# Metal Mediated Synthesis - I
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## Lecture – 5
## Cyclopropanation reaction

Hi there. How are you all doing? I hope you are studying about the Metathesis Reaction. Today, we will mainly discuss on the Fischer Carbenes, their synthesis and their reactivity pattern. And if then time permits, we will try to discuss the Cyclopropanation reactions. Now, let me quickly do one transformation on the Schrock carbine or the Ring closing metathesis that we were discussing in the last class. What we have seen in the last class is the Terminal Olefin put together to make an Internal Olefin or 2 alkyne can be even put together to make an Internal Alkyne. What if instead of 2 Terminal Olefin, you have 1 Olefin and 1 Keto, can you do the ring closing metathesis on the Olefin and Keto containing molecule?

The answer is yes, you can do that. Let us look at 1 of those examples.

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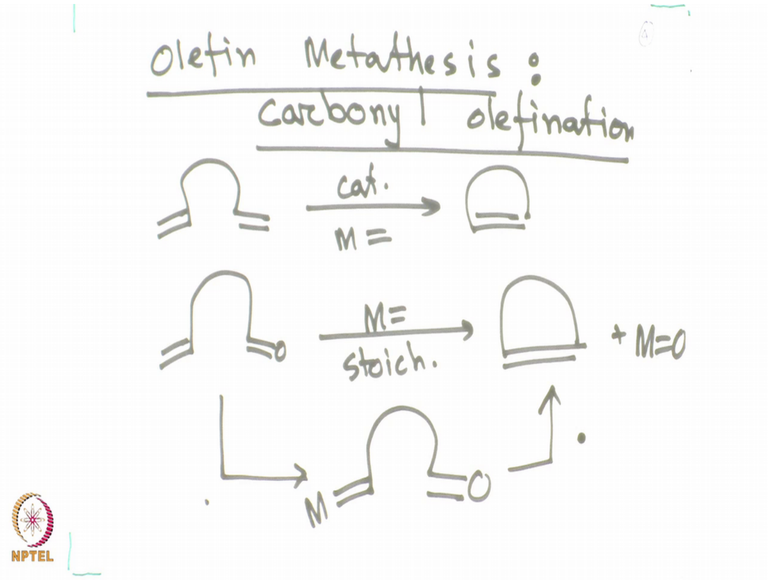

Now, this is the Olefin Metathesis you are familiar with. The catalytic metal carbine is reacted with die Olefin to give you a larger ring containing olefin compound. Now, what we have over here is a terminal olefin and a ketone and in these cases a once again metal carbene, but it has to be a stoichiometric version; in this case can give you the same product and without much problem. Of course, you are going to get a Metal Oxide in the process. The intermediate that is involved in this cases are the one as you can correctly predict. This Olefin reacted faster to or incorporate the Metal into the substrate. Subsequently this is 2 plus 2 and we did a 2 plus 2 sorry, yeah 2 plus 2. The total plus 2 gives this one. Once again, 2 plus 2 and retro 2 plus 2 would give you the Metal Oxide as the intermediate.

Now the next topic that we would like to move on is the Fischer Carbene. You have seen the example of Fischer Carbene, we will discuss in brief, the structure and bonding and their synthesis. Mostly we will be discussing the reactivity pattern of the Fischer Carbene. Now, Fischer Carbenes are also widely used just like your Schrock carbene. Fischer Carbenes are widely also used in synthetic chemistry. In lot of cases, it is used when traditional chemistry cannot have any solution and you desperately need that compound.

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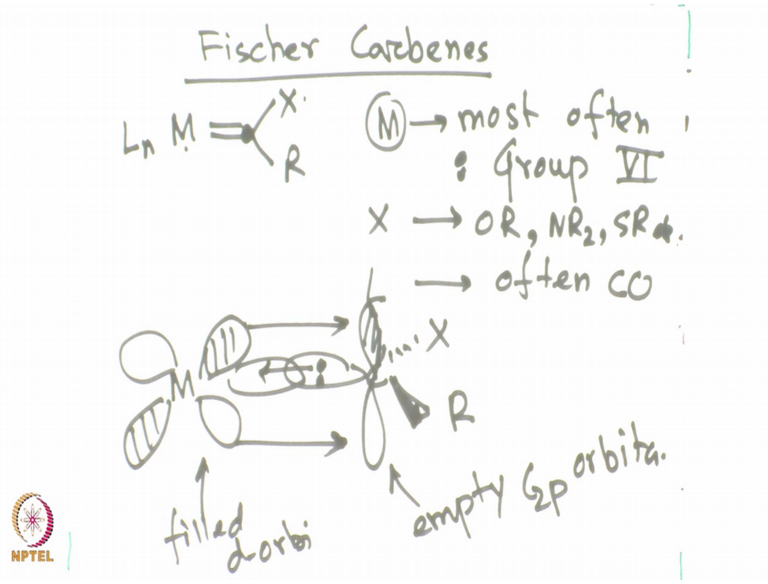

