Metal Mediated Synthesis - I
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Lecture – 1
Asymmetric Hydrogenation

Welcome to the first lecture of Metal Mediated Synthesis 1. With this first class we will be discussing mainly the Asymmetric version of the Hydrogenation reaction I am sure that all of you are familiar with the hydrogenation reaction, essentially we are talking about starting with an olefin converting that olefin into an alkane or you start with ketone you get an alcohol.

So, this is addition of hydrogen or 2 Hydride across an olefinic center or an alkyne or even a ketone center. The mechanism of this reaction can vary a little bit based on the organ metallic intermediate that is involved into these reactions; one of the best hydrogenation Catalyst is the hots rock osbourne catalyst. Now we will first look at the mechanism of this Schrock Osborn catalyst and then will discuss only one example to shed light into the asymmetric hydrogenation reaction.

Let us look at the shock Osborn catalyst and it is mechanism first of all we would for example, we would like to have these isometric reactions mainly to synthesize a number of drug molecules drug molecules such as Lipitor which is a multi-billion dollar drug, one of the best selling drug presently in the market something like 100 plus billion dollars is earned on this this is a drug marketed, by Pfizer and then of course, nowadays a number of generic versions are available in India it is known and let us say utter Vidal also in them in the name of Lipitor. Now this drug Lipitor if you look at carefully there is 2 asymmetric center, this a symmetric center in principle or in reality also are generated by the hydrogenation reaction, well before getting into the asymmetric hydrogenous and let us draw the drug Lipitor and then look perhaps how can be synthesized by a asymmetric hydrogenation so the Lipitor.

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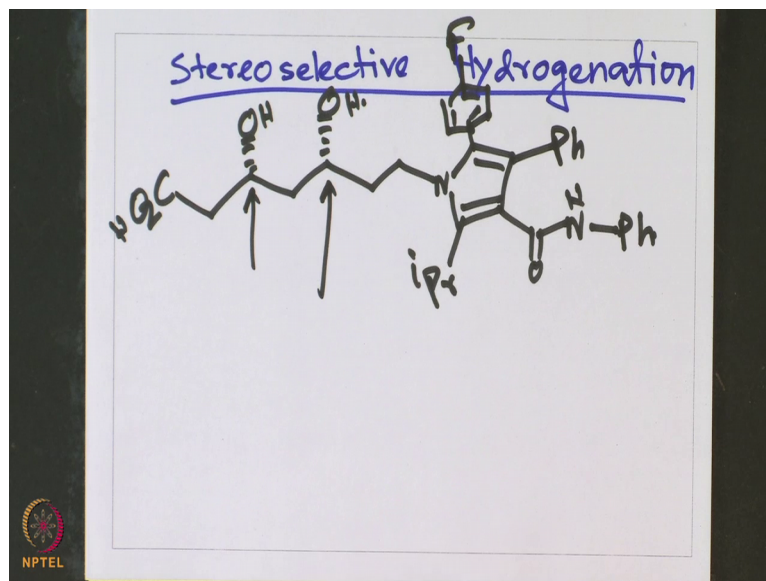
So, it has 2 stereogenic centers it is a rather big molecule as you can see well you can do a number of ways to synthesize this compound.

