Metal Mediated Synthesis - I
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Lecture – 4
Alkyne metathesis

Hello, welcome everyone, today we will continue on discussing the metathesis reaction. You have seen ring closing metathesis or rcm. In the last class we have discussed the last example about the 2 in and one iron reaction. So, die 9 reactions, the molecule was having 2 in and one ion, initially the organometallic intermediate was formed at one of the terminal in.

Subsequently, that organometallic intermediate containing sparked reacted with alkyne because, that was the more favored ring formation which will give rise to 5 membered ring, and those 5-membered ring containing metal a cycle, then reacted with another in, to give a fused 5 and 6 membered ring formation. Today, we will discuss some more example of these ring closing metathesis reaction. First of all, one problem always we have to encounter, and that is the geometry, controlling the geometry of the olefin, that is generated during this rcm reactions.

Well of course, the olefin can be cysts or trans in nature. Let us look at the first example, one example where 2 terminal olefin is undergoing ring closing metathesis, to give a huge something like 19 membered ring formation. And in the process what we see that the product is a mixture of cis and trans. So, let us look at one of those examples.

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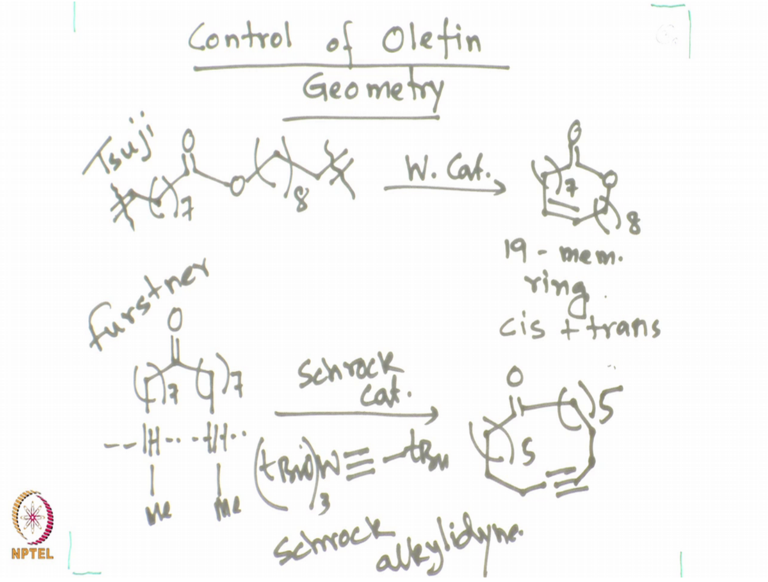

Control of Olefin Geometry

When we are looking at this molecule, this is reported by Tsuji. We have seen that the 2 olefins are there on the terminal position, they are interlinked by ester. Now in in presence of a tungsten catalyst, we have the ring closing metathesis in progress. Overall if we react this to terminal olefin, we will get 19 membered ring, 7 from this alkyl part, 8 from this alkyl part.

Overall it becomes a 19-membered ring; however, in these cases it gives a mixture of cis and trans product. Now there are not too many ways to control these cis and trans product formation. One of the way to control the cis and trans product formation, or that controlling the geometry could be reacting with, an alkyne instead of an olefin. So, these reactions are going to be alkalidi chemistry, where an alkyne instead of an olefin, is reacted with the organometallic intermediate.

During the process of course, if the 2 alkyne terminal position, 2 alkynes are reacted, those alkyne will give rise to the newer alkyne, where there is no problem of any geometry. Now that linear that alkyne the final product alkyne, if one is reducing with a suitable reducing agent, then one can control the geometry of the olefin. Let us try to look at these alkylidene ring closing metathesis reactions, and how to control the geometry in in those cases. The example which will discuss first is by Alois furstner. So, this is a terminal alkyne, not in truest sense.

But you know there is an alkyl group, on the on both the side of the alkyne. Now what furstner has done, now this compound he had synthesized and has taken schrock catalyst, that is the carbine tungsten catalyst, with carbine along with tertiary butoxide 3, this is the you know tungsten reagent, he has taken and this, you can called as schrock alkyli dyne in alkali dyne. Under this condition what one can synthesize, is of course these 2 alkyne will clip, and will give rise to this interesting compound.