So, let us look at the Fischer Carbene and its reactivity pattern. So, Fischer Carbene. Now Fischer Carbene are the one, where you have a Ligand Metal and X R. This is the carbene center M, your this M is most often not always, but most often it is a group VI metal X this X over here is usually alcoxide, NR 2, SR etcetera. Of course, L can be often CO, not necessarily always, but it is all often CO. If you look at the Metal electronic structure of course, there is a d orbital on the middle which is a filled d orbital.

Now, it can bind or interact with the Carbene. So, this is the lone pair. Now X and R is there on the Carbene Center. Now on the Carbon is having this empty C 2 p orbital. This is empty C 2 p orbital overall. Then you have the donation from this lone pair of Carbene and the filled d orbital can gives to the give electron to the empty C 2 p orbital. That is what the interesting part, you have a you know Carbene to electron given into the metal orbitals and metal d orbitals are interacting with the empty C 2 p orbital. Now let us look at you know, let us look at the synthesis of these Carbene. Synthesis of the Carbene is quite interesting and straightforward I would say.

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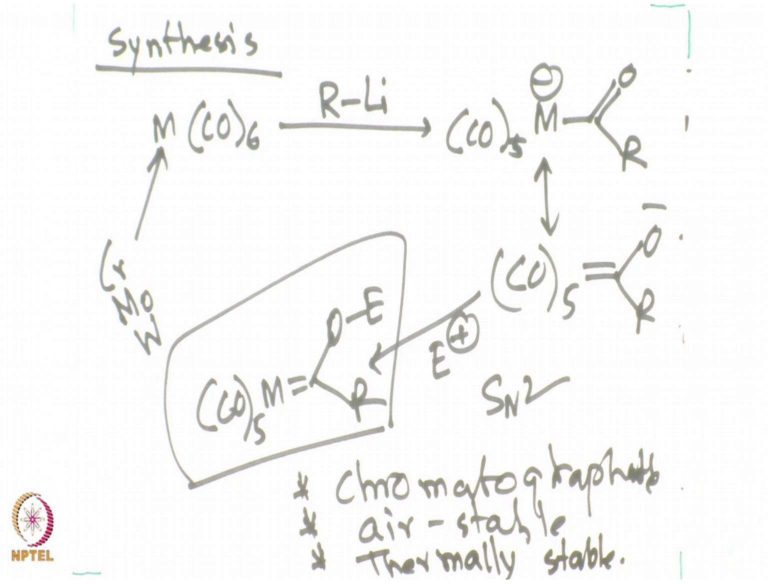

Lets say you have a Metal Carbonyl, Hexa Carbonyl species. This metal as you are saying it could be Chromium, Molybdenum, Tungsten and so on. You can react with Organolithium Reagent; we have discussed this briefly over the beginning part and from there on, you can have this intermediate where, this is a resonating structure between these 2 species and from which you can put an Electrophiles. So, basically this is an S N 2 reaction from where, you can get your product. That is the Fischer Carbene.

So, this is the Fischer Carbene that you are looking at. The most important part of these Fischer Carbene Synthesis, it is unlike other Organometallic intermediate species synthesis where, you have to take a lot of precaution here. Actually, this final compound are Chromatographon Chromotographable. You can run column on it. These are air stable. That is great from Organometallic perspective; if you can isolate purify and react it without any problem, that is going to be very very interesting. So, the characteristic of these species, this Organometallic intermediate are these are chromatographable graphable air stable of course, that is you know very very interesting properties and most importantly they are also thermally stable. Therefore, you do not have to worry about the reactivity pattern. Now the good part of the Fischer Carbene is they are equivalent to your carbonyl.

