Metal Mediated Synthesis - I
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Lecture - 12
Heck Coupling Reaction

Hello, welcome again to this class. Today, we will discuss the heck chemistry, of course, heck reaction, the one we were discussing in the last class mainly today's focus will be on the regioselectivity of heck reaction we have seen aryl halide or alkenal halide can be coupled with olefin now we have also drawn the mechanism of such reaction what we have seen is the halide; that means, the electrophile will oxidatively undergo addition to palladium under this oxidative addition we will have the olefin coordination at the palladium site subsequently the alkyl part or alkenyl or aryl part we will insert at the beta position of olefin leaving the alpha center to be attached with the palladium center.

Next step, we have seen the beta hydride elimination to give the product formation. Now as you can imagine with a given olefin we can have 2 position and proposition beta position or one 2 whatever way you want to describe it now whether this new group that is the electrophilic partner that is let us say aryl halide that aryl partner or alkyl halide that alkenyl partner will be attaching at the one position or 2 position of olefin it is something of a great value.

This cannot be really summarized in one word you have to understand the origin of the regioselectivity lets try to discuss the origin of the regioselectivity and the reactivity pattern that follows in the heck reaction right most importantly first of all look at the relative rates of olefin that reacts with aryl halide all the olefin will not be; obviously, reacting at the same speed depending on the electronic properties as well as the steric bias of the olefin, we will see the rate of the reaction varies dramatically let us look at different olefin and their relative reactivity pattern with respect to a given electrophile.

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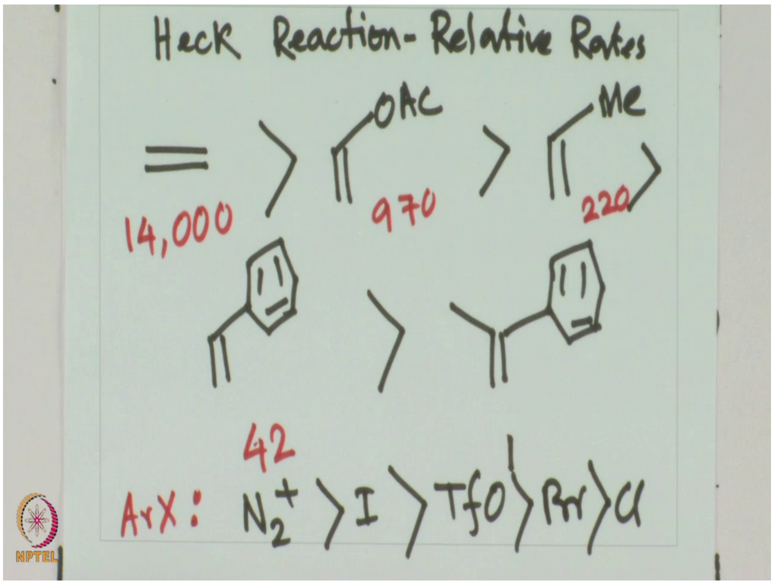

So, heck reaction and relative rates heck reaction and relative rates what it was found that in terms of olefin simple epithelium is most reactive then with acetate substituted olefin then a electron rich olefin such as this and this is more reactive compared to electron the styrene and subsequently we see alpha methyl styrene the relative rate if you are putting these to be one and with respect to that this is 42. This is 220, this is relative rate, once again, this is 970 and this is huge 14000 ok.

So, as you have seen in this example if you have no substituent on the olefin that is most reactive more substituent you have on the olefin reaction rate decreases therefore, it is a steric factor controlled reaction more importantly also electron withdrawing or the electron donating nature of the substituent influence the rate of the reaction will come more towards those discussion. So, we have seen the more substituted ones are least reactive least substituent ones are the most reactive in terms of electrophile also there is a reactivity pattern quite similar to what we have seen in other carbon-carbon bond formation reactions as well.

Let us look at the rate of reaction with respect to the electrophile; that means, aryl halide or diazonium salts and so on with respect to that with respect to aryl halide for example, or arx; what we see is diazonium salts are most reactive than iodo, then triflate and then bromo and then chloro; now of course, this is quite what we would expect in similar to what we have seen also in the oxidative addition pattern usually for heck reaction we do use other additives such as silver or tetra butyl ammonium acetate. So, on different derivatives make it makes the reaction faster usually by creating a cationic atmosphere around the metal centre; that means palladium center.

