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

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Lecture – 29
Dissolving Metal Reductions (Na,K,Mg) and McMurry Coupling Using Ti(0)

Hello everyone, I would like to welcome you all for today's lecture. Before we go towards the new aspects of reductions, we would like to see once more what we did in the last class briefly.

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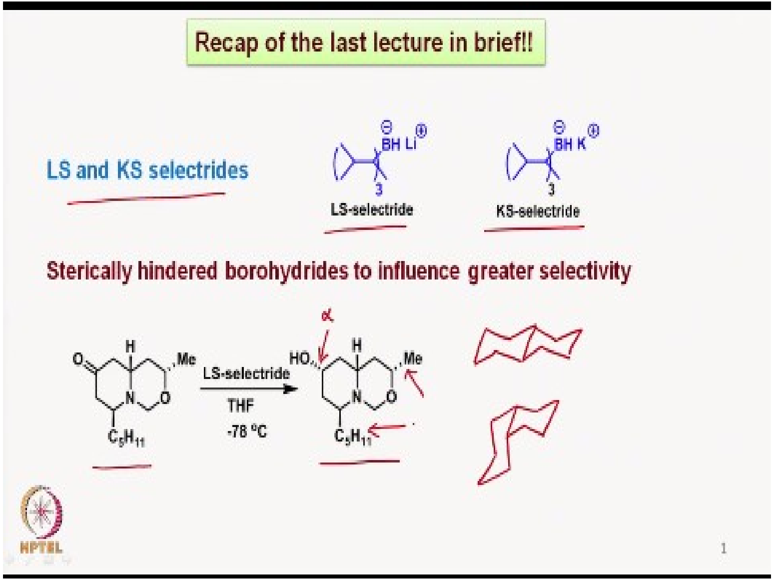

Recap of the last lecture in brief!!

LS and KS selectrides

Sterically hindered borohydrides to influence greater selectivity

For example, we towards end, we discussed LS and KS selectrides has are shown here. And these were considered to be very sterically hindered new reducing agents. And as I mentioned many times that the lithium ion based reducing agents are stronger than sodium or potassium based reducing agents because of the stronger binding of the oxygen with the lithium+.

Also, we looked at how sterically hindered borohydride these selectrides affect the selectivity in a great way. For example, this is, this example we consider last time and we saw that reduction leads to the formation of this hydroxy compound, where the hydroxy group comes from the reduction happens from the beta side and the orientation of the hydroxy group is towards the alpha side.

And for this, we did not consider under normal circumstances what we consider is trans confirmation. However, we considered the cis confirmation and how we saw that the steric hindrance leads to the formation of this particular molecule. So, it is not only the steric hindrance that we need to see, we also have to see the steric hindrance in conjunction with the conformation of the molecule that allows because in that case, the C5H11 group as well as the methyl group were both equatorially oriented. And thus, the reduction is guided by the conformation of such molecules.

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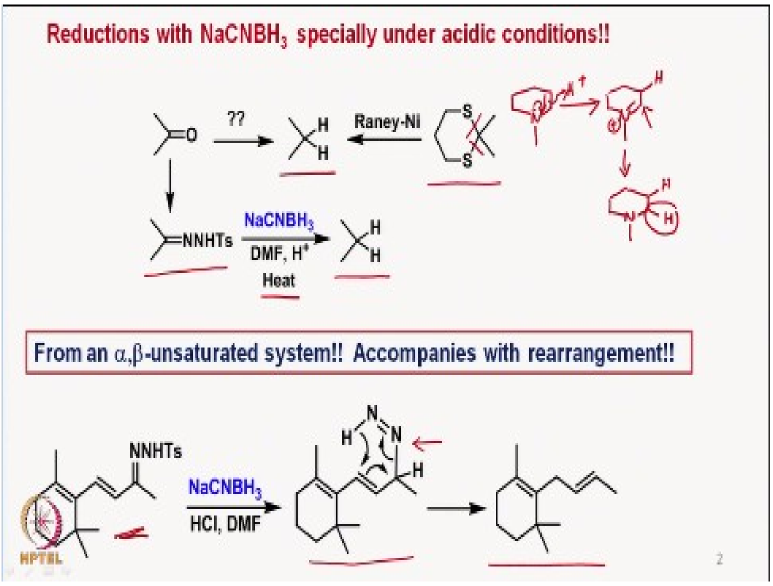

Reductions with $NaCNBH_3$ specially under acidic conditions!!