Now, most importantly as you can see these are the 2 stereo center that perhaps can be generated by asymmetric synthesis. Of course, you can think of a die keto center at these 2 carbon center and then do an asymmetric hydrogenation to come up with these centers that will effectively give you the desired molecule as, I said before getting into the details of these drug molecule synthesis let us try to look at the catalytic cycle, which is the fundamental of these hydrogenation reaction catalytic cycles will vary based on the catalyst also sometimes based on the substrate that is involved for the hydrogenation reaction. Today only one catalyst system we will discuss and that is Schrock Osborn catalyst.
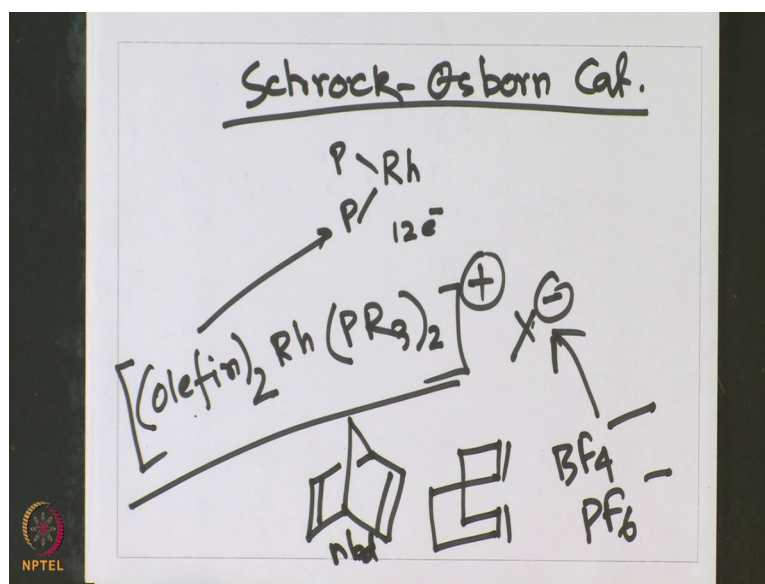
So, Schrock-Osborne catalyst mechanism well it is a rhodium based catalyst it is a rhodium Bis Phosphene complex, which is now a 12 electron species initially of course, this 12 electron catalytic species is generated from a pre catalyst.

Where it is a 16 electron complex usually we have a olefin coordinated 2 of them rhodium species that is commercially available along with 2 phosphine ligand bound with it and it is a cationic species, the anion X minus usually are the non coordinating one that is for example, BF 4 minus and PF 6 minus this is your Rhodium Catalyst. Now this rhodium catalyst is commercially available and known as the Schrock-Osborne Catalyst the phosphine ligands these ligands can vary the olefin we usually see it is a bis coordinated one for example, Cyclooctadiene or Normonadine this is MBD nor Bornedine Cyclo Octadiene can also be used for these reactions the species that we look at here is a 16 electron complex.

Now this species will undergo the hydrogenation of the internal olefin itself that is coordinated with rhodium to give rise to the alkane as well as the reactive intermediate that is going to be now a 12 electron intermediate, from this 12 electron intermediate we will start our catalytic cycle.

These internal olefin which are by coordinated such as norbornedine or cyclo octadiene are sacrificial olefin, since it is a hydrogenation catalyst itself the rhodium one it will be efficiently hydrogenating the internal olefin to gives norbornen and you know and corresponding alkene compound from whatever we have as bidentate ligand. Now from this sacrificial ligand which is providing the support for the pre catalyst we will get a very reactive 12 electron species coordinated by just 2 phosphates. These phosphine coordinated rhodium complex will now be the real active species for the catalytic cycle let us look at that.

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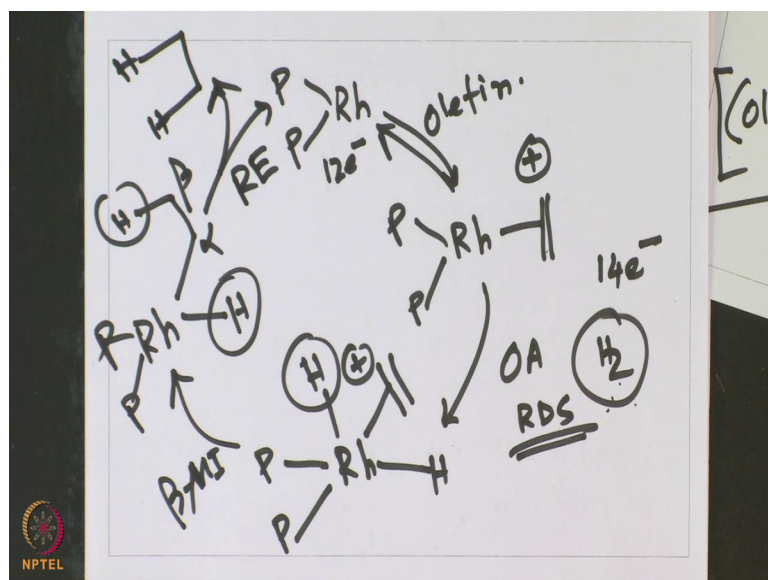
Now we have the rhodium Bis Phospene complex the counter n ion that is involved in these cases are BF 4 minus or PF 6 minus, which is giving enough you know opportunity for the rhodium center to be catalytically very active and subsequently we will see the major reactions that is happening at this rhodium center.