In a moment we will see this is 5 of them and that. So, this is the one which is going to be the final product, where 2 alkyne is reacted with an alkalynin, and it is undergoing ring closing metathesis reaction. Now that is a very interesting product, because 2 alkyne is giving rise to another alkyne, which is now really a huge membered ring in the process.

Overall if one is trying to clip between react between 2 olefin, namely, terminal olefin or even internal olefins during the process, controlling the geometry is extremely difficult. One way to solve this or rather not directly solving it would be taking alkyne. 2 alkynes will undergo the metathesis reaction in presence of an alkalidyne species. That is an organometallic species the one we have seen is from shrock, where tungsten alkylidene is reacted with the 2-alkyne substrate within one molecule to gives rise to that internal alkyne. In the process the huge ring that is formed, can now be reduced with for example, lindlar catalyst which is a palladium hydrogen catalyst. Now in presence of that now you can control the geometry of the olefin, which is generated from alkyne in a way you want.

Overall if you look at this product then we will see this alkyne to olefin conversion, and the product formation leading to a world-famous perfume, and which is which is very, very cool way to synthesize this perfume. Let us look at that molecule again that we have synthesized.

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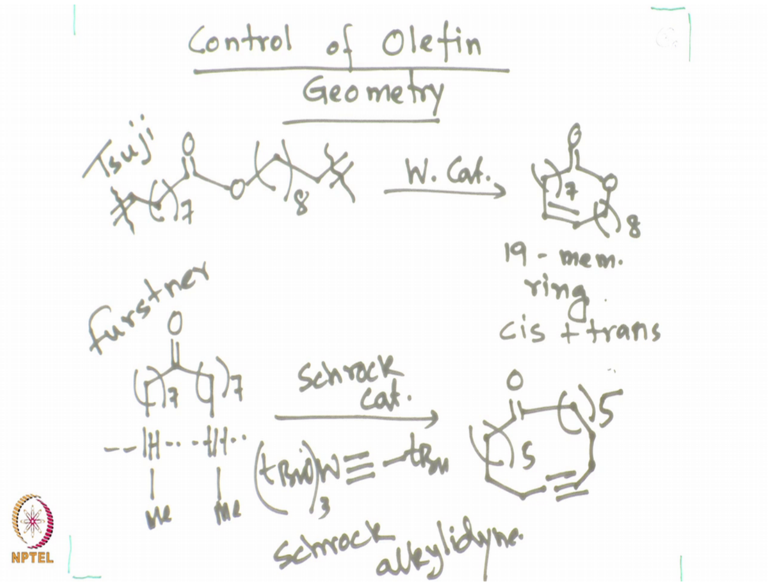

So, this is the compound we have synthesized, by using this shrock alkylidene species, and it has been reported by furstner from here on we can react it with palladium hydrogen, that is the lindlars catalyst, overall, we will be able to get, this civetone this is you the oldest perfume that is known, this is the ingredient of oldest perfume, and it is usually used in a kind of, extreme dilute condition. So, this is used very, very dilute, and you know it can be synthesized by a chemist quite easily. Now of course, this perfume industry is widely dependent on these ring closing metathesis reaction. I am sure all of us have used perfume, at one point of our life or almost some of some people may be using regularly.

Other perfume that is quite famous is muscone. Of course, there is a natural source, but you do not want to kill a lot of deer, to get that muscone, right. This is of course, illegal at this point and therefore, scientist has relied on synthesis of this perfume. And lot of these perfumes are now a days synthesized chemically, rather than utilizing the natural resources because those natural resources are scarce. And you know you do not want to go or push any animal into extinction, by doing extraction of this perfume.

So, the muscone for example, can also be synthesized by a similar pathway, that we have synthesized, or we have shown for civetone which is you know, which is the worlds oldest perfume known. And muscone is the one, which is now a days used quite widely. Let us look at the structure of the muscone, this is a again a ketone.

This is a very cool molecule, and this can be synthesized. So, this olefin can be generated, this olefin can be generated by utilizing the similar procedure. So overall what we have seen that, any huge ring can be generated, in the process of doing the ring closing metathesis reaction. Technically any terminal olefin or olefin, at any position 2 of those can be put together to generate yet another olefin.

