Introductory Organic Chemistry - II
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Indian Institute of Science Education and Research, Pune
Module 06
Lecture 42
Aldol Reactions: Specific Enol Equivalents - Part 01

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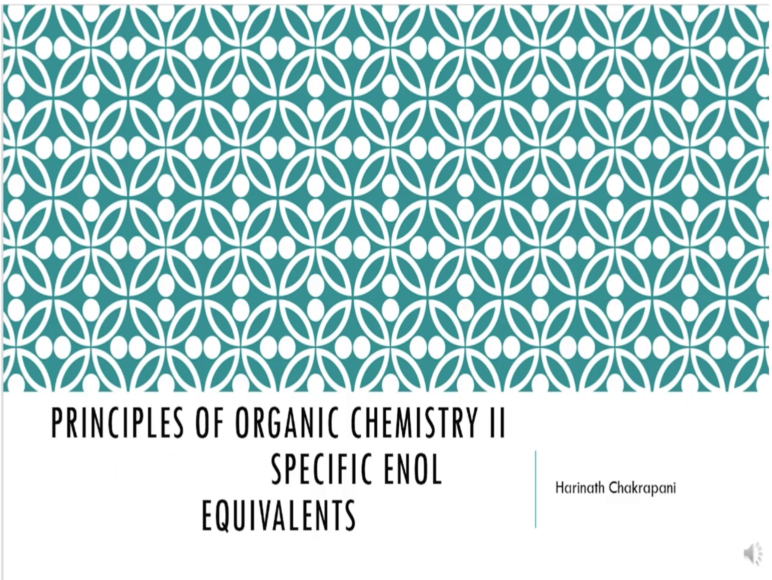
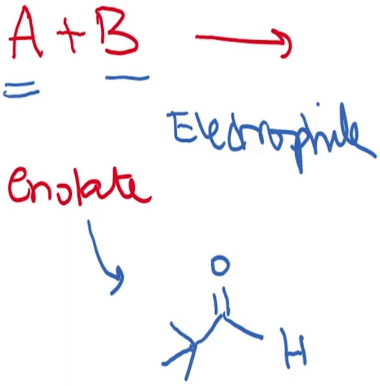


PRINCIPLES OF ORGANIC CHEMISTRY II
SPECIFIC ENOL
EQUIVALENTS

Harinath Chakrapani

Chapters: Reactions of Enolates with Carbonyl compounds Alkylation of Enolates



Welcome back to the next lecture. So, what we have been doing in the past three, four lectures is to figure out how to generate an enolate or an enol as the case may be. And we have also looked at the possibility of doing what is known as an aldol reaction where we react either an aldehyde with itself or we react ketone with itself or if you mix and match the reactivity appropriately then you may react an aldehyde with the ketone and so on.

So, however, I hope you will understand so far that, we still have some ambiguity in the whole process, because for example, if I pick any aldehyde and if I wanted to react with ketone for example, where I generate the enolate from the ketone, it is going to be challenging to do it with the methods that we have looked at so far. So, therefore, typically when you do an aldol reaction, so you have a component A, and if it is of course, reacting with itself, it is not a problem, but you have a component B.

And so, let us say A is the enolate and B is the electrophile. So, now, the problem is that you need to sort of figure out the reactivity of A and B properly. So, for example, the electrophile does not have any enolizable hydrogen at all. So, the examples that we have looked at for example, this tertiary butyl aldehyde. So, there is no choice here.

So, therefore, the enolate can only be produced from A and then the enolate reacts with this aldehyde and so on. Alternatively, you can also mix, you can have an electrophile that has enolizable hydrogen, but it should not be very reactive that is A should be much more enolizable than B. So, these are some criteria that we have looked at so far.

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Specific enol equivalents
Intermediates → have reactivity
of enolates but are stable
enough. | good yield

But, in order to solve this problem of trying to mix and match we generate what are known as specific enol equivalents. Now, we have looked at this earlier in the semester and for example, generating an enolate under certain special conditions we can do it. So, what these are basically, these are intermediates that have the reactivity of the enolates, the keyword here is the reactivity of enolates but are stable enough to be prepared and used.