In these cases binding of olefin takes place with the rhodium center to give you the rhodium olefinic complex cationic one and bisphosphene coordinated 1, this is was a 12 electron species now apu olefin binding it become a 14 electron species from here oxidative addition with hydrogen occurs. So, these are hydrogenation reaction you start with an olefin as a substrate and hydrogen as the other substrate olefin coordination occurs fast this is a Schrock-Osborn catalyst we are de discussing and then with hydrogen

oxidative addition happen and it was found to be the rate determining steps, we see the hydride formation dihydride formation these are dihydride catalyst it is not the mono hydride catalyst which we see in other cases.

Where one of the hydride is associated usually in the commercial from metal monohydrate species is taken and from their catalytic cycle start in these cases we do not have a monohydride to start to it into the organometallic intermediate or the metal complexes. Here we have a vacant coordination side a number of vacant coordination sites at the metal center then olefin vine and then oxidative addition into the hydrogen happens to give you the olefin coordinated dihydride intermediate, from here we have the beta migratory insertions; I hope you guys are all familiar with it I am not getting into the details of it where you see that at the beta position alpha beta beta position these hydrides are getting in and of course, your 2 phosphine ligands comes into the picture finally, reductive elimination gives you the product where this hydride and this whole alkane. Now, gets eliminated to give you the final product.

In this catalytic cycle therefore, you have seen starting with olefin coordinated organometallic intermediate and with a non coordinating and the ion the catalyst that is known as Schrock-Osborne catalyst will gives rise to a reactive intermediate, where in olefin is now no longer part of the metal catalyst, we have a very reactive 16 electron species to a 12 electron species formation by the loss of those 2 olefin which is a sacrificial olefin going to the alkane product, but our major reaction is an exogenous olefin reacting with hydrogen.

Where with the 12 electron species olefin coordination occurs subsequently we do see oxidative addition that is the rate determining step in these cases usually to gives rise to the dehydride catalyst rhodium dehydride species with olefin coordinated 1, from which we have seen a beta migratory insertion to give the metal hydride and alkyl species the final steps is the hydride and alkyl group beta or reductive elimination to give you the product formation and it regenerates the catalytic cycle, I am sure you are familiar with these processes. Now the major topic for our discussion is how this hydrogenation catalyst can be used for asymmetric reaction.

For example, if those phosphine ligand that we were discussing in Schrock Osborn

catalyst are having stereo center phosphine having stereo center can they give rise to a stereo center into the product of course, the answer is yes asymmetric version of the hydrogenation catalyst are quite popular. So, today we will see one or 2 particular examples where asymmetric hydrogenation reaction is taking place let us look at one such example alright. Let us look at one of the substrate and that is aspartame synthesis could be the sweetener famous sweetener or similar type of synthesis let us look at 1 of these.