So, if palladium center is cationic in nature then the coordination of the olefin becomes bit easier and the rate of the reaction overall not always most often we have seen that it the rate of the reaction can be faster by creating by adding some of the additives usual base for a heck reaction could a potassium carbonate for example, is a good one.

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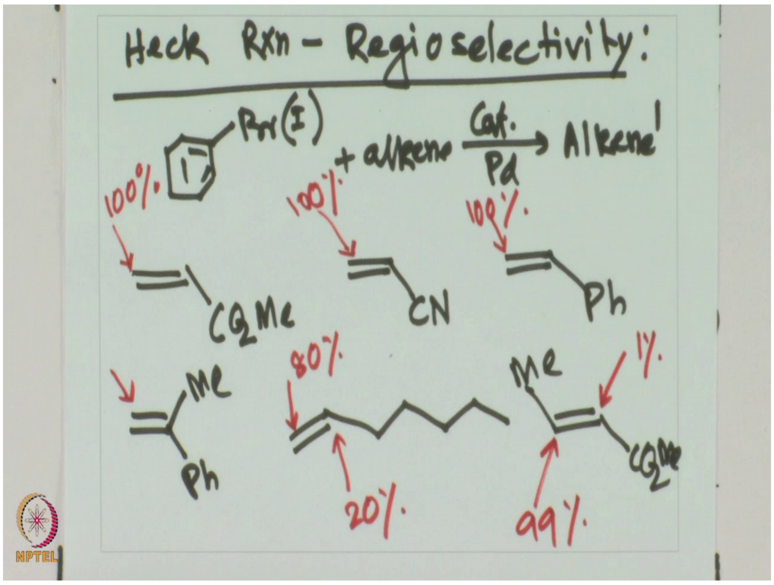

Let us look at the regioselectivity of the heck reaction. So, we have now the heck reaction regioselectivity regio selectivity.

Overall, you can have aryl bromide for example, or any iodide reacting with alkene in presence of catalytic amount of palladium to give alkene prime another alkene now this all the heck reaction, all it tells you is you are taking one olefin and the less substituted one in the process, you will get more substituted olefin that is the heck reaction is all about now that increases the substitution pattern on the starting olefin is going to follow some sort of rule what is those rule of selectivity or what is that rule of substituent is the one we would like to see.

We have seen that olefin usually prefers that terminal position or so, to speak less hindered position therefore, less hindered position will be substituted and we will get the corresponding more substituted olefin let us look at the relative rate of olefin and how or their regioselectivity what percentage of the alpha position or beta position gets substituted with an electrophile such as aryl halide. So, we do have; for example, if you take methyl acrylate and we do get selectivity hundred percent at this carbon that is good so; that means, that electron withdrawing group at the terminal position at the end we have hundred percent selectivity at this place.

Similar thing is too for acrylonitrile once again we get here 100 percent regioselectivity if you take styrene once again you get the similar 100 percent selectivity at this end, even if you take alpha methyl styrene you will get again the same thing over here if you get something like aliphatic olefin you get now a mixture of 20-80 percent for aryl bromide it is 80 percent and over here it is 20 percent if it is aryl iodide we using that would be 90 percent and this site will be 20 percent.

Now, that is very interesting right overall as you can as you keep on asking more and more questions with this different thing what we see here previously it was hundred percent over here now this is ninety nine percent and this is one person and. So, on well that remains the overall reactivity pattern for such reaction. So, you have to really be sure about the olefin that you are dealing with and therefore, the selectivity will be controlled accordingly.

If so, the rule of thumb is first of all the less substituted olefin gets substituted or less substituted olefin positions get substituted that is number one another thing that is more important is more electrophilic carbon center gets the substitution in a higher rate as you see the carbon center that is attached with the electron withdrawing group is not getting substituted the conjugated the other the beta center is getting substituted more frequently and in higher selectivity often we get the terminal selectivity, but internal product formation do happen in some cases and some cases depending on the both the electronic and then the steric factor, we should expect the selectivity to be happening at a desired position in a substrate.

Alright, let us look at some more of these discussions where we can take some more of the substrate of the similar type and then we might we will be able to get some sort of trend into this reactivity pattern. Now we will discuss a little bit more on those type of substrate where we have.

