Molecular Rearrangements and Reactive Intermediates in Organic Synthesis

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Lecture 43: Organoboron chemistry

Welcome back to this NPTEL online certification course in molecular rearrangement and reactive intermediate. In the last in the two classes I talk about the organoboron chemistry. So, I talk about the synthesis of organoboron compounds and then I talk about the different class of organoboron compounds. And today's class my plan is to talk about the you know more depth about the hydroboration reaction. So, in the previous class I introduced this reaction was discovered by Professor Brown. and he received the Nobel prize in chemistry for this important discovery.

In the today's class I am going to talk about several different variation in terms of the stereoselectivity and the enantioselectivity for the hydroboration oxidation reaction. So, let start with the class talking about the stereoselective hydroboration, enantioselective one and then of course, the hydroboration is not only limited to the alkene, it can also happen with alkyne we are going to learn about that. and then the catalytic hydroboration. So, this is a comparatively new topic and it was really explored in the over the year and I am going to briefly talk about some of the catalytic method.

Lets start with the where I left in the last class. If you remember I was talking about that if the the borane try to react with olefin. First it is react with olefin to form a BH_2. If you remember then the next there is another olefin can react to form BH and so it is dialkyl and BH, then the last one which will be little slower that third equivalent of olefin comes in the picture to form the corresponding trialkyl bond. And also I remember there are lot of cases the you know depending on the steric, it can be stopped after the monoalkylation like the monoborylation.

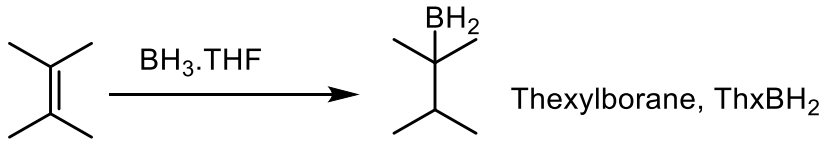
So, that the first example you can see here once you have this tetra substituted like tetra methyl ethylene. and treated with the BH_3.THF, it is going to form this compound. So, it is going to form this BH_2 and because of the steric you can see this compound can be isolated and is called thexylborane can be used as a hydroboration reagent. Because of the bulkiness of this you can find some the stereoselectivity in the outcome where you can see BH_3 might be giving a mixture, but using thexylborane might get stereoselective, then the other things I talk about the 9BBN.

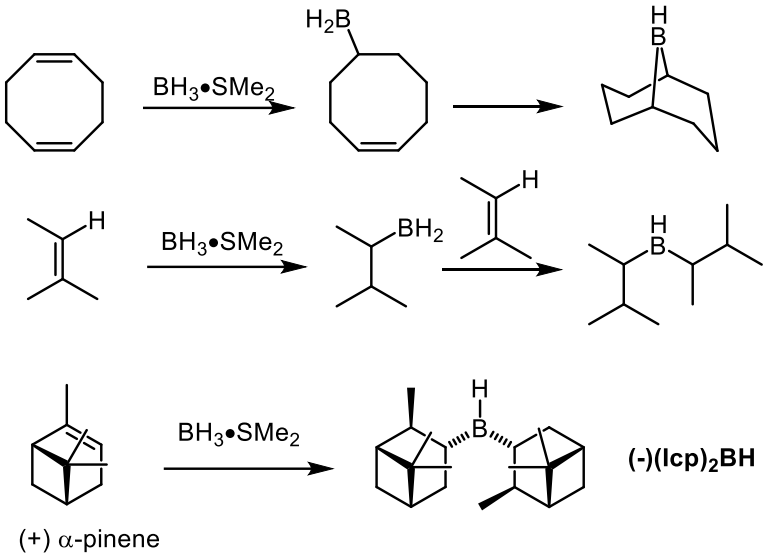
If you remember I was talking about this 9-borabicyclo[3.3.1]nonane or 9-BBN and you know previously only I talk about their structure but you might thinking that where it is synthesized, starting from cyclooctadiene, once you treat with $BH_3.SMe_2$, first there is a hydroboration of this olefin. form this BH_2, then there is a internal hydroboration with this olefin can form this 9-BBN. I also talk about the other class Disiamylborane. So, here also first thing is the hydroboration.

Now, you take 3-methyl group in the ethylene with 1-hydrogen. So, first it will go for the hydroboration in place of BH_3 to form the BH_2 and then it will take another equivalent of olefin to form finally this BH. So, now this Disiamylborane can be used as a for the monohydroboration. So, you can see there are several example I think in the last class I talked about where you can see if you have used BH_3, there is a mixture, but if you use a Disiamylborane you find the selectivity, particularly the regioselectivity I think last class I talked about. If you have a two different olefin and you want to get the regioselectivity then you have to use this type of bulkier hydroboration reagent.

And then I think I am going to introduce you know this one which is a chiral version starting from the α-pinene is called $(Icp)_2BH$. It is a Di-(isopinocampheyl)borane, you know borane or Ipc_2BH. So, I am going to talk about that. So, this is can be used for enantioselective, you know hydroboration because now what we are finding that in α-pinene having this chiral center, now once you forming this corresponding BH, now you have chiral center in the hydroboration. you know reagent which will be transferred to the product means if you have a double bond then you can have a hydroboration from a particular phase of the olefin that will generate an enantiomeric product.

Selectivity in Hydroboration





9-Borabicyclo[3.3.1]nonane or 9-BBN

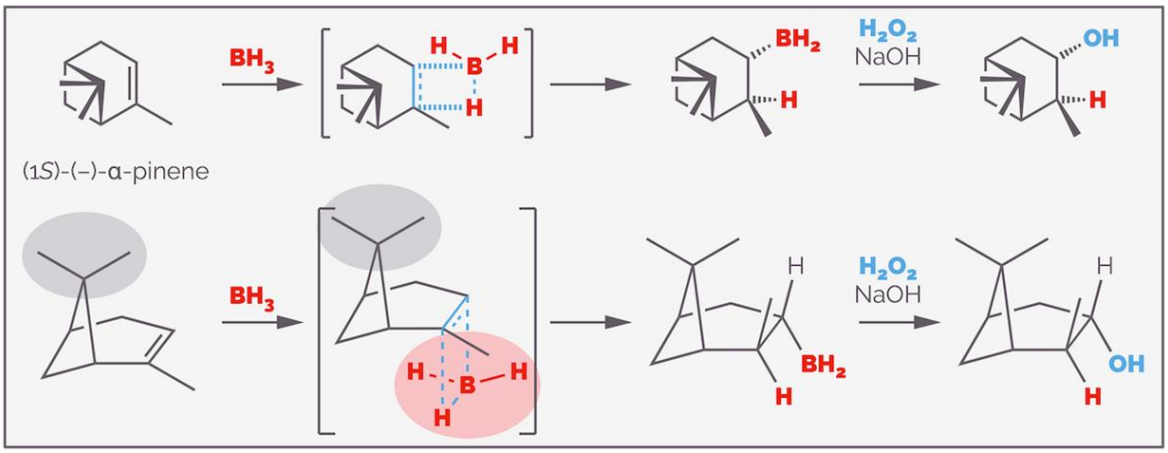
Disiamylborane or

(bis(1,2-dimethylpropyl)borane)

Di-(isopinocampheyl)borane; Ipc_2BH

So, lets talk about some of the diastereoselectivity, I think which I have not talked in the last class. So, if you have α-pinene and then once you treat the BH_3. Now, the question comes if you have a double bond here, the boron can come from either from the top phase or from the bottom phase. Now, if you see the structure of the α-pinene, now you can clearly see that in this phase when the boron can come from the top phase there is a sterically hindered dimethyl group. So, there will be a serious steric effect between this boron and this dimethyl, but once it the boron can be approach because if you remember from the last class I talk about this is a syn addition of boron and the hydrogen.

