enol Silyl Ether and Imine Based Chemistry Including SAMP and RAMP Based Asymmetric Alkylations

Hello everyone, welcome to today's lecture. I hope that you had the opportunity to go through what we discussed in the last class. In today's class we will take up some other aspects of C-C bond formations. But before that we will have a brief look at what we did last time. So we first took that how a ketone can actually be deprotonated.

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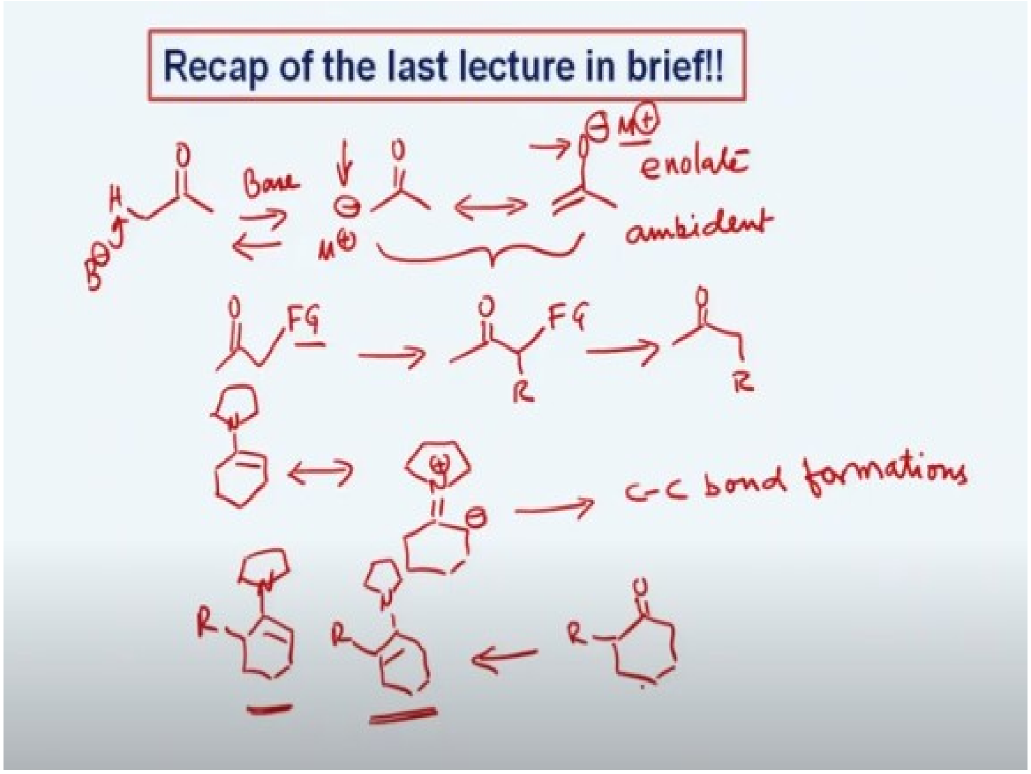

Recap of the last lecture in brief!!

And of course, we can have the formation of the corresponding anion and that anion can be in equilibrium with the original ketone depending on various factors such as the acidity of the proton, which is alpha to the carbonyl and also the strength of the base. And this will be in kind of resonance form with the O- here and then we discussed the ambident nucleophilicity of these type of enolates.

This enolate can react either through oxygen or through carbon and therefore the electrophile can come in either here or it can come in here. So this way we can tune the reaction and of course we looked at the solvent effect, the cation effect. Because here when we take a base, we also have a counter-cation here. So this counter-cation will also play a very important role.

So the effect of the solvent, effect of the nature of the M+ and the nature of the electrophile makes the O-alkylation or C-alkylation of enolates to occur. At the same time, we also discussed how the putting off an extra group here like for example, you have a functional group here which we can put it as an ester or a sulfonyl or a nitro and then we let the reaction go with softer nucleophiles to attack it here.

And then of course we remove the functional group where we can get the C-alkylated product. So we have the C-alkylation to go further. And then we introduced enamine chemistry, which is well known. And we saw how enamines can be allowed to form the C-C bond to take place and via this type of intermediates. Of course, we have the resonance structure of these and then C-C bond formation can be done.

But then we also saw the problems associated with this enamine chemistry. For example, it can be an N-alkylation or it can be that the formation of enamines when there is a substituent here on the left hand side. That is if we have a substituent here on this side, then generation of this type of enamines becomes difficult. So it is not easy to generate this enamines.

And these are the enamines that are formed from say for example, you have a ketone which is of unsymmetrical type. So these were the problems, but at the same time we also saw how the enamines can be allowed to react and form various natural products or complicated molecules in a easy fashion. So these problems of enamines or the problems of enolate chemistry can be to some extent avoided if we go for enol silyl ethers.