So, unlike an enolate, traditional enolate they are quite unstable, these enols equivalents can be even stored if needed. So, and also the critical part is that they have to produce the product in good yield. So, these are some criteria that we look at for specific enol equivalents. It will become clear and as we go forward what these are.

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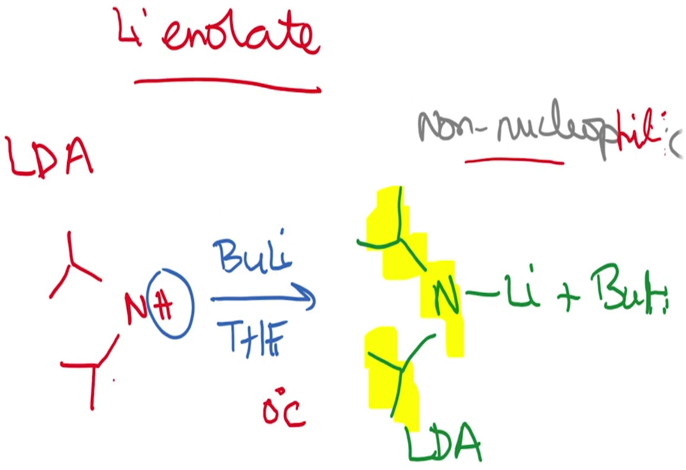

So, the first example of a specific enol equivalent is a lithium enolate. So, what we do here is we start with this molecule called LDA, which is I will just write it out here. So, this is diisopropylamine, now when I react this with butyllithium in THF. So, this is the proton that is going to be abstracted and we end up with $[(CH_3)_2CH]_2N\text{-}Li$, and this is called as lithium diisopropylamine.

Now, of course, the product that you get is butane, which I am just going to write it as BuH. So, this is very, very important, and of course, this reaction is carried out at pretty low temperatures like 0 degrees centigrade. And so LDA is a stable base, it can be made, it can be stored at low temperatures, it can also be prepared when you want to in the lab, you have to be very careful of course because the protonation of LDA is quite exothermic.

So, it is very, very commonly used in organic chemistry labs, as a de-protonating agent. Now, the important thing about LDA is also that because of these two Di isopropyl groups, this nitrogen is not a nucleophilic center. So, it is considered as a non-nucleophilic or poorly nucleophilic base. So, the idea here is that especially in this case you do not want this to be reacting as a nucleophile. So, you would much prefer that it reacts as a base. So, this is one of the examples of a non-nucleophilic base.

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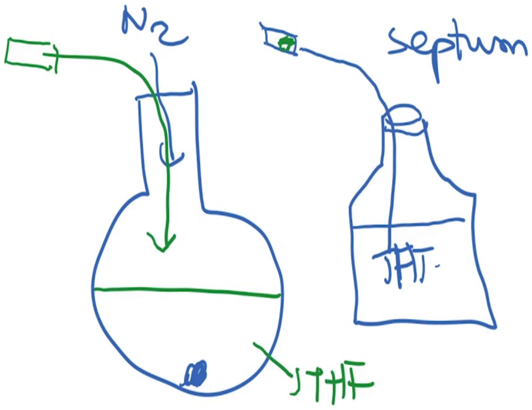

So, when we take LDA or when we take a ketone, what we do is we take, for example, a solution of the ketone, so you would normally keep this under nitrogen atmosphere. So, you add your ketone, you charge the reaction vessel with some of the aldehyde. And then what you do is you carefully distill out THF, so your THF is here. So, THF you freshly distill it and you cover this with what is known as a septum. I think all of you know what a septum is.

And so, this keeps it air-tight. And now, with the help of a syringe and a needle, you pull out the THF from here, to the adequate, whatever volume you need, and then that you will now transfer it to this container. So, once you transfer it, you have this much amount of, for example, THF. And now, what do you do is I am just going to write it on the next page.