Now, in a moment we would like to discuss, how can you compare the Fischer Carbene with Ester and Amide? Both Ester and Amide has a ketone unit CO right. Now how does it compare in reactivity pattern with respect to this ester and amide? That is the one we would like to discuss. What is the bond rotation energy between carbon and A or carbon and B, unit that is what we would like to discuss.

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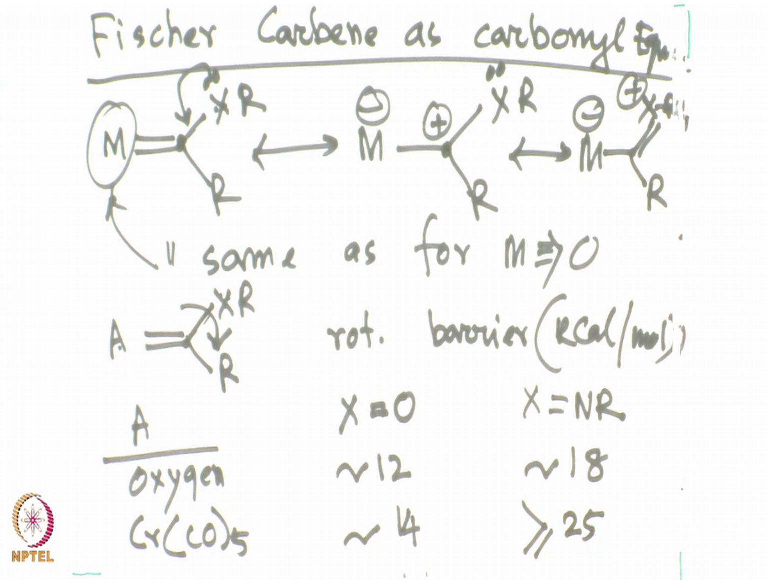
Fischer Carbene as carbonyl Eq

same as for M ⇒ O

rot. barrier (kcal/mol)

| A | X = O | X = NR |
|---|---|---|
| Oxygen | ~12 | ~18 |
| $Cr(CO)_5$ | ~14 | ≥ 25 |

So, this Fischer Carbene adds carbonyl equivalent; we have seen they can be quite interesting in this aspect and they can be very very beneficial, while we are interested in a desired transformation. Fischer Carbene as carbonyl equivalent, carbonyl equivalent, the 1st thing that comes to mind is let us try to put the lone pair, that is the integral part.

Now, you can write it down like M minus and this is your plus; this is what the characteristic of the Fischer Carbene. This carbon center is cationic in nature or positive and the one that you would like to draw further is the one where, you have a double bond character between this carbon center and this A or X R in the spaces right. Now this is a double bond character; that means, this is more of A in between it is going to be in between A double bond and single bond.

Now how strong are these bond compared to esters, that is where we are interested. So, this metal center as it turned out, this is same as for M equals when you want to put it an oxo; that means, Ester or Amide. Now we will compare let us say we put it A double bond XR, A where it could be Oxygen or Metal. This is we are got trying to compare with Ester and R and we will try to see that rotational barrier, rotational barrier. The unit we are following is Kcal per mole. If you have A, A as oxygen and then X, this X equals O; that means, it is a ester we are talking about r CO or the rotational barriers is nearly 12 Kcal per mole for this. This rotation we are talking now, X equals when NR or X equals N then, we are looking at 18 Kcal per mole.

If this is C r CO 5; that means, if Fischer Carbene, now we are dealing with here. Now this rotational barrier for Fischer Carbene, the CX barrier is 14 and if it is an N R, then the Fischer Carbene will have rotational barrier greater than 25 Kcal per mole. So, this is very interesting right. What you see therefore, then compared to ester and amide, normal ester and normal amide, your Fischer Carbene, this Carbon Hetero Atom bond rotation barrier is even higher; that means, it has a better double bond character indirectly it says that the lets say for example, this one is Chromium Pentacarbonyl, when your X equals chromium pentacarbonyl as opposed to O or oxygen for ester and amide, the rotational barrier is higher; that means, it is much more electronegative. Chromium CO 5 is much more electronegative compared to oxygen; that is a very interesting information qualitatively and quantitatively as well because the then we can compare and contrast the reactivity pattern of these Fischer Carbene with that of the known ester and amides.