Diastereoselectivity in Hydroboration

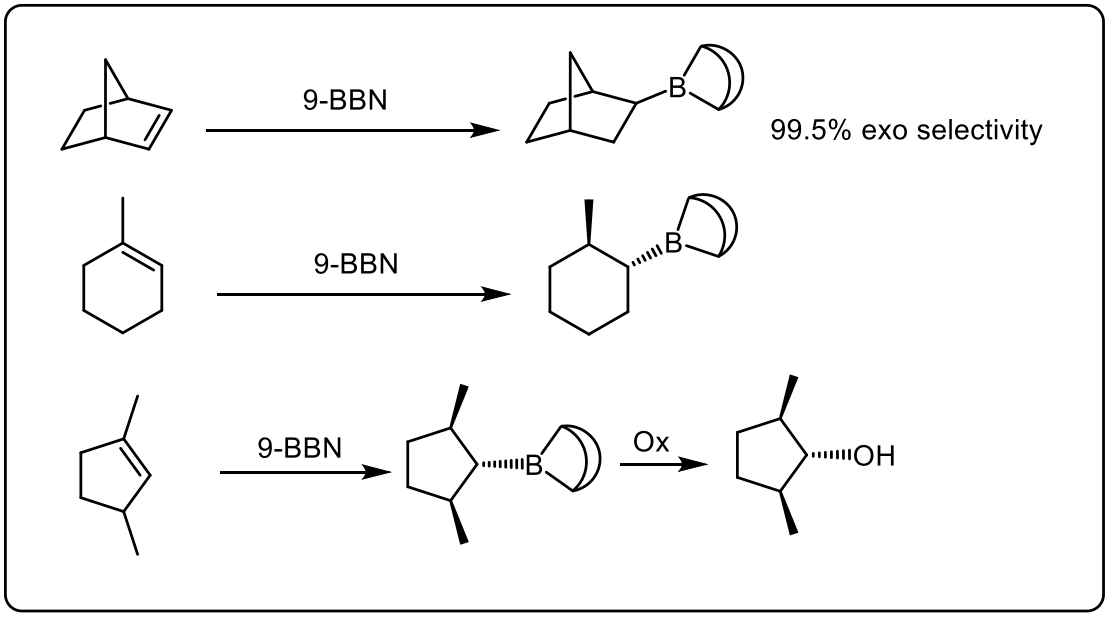


So, there is a two possibility either the boron can come from this side this way or it can come the other way where you know the hydrogen here the boron here. So, this is the two possibility you have. So, we have fixed that you know the boron going to come from the bottom phase not the top phase because of the steric. Now the question comes you know I think the last class I mentioned the steric is one of the important determining factor. So, that is why the boron will try to add to the olefin which is less hinder, it is an anti-Markovnikov addition if you remember from the last class.

The other important thing I have mentioned that if you think about this boron and hydrogen, I think I have mentioned you can think about this is as a δ+ and this is as a δ- and once it is adding to the olefine, you can think about the olefine. as a same time if you have a substitution. As a same time you have a substitution here, if you do not have a substitution here now you can think about a δ+ here and the δ- here, why I am saying here now between these two you know carbon if you think about a carbocationic character, then more substituted one will have a stabilized carbocationic character. So, that side this H- will be able to act.

So, that is why if you think here this H here adding to the more substituted position here and the boron is adding to the less substituted position to forming this product as the major product. I think a exclusive formation of this product, you can see and which will be after H_2O and NaOH oxidation, it is generating the corresponding alcohol.

I am going to talk about some more example. So, you have seen in the previous places we have seen endo selectivity, but here what we are seeing here in this particular case we are seeing a exo selective product, 99.5 %.



So, what is happening here why in the previous cases you have seen the hydroboration is happening from the bottom phase, but here it is happening from this phase. If you think about that if it is trying to approach from the bottom phase there is this two you know this CH_2CH_2 -group which is going to interact.

So, that interaction going to happen if the boron is going to approach from this phase versus if the boron is coming from this side, then it have only one CH_2 which is going to interact. And if you think about so coming from the bottom phase there will be two CH_2 versus top phase one CH_2 that is why this product will be form as major product. So, you can see once you are using a 9-BBN which is again a bulkier you know the hydrogen in reagent that can selectively add from the top phase to give you 99.5 %. Again, there is another example here I think in this particular cases if you use 9-BBN, you will get almost 99 % of this particular product, but if you use normal in the BH_3 you might get up to 95 % selectivity.

Again, what is happening here you can see you have a substitution here there is a methyl group here in this cyclohexene.

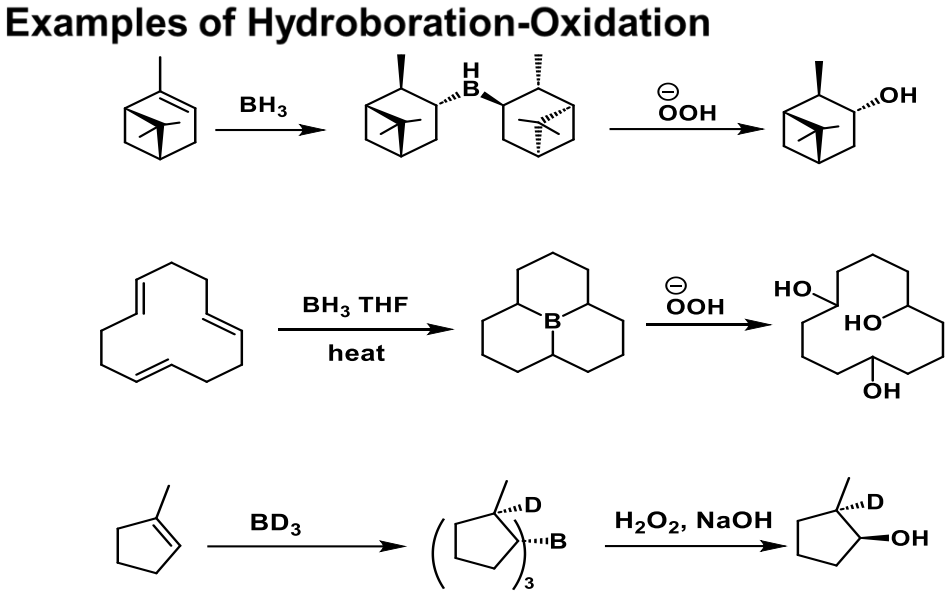
Now if you remember the hydroboration actually happen again if you see this rule you know the approach I think if you have a methyl group here then this will be the approach I am telling you several times the same thing that. So, they will be adding in a syn addition going to happen if you think about syn addition going to happen then what you are end up getting here that you have a methyl here if you think your methyl is up and this is coming from the H methyl you should remember that the boron will be below side.so this 9-BBN will be here. So, that is how you end up getting to the this product.