From an α,β-unsaturated system!! Accompanies with rearrangement!!

And we also studied the sodium cyanoborohydride based reductions. And we saw that since sodium cyanoborohydride is stable under acidic conditions up to pH 3, it was easy for carrying out reactions under acidic conditions. For example, we also, we consider reductions of enamines, which are possible, because the protonation allows the formation of this type of intermediate where the proton comes in here and of course, positive charge will come here.

So, you have the lone pair of electron pushing this double bond and protonation. And now, under these conditions, the reduction allows the full reduction of the immonium ion and sodium cyanoborohydride delivers the hydride at this particular position. And we saw many different types of reductions using sodium cyanoborohydride under acidic conditions. One of the last examples that we took was how to convert a carbonyl group to the corresponding hydrocarbon where both the hydrogens are basically coming from or during the cyanoborohydride reduction.

One of the ways as we have discussed last time was of course, you convert the carbonyl group to a dithiane protections and then you do the Raney nickel cleavage where the carbon sulphur bonds get cleaved. On the other hand, if we have to use sodium cyanoborohydride, then we convert the carbonyl group to the corresponding tosylhydrazone and these tosylhydrazone under acidic conditions in DMF in the presence of sodium cyanoborohydride and the heat conditions, gives the corresponding hydrocarbon.

And we looked at the reactions of alpha, beta unsaturated tosylhydrazone, such as this, which undergoes rearrangement and forms this particular molecule, where as I have shown here by mechanism that the reduction allows the shifting of the double bond due to this 6 member proton transfer or the hydrogen transfer. So, such kind of reductions accompany with the rearrangement. So, this is something very interesting because this normally does not happen.

So, therefore, we looked at various aspects of sodium cyanoborohydride, which are very useful and one of the other important reaction that we also saw was the conversion of a primary amine to N,N di-methyl amine, which is highly synthetically useful using formaldehyde and sodium cyanoborohydride under acidic conditions.

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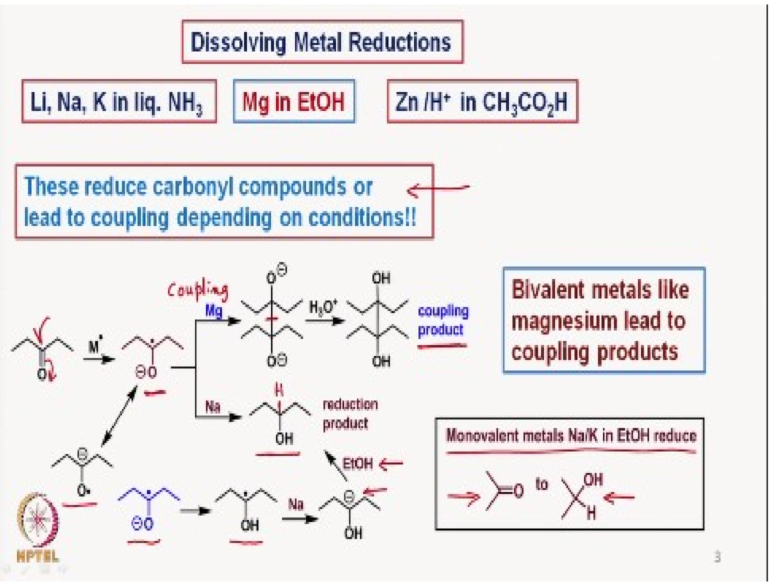

Dissolving Metal Reductions

Li, Na, K in liq. NH_3

Mg in EtOH

Zn /H^+ in CH_3CO_2H

These reduce carbonyl compounds or lead to coupling depending on conditions!!