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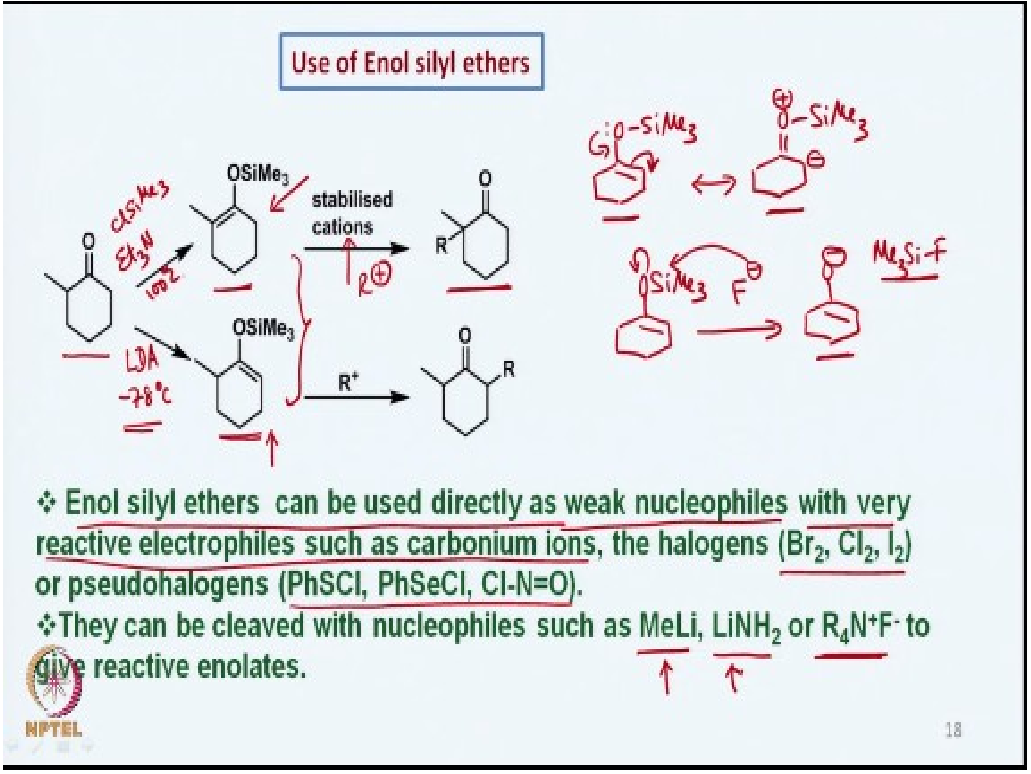

Use of Enol silyl ethers

- Enol silyl ethers can be used directly as weak nucleophiles with very reactive electrophiles such as carbonium ions, the halogens (Br_2, Cl_2, I_2) or pseudohalogens (PhSCl, PhSeCl, Cl-N=O).
- They can be cleaved with nucleophiles such as MeLi, $LiNH_2$ or $R_4N^+F^-$ to give reactive enolates.

So as you know that we can take an unsymmetrical ketone and at a high temperature, like for example if you have a triethylamine and chlorotrimethylsilane at say reflux temperature, so like about 100 degrees or so we can easily make the enol silyl ether of this kind. On the other hand if we take a base as strong as LDA and add -78 degree centigrade we do the reaction, then of course, we can get the enol silyl ether of this kind.

So we have conditions under which different types of enol silyl ethers can be procured. One is this is under kinetic condition and this is under thermodynamic conditions and then we can react with electrophiles; particularly these electrophiles need to be R+. That means they are cationic in nature. And then we have the formation of the corresponding C-C bond here.

Now it is important that we have this enol silyl ether and therefore the oxygen-silcon bond is strong. Oxygen is involved in this and therefore, the formation of these type of intermediates is not easily possible because you have a positive charge on electronegative oxygen. So if we look at this, this type of resonance structure is not a particularly favored, this is more favored.

And therefore enol silyl ethers are relatively poor nucleophiles and they react only with strong electrophiles. So as it is written here enol silyl ethers can be used directly as weak nucleophiles with very reactive electrophiles such as carbonium ions, the halogens or pseudohalogens such as this phenylsulfonyl chloride or phenylselenyl chloride and nitrosyl chloride.

They can of course be cleaved, say if we have an enol silyl ether and if you want to cleave, then you can cleave it with methyllithium or lithium amide or tetrabutylammonium fluoride. So suppose you have a tetrabutylammonium fluoride or any other nucleophile then this attaches on to the silicone here and then the negative charge comes out and you can generate now an enolate here.