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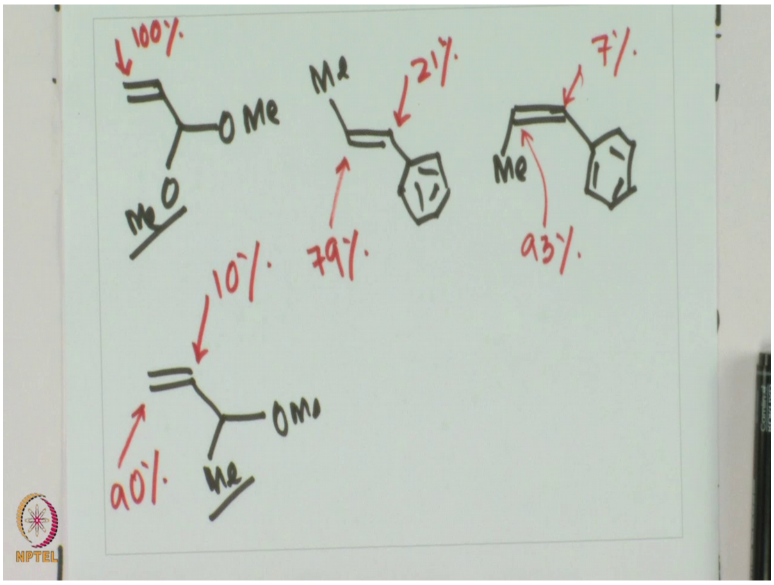

Let us say substitution like this and in this case we will get 100 percent selectivity at this side and the beta position if you have beta methyl styrene trans beta methyl styrene, we do have 79 percent selectivity, this is interesting now and we get twenty one percent selectivity for this one.

If you have on the other hand the cis one, then we do have a little bit different selectivity and that is over here we have 93.5 percent selectivity and over here we have 7 percent selectivity and if we have further substituted one and with similar to this, but now with methyl with respect to this one we now get 90 percent selectivity for this side and 10 percent selectivity of this side.

So, overall as you see well once again the same trend is holding towards or throughout the substrate throughout the olefin least substituted olefin are getting the new substitution that is coming from the heck reaction and second of all, we are also seeing that electron withdrawing group containing carbon center is not getting substituted of the olefin the other center other olefinic carbon center is getting substituted.

That is pretty much a good trend and once you deal with a variety of substrates let us say 10 different olefin, then and the ones we have discussed right. Now I guess the selectivity issue it should be should be solved or you should be able to understand why the selectivity is going to be by looking at that existing reports in the literature I hope the whatever we have discussed in last 3-5 minutes, we should be able to be you know predict the selectivity according to this discussion.

Let us look at some more of the regioselectivity issues using the heck reaction or the known heck chemistry that we have seen in the literature well another thing that is that is most important to discuss why the less substituted olefin is getting substituted with the aryl halide or the aryl partner of the aryl halide that is very simple that is because we do have the steric problem of course, that is the usual thing people say, but how really the steric issues are appearing can we draw it in a clear fashion and try to understand this approach why that sterically less substituted position will be substituted during the heck reaction.

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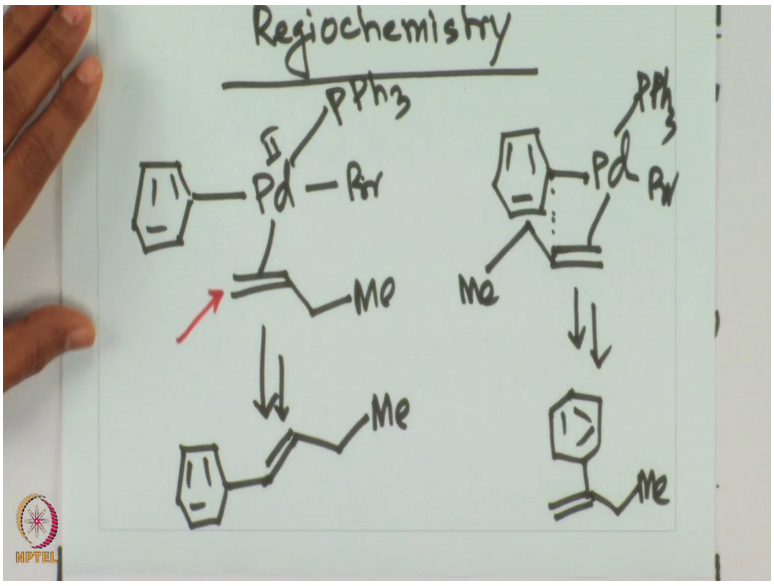