Bivalent metals like magnesium lead to coupling products

Monovalent metals Na/K in EtOH reduce

Now, we move on to dissolving metal reductions. In dissolving metal reductions, we have alkali metals, alkaline, earth metals and some transition metals for example, lithium, sodium and potassium in liquid ammonia can be used as a reducing system. And we can also use magnesium in ethanol as a reducing agent system and zinc and acetic acid or zinc and proton with an acetic acid is also useful as a reducing agent in which the metals dissolve and the reduction occurs.

Now, these reducing systems allow reductions of many carbonyl compounds or sometimes they also lead to coupling of 2 molecules, it depending on conditions. It is a very useful reducing system and the reduction as well as coupling lead to products which are both important. Now, if we look at the mono-valent metals such as sodium or potassium in ethanol, they reduce carbonyl group to the corresponding alcohol. Whereas bivalent metals like magnesium lead to coupling products.

First, we would like to see what exactly happens when a carbonyl compound is brought in contact with a metal either a mono-valent or bivalent. So, for example, once this metal transfers an electron to this carbonyl carbon, there is a movement of electrons and that leads to the formation of this radical anion which is here. Now, if this radical anion receives another electron from sodium and then undergoes protonation So, then we get a reduced product.

On the other hand, if this particular radical anion undergoes coupling, so that is possible with magnesium. So, it is basically undergoing coupling and this coupling leads to C-C bond formation. As you can see here, there is a to C-C bond formation here and this leads to this 1,2-dianion that under acidic conditions or during the reaction receives proton and then we get the 1,2-diols as a product. So, this is the coupling product.

One can of course, see that this particular radical anion would be in resonance with another radical anion of this time. So, there is a stability associated with it. So, what we are trying to look at it is that this radical anion which is what is here, this radical anion when under protic conditions as liquid ammonia gets proton to form this radical, which then again receives n electron to form the anion here and then that gets protonated with ethanol to form this particular hydroxy compound where this hydrogen also comes in here.

So, now we can see that there are conditions under which we can allow such reductions to take place.

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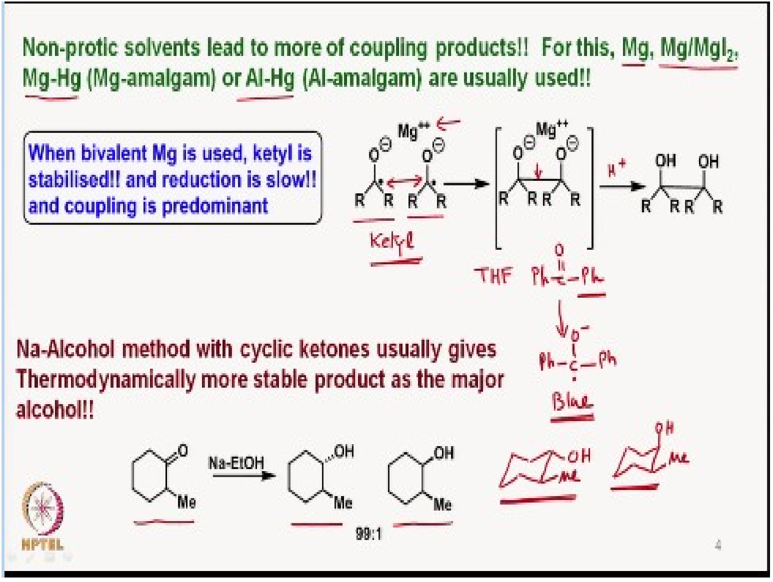

Non-protic solvents lead to more of coupling products!! For this, Mg, Mg/MgI$_2$, Mg-Hg (Mg-amalgam) or Al-Hg (Al-amalgam) are usually used!!

When bivalent Mg is used, ketyl is stabilised!! and reduction is slow!! and coupling is predominant

Na-Alcohol method with cyclic ketones usually gives Thermodynamically more stable product as the major alcohol!!

Non-protic solvents lead to more of coupling products, it is very clear that the protonation of the anion should not take place until it undergoes coupling. So, if we want coupling products to form, we have to preferably use non-protic solvent, we can always protonate towards the end of the reaction during the workup. Now, for this coupling to take place, we need to use magnesium or magnesium, magnesium iodide, this mixture or magnesium amalgam or aluminium amalgam, these are generally the metals or the systems that are usually used.