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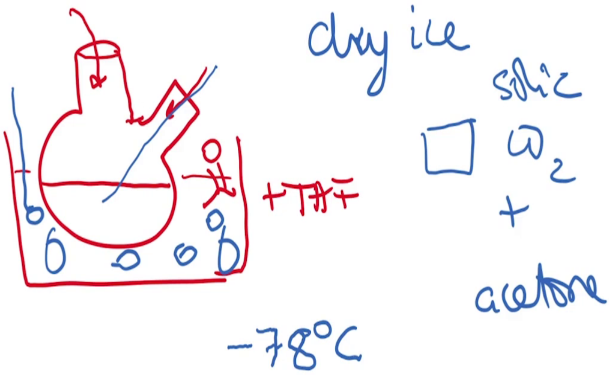

All this while you keep it under a nitrogen atmosphere. So, one of the ways to do that is to use a two-neck flask, so this is kept under a constant flow of nitrogen for this and you can do all your transfers from here. So here is your ketone or aldehyde with THF in it. So, carbonyl + THF. Now, what you do is you keep it under a trough which contains dry ice and acetone. So dry ice is you get these chunks of dry ice, which is basically solid CO_2, and acetone. Acetone is very widely used in organic chemistry labs.

So, you mix this dry ice and acetone in this. And what it does is it is a very, very inexpensive way of maintaining low temperatures, specifically, the temperature that we are looking at is around minus 78 degrees centigrade. And so, what this does is that once you put this two-neck RB into the trough, which contains dry ice and acetone, then the THF gets cooled down, and you are maintaining a very low temperature.

Of course, you can also insert a thermometer here, just to look at what temperature it is at, you can also insert a thermometer, you can also have an external thermometer to find out what the external temperature is. So, this is a pretty standard practice that is followed in organic chemistry labs.

And what you need to do is you need to give a little bit of time for the THF to acquire the temperature that you wish. So, you may need to give 5 to 10 minutes' time. And one way to monitor the internal temperature of course, as I mentioned is to use a thermometer and then to this reaction vessel, what you do is you can add LDA to it.

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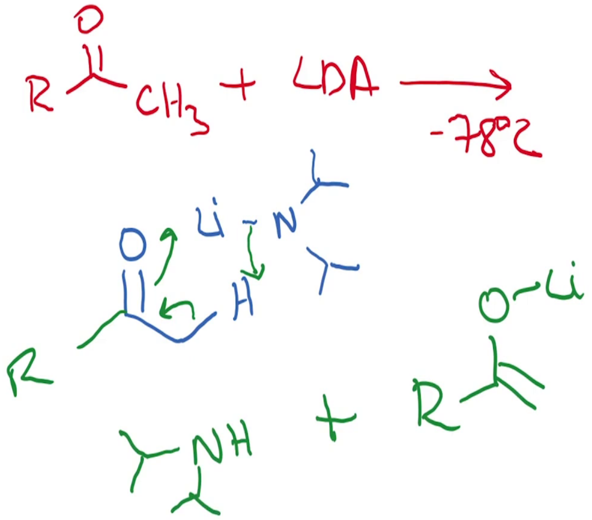

And so, the reaction now is, let us say we take this plus LDA at minus 78 degrees. And what we expect here is the following. So, you have $RC=OCH_3$, and you have your nitrogen enolate here, and there is a nitrogen base here. And what can happen is, you have the abstraction of hydrogen, followed by the reaction of the oxygen with lithium, and you get the product as $RC(OLi)=CH_2$. And of course, the by-product is Diisopropylamine. And so, this is one very good way to generate the enolate.

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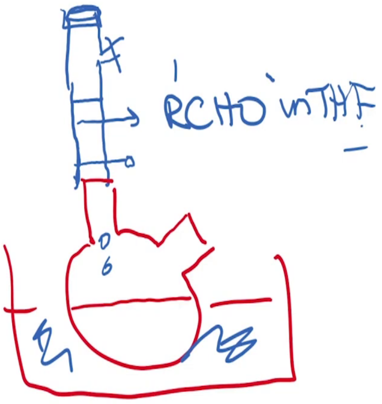

So, in this reaction vessel, as you recall, we now have the ketone, and we have added LDA. And you can measure out the exact equivalents of the LDA that you are adding. And you can very carefully generate the enolate, maybe in 20-30 minutes or so, depending on the reaction. So, what you do is you maintain this whole vessel at minus 78 degrees centigrade. And then, now I will give you another piece of information, another possibly experimental situation that you may deal with.