Let us look at that, how to compare the reactivity between these 2 species?

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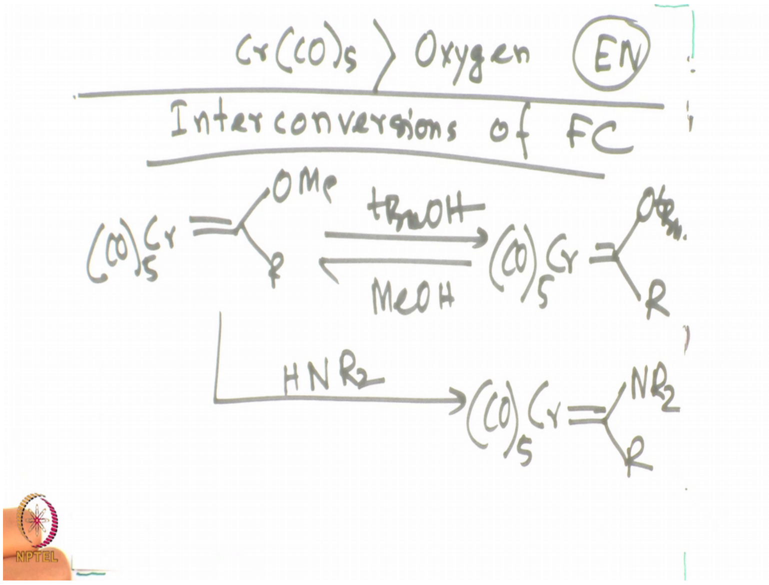
Cr(CO)5 > Oxygen EN

Interconversions of FC

What we have then? Chromium penta carbonyl is much more electronegative than oxygen in electronegativity right; that is a interesting phenomenon. What we can then do try to do is the inter conversion right, we know that ester can be 1 is to transesterification is a famous phenomenon. We can, can we convert one Fischer Carbene into another Fischer Carbene much similar to what transesterification does. So, interconversions of Fischer Carbene. Now if you start with this, chromium penta carbonyl species and react it with another alcohol for example, Tart Butanol; of course, this is going to be a reversible reaction what you can get is the tart butyl oxide or tart butanol replacing methanol to give you that. Of course, since its tart butanol you cannot do SN 2 reaction.

It has to be the one, where you know you see the reactivity pattern similar to the one, we have with amine as well. So, you can interconvert or you can exchange alcoxide with amine unit or alcohol with an amine counterpart right. Now that is having said that, then that sets of the right platform to do in number of interconversion that tells you that if you have one Fischer Carbene from there on, you can synthesize plenty of other Fischer carbene just by simply exchanging the different alcohol or different other amine. That means, of course, there you have seen there moisture stable or a air table, they are air stable, they are thermally stable and of course, they are also chromatograph able; that means, synthesis of these Fischer Carbene becomes much much easier and without problem we can synthesize a variety of them.

Now one reaction that really comes quickly to mind is the Diels-Alder reaction of ester. Because it is a dyne dynephile reaction; your dynephile has to be electron withdrawing in nature and that is how the Diels-Alder reaction goes. Now how does it compare? What do you expect from Fischer Carbene? Can it participate in the Diels-Alder reaction? Of course, let us try to figure that out the Diels-Alder reaction.

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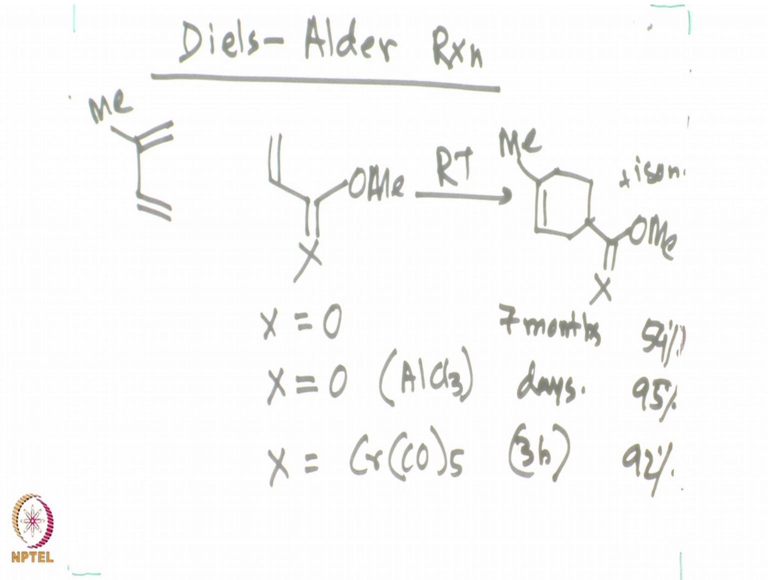