When we use bivalent magnesium, the ketyl, this is what is called ketyl or the radical anion is basically stabilised of course and reduction is slow and coupling is dominant that is because you have 2 molecules of this radical anion or the ketyl they come in contact with the magnesium2+ and bring into the closeness and thus, there is a very easy possibility of coupling of these 2 radicals leading to the formation of this particular C-C bond.

And then the protonation allows the 1,2-diols to form. So, this coupling is easily possible in a non-protic solvent. This is also something that is used when we are trying to dry THF, when you will take a THF and try to dry by using sodium as a metal, then we use a small amount of benzophenone into this THF. Suppose you have 2 litres of THF and use a one gram or less than a gram of or even less than that of benzophenone which and of course, you use sodium wire into this to make sure that moisture is not present.

How do you make sure that the moisture is not present? That all the sodium all the moisture which is present has reacted with the sodium and that is the reason why we use a small amount of benzophenone, which allows to form the radical anion or the ketyl, this is what is its form similar to the ketyl that is here. Now, since this is a tool, there are 2 phenol groups attached the radical here is highly conjugated and because of this conjugation, this gives a dark blue colour.

And so, if we see that, when we take THF and which is already pre-dried with some other like calcium chloride or something and then you add sodium wire into it, you press sodium wire into it and reflux it and add a pinch of benzophenone, if the blue colour comes that means all the water has reacted, sodium has a preference of reacting with water first and then the it can react with the benzophenone.

So, this is basically an indicator which is used to which I am sure many of you would then later on, use it in your practicals in during your research or PhD. Now, sodium and alcohol reduction with cyclic ketones is also very interesting, because if you have cyclic ketone like 2 methyl cyclohexanone and reacted with sodium and ethanol, we can see that there are 2 possibilities.

One is a trans product and the other is a cis product. So, the trans product is formed in 99 ratio is to 99% and of course, the other one is from in 1%. So as you can imagine the conformation that if we have the hydroxy group like this, the methyl will go up like this and this is what is the trans product. On the other hand, if we take the cis product, then we can see that we will have the hydroxy group and the methyl group oriented in this fashion. So, obviously, thermodynamically, this is more stable.

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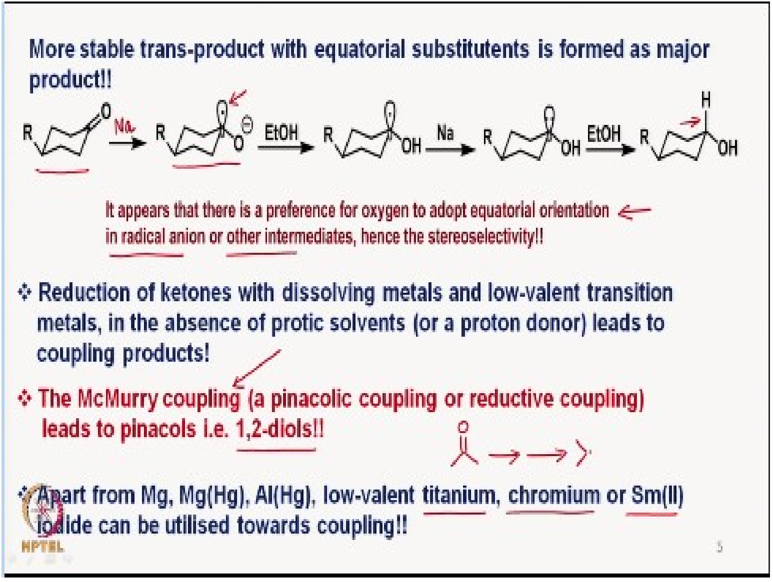

More stable trans-product with equatorial substitutents is formed as major product!!

It appears that there is a preference for oxygen to adopt equatorial orientation in radical anion or other intermediates, hence the stereoselectivity!!

- Reduction of ketones with dissolving metals and low-valent transition metals, in the absence of protic solvents (or a proton donor) leads to coupling products!
- The McMurry coupling (a pinacolic coupling or reductive coupling) leads to pinacols i.e. 1,2-diols!!
- Apart from Mg, Mg(Hg), Al(Hg), low-valent titanium, chromium or Sm(II) iodide can be utilised towards coupling!!