So, now the methyl and the 9 BBN actually trans to each other. There is another example here you want to see about dimethyl here that is also end up making this product where you see this is the trans. So, you can see there is a H here and then after oxidation it is going to end up giving product, you know some more example I already talked about this example at the beginning formation of this product you know selectively by approaching from the bottom phase. Here there is another example if you have three double bonds, you treat with BH_3. So, if you remember, I talked about the synthesis of a 9-BBN.

So, there was two double bond first there is a hydroboration happening then there is so in the cyclooctadiene. and then the next is another hydroboration to form this then the 9-BBN. So, here what is happening you have three double bonds. So, first there is a hydroboration going to happen with one double bond that will end up forming this BH_2. So, that BH_2 will go for another hydroboration intramolecular to form the BH then that BH will also go for another intramolecular hydroboration to form this compound.

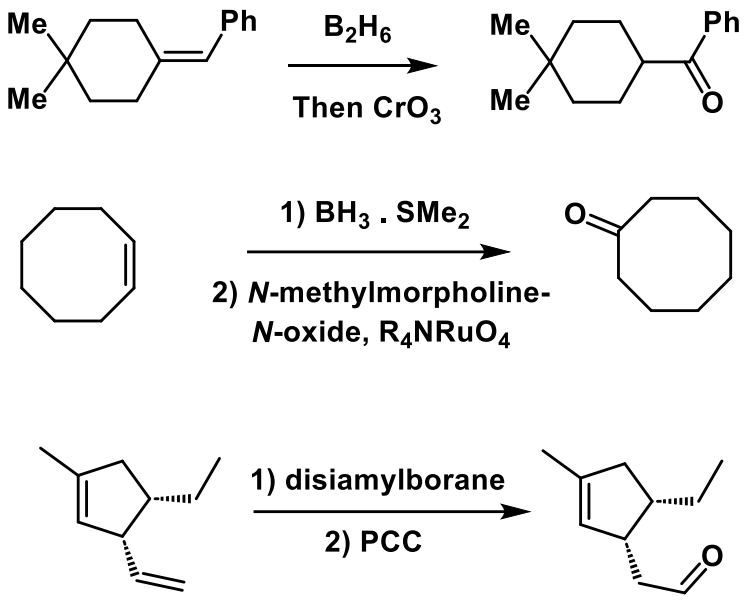
Once you have formed this compound you treat with the H_2O_2 / NaOH that will going to end up forming this compond and introducing three hydroxy group into the molecule.

So, this is a one sort you can form the double bond you can introduce three hydroxy group. then if you have this compound instead the BH_3, if you include BD_3, you say deuterium then you can introduce a deuterium here in the methyl carbon to form this product. we have already explained that if the addition is happening we should be end up forming I think there is a problem with the stereochemistry. So, this should be down not up.



So, please correct that I think I will also correct the slide because you have to understand that the deuterium and this the boron will act from the bottom phase. In this example you can see tri substituted olefin and again the tri substituted olefin if you treat with the BH_3 or the B_2H_6 what is going to happen now there is boron will be approach in this way as this is a more sterically hindered. So, it will add this way to first there will be hydroboration and then you know oxidation using chromium oxide which will oxidize the alcohol to all the way to the ketone. then you have another example here double bond which will be first you know in hydroboration then once you use the N-methylmorpholine, you know N-oxide and the ruthenium oxide will take you all the way to ketone. In this example you have two different olefins.

Examples of Hydroboration-Oxidation



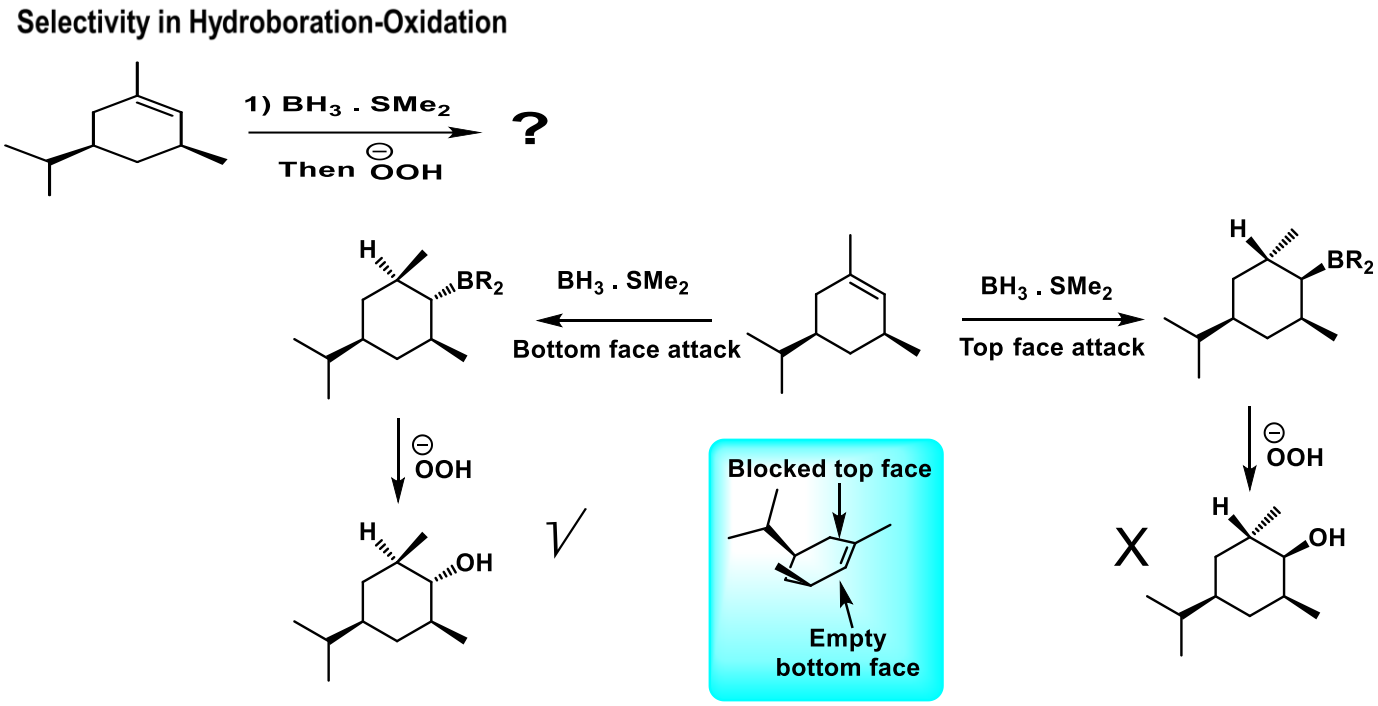
So, this is a tri substituted versus terminal one. If you use this disiamylboraneborane then it is going to the selective to the terminal one which is you can see again this is a less hindered So, it is going to add here and then once you treat with PCC it will oxidize to the corresponding compound. There is another example here now if you have this isopropyl group and this methyl group both are up then the hydroboration can only happen from the bottom phase you can see here because of this groups are blocked the top phase.

