Molecular Rearrangements and Reactive Intermediates in Organic Synthesis

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Lecture 42: Organoboron Chemistry

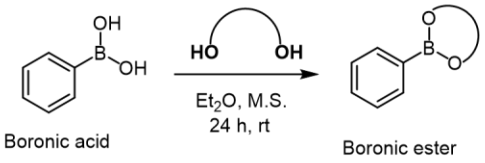
Welcome back to this NPTEL online certification course in molecular rearrangement and the reactive intermediates. In the last class, I started talking about the organo-boron chemistry. So, in this class I am going to talk about the one of the important reactions called the hydroboration correct. I already showed you the reaction in the last class, but in this class, I am going to show several examples of that and also the other important aspect is what are the different protecting groups for the boron. So, you have seen only the pinacol correct, what are the other different protecting group for the boron and what are their structure their stability can be also varied. So, let us go through them.

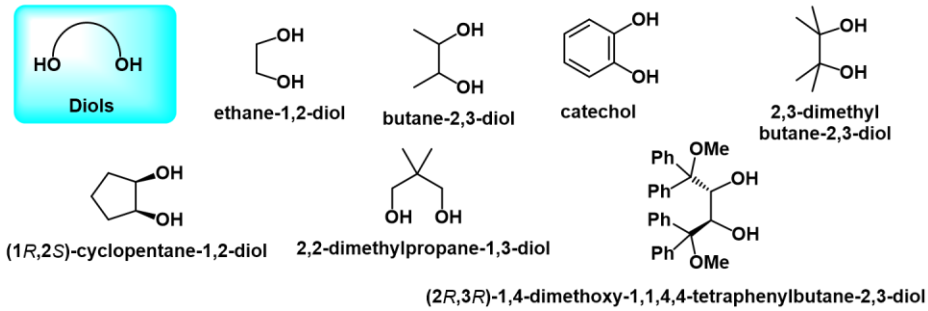
So, let us talk about some of the synthesis of different types of boronic esters and then we are going to learn about their structures of the different protecting groups and then their stability. And then we are going to talk about some of the multi-boron compounds, majorly trying to focus on the hydroboration reaction. So, here you can see here this is an easy method I think I told you in the last class that one of the very easy methods that if you have a boronic acid and if you take some sort of a diols or there are of course, there are more variation you can see there are several different diols. It could be ethane diol like a butane, catechol and then you have 2,3-dimethyl butane-2,3-diol.

You can see what is happening from the butane to 2,3-butane you can see slowly the steric is playing important role here. Then there are some chiral diols ok. There are 2,2-dimethyl propane 1,3-diol and then of course, there are other chiral diols. So, this is a very easy reaction as I said if you take the boric acid in place of the diethyl ether and molecular which can take this 2.0 equivalent of water you can form this boronic ester.

But the question comes depending on this diol your stability will be varying. Why we are talking about stability? Because if you are forming a boronic ester you have to understand that in that particular compound by taking this compound you might want to do some other transformations. At the time, if your boronic ester is unstable, then you cannot do multiple transformations using this organoboron compound. That is how we are quickly going to learn about their structure and stability.

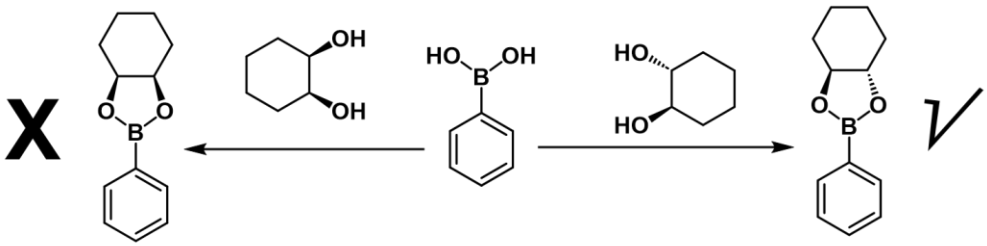
The easiest method to access the boronic ester is from boronic acids





So, one of the important facts here that if you have this cis 1,2-cyclohexane diol versus you have trans 1,2-cyclohexane diol.