So, why is it that the more stable trans product is formed is, because if we consider this cyclo hexanone conformation, the when the radical anion is formed by the transfer of an electron from sodium, the preference of the oxygen is to adopt equatorial orientation like this in radical anion or other intermediates, that is because the orbital containing this particular radical is relatively small.

And the carbon oxygen bond is a bit and the oxygen is bigger and therefore, it prefers to remain in an equatorial position, which then gets protonated and then again sodium gets transferred and eventually the hydrogen comes in. So, this is the reason why the reduction of cyclic ketones, the OH group generally prefers to come to the equatorial side. Reduction of ketones with dissolving metals and low-valent transition metals in the absence of protic solvents or a protic donor, proton donor leads to coupling product.

This is what we saw when we looked at the magnesium based coupling. Now, there is also something very useful interesting reaction which is called as McMurry coupling. Basically, it is a pinacolic coupling or reductive coupling that leads to 1,2-diols in a very effective manner. Now, apart from magnesium, magnesium amalgam and aluminium amalgam, that what we saw even low-valent titanium, chromium or Samarium iodide can also be utilised towards coupling.

So, there are a variety of methods or approaches to allow the coupling to take place. Now, why is it that the coupling is important because, if we allow the carbonyl groups to couple of course, we can get 1,2-diols, but under certain conditions, they also lead to the formation of corresponding olefin that means if we have a carbonyl group something like this here and we allow the coupling followed by elimination of the hydroxyl groups, we can have the 2 molecules form a corresponding olefin. This is what is called McMurry olefination or McMurry coupling.

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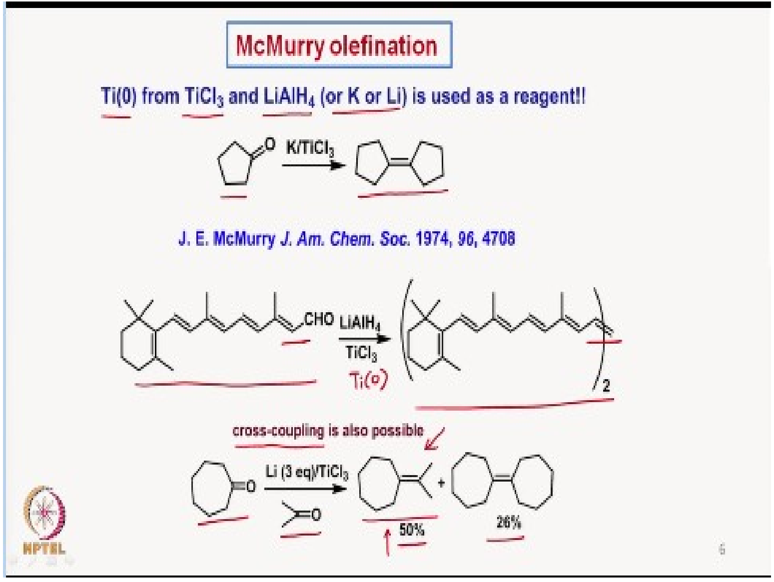

McMurry olefination

Ti(0) from $TiCl_3$ and $LiAlH_4$ (or K or Li) is used as a reagent!!

J. E. McMurry *J. Am. Chem. Soc.* 1974, *96*, 4708

cross-coupling is also possible

So, we will discuss that in detail now, McMurry olefination. Somewhere in the 70s, this particular reaction was established and developed by McMurry, where he used to titanium zero which was derived from titanium tri chloride and lithium aluminium hydride or reaction with potasium or lithium as electron transfer. So, basically a TiCl3 was reduced to the corresponding Ti(0) that is titanium zero using a either a reducing agent or a metal electron transfer from potassium or lithium.

And that allowed, say, for example, cyclopentanone would give such a molecule and this type of molecules are very difficult to make under normal conditions and therefore, it has a lot of importance. For example, we can also take an aldehyde, even if it is an alpha, beta unsaturated aldehyde, it undergoes coupling and forms such a large molecule very, readily available by using this titanium zero derived from titanium tri chloride and lithium aluminium hydride.