So, the boron can approach from the bottom phase the BH can approach which can end up forming this product as a major product not you know the other pathway. due to the steric which can be after the oxidation you can convert this boron to the corresponding alcohol using the H_2O_2 / NaOH.

So, I talk about some example about you know the hydroboration using several different type of bulky group, the borylating agent and you have seen that there is some advantage there for getting stereoselective product. So now the things about if you can introduce a chirality on those type of hydroboration agents then you can introduce the chirality in the product as well.

So the brown group actually developed this one that starting from the α-pinene once you treat with $BH_3.SMe_2$ you can able to make to this $(Ipc)_2BH$, I have already explained at the beginning that you able to make this.

This is going to react first here from a BH_2 then it is react from this BH.So, this could be a diisopinocamphenylborane at the same time this monoisopinocamphenylborane can be also used.



So, you can take the α-pinene and you can able to isolate this (Ipc)BH2. So, that can be also used for the asymmetric hydroboration. So, both of these reagent are used and I am going to show there are some complementary effect of both these reagent. I think you know before that I am going to talk about that not only this is the only example, there are more example also developed like there are also you know other natural product like limonene. Limonene can be from the limonene this type of hydroboration agent was developed which again chiral from carene, from longifolene.

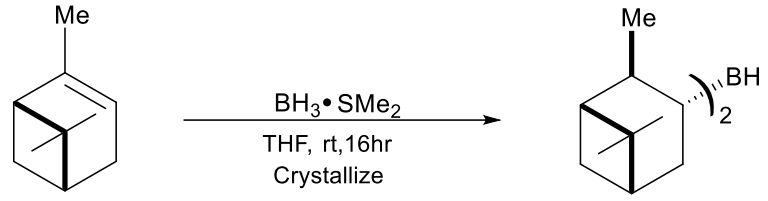
Asymmetric Hydraboration

Asymmetric hydroboration were amoung the first examples of non-enzymetic trasformations to proceeds with high enantiomeric excess.

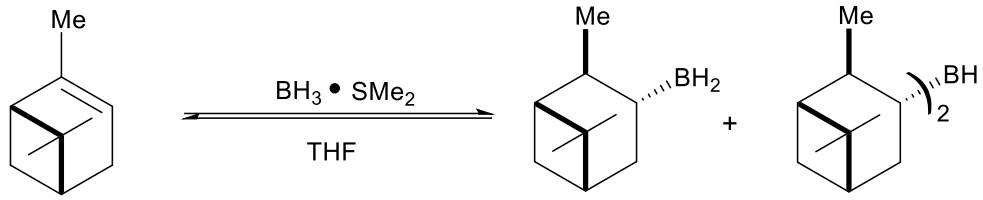
Several reagents have been developed , but those derived from α-pinene (Brown) are still the most widely used.

So, there are several different chiral hydroborating agent was you know developed. So, this can be also used for the asymmetric synthesis. and then of course, this was also developed which is also a very good hydroborating agent, I am going to talk about that as well.

Diisopinocamphenylborane - sterically demanding reagent reacts with unhindered alkenes.

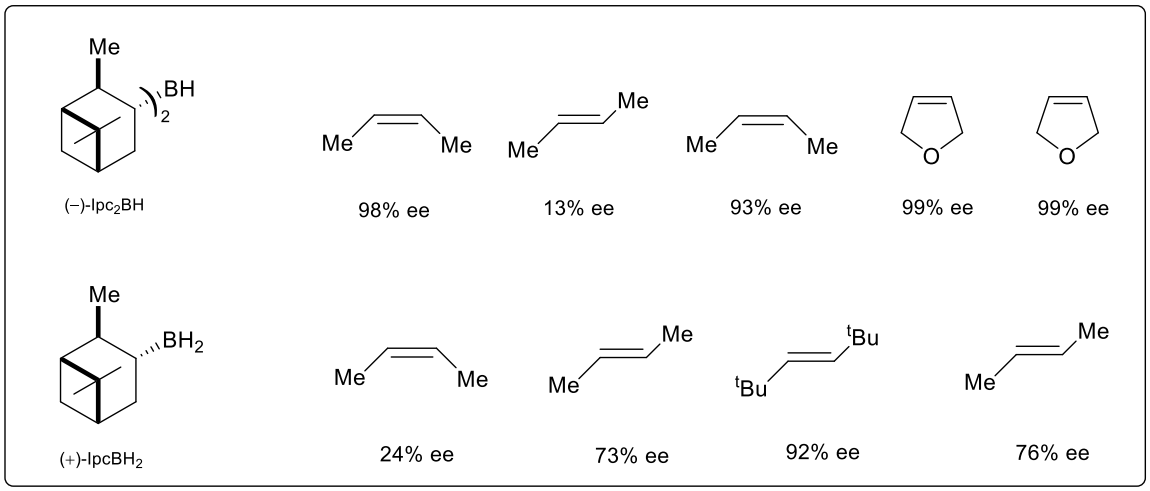


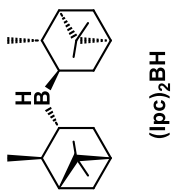
Monoisopinocamphenylborane- unhindered reagent reacts with all classes of alkenes.