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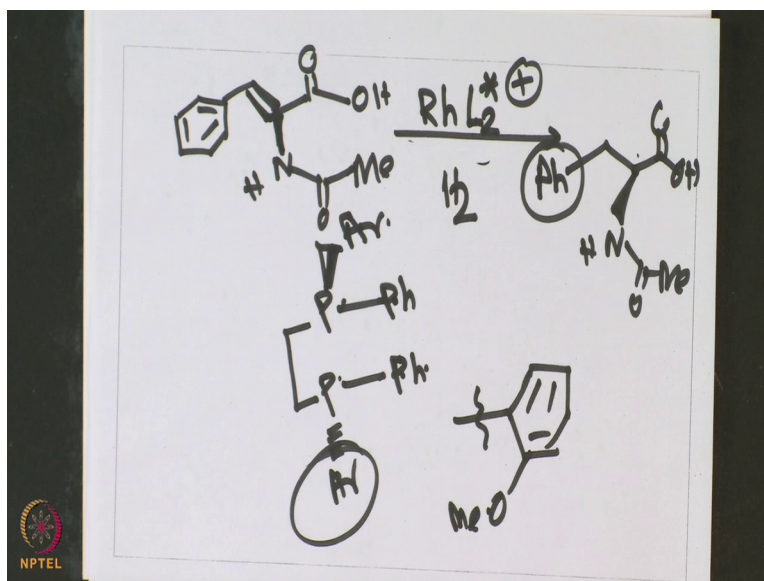
Where you have an acid and in H CO Me these are the 2 coordinating group, but the major interest our major interest is at this olefin we want an alkane formation or you know saturation of this unsaturated partner to give you the stereo center in this particular case, the catalyst that will be used is the rhodium die coordinated ligand complex of course, there is this is a chiral ligand and you have a cationic complex.

We use hydrogen to give overall a species that is going to be very interesting for asymmetric reaction. So, we are just putting phenyl over there. Now the ligand this ligand that is used in this case or the bisphosphene ligand where you have this phosphine center having the chiral ligand center and this aryl group for example, this is a phenyl this is a phenyl these 2 are aryl this aryl group could be like ortho methoxy one unitual partner and so on. All if we have the amine instead of phosphine in these cases these ligands are not going to be asymmetric or these are not going to be chiral center, because as you know

the inversion energy or the inversion barrier required for the amine is pretty low which is achievable at room temperature, but for phosphine asymmetric ligand synthesis or a nuncio selective catalysis is possible with the phosphine ligand because we can make the chiral version of the phosphine ligand and this is one of the ligand that is used for these cases.

Now let us look at the mechanism of these reactions of course, we also know that since the ligand is having chiral center, with respect to the ligand we can bind the olefin in 2 fashions which is leading to the 2 products 2 stereocenter containing product. One would be the R product from the starting material; another would be the S product from the starting material.

Now we will try to discuss what is getting generated and how it is genre generated what would be the mechanism of such reaction, let us look at the product formation for these 2 cases and the possible stereo center generation steps that will require then a rhodium complex with chiral ligand with respect to that chiral ligand, now the substrate will be oriented in a way. So, that in one conformation it can give you the R product hydrogenated product the substrate can also orient in n in another way where it is leading to the S product. Now from there on we will see what is the experimental observation and how that can be explained further in detail.

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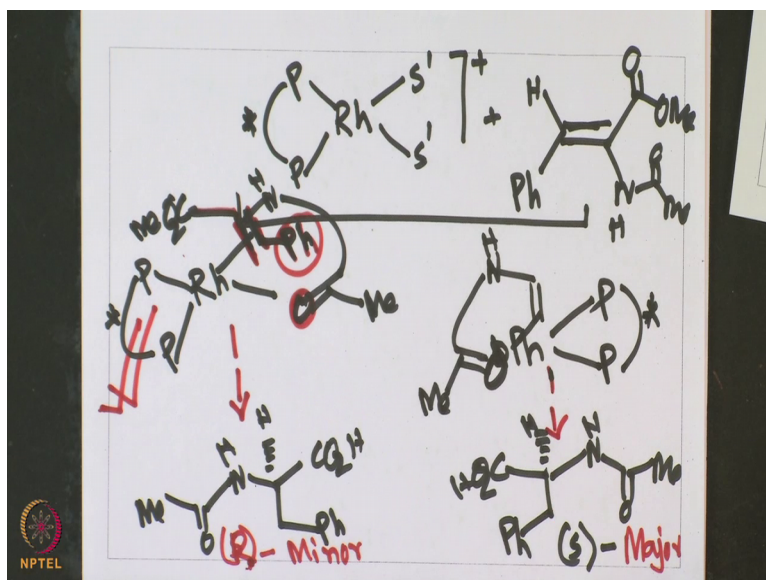
Now we are we are going to draw a catalytic cycle O R semi catalytic cycle we are assuming that phosphine ligand is rhodium P P and we are giving a star over there and we are going to have let us say usually a solvent coordinated species, which is usually the case and we are going to take the substrate which is the one which we have discussed in the last slide. So, we have co 2 me and NH C O Me.