That we would like to do with these Fischer Carbenes. Diels-Alder reaction as you know we can do with a leaf you know in and ayn. So, dine and deinofyne. So, if this is your butane, if you are taking diene and usually we are familiar with an ester over there; let us say for OM e, if you want to do this reaction at room temperature one, you are in for trouble this reaction when even it is X equals O. This reaction does work, but at is as it turned out it is little bit longer.

How long is it of course, you have other isomer as well. If X equals oxygen and if X equal oxygen with Luis acidssuch as AlCl 3 and if X equals Cr CO 5, what would be the timeframe that we are looking at? Well, that is a very interesting one, that is how perhaps you know PhD students are therefore to figure it out, how easy or difficult these reactions are. If you are interested in doing this Diels-Alder reaction with an ester for example, the dienophile if X, that X equals oxygen, can you imagine how long it takes? It takes 7 months. I donot know how did they do it, perhaps they set it and then waited for 7 month.

I hope they have controlled it nicely, but overall what we know about this reaction is it takes 7 month to get even 50 percent, 54 percent yield to be precise for this dynophile and dyne to react to gives the Diels-Alder reaction. Now that is quite interesting 7 month it takes, but when you are interested in putting some luis acid; that means, you are making the dynophile much more reactive then the reaction is done in days.

That is very promising, but can you imagine when you take this X equals Cr Co 5 chromium pentacarbonyl; that means, a Fischer Carbene. Well, that gives the reaction in hours; that tells a lot about the utility of this you know Fischer Carbene reaction. How reactive they are compared to your traditional organic reagent. Let us look at the yield of this reaction this takes 7 months give 54 percent yield. This takes nearly, you know nearly days I guess days; days it gives 95 percent yield. If this takes 3 hour; it gives 92 percent. Now this tells you that this chromium penta carbonyl species, they are the one acting more of a more like a activated you know ester activated with a luis acid.

Of course that because chromium penta carbonyl is much more electronegative compared to your oxygen atom. So, the ester oxygen or this Fischer Carbene oxygen, Fischer Carbene, this chromium penta carbonyl can be compared directly and can be accelerating the reaction quite efficiently as one would expect. Now that is a very interesting reactivity pattern comparison as you have seen chromium penta carbonyl or the Fischer carbonyl can make the reaction very very fast compared to your traditional Diels-Alder reaction where, dynophile is used as ester as compared to as compared to your you know Fischer Carbene reaction.

Now lets try to compare it a little bit more and try to see how they compared with the Enolate chemistry because all we are trying to compare is how the ester reacts and how the Fischer Carbene react. Then the in a Enolate chemistry we should be able to comment on that we should be able to comment their reactivity pattern and how efficient they are in in this business.

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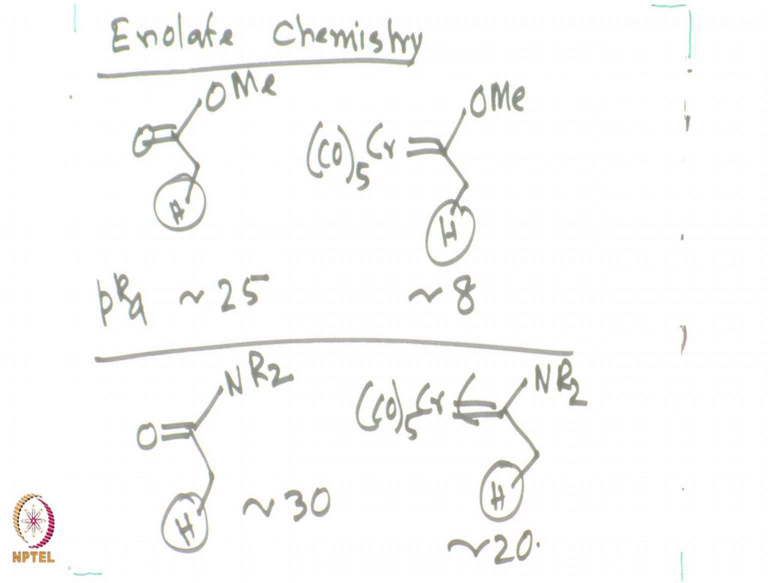