Of course same is true for alkyne one can put together, 2 different alkyne together to form a new alkyne in the process. But let us look at that chemistry of the alkyne lindens tungsten species, which has been studied in details. And even there exist crystal structure, which gives the idea about the intermediate that is involved during the process. Let us look at the mechanism.

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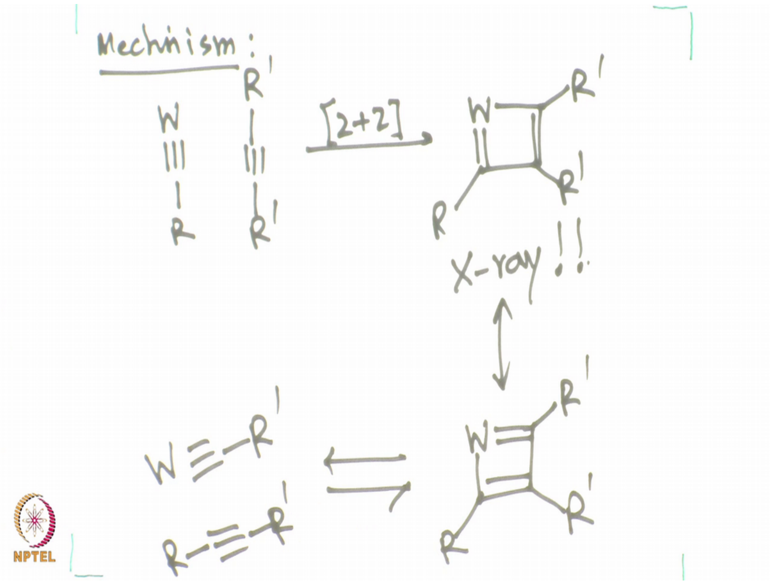

So, mechanism for this alkyl alkylidine species so, we are taking the tungsten alkylidene reacting with an another alkyne. Overall it is a 2 plus 2 reaction, to give you tungsten intermediate the most inter interesting part of this is; now characterized by x ray, what in x ray it is found that all the bonds over here are equivalent, all bond lengths are equal. Overall you can give a canonical structure for this, in the double bond, then shifted based on the fact that all the bond lengths are equal. You can see that you can say that, this is a resonance structure, between these 2 species right.

So, these are resonance structure, and subsequently if one is undergoing, retro 2 plus 2 O we can get the tungsten with another alkyl leading moiety. And this is this has to be really interesting, at this point because you know we overall, we get these new tungsten, alkylidene intermediate. So, we started with a schrock catalyst that is tungsten alkylidene, we reacted with a alkyne. Overall it is a 4-membered transition state, or 4-member intermediate that that we find this is crystallographically characterized, which clearly suggests that between the 2 structures, there is a resonance.

And therefore, all the bond lengths are found to be equal, and this gives rise to the a clear mechanistic idea how this might will be happening during those a ring closing metathesis reaction. Next topic, that we would like to discuss is, carbonyl olefination. Now all of us are familiar with, carbonyl olefination. In our undergraduate studies, or graduate studies this olefin you know of converting these carbonyl olefination reactions, are mostly known in terms of this utig reaction, right.

Of course, there is no organometallic intermediate involved. Although, utig reaction is quite popular. It is every reason to be popular. But a number of cases, utig reaction does not work, then if you want those utig like product. What is the alternative or, you have this metathesis reaction to rely on to get those utig like product. Now let us look at the pros and cons of this metathesis reaction, to synthesize the carbonyl olefinated product. Carbonyl olefination is the next topic that we would like to discuss.