So, that region chemistry regiochemistry is at the less substituted position we will be getting the substitution right; the aryl substitution. So, we are drawing the olefin coordinated intermediate right. Now let us say, this is the olefin, this is a you know the track ordinate and palladium it is a palladium 2 plus. So, minus minus palladium 2 plus of course, palladium 2 plus will be the eight system it is a square planar in nature from here on what we see the product formation that gives the right chemistry for these cases is this one, right.

The other one the why the; so, therefore, the less substituted carbon center is getting substituted as you and see the other center if we are to substitute this position of course, that position has to be close with respect to the born newborn forming processes. Let us look at that orientation. So, if it has to you know substitute at this position. So, these 2 carbon centers should be close to each other. So, let us say that is close to each other and during that orientation what we see that this alkyne substitution is bumping into the aryl ring right and therefore, we are going to get this product formation and that is going to be something like this right.

So, this is the alpha substituted one and this is the beta substituted one or whatever way you want to call it this is not going to happen because there is a steric hindrance between the substituent of the olefin and the aryl ring of course, another thing. So, this is the regiochemistry is controlled by the steric factor; of course, that is very clear, but we have also drawn right. Now how this steric factor might will be coming into the picture while the carbon-carbon bond formation is happening during the heck reaction.

Another thing that we also have to be aware of as we are discussing that is the electronic factor let us look at how electronic factor controls the regiochemistry of the addition or regiochemistry of the aryl partner when it is incorporated into the olefin let us look at that now that regiochemistry also is determined by electronic factor we have seen the steric factor.

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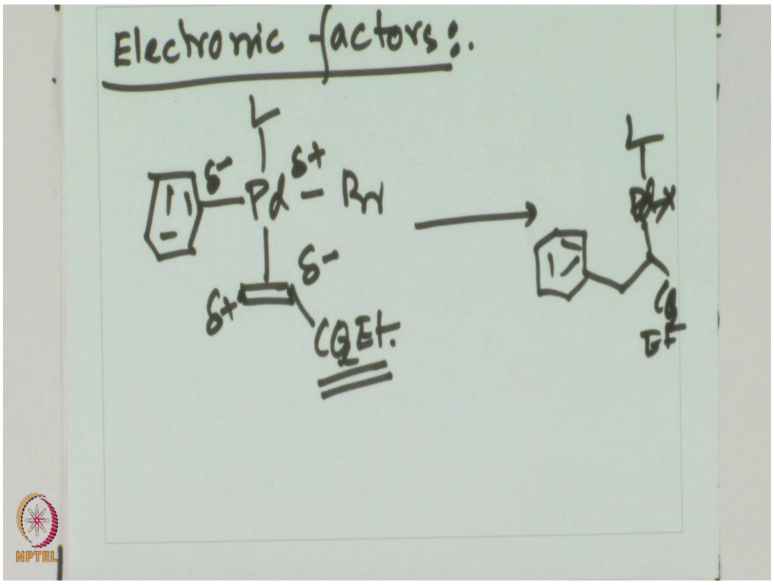

So, electronic factors also dominates or transferred to most electron-electron deficient site right. So, let us draw at the oxidative addition olefin coordinated intermediate after oxidative addition we get the olefin coordination that intermediate, if we draw this is the intermediate right.

Now, this is delta plus because this is electron withdrawing this is relatively delta minus, now this is your delta minus and this is your delta plus. So, that is also plus and minus will combine to give the product and that is how you get the selectivity in terms of the less substituted position as well as the electron withdrawing group containing carbon is not getting substituted the one which is positively charged is its usually getting substituted by this process ok.

So, that is both the electronic factor we have seen and the steric factor we have seen during the heck reaction now another factor that comes into the picture what happens when the beta hydride elimination is happening how the region chemistry or the cis and trans product formation not only the positioning where regiochemistry, but the stereochemistry is also important where this substituent is interacting or where it is entering if you already have a substituent in the olefin with respect to those existing olefin substitution where the new substitution is going to occur let us try to look at that.