What is happening? In case of trans, we are seeing that it can able to form this corresponding boning ester comfortably, but once you have this cis diol by looking into that you might think sir, I think this look cis they can form bonds but that is not the fact. So, this is going to form an unfavorable the boron ester geometry ok. So, that can be explained from the basic the stereochemistry background.



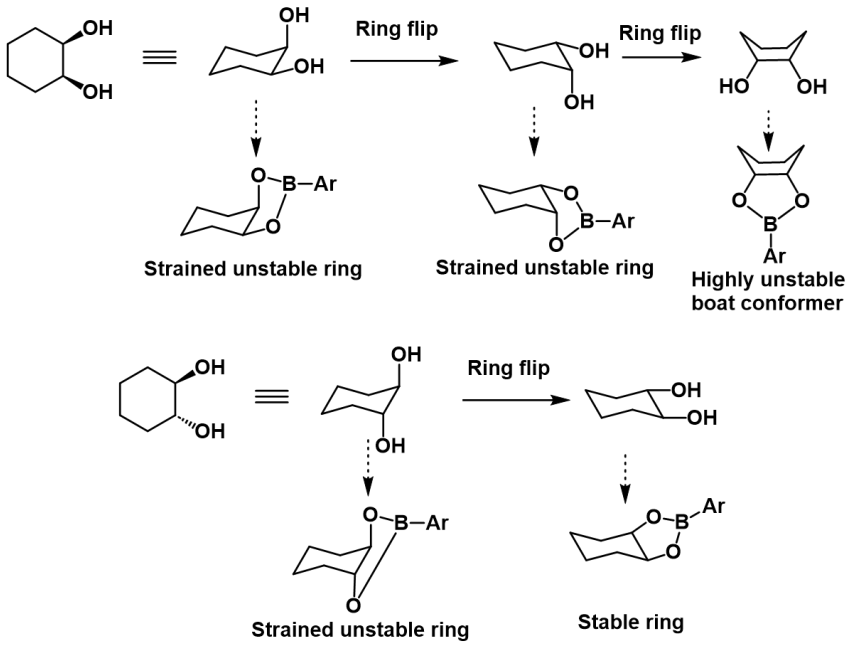
***cis*-1,2-cyclohexanediol failed to provide the corresponding cyclic ester. This is on the basis of the unfavorable diol geometry of the substrate due to the boat conformer of *cis*-1,2-cyclohexanediol, which is thermodynamically unfavorable.**

So, by looking into this structure you just cannot be thinking ok these are two -OH in the same site, but that is not the fact once you try to draw them suppose here you have this cis

1,2-diol correct. So, if you try to draw them from cis then one will be axial another will be in equatorial correct.

You can do a ring flipping. So, here you have one will be axial another will be equatorial correct, but in every case there will be one axial one equatorial correct. Now, if you try to form a boronic esters from here, you will form a strained unstable ring. in both the cases you end up making a strain unstable ring correct. And then if you do another sort of a ring flip just to try to make them in the boat conformation you can able to make them in the boat shape, try to put them two OH in the same side, but that is going to make again highly unstable a boat conformity ok.

So, what you are seeing here that once you can see that you are forming this strain type of unstable ring, but once they are trans then that could be two diaxial or they could be both equatorial. So, there will be both axial or both equatorial ok. So, now, you can see here that once a both axial this will be strain unstable ring, but once they are both equatorial now, they can form a very stable in a boronic ester.



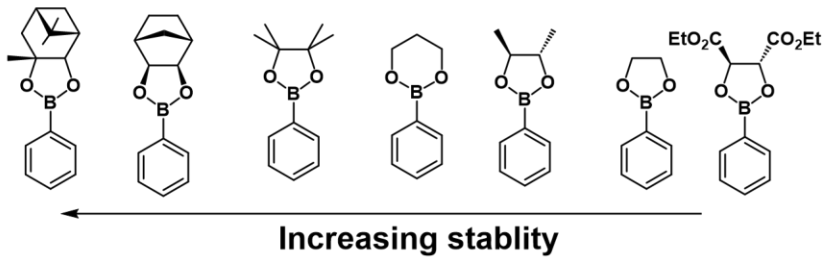
Now, you can see here that there are could be different boronic esters as you see from here, in this case, once you have this pinene 1,2-diol, all are here the steric around this boron is getting increased. So, once you see that the you can see if you compare this one versus this one versus this one.