So, here is your reaction vessel, and here is the bath at minus 78 degrees. And now, you have the ketone, and LDA in this, so, based on prior experience or based on reported protocol you know how much of time it takes for the enolate to be produced. And now, what you do is you can predetermine this, you have what is known as an addition funnel.

So, the addition funnel is nothing but an addition that goes here, you have a small tap, you can add your reagent, you again have a septum over here, and you can add whatever reagent that you want, let us say here is the aldehyde in THF again. And what you can do is to also maintain the THF here at low temperature, there are ways to do it. But as a concept, what we will do is we will prepare the solution of the aldehyde in THF.

And then when you open this, there could be a tap here as well. And when you open this tap slowly, you will have drops of this aldehyde in THF falling into this. And the moment you are adding this here, the enolate is now exposed to the aldehyde. And then the reaction can occur. Now, let us go to what reaction we are talking about.

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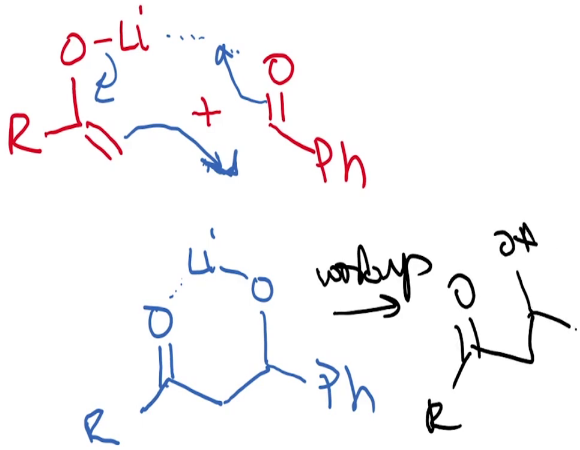

So, the reaction here is RC(OLi)=CH_2. So, let us say we start with benzaldehyde. So, you can have the attack of the carbonyl on this position like this. And you get the following. It is a six membered reaction transition state and you end up with C double bond O, and you can imagine that the lithium is coordinating to this carbonyl and you get R, a new bond that is being formed, O Li, now there is an actual bond between oxygen and lithium, and then there is going to be a coordinated bond here.

So, then what you do is, to this reaction vessel, you wait, after the complete addition of the aldehyde, you wait for about half an hour, one hour or whatever time, maybe a couple of hours, and then you warm it up to room temperature, the way you warm it up as you remove the dry ice and acetone and slowly it warms up to room temperature. And then at this point, you need to very, very slowly work up the reaction.

So, the way you work up the reaction is by adding a few drops of water very carefully, you may want to keep it under ice or at a low temperature so that the reaction whatever remaining base if there is a small amount of base that is remaining, and so on, they are going to react very violently with water. So, you are going to do a work-up with water very slowly and then you get the aldol product.

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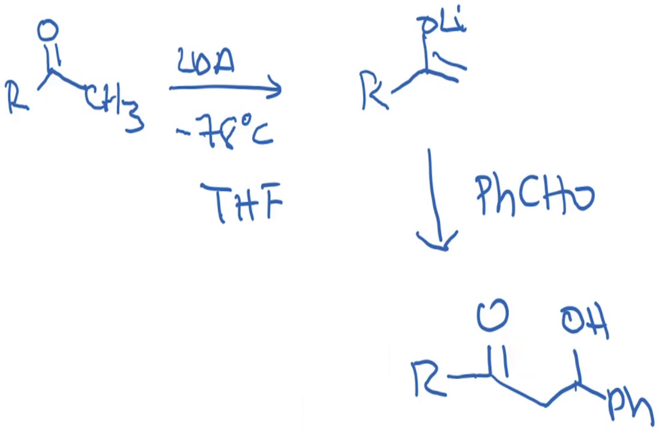

So, a quick recap on the lithium enolate reaction. So, the way we would do this reaction is we would first generate the enolate from using LDA and we would use minus 78 degrees centigrade, and typically these reactions are carried out in the solvent such as Tetrahydrofuran. So, this gives us the enolate and then the next step is when we add aldehyde, for example, we add benzaldehyde, and the product that we get would be $RC{=}OCH_2CH(OH)Ph$.