It is also possible that we can conduct a cross coupling that means, we take say for example, cyclohepentanone and we take acetone and we use the lithium and titanium tri chloride. What they have observed is of course, a formation of this type of cross coupled product that means one molecule of acetone and one molecule of cyclohepentanone, they react to form one molecule of this which is formed in around 50%.

And of course, cyclohepentanonee can also coupled with itself and that forms 26% of the product and of course, remaining will be acetone coupling with itself also can form. So, this kind of cross coupling is also very important because even if it is 50% yield, it is not easy to get and therefore, it is a useful alternative for getting such olefins, where the 2 parts are from different ketones.

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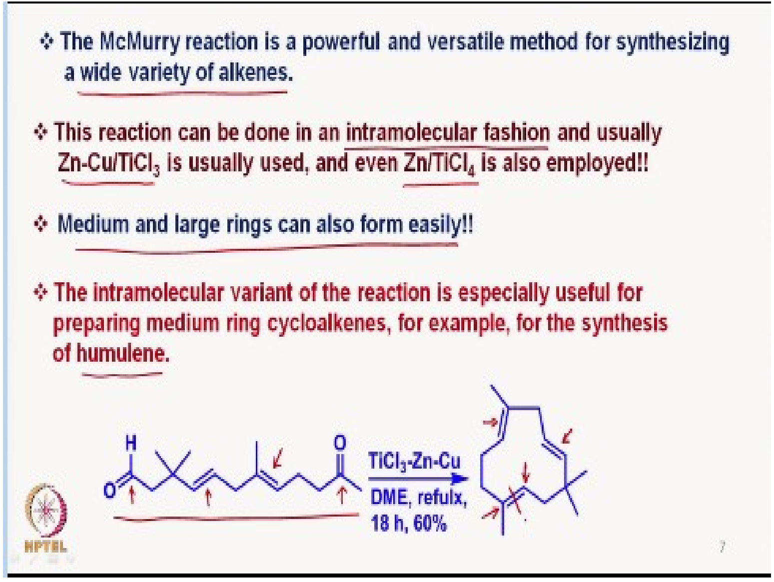

- The McMurry reaction is a powerful and versatile method for synthesizing a wide variety of alkenes.
- This reaction can be done in an intramolecular fashion and usually Zn-Cu/$TiCl_3$ is usually used, and even Zn/$TiCl_4$ is also employed!!
- Medium and large rings can also form easily!!
- The intramolecular variant of the reaction is especially useful for preparing medium ring cycloalkenes, for example, for the synthesis of humulene.

It is a powerful and versatile method for synthesising a wide variety of alkenes. This reaction can also be done in an intra-molecular fashion, which is very interesting because you can derive, you can make a large number of cyclic molecules and not only just intra-molecular fashion reactions, but also they can lead to medium and larger rings. And that is something very, very much useful.

For that you can of course, use many reducing agents such as what we discussed lithium aluminium hydride or potassium or lithium, but they also have this zinc copper coupled with TiCl3 or even zinc and titanium tetrachloride is used essentially, the idea is to get titanium zero, which allows an electron transfer to take place. This intra-molecular variant of the reaction to form large or medium sized ring is very useful.

As you can see, we can take such an example, where we have already 2 double bonds, which are present here and we have towards an a ketone and an aldehyde which then is allowed to react as you can see that this is the part which has come and this is the part which is the aldehydic carbon and this is the one that is a ketonic carbon and rest of the part of the double bonds and the other parts of the molecule remain as they are.

So, this is this molecule is called humulene and its synthesis has been done using McMurry coupling in a very easy way. And therefore, once we have the double bonds in a proper orientation, as we can see, here, we have got the during the coupling, we have got the trans product in this particular case, where there is a medium sized ring.