And then you have a strong silicone fluorine bond is formed and to make this trimethylsilyl fluoride. And this is now a better nucleophile. It is like a any other enolate. Same thing we can do it with methyllithium and lithium amide for example. So this way the relatively weak nucleophilicity of an enol silyl ether could be modified and can be made into a more nucleophilic enolate ion.

On the other hand, if we have a very strong electrophile reacting with enol silyl ethers, then of course the reaction takes place. So either you increase the nucleophilicity or you react with highly electrophilic species for the reaction of enol silyl ethers.

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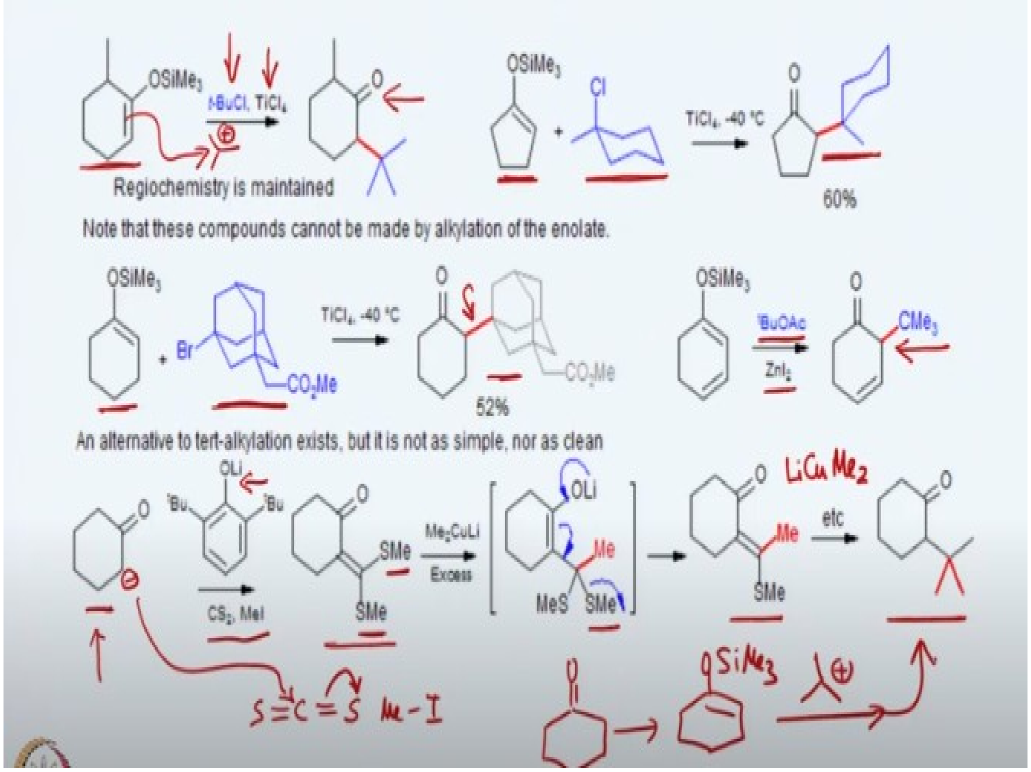

Regiochemistry is maintained

Note that these compounds cannot be made by alkylation of the enolate.

An alternative to tert-alkylation exists, but it is not as simple, nor as clean

Now there are several examples in the literature, for example if we take an enol silyl ether of this type, which we can make it by kinetic deprotonation and react with tertiary-butyl chloride for example in the presence of titanium tetrachloride, then of course as you can see that we generate basically a tertiary cation and then tertiary cation then reacts with this enol silyl ether to form this ketone.

Such a reaction is not possible with say enamines very easily or even enolates very easily. In a similar fashion this enol silyl ether reacts with this tertiary chloride in the presence of titanium tetrachloride and then we have this carbon-carbon bond formed. And also similarly, this enol silyl ether forming the C-C bond at this particular alpha position of the carbonyl group here.

Now if we take a tertiary butyl acetate and Zinc iodide, then this dienol silyl ether leads to the formation of this particular tertiary butyl group that is attached. If we see in the literature that how such kind of tertiary butyl groups need to be introduced, there are not that many straightforward methods. So enol silyl ether is a very easy way by which we can introduce the tertiary groups alpha to the carbonyl group easily.

As for example, we can take a ketone and then react with this particular base and then carbon disulfide and metal iodide. So basically we are deprotonating here and reacting with carbon disulfide in this way and then trapping the. So if we had reacted with this particular anion to the carbon then you generate this carbon-sulfur bond as a carbon S- and then that reacts with methyl iodide to form SMe bond.

In a similar fashion we can use the second proton and then we form the second SMe bond. So this is how the carbon disulfide can react and then if we use an excess of lithium dimethyl cuprate then first one attacks and then it leaves the S methyl as a leaving group forming this intermediate. And similarly we can add one more time lithium dimethyl cuprate to it, two times in fact.