So, if you coming from here to here and from here to here you can see the steric environment around the boron is getting increased. Because, what is happening? Why this

boron ester become unstable because you can able to. So, they are going to cleave this boron-oxygen bond through a transesterification that means, we have one ester now you can bring some another alcohol like you know 1,2-diol not alcohol 1,2-diol which will be forming a more stable boronic ester. Then they can replace the less stable boronic ester into a more stable boronic ester through a transesterification So, what we are seeing here? So, that is also depending on the stability, which clearly depend on the environments around these organoboron compounds, because if it is sterically hindered then it will be very difficult for the nucleophile to approach to the boron correctly. So, that is how you can see here by going from this one to this site in this direction we are seeing the stability is getting increased.

So, that is why this is the one getting the most stable compared to this. So, that is that can slow down the hydrolysis ok.

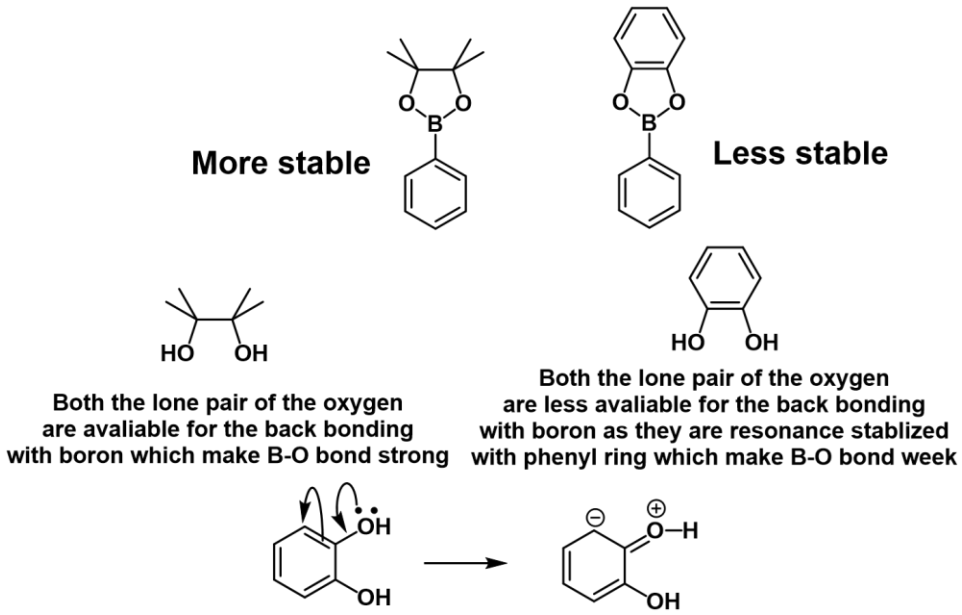
Rigid, preorganized diols like pinanediol provide the most robust esters and it was also found that six-membered esters are generally more stable than the corresponding five-membered boronates. Presumably, the stabilizing effect of B-O conjugation via overlap of boron with oxygen lone pairs is geometrically optimal in the larger rings



Hydrolysis can be slowed down considerably in the case of hindered cyclic aliphatic esters such as the C2-symmetrical derivatives and pinacol pinanediol etc as the increase of steric effects on neighboring atoms oppose the incoming water to attack to boron.

Now, the question comes if you try to compare between these two, one is the pinacol boronic ester another is the catechol boronic ester. Now, why we are saying that this is more stable, but this one is less stable So, if you think about both this alcohol you can see here you have this oxygen lone pair is there on the oxygen there is it is not available for the back bonding to give into the aromatic ring because here, because it is a resonance stabilized compound this kind of catechol the oxygen lone pair is also getting involved in the phenyl ring through the resonance. So, that can participate in the resonance so that means, when is forming the boronic ester the lone pair in this particular scenario is completely given to the boron forming a very stable bond, but once you have this case here in case of catechol that is not there.