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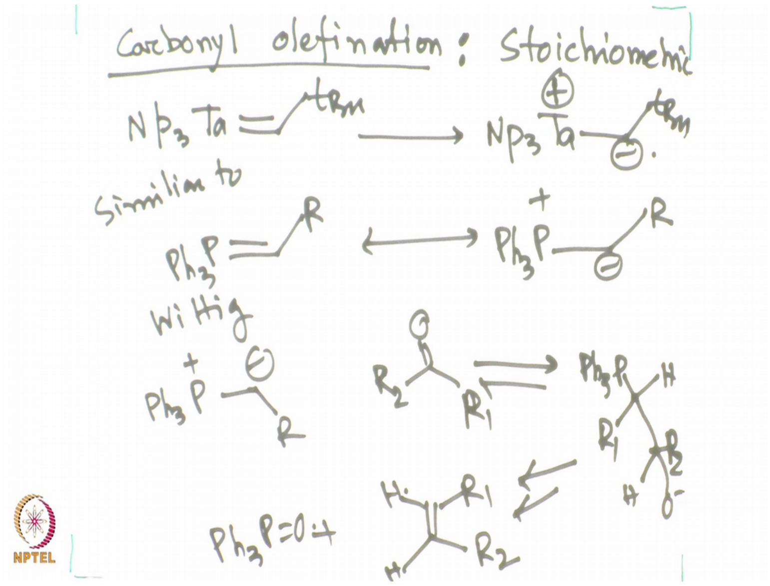

Carbonyl olefination also alkylidene chemistry, these are stoichiometric reaction. Of course, that is true also for the utig reaction the chemistry, we would discuss today, is the is with the schrock carbene, this is the schrock carbene. This you can draw in a different fashion, as we have discussed schrock carbene, is nucleophilic at the carbon center. This is similar, similar to what you know about the utig reagent, this is your utig reagent, and this is a equivalent thing, for a schrock carbene reaction.

Now overall what you do in the utig reaction, is this triphenyl phosphine, and this alkyledene equivalent, you react with let us say R 2's aldehyde overall to give, a intermediate where you have H R 1 and let us say H R 2 O minus, from there you get, R 1 and R 2 H H along with triphenyl phosphine oxide. Now if you look at this chemistry of the utig reaction. Of course, you are able to generate, a olefin from an ketone. Now similarly, if you are using this carbine chemistry those of, schrock metathesis reaction metathesis reagent, shock catalyst, if you are using and reacting with olefin you can get exactly similar product as you get in utig reaction. Let us look at one of the example, where schrock carbene is used for the utig reagent.

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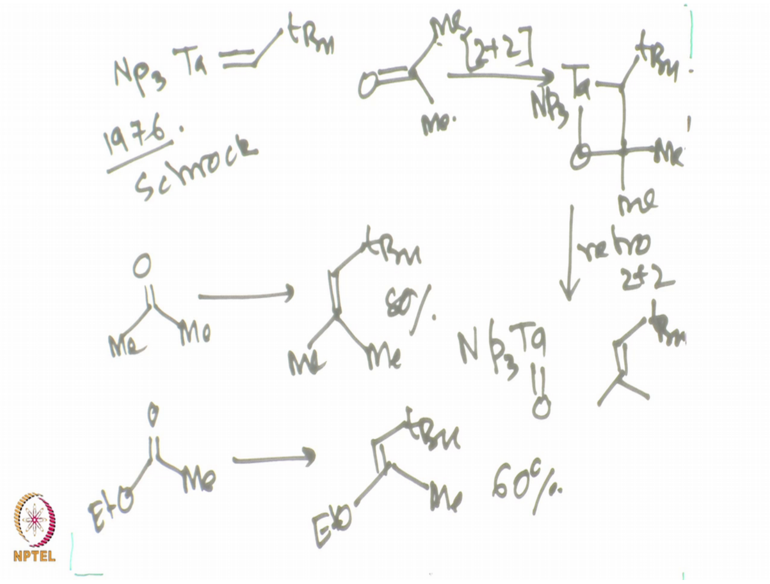

Now this is done by schrock in, early 18, 1976, rather 1976 by schrock.

He reacted it he schrock catalyst, which become famous letran reacted with a olefin, to give an intermediate which looks like just your utig reagent, utig intermediate. Now if you do that overall you have a 2 plus 2 and a retero 2 plus 2, to give you the tantalum oxide, is much similar to your phosphine oxide, and the product that you get in the process, has the terbutyl part. Because the terbutyl you started with the reagent, now terbutyl ended up with the product. Now this reagent, if a similarly if you want to react with a lot of other reagent, you can react with a number of ketone, to get the corresponding product.