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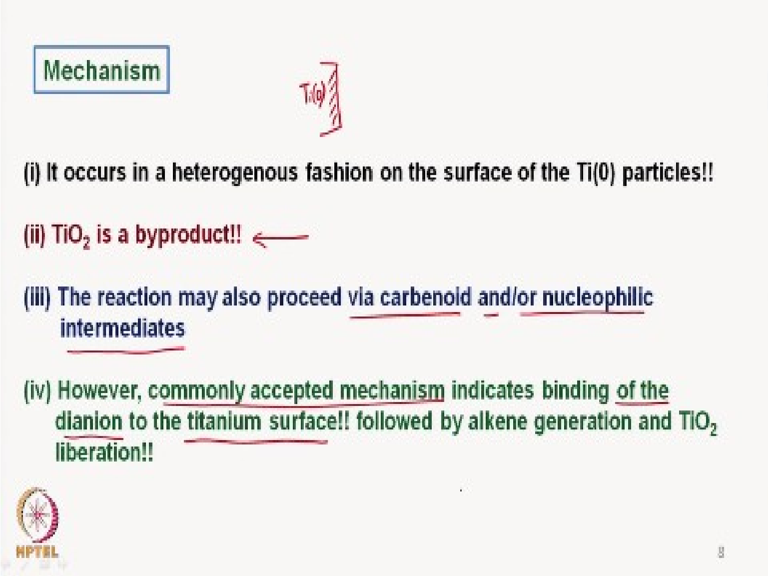

Mechanism

(i) It occurs in a heterogenous fashion on the surface of the Ti(0) particles!!

(ii) TiO_2 is a byproduct!!

(iii) The reaction may also proceed via carbenoid and/or nucleophilic intermediates

(iv) However, commonly accepted mechanism indicates binding of the dianion to the titanium surface!! followed by alkene generation and TiO_2 liberation!!

What is the mechanism of such a reaction? It occurs in a heterogeneous fashion on the surface of the titanium zero particles. So, essentially what is suggested is that we have here titanium zero, which is present here as a surface and there is an adsorption of the carbonyl group. We will discuss the mechanism in a minute, but everything happens on the surface of the titanium zero.

Now, titanium dioxide is formed as a by-product after the reduction is over. It is also possible that the reaction may proceed via carbenoid and or other nucleophilic intermediate but commonly accepted mechanism which is generally believed indicates binding of the dianion. We will see how the dianions form to the titanium surface and followed by generation of alkene and loss of TiO2. So, it is generally on the surface of the titanium zero with where the reaction occurs.

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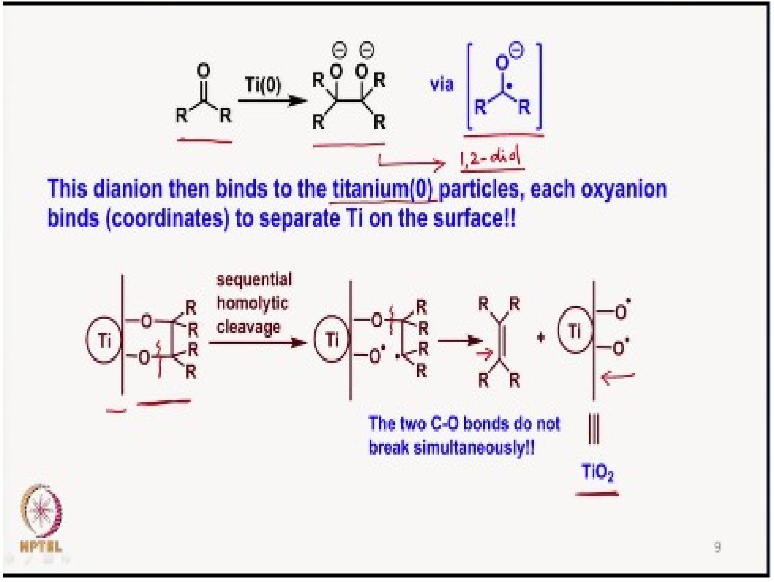

This dianion then binds to the titanium(0) particles, each oxyanion binds (coordinates) to separate Ti on the surface!!

The two C-O bonds do not break simultaneously!!

Now, what is happening is, this is the simplest way of indicating that we have a carbonyl group here, carbonyl compound and the titanium zero transfers one electron similar to the ones that we discussed with sodium or potassium or lithium or even magnesium. So, the radical anion is formed by the transfer of an electron from the titanium zero here and we obviously go to this ketyl radical or which is called as radical anion.