Enantioselective Hydroboration

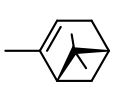
Di-(isopinocampheyl)borane; Ipc_2BH, which can be prepared in 100% enantiomeric purity from the readily available terpene–pinene



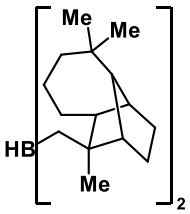


BH_3

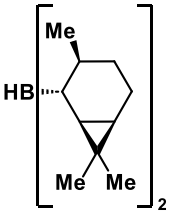
+



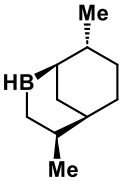
Other chiral Organoborons:



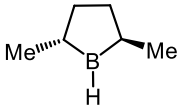
From longifolene



From 2-carene

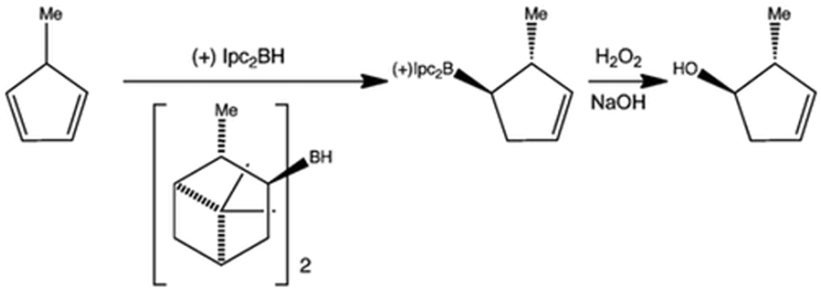


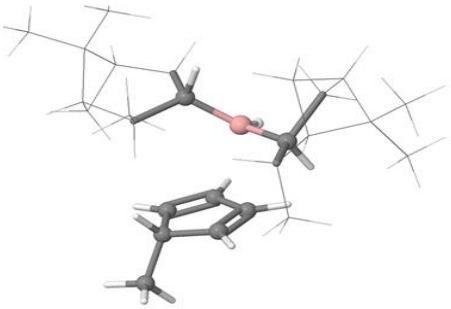
From limonene



You are going to see that I think I do not have time to talk about all the details, but this was a very good reagent you know lot of time when this $(Ipc)_2BH$- is giving very poor selectivity, this is giving you know very high selectivity. So, here is an example I have given here.

So, if you see using this $(Ipc)_2BH$- if you know go for the hydroboration. If you have a cis olefin, if you have a z- olefin then if what you are seeing the selectivity is very high 98%. So, I think there will be a ethyl here, there is a error here this will be a ethyl then this is 93 % which is kind of you know consistently showing that if you have the z-olefin, then you are getting very high selectivity if you have a some sort of ring system Then of course, in this system also you can see this is a Z- selective bond giving 99 %, again this is I think you know this will be a thiophene here this is also 99 %. But then the problem comes once you have a trans olefin specially once you have a trans olefin which has a you know the the both side has same substitution those are giving very poor ee but once you come to $(Ipc)BH_2$ in this hydroborating agent, the Cis or Z- is giving poor ee, but the trans is giving very very good ee. Again this will be ethyl here instead of the methyl So what is happening here what we kind of you know try to conclude as I was telling these are complementary because in one cases the Z- is you know very good, but other cases the E- is very good using the $(Ipc)_2BH$ that means the monomeric one is you know very good for the trans or the dimeric one is very good for the cis.





So, now the question comes why that is happening. So, there is you know lot of calculation was done by the Haug group for you know has done lot of calculation to establish that you know why that is happening and one of the concept that for $(Ipc)_2BH$- once you can think about. So, what they have done in this model they try to show these types of groups as that the boron is attached with a carbon. So, suppose they are saying that the boron is attached with a carbon where you have different type of group attached like you can tell them small, medium and large. As you can see it you know this side could be a larger side you can see this part and now you have a H- here that could be a small and this could be this CH_2 part could be a medium.

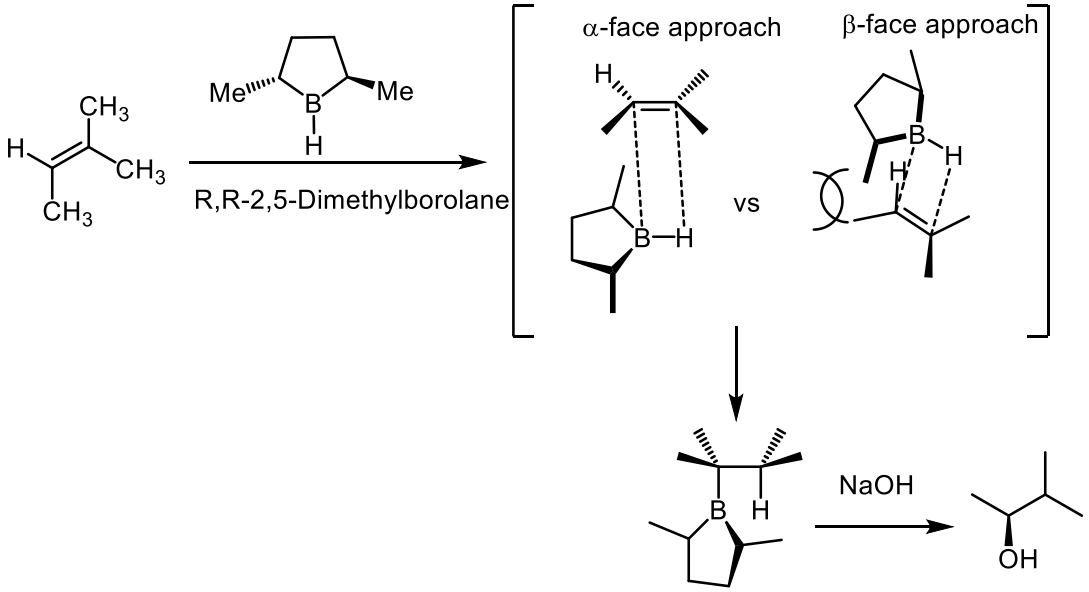
So, now this is going to approach. So, this particular in case of $(Ipc)BH_2$ this is going to approach to olefin. Now the question comes once you have the Z-olefin or Cis-olefin then in the transition state the interaction of this R-group and this S-group which is going to approach or the M-group which is going to approach is really minimum. Because you have to understand to get a high ee the substrates and the catalyst interaction is very important. So, that interaction get decreased once you have a Z-olefin which is reacting with the $(Ipc)_2BH$. You can understand that these group are far when this is coming the interaction between these groups are getting minimum.

But on the other side once you have this $(Ipc)_2BH$ and you have a trans, now once you have a trans scenario because in case of $(Ipc)_2BH$, you can see this structure is little different because now you have a BH- here which have a single hydrogen here. which attached with two carbon if you think about I am just going to write this way for simplify this, if you have a small, medium and large and both side you will have a very similar structure. so now once this is approaching to olefin where you have a both the groups attached. And now if you think about this actually this BH- is coming and adding to this forming a four member. what is happening both side so there is not much selectivity from approaching from the up or down because you can see if it is approaching from the up or approaching from the down if you are both the methyl are same then you will have a very similar there is not much selectivity going to approach from a particular phase.

If you do not have a selectivity to approach from a particular phase of the olefin then you will not get a selectivity in the product. So, you will not get a good ee. So, that is the reason you find out there is a poor ee, once you have this type of substrates there.