And then eventually the tertiary butyl group comes on to the alpha position. So it is something not very easy. That means, you start with a ketone, and then you make this particular intermediate and then go via this. So it is a little longer route to form this. On the other hand, if we use enol silyl ether chemistry, so we can start with the same ketone, make an enol silyl ether and then directly react with a source of tertiary cation here and then go to the same molecule like this. So this is the advantage of enol silyl ether based chemistry.

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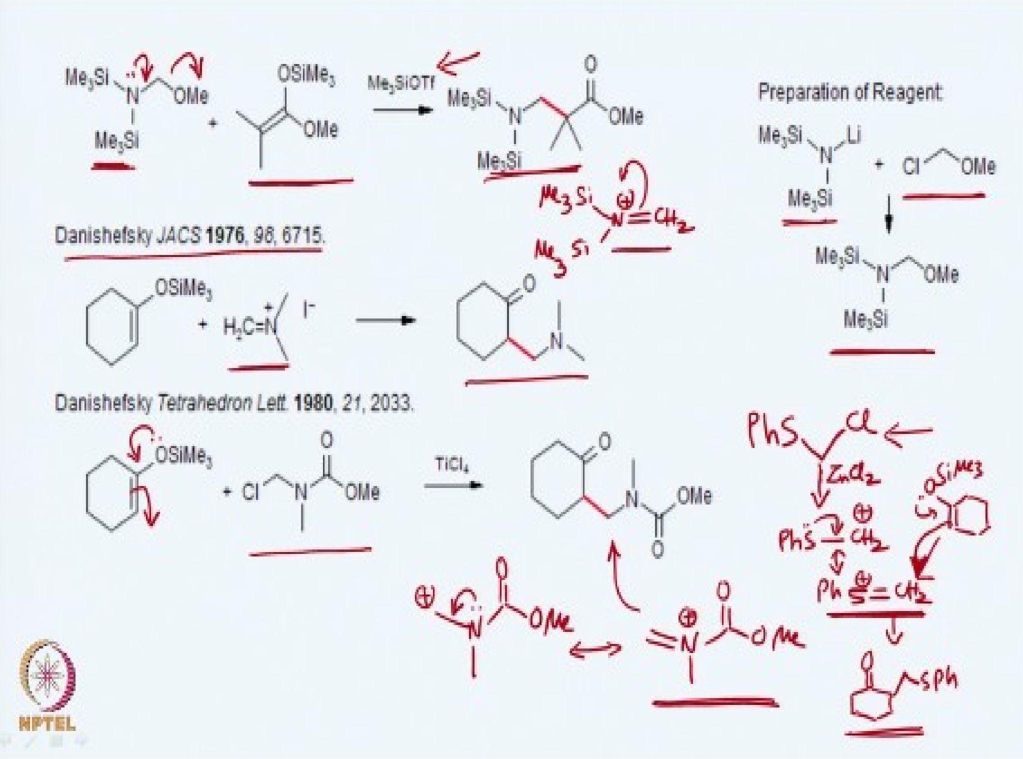

Preparation of Reagent

Danishefsky *JACS* **1976**, *98*, 6715.

Danishefsky *Tetrahedron Lett.* **1980**, *21*, 2033.

And it has also been seen that the enol molecules generated from the ester can react with these type of molecules in the presence of trimethylsilyl triflate as a Lewis acid and we can generate say in the presence of Lewis acid, we can expect to form something like this as an intermediate where now you have a cation that is stabilized by the nitrogen.

So now your enol, this ester here reacts on to this carbon and then you generate this species here. And how can you make this? You can start with this and react with the chloro(methoxy)methane and then you can generate this. So basically, this is a very important way of generating this type of species, which are useful for the making of C-C bond for example.

So in a similar fashion, the enol silyl ethers also react with this type of mannic type of intermediates to undergo reaction leading to C-C bond formation. And of course, we can also make use of this type of intermediate with $TiCl_4$ generating again as we discussed earlier, that you can generate a positive charge here.

And of course, you have the remaining part of the molecule, where we can think about having a species of this kind reacting with the enol silyl ether. So this is how the species that reacts in this way it will come and it will react with this part and then lead to the formation of this. So this is how the C-C bond reaction occurs with enol silyl ether.

So this is an advantage because you do not have to deal with enolates or enamines, and of course you can even use tertiary butyl groups if the cations can be generated. But then they are disadvantages. Of course, at the same time that you need a molecule that can generate a cation. For example, we can also take say you have a phenyl S CH_2Cl and you can generate this phenyl S CH_2^+, which is now stabilized by the sulfur.