And then they couple to form this 1,2-dianion and this dianion then binds to the titanium zero particles and actually, it is more of a coordination. So, if this is the surface of the titanium zero, then we get this type of binding on coordination onto the surface through the oxygen or the dianions and as we can see that we can cleave this particular carbon oxygen bond, where a di-radical is formed radical on the carbon and radical on the oxygen.

And in a similar fashion, it will also happen on the other carbon oxygen bond and they will couple to form the olefin, the C-C bond formation and the released oxygen which is now sticking onto the titanium surface basically leads to the titanium dioxide formations. So, this particular type of mechanism, we will discuss a little bit more in detail when we talk about another reaction.

Where we can take this dianion which is also possible that we can trap it as a diol, 1,2-diols that is if we logically see that if this dianion is forming, then it should also be possible to trap it as a 1,2-diols and then we can see that 1,2-diols also leads to the corresponding olefin under the same conditions.

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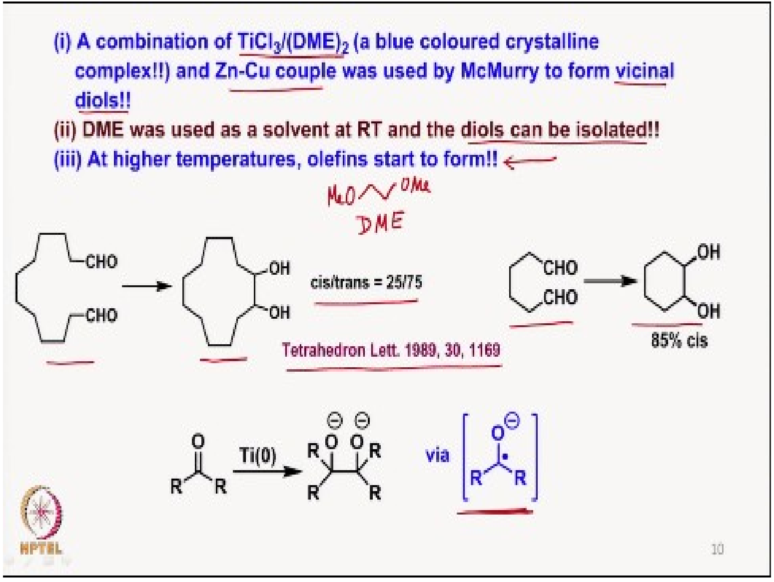

(i) A combination of $TiCl_3/(DME)_2$ (a blue coloured crystalline complex!!) and Zn-Cu couple was used by McMurry to form vicinal diols!!

(ii) DME was used as a solvent at RT and the diols can be isolated!!

(iii) At higher temperatures, olefins start to form!!

MeO/\/OMe

DME

cis/trans = 25/75

Tetrahedron Lett. 1989, 30, 1169

85% cis

It was found by McMurry that a combination of TiCl3 and this is a di-methoxy ethane, 1,2-di-methoxy ethane. You have this, this is what is DME and this forms a blue coloured crystalline complex. So, that particular complex and zinc copper couple was used to form vicinal diols by from the two ketones. DME was used as a solvent at room temperatures and the diols could be isolated. At higher temperatures, then the olefin starts forming that means that during the coupling, obviously, once the radical anion is formed.

The diols can be formed and do form as intermediates which decompose at high temperature. So, from this particular medium sized di-aldehyde can be converted to a medium sized alcohol where cis-trans ratio is 25 to 75. If we have a smaller ring formation needed, then of course, we get a cis diols as the product and as we discussed it, such a reaction proceeds via radical anion of this type.

So, we will stop it at this stage today and take it up next time further aspects of these titanium based reactions, McMurry coupling, but as you can see that we can very easily allow the coupling of aldehydes or ketones and stop at the stage of diol. And also if required by heating, we can convert that into corresponding olefins.

So, you can study these some references I already mentioned, for example, here, this particular Tetrahedron Lett in 1989, where this diols formation was first reported and then we get ready for the next class. Thank you. See you next time.