As you know utig reagent really does not work with ester. That is one of the limitation of the utig reaction. But if you are interested in this schrock carbene for example, you can react with ester, of course aldehyde ketone ester, at will to get the product, that you desired from the ketone, to corresponding olefin product you can get in acceptable yields. The same thing, we cannot tell about the utig reagent, because utig reagent fails with the ester.

Let us look at one of those example, where ester is reacted with the schrock carbene, to give you the newer olefin. First of all, let us look at one of the ketone example, I think that we have discussed, during this process overall, we get this t butyl containing ketone in, 80 percent yield. That is great. Interestingly, as I was telling that ester, also react to give you the corresponding olefin, in in 60 percent yield. Now utig reaction of course does not work with the ester, because ester is less nucleophilic in nature. Now another case where utig reaction does not work, is the let us say you know dmf, if you want to do utig reaction on dmf, can you do that? Of course, you cannot because, it is you know that aldehyde center is less nucleophilic in nature.

You cannot a utig reaction with the dmf. Now dmf or even ester. Any ester you cannot do. And this is where this schrock carbene, or the metathesis type of reaction becomes, much more interesting, and can give the product, and it is used industrial in lot of cases where utig reaction is failing. And these reactions are now used, as an extremely dependable alternative, for the utig reaction. Let us look at one more example with dmf. Now dmf is the one this one.

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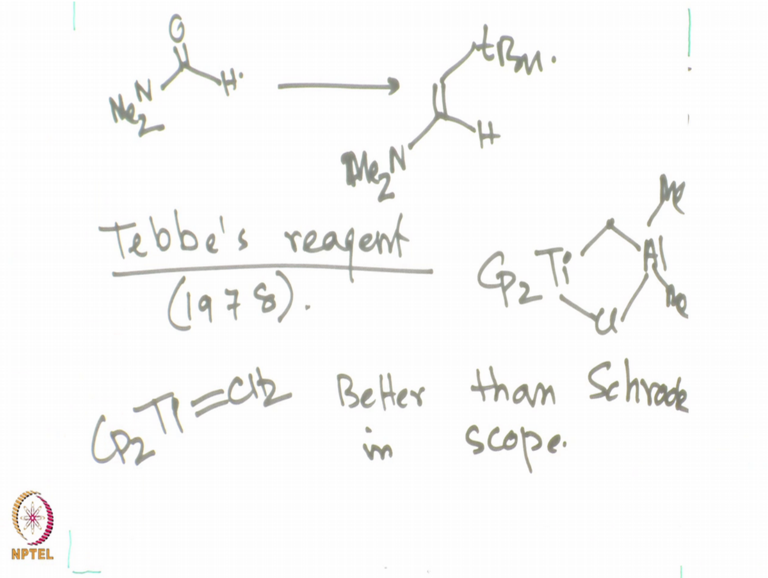

So, these are even less or lower nucleophile, compared to aldehyde, from there on you can get, using this your schrock al schrock carbene you can use the reagent. Now that is that is fine, when a lot of limitations, is there in utig reagent. You can utilize these carbene chemistry, to get the desired product namely ester and amide, which never really participates in the utig reaction.

But there is a problem in these cases because, as you see in all the product the final compound, if you look at carefully there is a terbutyl unit invariably, whatever you want to do that comes in. So that got to be the limitation of such reactions, where you cannot have any other alkyl groups at the olefin partner. Now if you are with the terbutyl group, if your target molecule requires to be terbutyl, that is fine. But if you do not want that, this is when the tebbes reagent becomes much more useful, and it is actually found to be quite versatile, even more versatile, then then schrocks this carbene chemistry.

So, let us look at the tebbes reagent, and let us try to see, if what it can do. A of course this step this reagents are alternative, to thus utig reaction. When utig reaction has no way to deal with the product formation, utig reaction fails completely. Then when car schrock carbene comes into picture, and of course the your tebbes reagent comes into picture schrock, and tebbes reagent of course works very well for aldehyde ketone.

And every other things, but one may not want to use them, when utig reag reagent is working ut, but when utig reagent is not working, this is the only way to move forward, with the ketone to olefin product formations. So tebbes reagent as you know tebbes reagent is a titanium species, this is cyclopentadienyl titanium species, which is ready to give you the active catalyst from their own.