So, this is an example of the enolate that is produced by using LDA. So, there is one important aspect of this is that this reaction that we carry out at minus 78 degrees, it is pretty much an irreversible reaction. So, what happens is that once the enolate is produced, it really does not go back to give you the starting material. So, what you normally do is you, like we discussed last time, is you generate the enolate. And then you add the aldehyde drop-wise.

So, what it does is that the enolate is quite reactive here. And then once it, there is a plenty of enolate in solution, and there is a small amount of aldehyde that is added. And so, the reaction would favor the formation of aldol. So, now, in continuation with this topic, we shall now look at how to make and how to use what is known as silyl enol ethers.

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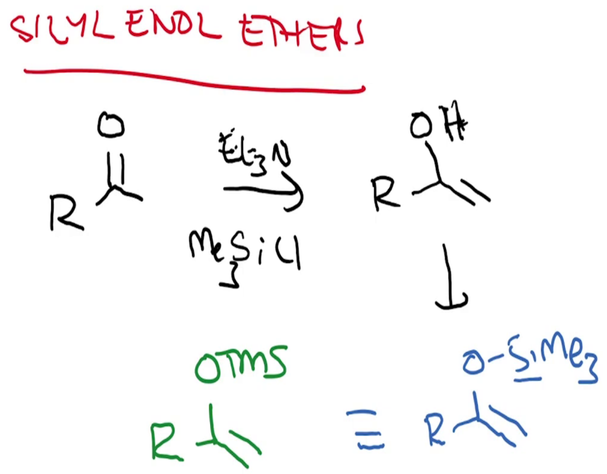

So, we have already looked at this in the previous lectures. So, silyl enol ethers, we saw them during the production of enols. So, the strategy here is that take a ketone, and then react this with triethylamine in the presence of a Me_3SiCl, which is trimethylsilyl chloride. And what this does is it first gives you the enol and then the enol is going to react and give you the silyl enol ether.

So, this is an enol, and if you have a methyl group instead of Si here, that would be an enol ether. So, this is called a silyl enol ether. Sometimes this is also represented as

$RC(OTMS)=CH_2$, which talks about trimethylsilyl group. So, this is the key reagent in this reaction.

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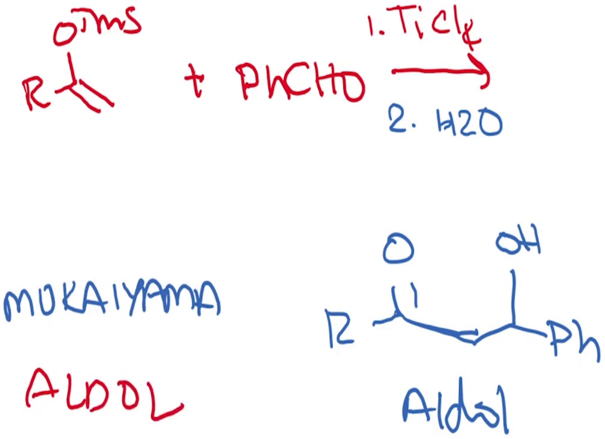

And so, what we do with the silyl enol ethers is that when you take RC(OTMS)=CH_2 and then you react it with an aldehyde, let us say we take benzaldehyde, okay, there is pretty much no reaction that happens. But when you add in a Lewis acid, if you recall, we have done for example, electrophilic aromatic substitution reactions, we have done in the presence of Lewis acid. So, in this case, the Lewis acid that is used is Titanium tetrachloride.