Now in these cases in this particular case as we have drawn we are getting overall the final product as the s product right. So, the product from the hydrogenation of these reactions we are getting is the s product that I am trying to draw in here NH Co Me. So, essentially this olefin double bond is now getting hydrogenated one of the hydride is coming over here another hydride is coming over there. So, this is the S product and that is turned out to be the major product this is the major product, the other product is the minor 1 or very little one since it is a very good asymmetric reaction and that is the S product and that we are going to draw right now this is the one where the mirror image of this one which essentially have drawn the mirror image of that one and that is the S product and this is the sorry this is the R product and that is the minor product.

Now the catalytic cycle, which we have drawn for the Schrock Osborn catalyst is also valid in here where we have seen Bis coordinated phosphine ligand in this case asymmetric version of the ligand will be interacting with the metal center and you have an olefin associated with it. We will also see the di hydride species formation from the oxidative addition of hydrogen from their own a beta migratory insertion into the olefin will take place where hydride attacks the olefin.

Now this mode of olefin binding will determine whether this is going to be an R product or S product and the mode of olefin binding will be in turn related or governed by the chirality of the ligand center or the substituent having the preferred sterics configuration or steric demand will force the olefin to bind in only one manner, but what in this case in particular case we were seeing is selective S product formation, but if you look at the mechanism of these reaction intermediate isolation indicates that intermediate that can be characterized should lead to the R product.

So, let us look at the scenarios in hand 2 different product is possible one is the S product another is the R product. The reaction mechanism study for this reaction indicates that

intermediate that is forming or that can be characterized are similar or should lead to the R product, but in reality we are getting S product.

The question is how that is possible when R product intermediate is characterized, but the product in reality we are getting is S. Let us draw the mechanism or let us draw the corresponding intermediate, the intermediate that was characterized is having this phosphine ligand and where we have seen that the olefin is coordinated in a fashion we have Nh over there and then we have Co Me and from this side Co 2 Me is attached. So, this is the olefin coordination olefin is coordinated and you have a Phenyl over there and Co 2 Me very this side and the ketone that is Nh Co Me that is associated with the rhodium in this fashion.

Now this one in principle should lead to the R product this is the only observed intermediate, but the product that we see is the S 1 the corresponding intermediate let us draw it over here is not really going to give us the desired product, but in reality this is what we are getting in the process. I will show you the intermediate in a moment where I have already drawn it and that would be little bit clear and from here this is the intermediate that is getting generated and the product being formed. Let us look at the intermediate in little bit clearer way if you can see over here.