This is done in 1978. So, these are methyle linates. The reactive species, are the one where this is dicyclopentadiene titanium methyle, linates is forming, and this better in scope compared to, even the schrock one. Better than schrock in scope. So, by using the tebbes reagent one can use, of course one can react with aldehyde, ester, ketone, amide and whatever other reagent which is incompatible with the utig reagent can now be incorporated quite efficiently.

Let us look at one of those example by which, this tebbes reagent can be of great use. First of all, let us look at the ester, of course as we have discussed these are not compatible, with utig amide ketones all can be aldehyde, everything can be reacted with tebbes reagent, the one example that we will discuss specifically, is the one where you have analyzable proton.

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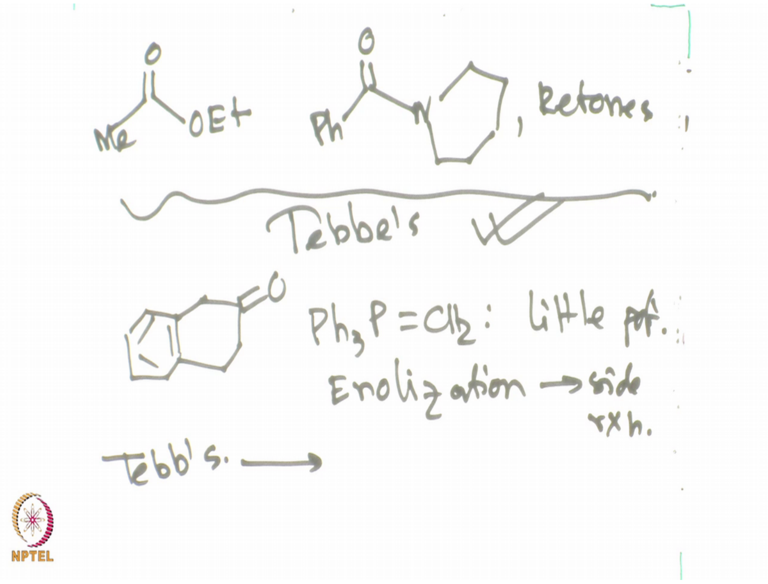

For example, this ketone now this, there if you are reacting this reagent this ketone, with utig reagent you get very little product. Because utig there is a analyzable proton which is not compatible with the utig reagent. Now so, therefore, if you take Ph 3 P double bond C H 2 this is very little product you get enolization as the side product or side reaction. Now these are tebbes reagent are tebbes reagent can be used over here very beautifully, because these are less bronsted basic and therefore, lesser ability to accept proton.

So, less enolization you can expect. So, less bronsted as in tebbes reagent is less bronsted acid. And therefore, it is not promoting the enolization that very effectively and overall, we can then get quite a good reaction with this with this tebbes reagent. So, this ketone which are enolizable they usually give you the side reaction as the enolization as the side reaction, which is what the problem with the utig reaction is. Now using tebbes reagent you can get or convert this ketone into corresponding olefin without any problem.

Once again, then what we have discussed in this class that utig reagent is a reliable reagent for converting aldehyde and ketone to corresponding olefin; however, in a number of cases utig reagent does not work and this is where schrock carbene can be extremely beneficial. And the problem with the schrock carbene is, it leaves a terbutyl or the you know the carbene terminal is getting incorporated into the product, often we may not want that into our product.

Although, it works decent with ester it works well with even the amide. This is when the schrock carbene cannot be utilized for a some of the substrate tebbes reagent, I would say is most versatile, and can be used widely of course, it can react with aldehyde ketone ester amide these works beautifully. So, it is a very good reagent with respect to the utig reagent. Now whenever utig reagent fails I would like you to think about the tebbes reagent.

Even for those ketone which are having enolizable proton one can react those reagents to get the corresponding ketone to olefin product formation, alright. So, in the class so far, we have discussed about mainly the schrock carbene. And it is reactivity we have seen how the schrock carbene has developed, and some of the reactivity pattern of the schrock carbene. In the next class we will get back to Fischer carbene, and their reactivity pattern. Till then, keep studying, will see you in the next class.