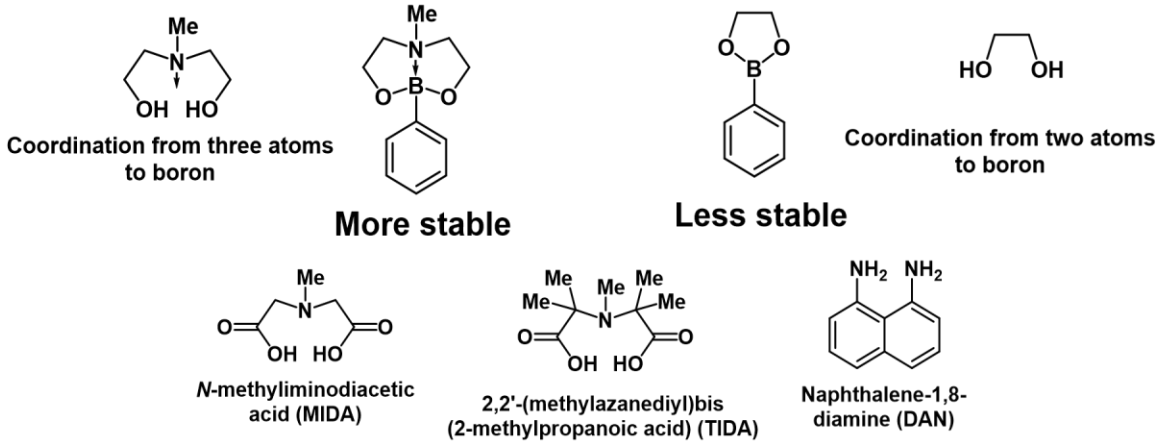
that is one fact the other fact is in case of this the pinnacole, you have this tetramethyl group. So, that is also forming a more steric environment compared to catechol as well.



So, now, what happen after that from diol there are some so many other types of boronic ester group were developed. So, the idea is that after giving this oxygen to stabilize more can we bring another Lewis based atom which can give the lone pair to stable the boron even more ok. So, that brings to the nitrogen into the picture ok.

So, so that kind of bring now you have seen the boron ester which is now getting really stabilize more because not only there is two oxygen there is also a nitrogen which is giving redundancy to the boron ok. So, these are even more stable to this compound not only that if you think about the pinnacle also compared to them also these are these are these are more stable. And that slowly brings to the the discovery of a compound called N-methylimidodiacetic acid or MIDA ok. This is a better protecting group, which can even stabilize the boron ok. And then there are other group like DAN where instead oxygen you have these two amines here which can also form the boronic ester by coordinating with this two nitrogen atoms.

N-substituted substituted diol further increase the stability of the boronic ester via the internal coordination between the nitrogen lone pair and boron's vacent orbital constitutes a unique structural characteristic of these tetrahedral derivatives.

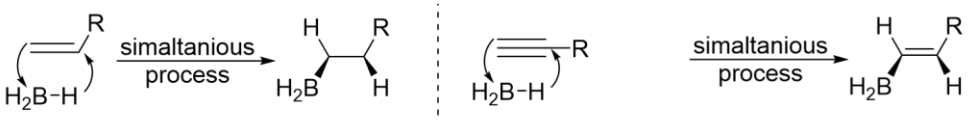


So, we have learned about first part that, what are the stability of different boronic ester. But now we are going to talk about the very important reaction which was discovered by Professor Herbert Brown which is called the hydroboration. So, if you have an olefin as I mentioned and if you treat with the BH_3, what is going to happen? It is going to add to the corresponding olefine and then it is going to first add and then it is going to add, again and again to form this trialkyl boron. Again, we are going to come back to the addition you know whatever addition is happening in this reaction we are going to come back to that in a minute. So, this reaction is not only happening to olefin, it can also happen to alkyne.

Remember that it is not only happening to the alkene it can also happen to alkyne and you can now end up making some sort of a vinyl boron compound ok.