So, we are trying to discuss the positioning of the incoming substituent that might will be happening during these cases ok.

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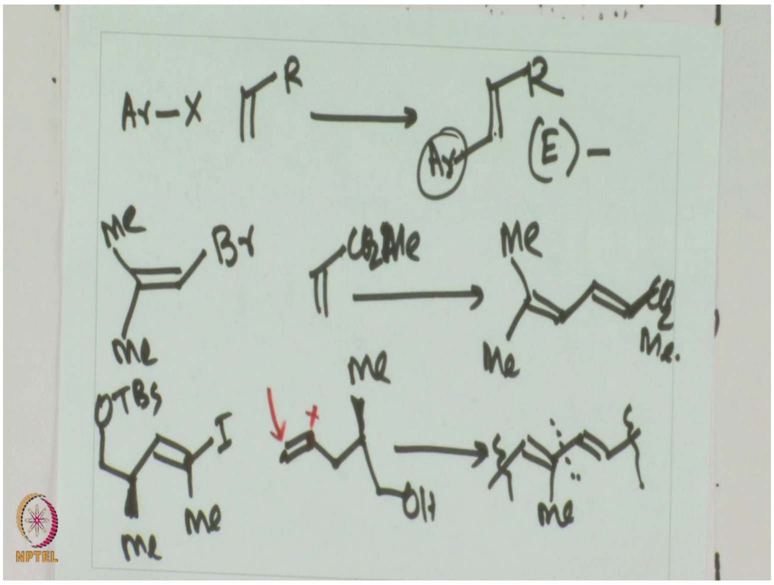

We will take again aryl halide in this case and a olefin R group overall we usually draw the trans chemistry; that means, e products predominates well it is of course, it is sensitive towards the reaction condition, let us take some more example of the e product. So, as you see this aryl group could be on this side on this usually R on this side aryl group on this side of course, that way steric factor is also controlled.

now if we have an olefin or alkenal halide as a coupling partner let us say with ethyl acrylate or methyl acrylate what we have seen is again these are the examples directly from the literature. So, that should be supported quite well. So, that is what the product formation it is if you have further other substrate of similar types as you see this is trans with respect to the other substituent. So, always this is the e product again e product well if you take another example of similar type what we see once again the e product is for will form in these cases as all and you know irrespective of the center that we take it is going to be the same product formation again and again.

So, that is the e product; that is dominates the chemistry for such cases. So, let us not draw the whole part. So, this is the new carbon-carbon bond that forms between this carbon center and this olefin and that is how we see that it is getting substituted at the less hindered position not at this center. So, substitution is not happening at this carbon centers its happening at this carbon center it is not happening here and more importantly we see with respect to this substituent. So, it is always trans. So, the incoming one is going to be on this side that is how the product formation is going on.

So, always in these cases we do see the trans product formation at that less substituted position and part from the electron withdrawing group that is quite amazing now another thing we need to look at how the stereochemistry or region chemistry would be and how the stereochemistry will be when we have disubstituted compound let us say if you have a the disubstituted olefin how the product formation is going to be controlled at which carbon center it is going to be the new substituent is going to join that is one thing we really need to understand because as you know for the beta hydride elimination we need the same elimination.

So, the same chemistry same stereochemistry has to be maintained during the beta hydride elimination accordingly the substitution pattern has to be controlled or the relative orientation has to be placed. So, that orientation is coming during the beta hydride elimination. Let us look at one mechanistic drawing of that. So, acyclic disubstituted olefins we are going to draw.