And again, there is a example here if you have this cyclic cases the things are different once. You have this the diene scenario here in case of diene also this reaction works, but again you can see here this is you can see these groups are again you can think about that way.

So, now if this olefin is reacting with the $(Ipc)_2BH$ you can end up getting a very good ee for this product which can be further oxidized to to form the alcohol. Now you can see in the transition state one of the important thing you have to understand this methyl group will be try to be away if you see in the transition state this is the methyl group of this substrate. So, it is in a different phase where from the boron is approaching because to avoid the steric interaction that is why you end up giving to the this particular product. Then you know there is enantioselective hydroboration using this particular hydroboration, as I mentioned this was used a lot and only thing there was some limitation for the synthesis of this that is why it was not become that popular compared to the Brown's chemistry.



But again, this was also reported for several substrates where you know with the tri substituted one I think one thing I missed in the last slide that if you have the $(Ipc)_2BH$ then that is not even reacting very well with the tri substituted because of the steric bulk.

But if you have $(Ipc)_2BH_2$, then it is reacting with the tri substituted one giving I think it is you can say a good to moderate ee, but here in this particular hydroborylating agent can give a very good ee for the tri substituted reagents.

Again, there is two different approach it can approach in a facial way in a α-phase approach the BH is approaching the olefin in the α-phase approach or it can approach through a side approach it called a β-phase approach. The β-phase approach in case of this methyl group have a steric interaction with this methyl group. So, α-phase approach will be the viable and you know that is how it is going to end up forming this product which after oxidation

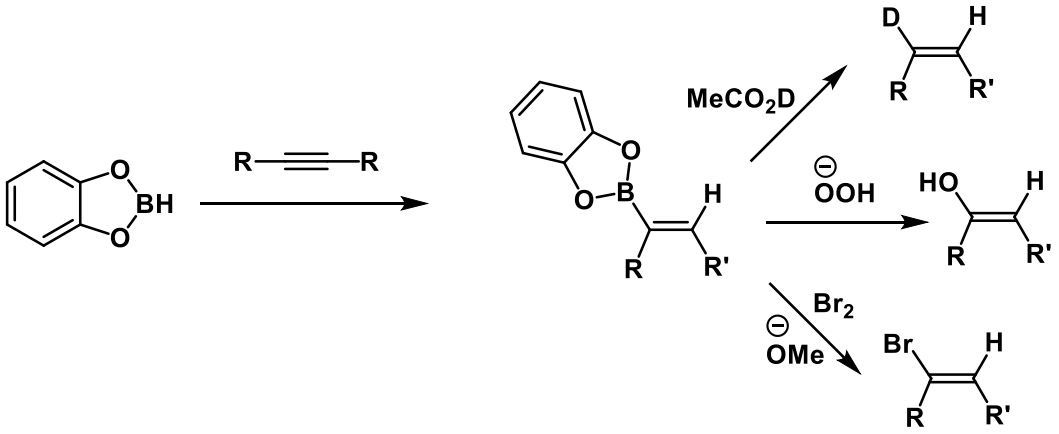
end up forming this product as a good. So, I talk about lot about the hydroboration in the olefin, but now I am going to talk about the hydroboration of alkyne very similar to olefin.

The hydroboration of alkyne also takes place using catechol boron. Once you take the catechol boron and take alkyne that can go for a hydroboration that can act to the alkyne to form this species here. So, depending on the condition there are I am going to bring you different condition in a minute. So, that you can see that once you have these groups are similar R and R- then you do not have to worry about the stereoselectivity of the product. But as soon as R and R'- will be different now you are going to see depending on the hydroboration agent you will see a selectivity difference.

Once you have this product if you treat with this $MeCO_2D$- this bond between this carbon bond is weak that can get a cleave to form introduce the deuterium or it can oxidize to the -OH, which is a enol which is you know convert to a ketone and also you can have if you treat with the alkoxide and the bromine you can also replace this the boronic ester to introduce a bromine here, so now i am going to talk about some of the unsymmetrical one so if you have a n-propyl versus a methyl So, now how to control the selectivity because you can see here if you are using you know n-propyl versus a CH_3- using the silylamyloborane it is giving 60% and 40% only. That means still you can see that the it can able to differentiate, but not much.

You can see, this is giving 60%, where it is adding from the less hindered side. But once you have a isopropyl versus methyl now that can be differentiated by silylamyloborane.

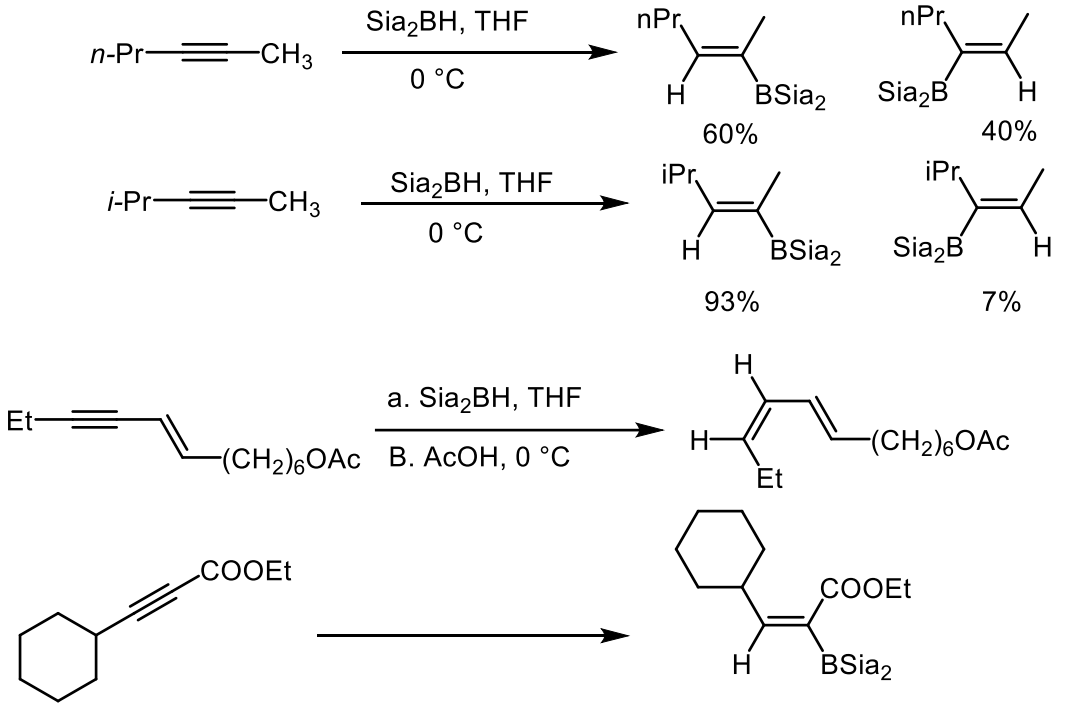
Hydroboration of alkyne



So,now you can see it can improve up to 93%. So, that is the difference. So, I am saying the substrate varying substrate you can see the selectivity can be improved if there is a steric difference between those two substitutions which are present in the alkyne terminal.