And therefore you have this type of species formed. So you have the resonance between these two. And then the nucleophile from the enol silyl ether can attack on to this particular species, carbon atom. So one can carry out this kind of reactions and this will give, what will it give is a ketone here and then CH_2 S phenyl. So this type of molecules can be made.

Now this is possible only because directly the reaction will not take place. And then unless and until we use a Lewis acid to it. Say for example, you have a zinc chloride or any other Lewis acid that takes away the chlorine from here generating a positive charge on the primary carbon atom which is stabilized by the sulfur.

And therefore, this stabilized carbocation or sulfonium ion then reacts to form C-C bond and then reaction occurs. So these are the various ways by which enol silyl ether can be used.

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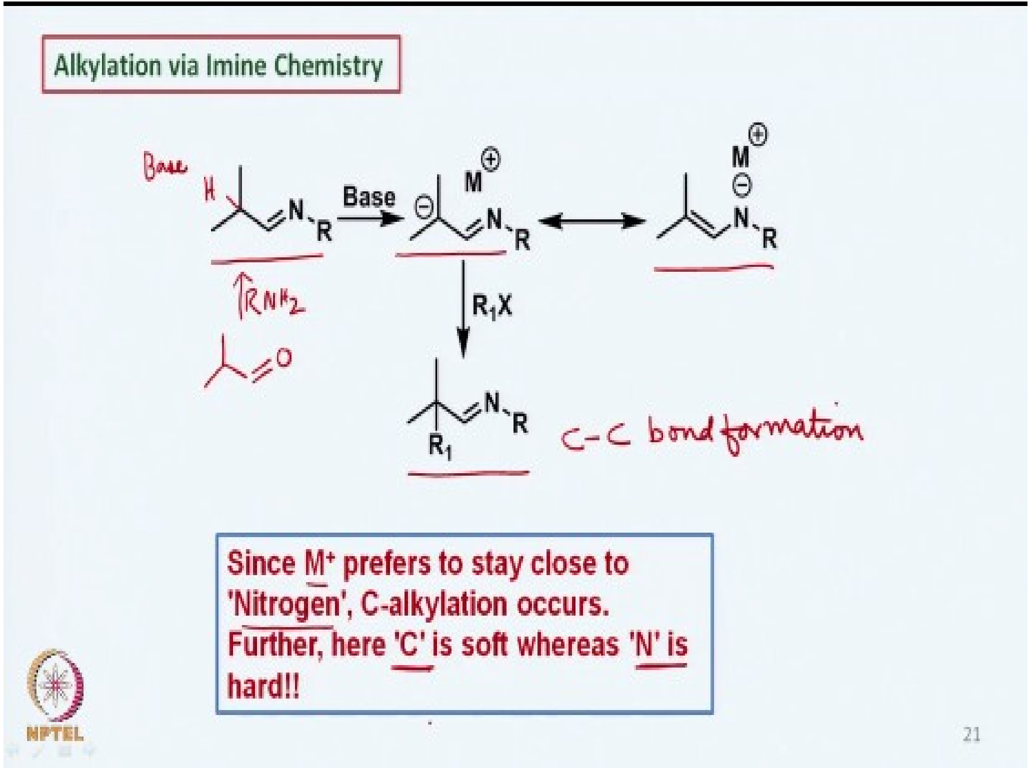

Alkylation via Imine Chemistry

Since M⁺ prefers to stay close to 'Nitrogen', C-alkylation occurs. Further, here 'C' is soft whereas 'N' is hard!!

Now there is another way of using imine chemistry for a C-C bond formation. So far what we discussed was that we start with an enolate based chemistry and then of course, we can change into electron withdrawing group attachment alpha to that so that C-C bond formation can be done. Then we saw enamine based chemistry and then there are problems of different kind associated with enamine chemistry.

And then we saw silyl enol ethers and then we saw the also the advantages and disadvantages of silyl enol ether chemistry. Now we look at alkylation via imine chemistry. So if suppose we are in a position to make an imine of this type, say for example with a carbonyl group like an aldehyde from here. So if we react with NH_2 here and R group here, then we can get the corresponding imine.

Now we can do the deprotonation of this hydrogen by base. So what we have is removal of this proton leading to the negative charge which is stabilized alpha to the imine group. And this can exist in this form or it can exist in this form. And then when the reaction occurs of the carbon then we have a C-C bond formation here.

And now what happens that we have preference of the M+ to stay close to nitrogen because nitrogen is more electronegative and then the C-alkylation occurs. That means, the same situation as we discussed earlier, when we were talking about the enolate based chemistry is that the counter ion M+ has to be very close to the nitrogen or oxygen so that the reaction occurs to form a C-C bond rather than O-C or N-C bond.