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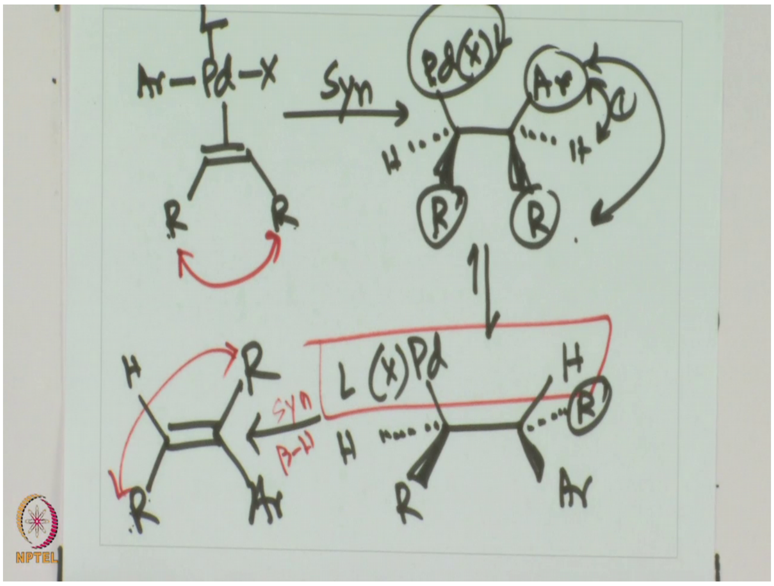

So, it is going to be aryl palladium x substituent and l it is reacting or interacting with 2 substituent let us say R and R 2 different substituent

So, acyclic disubstituted olefins well not that many examples are known and you know sometime an x this is an excellent means to prepare the stereo defined trisubstituted olefin as you can see this is a disubstituted olefin from disubstituted olefin you are going to incorporate an aryl group, but this is going to be an exciting way to look at the stereochemistry what we have not done is we have not taken 2 different R we are taking the same r. So, what we know about these addition is its going to be a Syn addition. So, let us draw the Syn addition product of course, aryl and palladium x and l always going to be attached with it.

So, this is the Syn addition both the aryl and palladium attach at the same position and from there on or from the same side and from there on we do see that R and R of course, they are on the same side we do get them in the same side what we get the hydrogen is on the other side. So, R and R on the same side palladium and R at the syn; Syn addition and overall then what from here on we will see that there is a rotation because of the Syn elimination is required right. So, you can exchange between these 2 and then the remaining that is first and then second you can exchange between this one and that one

Overall you get the substituent where h is above or h is in the plane and then, then overall we have R prime in there or R in there and aryl group is in this substitution position and R overall comes in the above plane and h is below and palladium stays in there in the plane. So, what we have done is we have taken the h over here and aryl over there and then aryl and R we have showed, right.

So, overall during these processes during these drawings what we try to do is aryl group insert into the olefin after that we need to see the same elimination that is the beta hydride elimination in order to bring the hydride or the beta position hydrogen and the palladium at alpha position in the same plane we need to rotate the bond double exchange can be equivalent to a rotation we have done that now h and palladium are in the same plane we will see that now they are leaving from there right overall lets we will say we will see then the beta hydride elimination from this intermediate this is the beta hydride elimination intermediate we will get.

Now, the product where h is on that side. So, this one below the plane this is above the plane R is on this side and overall the other R is on the other side and aryl group and the other side. So, what you see you have started with R in the Syn position. Now in the product you see that R is on the you know diagonally opposite to each other. So, that is actually the chemistry that we need to really simply understand if it is a disubstituted olefin alpha beta or 1 2 substituted olefin the substitution wherever they were it will change.

So, overall if you drop start with cis substituent 2 substituent on the same side those 2 substituent will go trans with respect to each other well that is really a powerful technique for getting substitution now the new substituent will be at either at the alpha position or beta position it does not matter, but if you are starting with the olefin where 2 substituent disubstituted olefin 2 substitutions are opposite to each other during the heck reaction these 2 substituent that 2 particular substituent will be cis to each other fine that is very interesting let us look at this example one more time in the drawing what we have drawn so far.

We have seen R-R on the same side of the olefin that is our starting material during the process it is just the Syn addition and this beta hydride Syn elimination Syn elimination beta hydride elimination during the process what we have seen that the rotation is such that or rotation has to be such that now the R and R these 2 R are opposite to each other and this 2 are on the same side to each other. So, that is the product formation.

Well, today's class, we will stop here, we will discuss more on the heck reaction in the next class you must appreciate the regiochemistry and the stereochemistry of heck reaction that is a very simple and powerful way to synthesize more substituted olefin from disubstituted to trisubstituted olefin from unsubstituted to monosubstituted olefin from monosubstituted to disubstituted olefin during these heck reactions.

Well, we will continue discussing on the heck reaction and also in the next class we will try to see the palladium catalyzed carbon nitrogen bond formation reaction till then keep studying we will come back soon.