Now another example here first thing is they have done the hydroboration and then you treat with acid. So, it can able to the hydroboration, the boron you know can be removed to introduce the H. So, that you can see both these H coming from the same phase to give you to this type of 1,3- diene.

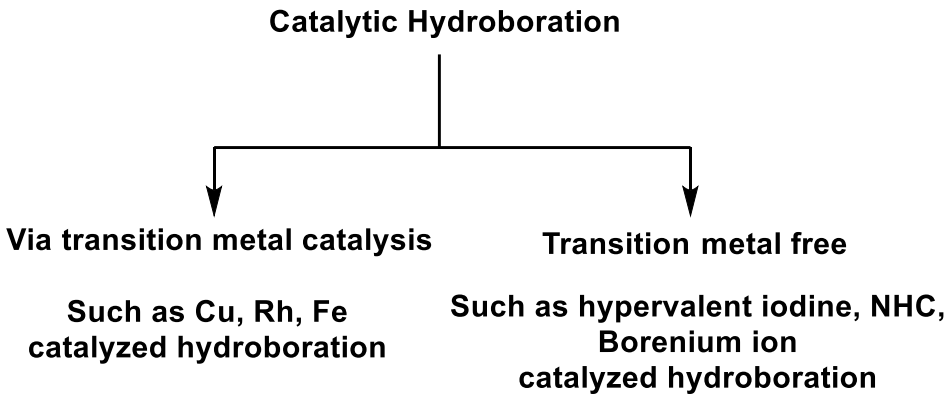
And now there is a interesting problem here, you have a -COOEt here and you have a cyclohexyl here in the alkyne. Now things that if you treat with the Sia_2BH H in THF, you know what is going to happen here. So, if you treat with that now if you think about you know understand the electronics of it, if you remember in case of the hydroboration I was explaining that once the you know COOEt- can pull the electron density it is going to create a more δ+ here in the β-carbon. so that is why you can see the approach of this Sia_2BH. So, this will be approach in this way, that will end up giving you this product. So you can see the electron is also going to play a important role not only the steric, the electronics can also play important role to give the selectivity in the product So I talk about lot hydroboration where you have to use a stoichiometric reagent that means you have to make a chirality then you have to bring a reagent which you have to use an equivalent amount which can form the boron and you can oxidize and do other transformation.

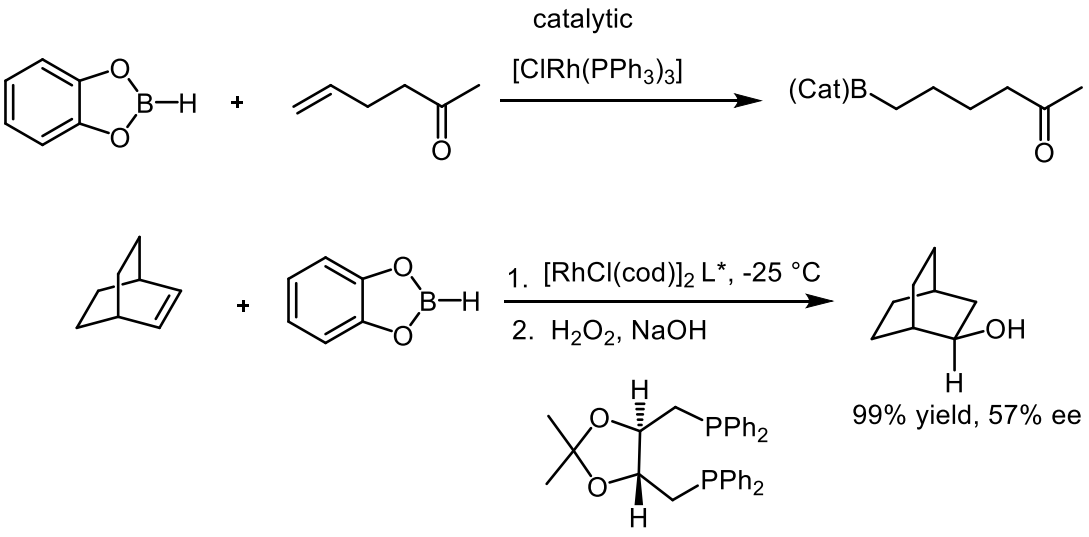


But I am going to talk about some of the chemistry where you can do catalytic hydroboration. So here you can use a transition metal catalyst to even bring asymmetric.

So, there is a vast area of this I think there are still in lot of publication coming every other day about the asymmetric hydroboration using transition metal catalyst and then there are also lot of several transition metal free method was developed over the year. Again you know this could be this is not going to cover a much in this particular lecture, I am going to only briefly talk about some of the important discovery about the catalytic hydroboration. So first catalytic hydroboration using the Wilkinson catalyst using the catechol boron as a borolytic agent.

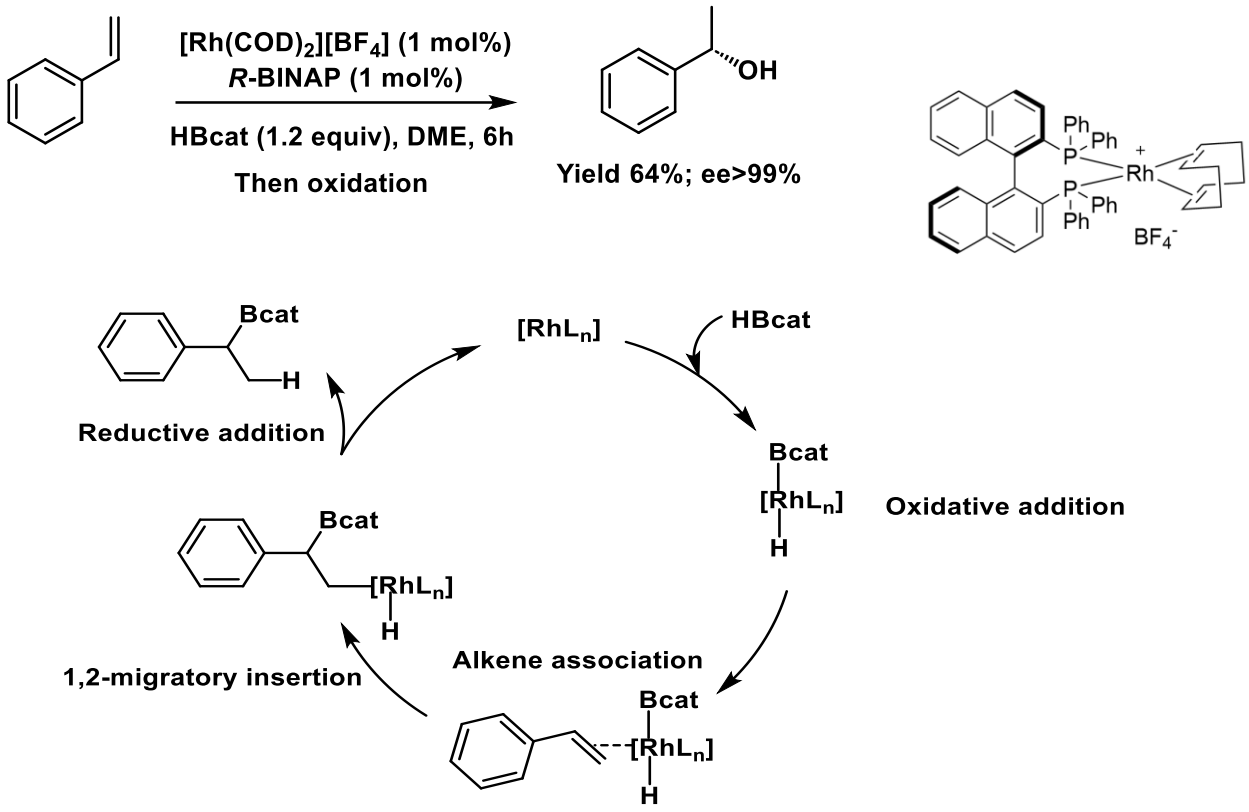
Besides there are several other catalytic hydroboration methods have been developed.