So, Enolate chemistry. What we have traditional Enolate, let say if you want to compare this ester with chromium penta carbonyl, this reagent that we get from the Fischer Carbene. Now as you know lower the pk a value higher the acidity where the pk a of this one versus that one; if this is nearly 25, what it is found is nearly 8, that is again very very exciting. If you have an amide, now of course, acidity of this pk a or acidity of this is nearly 30, pk a is 30; if you have the chromium equivalent for the same thing, now you have with this chromium reagent you have quite acidic CH this CH is nearly 20.

So, this tells you that this is directly comparable the Enolate chemistry or pk a value you can have is quite low pka low means it is a better acidic much more acidic. This reagent or this part when you have this CH 3 attached with a chromium penta carbonyl, that is much more acidic compared to when the CH 3 is a part of an ester; that means, if it is more acidic therefore, what you can think of subsequently is doing the Aldol chemistry as you know very familiar with the Aldol chemistry, how Aldol chemistry would be? Well, I would say it is going to be very very reactive and it is going to be very very active partner in the Aldol chemistry right.

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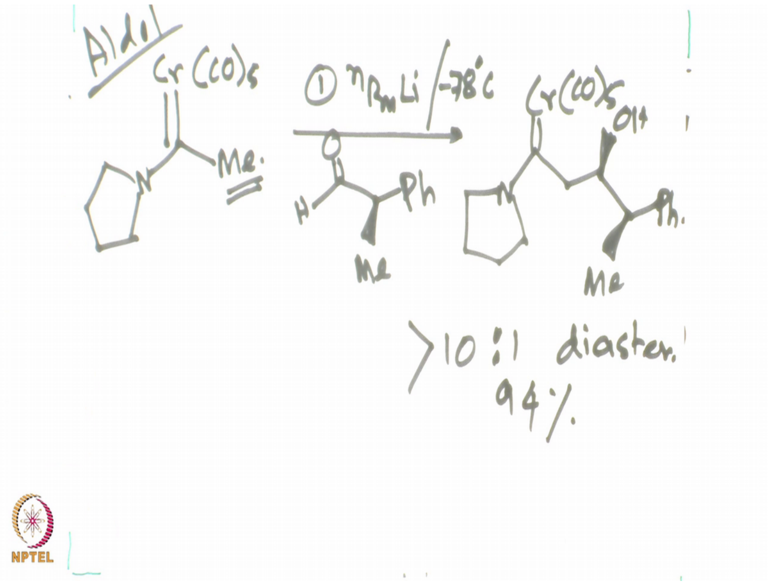

Lets look at one of the Aldol reagent or Aldol chemistry. With this, Fischer Carbene reagent and we should be able to demonstrate the efficiency of such reaction. The chromium penta carbonyl reagent, we have and then it is reacting with Methyl counterpart now this is the one which we have seen the acidity is quite good and if you have n Bu Li at even minus 78 degree c and you are interested in reacting with an aldehyde, we are doing a Aldol reaction. Let us write it down and Aldol reaction we are trying to do and we get the product quite efficiently in these cases and what we get is the expected Aldol product with a very high dia stereo selectivity, that is done at minus 78 degree you know centigrade; we get greater than 10 to 1 diasterio selectivity, diastereo selectivity and we have nearly 94 percent yield.

Now so, I think with that we would like to close on this reactivity pattern of the Fischer Carbene as you have seen this is quite interesting, you can have a number of or any example that you know with the Aldol reaction, you can possibly think about Fischer reaction not possibly definitely you can think about the Fischer reaction right. These are these are much more acidic the methyl group or the part not that is associated with the Fischer Carbene. Its much more acidic, any Aldol reaction that you can think of you can do. You can do the inter conversion of ester to amide or you know the corresponding Fischer Carbene to one Fischer Carbene to another Fischer Carbene and so on.