Hydroboration means the simultaneous addition of hydrogen and boron

a) General scheme for hydroboration



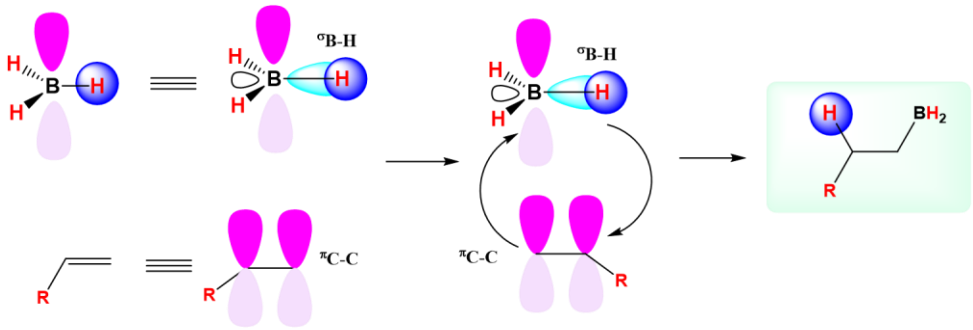
Addition to alkene

Addition to alkyne

The reaction was first reported by Herbert C. Brown in the late 1950

So, you can see the boron has this the boron hydrogen σ-bond here correct these are the σ-bonds and this is the Π-bond. So, these are the interaction happening, the σ-bond(B-H) actually interacting with this Π-bond in a concerted manner to form this product. So, we are going to come back to some of the Markovnikov or anti-Markovnikov thing or you know all these discussions we are going to come back in a minute, but before that I think a important questions we ask. So, you know in this particular problem that you want to synthesize this compound.

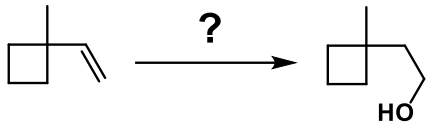
So, we are talking about one of the important things that in this transformation, if you want to get to this product then you have to use this hydroboration.

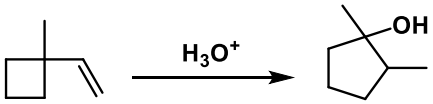


The addition as takes place by interaction of the filled alkene orbital with the empty p orbital on boron, accompanied by concerted C–H bond formation

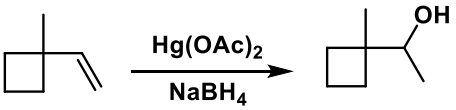
If you try to use something other condition like if you try to give a acid strong acid, then it will go for a carbocation rearrangement, we have learned about those and it is not going to form the same the product we want, it is going to form a ring expansion happen a ring

expand product. And now if you go for oxymercuration of alkene ok, which we have learned I think you have learned before in the soft more organic chemistry, then you end up getting to the forming this secondary alcohol, but if you want a primary alcohol here, we had to follow the hydroboration oxidase. So, now I am going to talk about that reaction which is the hydroboration.