And further we of course have to have C is soft, therefore and nitrogen is hard and therefore, C-alktlation will occur with softer electrophiles. So this is how the imine chemistry's basic requirements are needed to be fulfilled.

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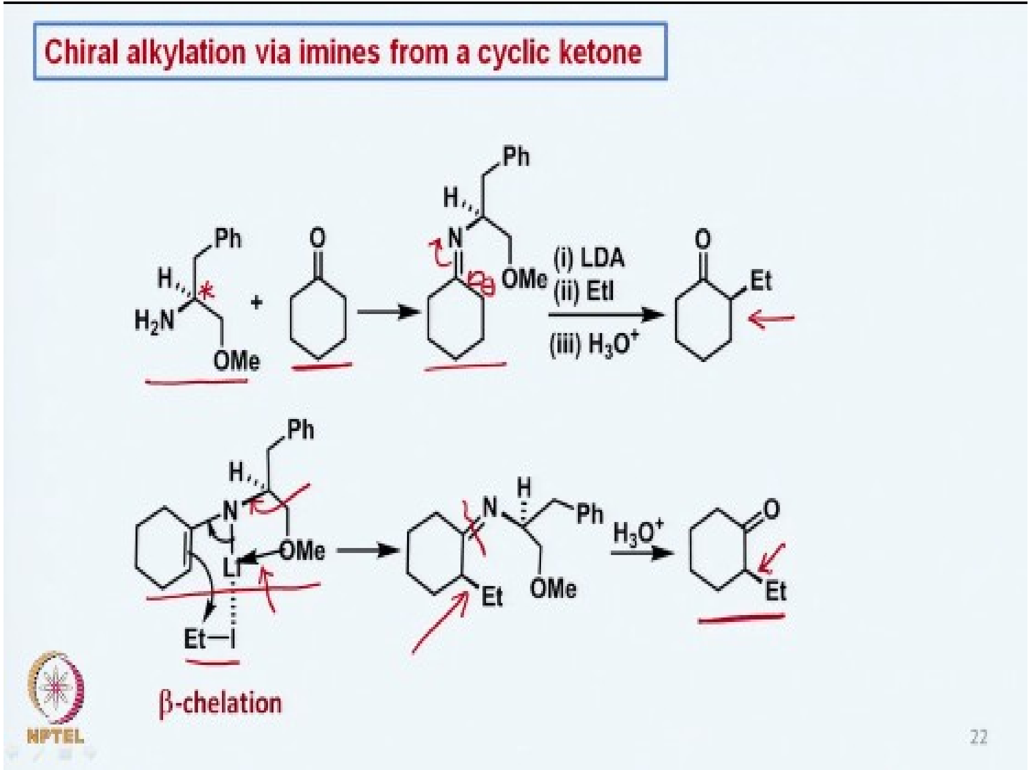

Chiral alkylation via imines from a cyclic ketone

β-chelation

Now if you take a ketone and make a reaction with a primary amine, which is a chiral amine. So we take this as a chiral center and we make this particular imine, which is now a chiral because the amine was the chiral. And now if we take the LDA as a strong base and ethyl iodide and then finally do the hydrolysis, this is what is obtained and this particular alpha ethyl ketone is optically pure.

So what happens here is that the geometry of the final molecule is dependent on the intermediates that are formed and then the anion, when the anion is formed from here, this anion, this anion can be resonance stabilized and therefore this kind of enamine is formed. And this enamine is such that the chosen part of the amine allows the O-chelation with the lithium. So if this is beta oriented, the whole molecule is beta oriented.

And therefore the methoxy group which has a coordination with the lithium is also on the beta side and then the attack also take place at the ethyl carbon from the beta side and then we get the introduction of the carbon-carbon bond from the beta side, because the beta-correlation is the one that is guiding this. And then eventually, after the hydrolysis of this carbon imine double bond N bond or the imine bond that leads to the formation of the ketone, where this is beta oriented.