Transition metal catalyzed hydroboration

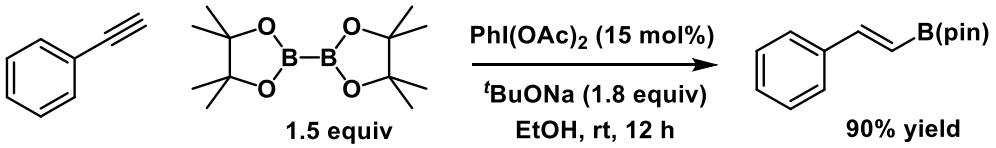
So, it was found that it can give a mixture of this where it can as you can see the boron will prefer to be add to the terminal position to form this product plus something will be where there will be internal as well. But later on what happen in this reaction if you start the reaction with this steps you know substrate where if you add from either this side or that side you will still end up making a chiral center there. So, here what is happening using this $[RhCl(cod)]_2$, you know cyclooctadiene in place of the diop as a chiral ligand. So, if the diop as a chiral ligand and at -25°C, then this hydroboration can be happened. So, it can able to now there is a control of the facial that means, now it can able to get an enantioselectivity in the product with 99%, Now after that there are you know several more discovery you can see there is another example using BINAP-here.

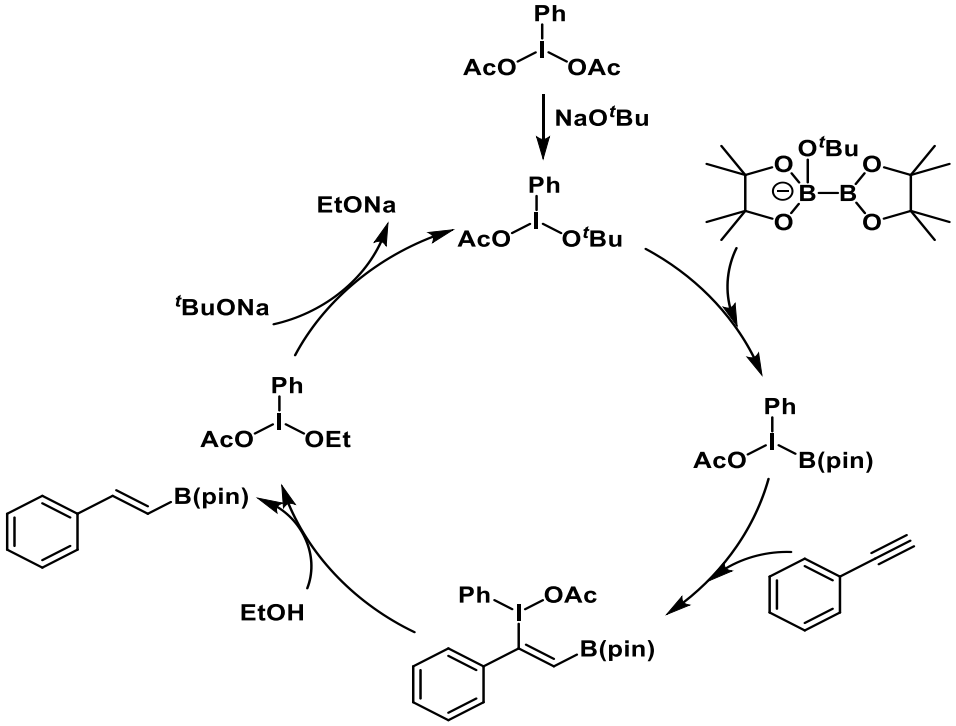


So, this is for the styrene you can see. So, this is a very important transformation from styrene you can able to get this type of secondary alcohol here. So, here the BINAP- has actually you know used as a chiral ligand which actually bound with this $[Rh(cod)_2][BF_4]$ to form this species here. So, you can see this is a bidented ligand the phosphorus binding two of the phosphorus the rhodium which can treat with this the catechol borane, it is going to go for oxidative addition first with the rhodium. Then there is a alkene association with the rhodium happening here and there will be 1,2- migratory insertion followed by a reductive elimination and the catalysis going back to the catalytic cycle again.

That is how we can able to make this product with a good as you have the chiral backbone here in the ligand that can control this particular step here while you are from this step to this step where the 1,2-migratory insertion can happen.

Then I am going to talk about I am going to finish this part with one example of catalytic hydroboration where you do not need a transition metal here. You can use a PIDA which is the phenyl iodide diacetate using tart-butyl ethoxide and ethanol as a solvent. So, using this bis-pinacol diborane and a phenyl acetylene can end up giving phenyl vinyl boronic acid. Again, it is a very simple reaction if you treat with the base with this PIDA, it can introduce O-t-butoxide here to get it to the acetate that O-t-butoxide can act to the boron if you remember in the class I talk about that it can nucleophile can act to this type of diverse species. Now once it will act this other boronic, boron group will be going to act as some sort of a nucleophilic character, we will get here that will form these species.





So, this O-t-butoxide will be removed to get the B(pin), it will now add to the alkyne followed by a ethanol comes into the picture replace you know this part and get the phenyl vinyl boronic ester out, then it is going to get back to catalytic cycle again. Again, there are some references for this part you can able to go through some of the references and the publications which mention here again, thank you so much for coming to the class and i am going to see you guys in the next class. Thank you.