Via carbocation rearrangement



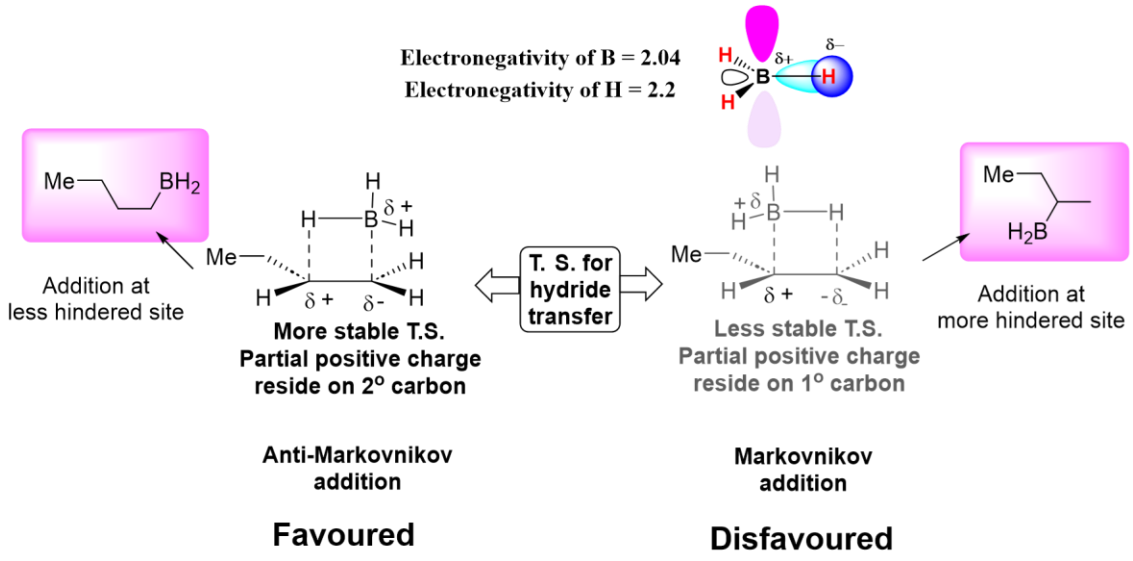
Oxymercuration of alkene

If you first think about the electron native difference of the boron and the hydrogen, you can see the hydrogen is more electron native than the boron.

So, what is happening if you think about that the boron and hydrogen bond then the electron density towards in hydrogen. So, the boron you can think about the boron having some sort of a delta positive and the hydrogen having some sort of a delta negative. Now, if you think about when it is adding to the olefin, it is adding in a syn fashion. So, the B-H bond coming in a syn fashion to add to the olefin, but the important question we are trying to answer in this slide that why the boron is adding to the terminal position. That means, we are talking about we are getting to a anti-Markovnikov selectivity you show the Markovnikov selectivity what is happening here.

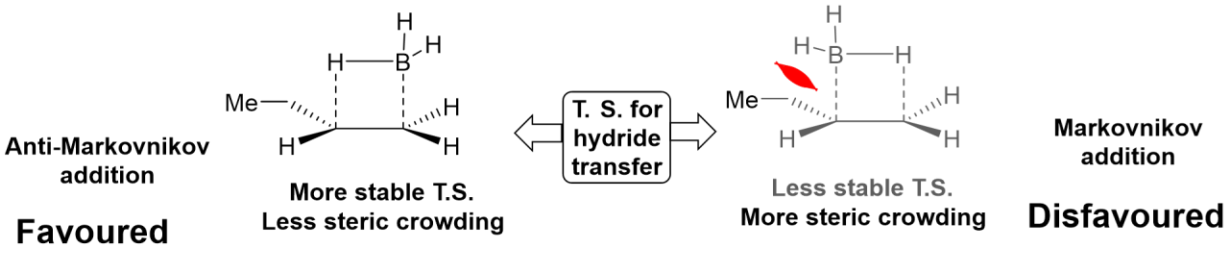
So, if you think the boron is as I mentioned the boron have some sort of a $\delta(+)$ and the hydrogen have some sort of a $\delta(-)$. Now if that is approaching to the olefin, now you can think about the olefin you can also think about if you have a hydrogen as a $\delta(-)$ then that is going to interact with a carbocation which is have a $\delta(+)$. Now if, you think about this one versus here, here the hydrogen is coming, I think here there is a error this will be a $\delta(-)$ and this will be $\delta(+)$. Now you can think about here you are forming a $\delta(+)$ or some sort of a partial positive charge into 1^{o} carbon. Here you are forming this partial positive charge in a 2^{o} carbon correct.

So, in an electronically I think the formation of the carbocationic character in a 2º carbon will be more stabilized compared to 1º carbon. That is why the hydrate transfer will be more favorable through this transition state which allow the hydrate to comes to the internal position and the boron to the terminal position. So, that end up giving you this anti-Marconikov variation product as a favorable. That is why you end up getting to this product not this product. Again, the other explanation which you always say about the study.



There once the boron as it is approaching in a Cis in addition. So, there is a steric could be play another important role here. That means, this boron with two hydrogens they can interact with this alkyl group in the internal position correct. If that interaction is happening so, that can so, this then that this tangent state will be less stable compared to this one which will be more stable transition state because there will be not that because now if there is two hydrogens here. So, compared to the two hydrogens and this methyl and alkyl group here in this transition will be more stable.