And then that is step number 1, and step number 2 is just water and work up. So, we get the aldol product. So, this is a wonderful reaction, it works really well. And let us look at the mechanism now. But this was developed by Mukaiyama and is referred to as the Mukaiyama aldol reaction. So, the strategy that we will use here is to generate a silyl enol ether, and then use the silyl enol ether and go forward with the aldol reaction.

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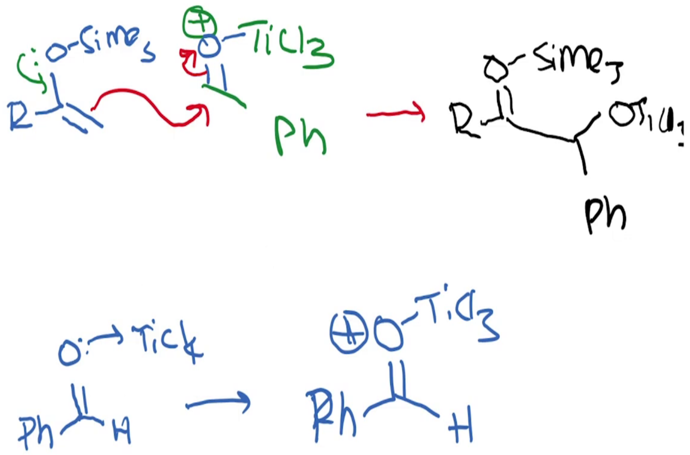

So, now let us look at the mechanism. So, we have already looked at the mechanism to produce the silyl enol ether. So, I am not going to repeat that. So, this is your silyl enol ether. And now, we know that carbonyl compounds can react with Lewis acids. And so, I am just going to draw that here. So, you have benzaldehyde and react with $TiCl_4$ to give you Ph HC=O^+ $TiCl_3$.

So, this is going to have a full positive charge on it. So, this is got to be quite activated. So, if we generate species such as this. Now, what we can propose is that the silyl enol ether is activated enough that it would come here, attack here and neutralize that positive charge that we have seen. So, the product that we would get is O $SiMe_3$ O Titanium Cl_3 still there and then the Ph is still here. So, I am just going to redraw this next page. So, you can look at it once again.

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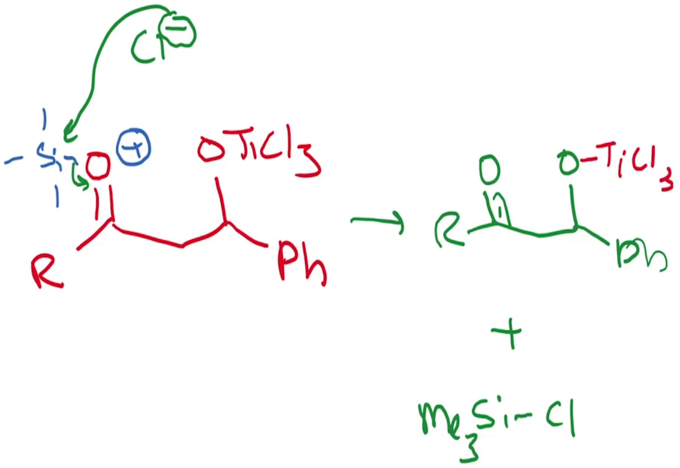

So, let me just redraw this intermediate for our convenience, $RC{=}OCH_2CH(OTiCl_3)Ph$. So, keep in mind that the silyl group is still here, and there is a positive charge over here. So, now, we can envisage that this silyl group is quite activated, and we have some chloride floating around.

So, chloride can come and attack this silyl group and free up the carbonyl group here. And so, the product that you would get is $RC{=}OCH_2CH(OTiCl_3)Ph + SiMe_3Cl$. And now, we can move to the next slide, I just write it once again.