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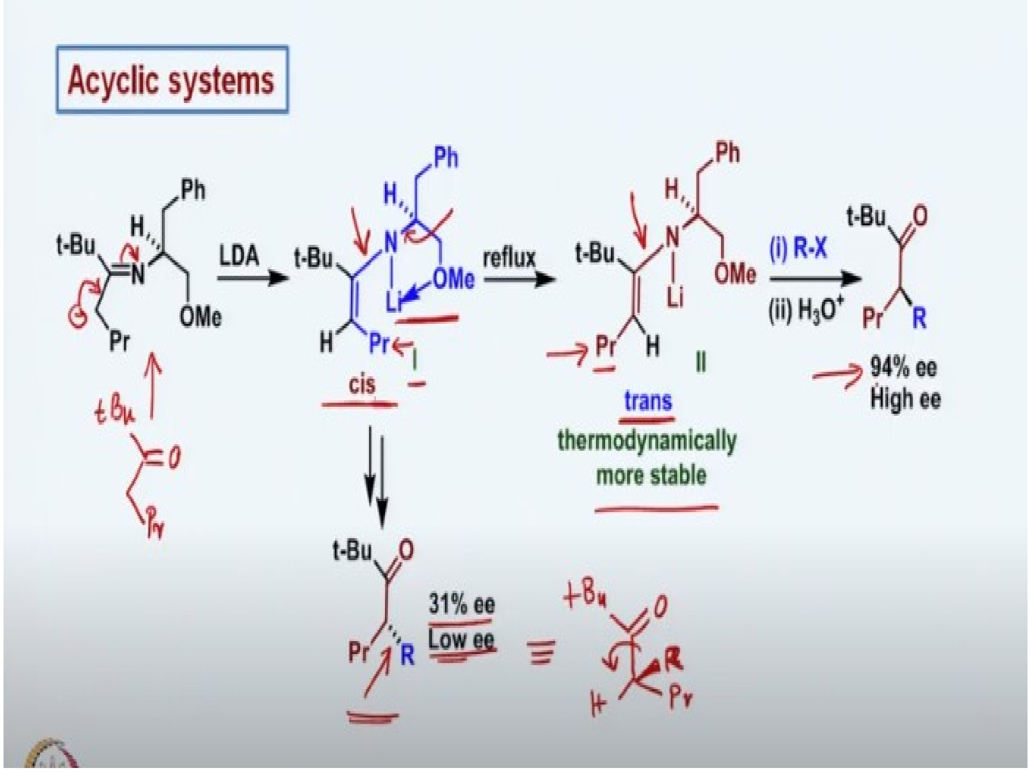

In the acyclic systems, it is somewhat different. Like if we take a similar type of amine, chiral amine and react with tertiary butyl, this is obtained from tertiary butyl and this part of the ketone, and this can give the optically pure imine. And when this is deprotonated from here, this deprotonation occurs. Then what we have is this intermediate which is of course stabilized to the oxygen as we saw earlier time.

Now if this is of course beta oriented and therefore everything is beta oriented and the reaction should occur from the beta side. So as you can see from here that this particular, since the ketone is acyclic, therefore there are two possibilities, one is cis and the other one is trans imine or the enamine to form. So when the deprotonation takes place, we can get this cis enamine, where this particular group and this group here are cis to each other.

Or if we heat it, then of course we have this group and this group are trans to each other. So this is thermodynamically more stable because the group here, propyl group and the nitrogen based group are trans to each other. So if we allow this particular electrophile to react with this enamine, then we can expect that tertiary butyl ketone and here when H is here, Pr is here, then this particular R group should come from the beta side.

And if we look at this and so this and this are the same, because if we rotate it here, then the Pr will come on the left hand side and the R which is beta oriented will become alpha oriented. So this is how the molecule can be written up. So essentially the alkylation is taking place from the beta side.

But then it is of low enantiomeric excess because, when such a reaction is done, you will definitely prefer that much of trans product is formed and less amount of cis especially at a little bit higher temperature. And therefore this low enantiomeric excess is formed because much of it will go to the trans product. Now if in the trans product when the reaction takes place of course, the R group comes from the beta side.

And as you can see that it is high enantiomerically pure compound, is close to 94% enantiomeric excess. So this is the reaction of the acyclic systems. So there are advantages and there are of course, disadvantages.

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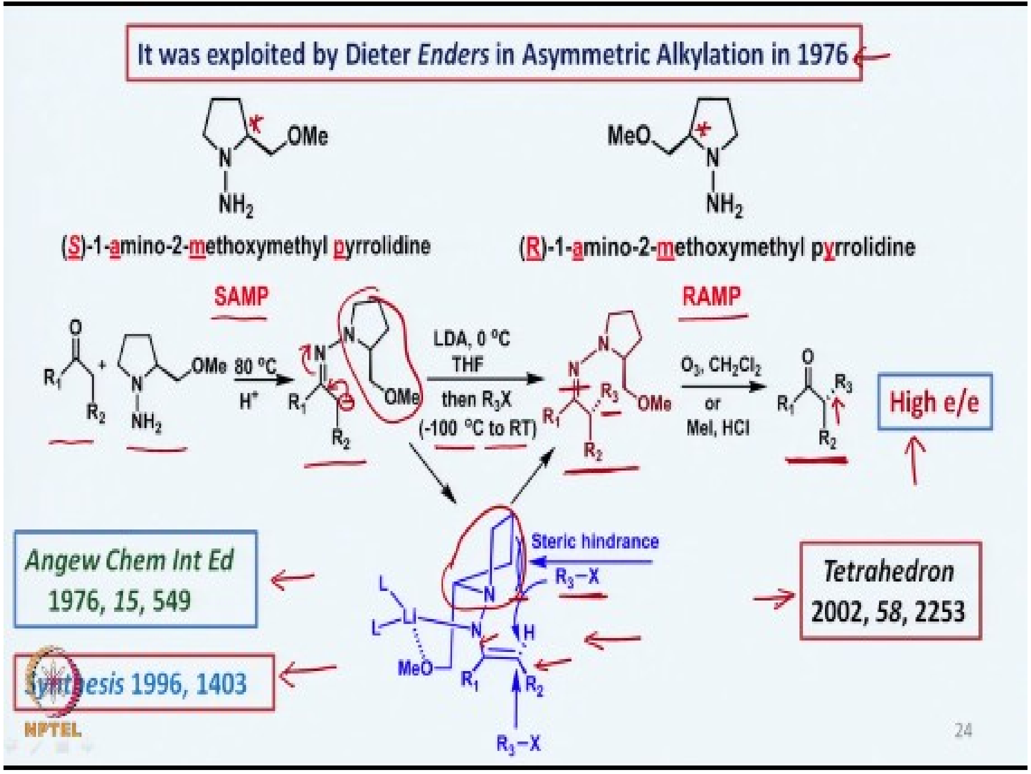