So, that means, that is so what is he saying that the hydroboration reaction there is both effect there is steric and electronic as I explained through steric effect you understand the it is going to go through this stable transition state to avoid the steric between the boron and the group which is present in the internal position that is why it is going to go to the terminal position. Again, this reaction happening in a concerted manner and it is happening from the same phase both boron and hydrogen going to come to the olefin on the same face of the olefin.



Hydroboration is highly regioselective and stereospecific
Hence boron will add to the less hindered side

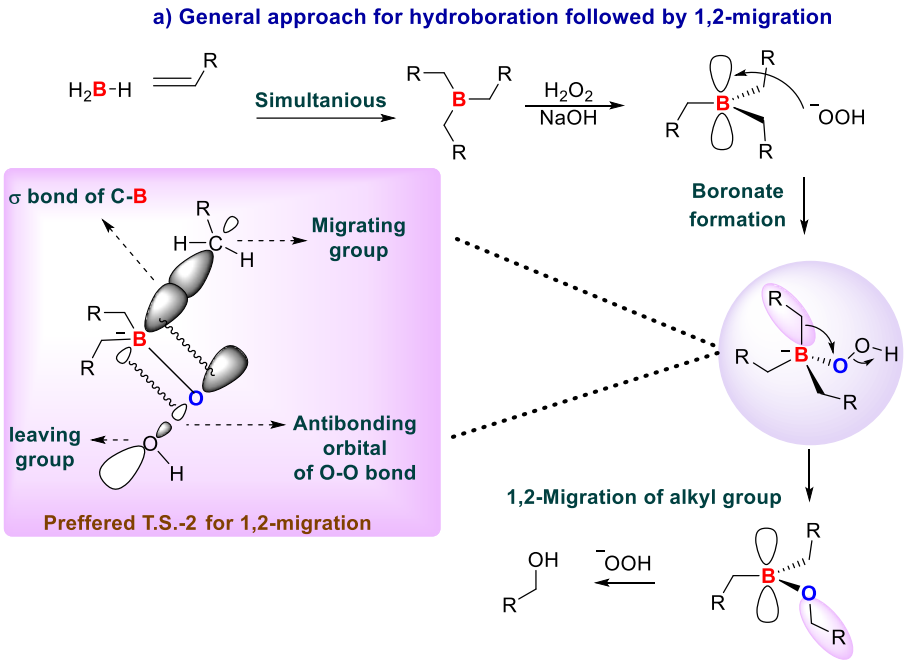
Hydroboration is a stereospecific *syn* addition that occurs through a four-center TS with simultaneous bonding to boron and hydrogen. The new C−B and C−H bonds are thus both formed from the same face of the double bond.

Now, we are we are going to talk about the next part. So, first is the hydroboration happens. So, from here once you form this first is going to form the BH_2 and then the BH_2 going to constantly add.

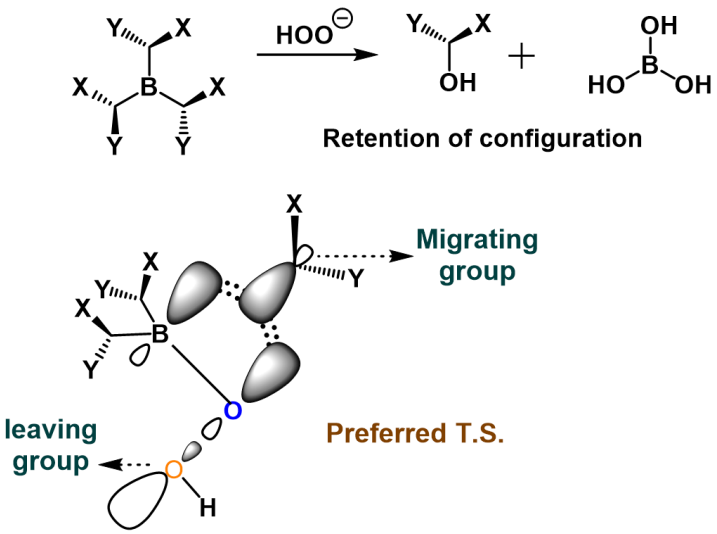
So, there will be you think about we end up making this BH after the hydroboration and then this can act to another you know olefin here ok. So, what is happening? This compound can now act as a hydroboration agent. So, I am going to come back to that you know discussion. So, that idea was further used to make some sort of a bulky boron agent ok. So, now that can react with 2.0 equivalent of this to form this corresponding trialkyl.