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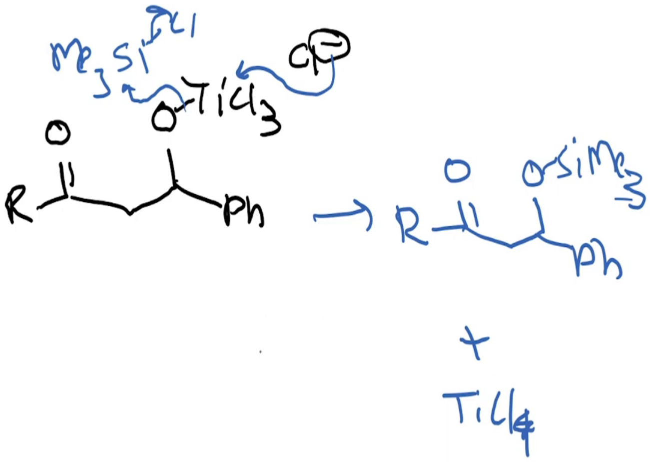

We have $RC=OCH_2CH(O-TiCl_3)Ph$ and you have this trimethylsilyl chloride, that is floating around, you have chloride which is still present and so you have a reaction over here. Now, which then eventually picks up this silyl group from here and the product that is formed is $RC=OCH_2CH$ (O- $SiMe_3$) Ph.

So, and titanium tetrachloride is also a product that is formed. Now, there are many versions of this mechanism. And they all have some common features. For example, this proposed mechanism may not be completely accurate, but you know there are some aspects of this reaction that are important for us to discuss.

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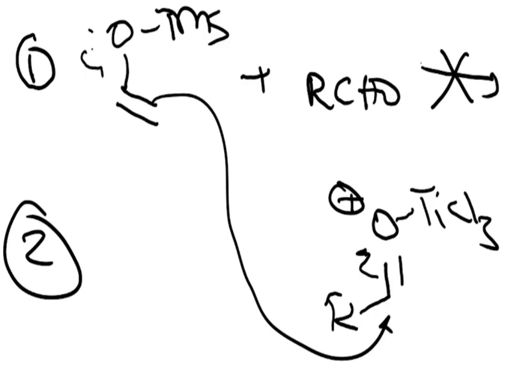

So, the first one is that if you just add the enol and the aldehyde, there is no reaction. So, without the Lewis acid, there is no reaction, the enol is extremely stable, and the carbonyl group here is not that reactive for it to react. And second thing is that the key step in the reaction is the reaction of the silyl enol ether with the Lewis acid complex electrophile, that means that your electrophile is going to be complexed to $TiCl_3$, for example.

So, now this reaction is the key step in the reaction. So, after this the steps that we discussed. They are of course important, but from a mechanistic standpoint, they are not that important. Now, let us look at one example.

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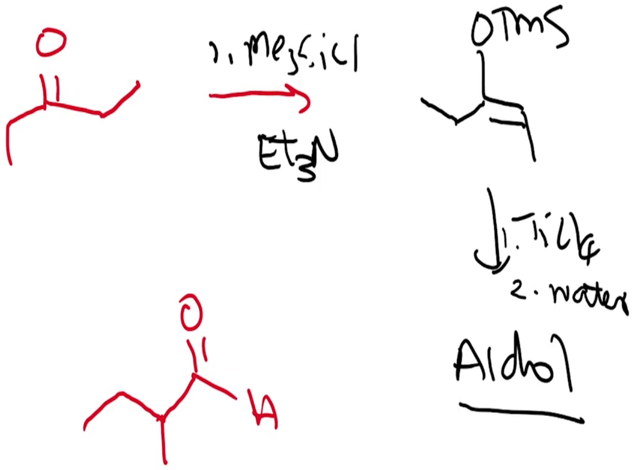

The example that we want to look at is we start with triethyl ketone. And if I want to add, let us say, we add this with this aldehyde. So, what we could do is step number 1 would be, Me_3SiCl, in the presence of triethylamine. And this is going to generate the TMS, right. And then the next step would be to react it with this aldehyde in the presence of titanium tetrachloride. And that is going to give me the product, the aldol product. And I would urge you to draw it out yourself, that will be, of course, number 1 would be this and number 2 would be water.