It was exploited by Dieter *Enders* in Asymmetric Alkylation in 1976

(S)-1-amino-2-methoxymethyl pyrrolidine

SAMP

(R)-1-amino-2-methoxymethyl pyrrolidine

RAMP

High e/e

Angew Chem Int Ed 1976, *15*, 549

Synthesis 1996, 1403

Tetrahedron 2002, *58*, 2253

Now this was exploited by Dieter Enders in asymmetric alkylation in 1976 and there are two very well-known SAMP and RAMP as two ligands, which are chiral ligands which are prepared and used as you can see it here. So there is an asymmetric center here and there is an asymmetric center here. So this is (S)-1-amino-2-methoxymethyl pyrrolidine and the other one is (R)-1-amino-2-methoxymethyl pyrrolidine.

So one is SAMP because of this SAMP and the other is RAMP. And that is how they are known as SAMP and RAMP hydrazines introduced by Dieter Enders. Not much is now being done on these but they are very popular. They were once upon a time very popular and even now Dieter Enders and others do make use of this in many reactions.

Now what exactly happens we need to understand it is that if we take a ketone of this kind and react with one of the two SAMP and RAMP hydrazines then we get, at 80 degrees we get this imine that is formed. And when this is reacted with a base at zero degrees and lowered the temperature to 100 degrees and then eventually slowly bring to the room temperature, then this reaction leads to the introduction of the R3 group as an electrophile and the C-C bond is formed.

And then you need to cleave this by ozonolysis or methyl iodide or hydrochloric acid. Say ozonolysis directly gives this one. If we have a methyl iodide then of course you have methylation on the imino nitrogen followed by a cleavage of the imonium ion. And that gives this ketone a very high enantiomeric purity of these ketones are seen.

Now how does this reaction occur is something that you can see it from here that you do the deprotonation and then the deprotonation leads to an enamine of this kind here and we are looking at thermodynamically stable trans enamine where this and these are trans to each other. And if we look at the same thing and orient this particular part, which is what is this part here.

So we orient it, turn it around and put it in such a way that there is a chelation of this nitrogen with this lithium and methoxy group. So you have this nitrogen, nitrogen, carbon, carbon oxygen. Same thing is here. And the only thing is that the LDA allows lithium and of course the other ligands attached to it in this fashion and then there is a chelation.

This chelation allows the cyclic intermediate or the transition state having these cyclic forms, bicyclic forms as a matter of fact. And then as you can see, that the double bond is ready to react with an electrophile R_3-X. But then, whether the electrophile comes from the top or from the bottom is the one that will determine whether the reaction use R_3 into alpha orientation or beta orientation.

As you can see from this particular transition state, that the top approach of the R_3-X is prohibited because of the steric hindrance caused by this large group which is present here. And therefore, the R_3-X attaches from the lower side leading to the formation of the carbon R_3 bond in an alpha orientation. And this is how the reaction occurs.

There are three references which I have mentioned, which you can go through and see if you need to go into details of these particular reaction. So this is one of the examples of how this RAMP and SAMP based hydrazine reactions have been exploited in organic chemistry to let asymmetric induction to occur. Now we will see in the next class, what are the other usefulness of these hydrazones.

Basically when you react this ketone with this hydrazine, then you are generating hydrazones and then after the C-C bond formation is done, then what is the what are the further reactivity of this imines, that can be taken up. At the same time what are the further developments in asymmetric C-C bond formation that also we will see in the next class. Till then bye and thank you for today’s class.