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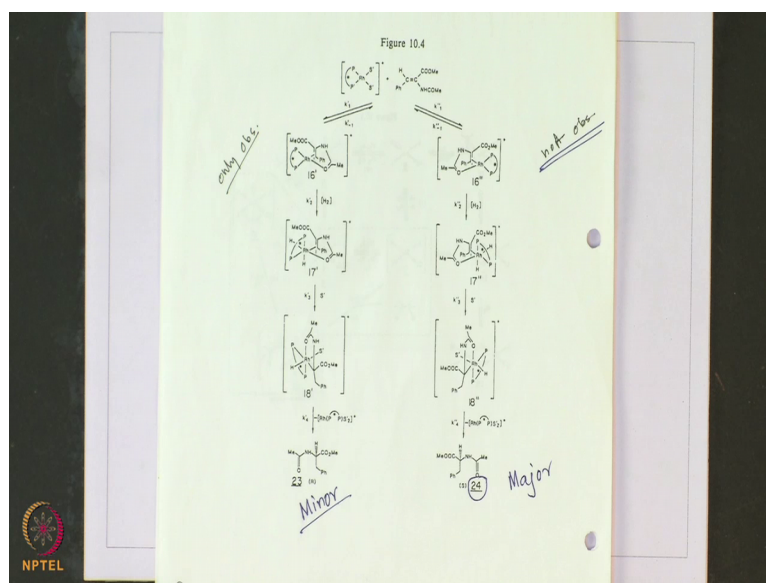
Well let us look at this intermediate in a little bit better drawn fashion, because drawing over here with the with the pen is becoming little bit critical. Let us look at this in a pre-drawn manner which I have done before from the original reference that has been given that has been published earlier. Let us look at this rhodium intermediate where your rhodium is having this chiral ligand and solvent coordinated from there on this olefin can coordinate.

With this rhodium center in 2 fashions as is drawn here in the form of 16 double prime, on the other hand the 16 prime as you can see on the left hand side is the intermediate that is only observed. The 16 double prime intermediate is never observed whereas, the only observed intermediate is 16 prime; this 16 prime intermediate is not leading to the corresponding compound that is 23 in this case, but this is observed as the minor product.

So, the intermediate 16 prime is observed intermediate only 16 double prime is never observed, but the product formation is not governed by the 16 prime original product formation is actually governed by 16 double prime. So, this is somewhat little bit confusing, but this can be explained by what is known as Curtin Hammett principle.

Let us look at the Curtin Hammett principle and then we will try to come back to this problem again and discuss it further. So, Curtin Hammett principle tells you that from one reaction if you are expecting 2 different conformer or 2 different intermediate. So, your starting material are going to give you 2 different intermediate if these 2 different intermediate formations are not going to be very much energy demanding; that means, they can be in equilibrium or one can go back to the other one very easily under that condition the product formation step from those 2 intermediate will be determined by the next transition state coming out from them let us look at this phenomenon one more time in the form of this energy diagram.
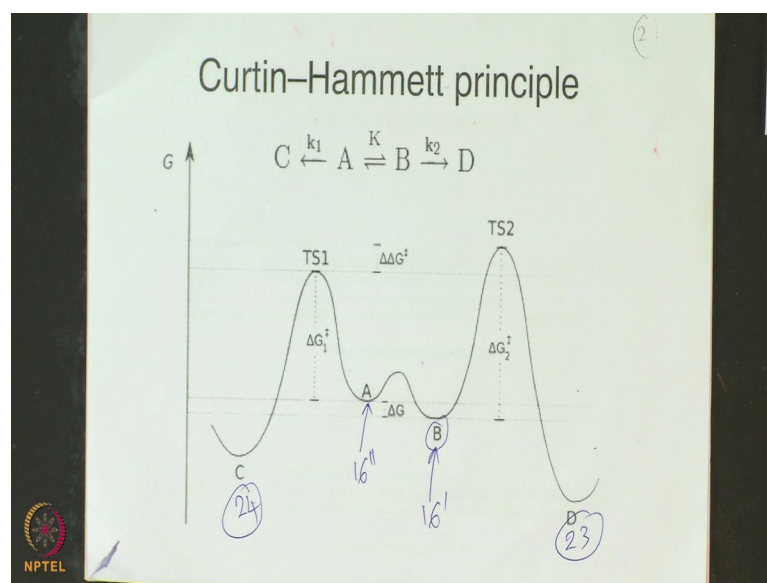
Let us look at the energy diagram you have A and B 2 intermediate A and B 2 intermediates that that are in equilibrium with each other. Now from intermediate a product C is forming and from intermediate B product D is forming. If you look at the relative energy from intermediate A this TS 1 is the shorter one whereas, from intermediate B the product that is D forming that intermediate and at that product formation energy or energy barrier is quite high. So, delta G 1 over here is smaller delta G 2 over here is larger. So, this is smaller this is larger; this is a small part and this is a large part. Now although you see that A is having higher energy B is having lower energy if these 2 are intermediates you will usually see the formation of B only from the reaction mixture. So, the characterization of intermediate in this particular case is going to be the B you will be able may be able to isolate or characterize B, because A is having higher energy, but from A the product formation is of lower energy, but from B product formation is having higher energy. So, in this reaction mixture although A is having higher energy B is having lower energy overall the product formation actually going to be C not D.