You can also have a very good Diels-Alder reaction as we were saying Diels-Alder reaction. So, whatever reaction you can think of with ester, I think you can pretty much parallel those reactions we and with much more efficiency and shorter reaction time perhaps in most often better yield and so on and once again, these reagents are very very user friendly right. You can you can isolate it, purify it and chromatogram it and you know you can, it is air stable and it is also thermally stable. So, therefore, you know you can pretty much deal it with as if like you are dealing with Esther and Aldehyde right.

Now having said that now, next topic that we would like to discuss perhaps in the next class mainly is the Cyclopropanation reaction. Now Cyclopropanation reaction maybe we will introduce a little for this class and then, we will try to close todays class with us with the beginning of some Cyclopropanation reaction. Cyclopropanation reaction is a very interesting topic where, Olefin is converted into Cyclopropane by using often as you see diazomethane chemistry and there are various reagents are various catalyst that we use most often the rhodium catalysts or of course, you have seen the copper and palladium combinations and different other combination.

As nowadays has come up let us look at the Cyclopropanation reaction briefly and then, we will close todays class.

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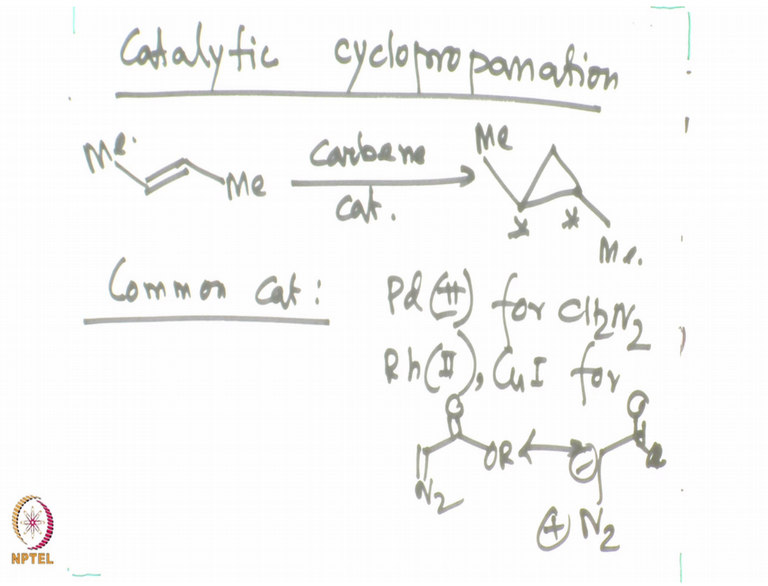

So, Catalytic we will discuss only the Catalytic. Catalytic Cyclopropanation reaction. So, we are interested in starting with an Olefin, we want to react it with a Carbene, Carbene equivalent, Carbene catalyst. Overall what we would like to get a stereo center of course, this. So, the Common catalyst that you found for this cases is the Palladium one that for diazomethane chemistry; rhodium 2 and copper iodide for ester diazo ester chemistry. So, this is in equilibrium with you can see that nitro plus and this is (Refer Time: 27:11) minus CO OR.

Of course, you know you can think of this diazo reagent, diazo methane CH 2 N 2 and diazo ester and so on. Of course, palladium and rhodium are the 2 metal that is used rhodium is usually often used in conjunction with copper, but it is always it is as if like Metal Carbene, metal double bond Ch 2. This is the chemistry that is used for Cyclopropanation chemistry right and this is a quite powerful technique and can give you Cyclopropane which are found in a number of pharmaceuticals and industrially it is very very interesting reaction than Cyclopropanation.

So, will in the next class we will try to discuss the Cyclopropanation reaction. Their asymmetric version and also we will try to discuss the application of this in drug molecule synthesis or pharmaceutical synthesis, industrially it has been used and it is quite an efficient reagent for doing the reaction in both in both in academia and in industrial setup. Well till then, you start reading more on the Fischer Carbene and maybe some on also on the Cyclopropanation reaction. We will come back shortly with the more information, more materials on the Cyclopropanation chemistry. Keep reading. Bye, bye.