That is because if A and B are interconvertible they can be form in equilibrium under that situation and this energy barrier is very less and therefore, under that situation B can always go back to A and then A to C product formation, that is the lower energy formation compared to lower energy requirement compared to the subsequent B to D

formation.

So, intermediate characterization can sometimes be misleading maybe it is indicating the other product formation if it is under the Curtin Hammett principle. So, what we have seen here in this particular energy diagram is A and B although are in equilibrium B is having lower energy. So, you might will be able to characterize B, but the product formation is actually observed finally, from A because a to product formation C is much facile compared to the B to D deformation.

So, this is what essentially is the Curtin Hammett principle where the equilibrium between the 2 intermediate can be determining the product controlled step and that is the 1, which is having the lower energy irrespective of the energy between the 2 product formation steps the as long as A to B transition is smaller we will see always the product formation C. Let us get back to the original this hydrogenation catalyst 1, where we will see that starting from these rhodium complex we have this 16 prime and 16 double prime possible formation we only in the reaction mixture we see 16 prime, but we are not going to see the product formation 23 in this case this is turned out to be the minor product, because from 16 prime to 23 is a higher energy relatively higher energy steps whereas, from 16 double prime to 24 is a lower energy steps compared to 16 prime to 23.

So, 16 prime will be converted to 16 double prime and then 16 double prime is going to give you the product formation, this is what roughly is the Curtin Hammett principle where equilibrium in terms of the intermediate will be the key factor whereas, the corresponding transition state will dictate the term which intermediate should give you the product formation.

The characterization of one intermediate does not necessarily mean that that intermediate will firm the product in some cases this intermediate can be converted to a further lower energy intermediate in this case it is happening and therefore, we further even the higher energy intermediate case can be possible and from there product formation as long as it is favorable we will be ending up seeing it.

So, what we have seen in this class then asymmetric hydrogenation is quite a powerful technique we might will not be discussing too much of asymmetry hydrogenation

anymore. So, idea simply is if you have an olefin and you have a the hydrogenation reaction if there is a possibility of generating a stereo center the stereo center can be controlled by the ligand on the metal center.

Of course, you need a stereo center at least in the ligand it could be 2 stereo center in the ligand overall an asymmetric hydrogenation reaction is an extremely powerful technique for synthesizing a number of valuable drug molecule one of those is the Lipitor, from here we can see that this hydrogenation reaction is now really applied in industrial scale to give a number of value added product which are often the drug molecule presently in the market.

So, in the next class we will be discussing not the hydrogenation reaction anymore, but we will be getting into the carbon reaction. So, you can study about the asymmetric hydrogenation in detail due to the shortage of time and that overall syllabus coverage will be mainly focusing on the carbon reaction from here on and after that we will be getting into the cross coupling reactions namely carbon nitrogen, carbon oxygen, and the carbon other hetero atom bond formation reaction also.

Various other Organo metallic reactions where metal plays a crucial role without the metal center and the organometallic intermediate the synthesis would not have been possible and literally there is no other alternative that is available for such catalytic reaction or for such brown formation.

So, will discuss more on that in the next class till then keep studying may be let us look at the asymmetry of hydrogenation little bit into the detail first look at the hydrogenation mechanism and after that try to look at some of the examples of the asymmetric hydrogenation reaction all till then see you; bye.