Once you have this trialkyl boron now if you treat with H_2O_2 /NaOH it forms the corresponding alcohol at the end. So, what is happening here? So, once you react with H_2O_2 /NaOH what is happening because from H_2O_2 if you take one hydrogen out it is generating in place of NaOH it is generating $HOO^{(-)}$ correct. So, this OOH minus going to attack to this So, this hydro peroxide anion going to attack to the boron empty orbital to form this boronate complex ok. Now, what is happening because now this boronate complex wants to here, this R group which is here going to participate in a 1,2-migration. So, this this can move from the boron to the oxygen to eliminate this group as a leaving group that can generate this you know BR_2 and this OR which can take part with another 2.0 equivalent of this.

Hydropoxyanion is going to add here to and then finally, it will going to form this compound which is going to get hydrolyzed to form your desired product ok. From there it is going to get hydrolyzed to get to the corresponding alcohol ok. So, the important fact is how this migration is happening? if you think about this migration happening this is a migrating group here in the boron which actually interacting with the σ*-orbital with the oxygen boron. So, this σ*-orbital is getting electron density. So, there is migrating here from this group is migrating here by giving the electron density to the σ*-orbital.



So, the question comes if you have a chiral center suppose you would have done a hydroboration you generate a chiral center. So, what is going to happen? You end up seeing a retention or inversion in the alcohol product, you end up seeing a retention. Because if you think about this when this group is getting migrated ok, because once you have this trialkyl boron, once you generate this trialkyl boron and you treat with this OH minus or NaOH, what is happening? This group is getting migrated from this from boron to the corresponding oxygen by giving electron density to the corresponding σ*-orbital. So, here the migrating group geometry has not changed anything it is just. So, the migrating the configuration of the migrating group remain unchanged there is nothing happening on that carbon the only thing is happening it is this you know this bond is getting flipped it is getting migrated from this boron to the corresponding oxygen.



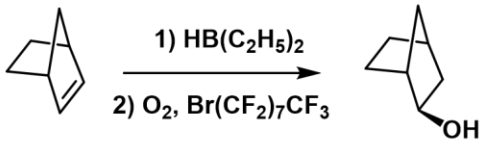
Swiping of the alkyl group occurs from boron to oxygen

So, not only this H_2O_2 only works, there is other oxidant like oxone can also able to oxidize or the molecular oxygen can also oxidize the boron to the alcohol, sodium peroxide carbonate, amine oxides, N-methyl morpholine N-oxide. So, there are several different types of N-oxide also developed. You can think about sir how this. So, how this thing works? If you have this morpholine N-oxide, it can react with the boron now if you think about this is reacting with the boron. with the R group here can generate this minus correct which can migrate here and this group can act as a leaving group here ok.

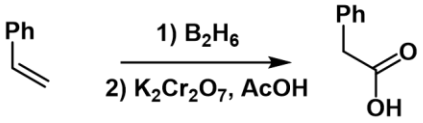
That is how these groups can also the N-oxide can also you say trimethyl N-oxide can also use here to act as an oxidizing agent for the boron. So, here is an example also oxygen can be also utilized for this type of things first hydroboration and then oxidation to the corresponding alcohol. Now, the chromium reagent can be used for this, but if you use the chromium reagent as your oxidizing agent, it will not go to stop as alcohol it is going to oxidize all the way to the corresponding acid. So, if you start with this and then use this $K_2Cr_2O_7$ after the hydropotassium it will take you all the way to the acid.

Other oxidants can be used to effect the borane to alcohol conversion

Oxone ($2K_2SO_5 . KHSO_4 . K_2SO_4$), Molecular oxygen, Sodium peroxycarbonate, Amine oxides (N-methylmorpholine-N-oxide).

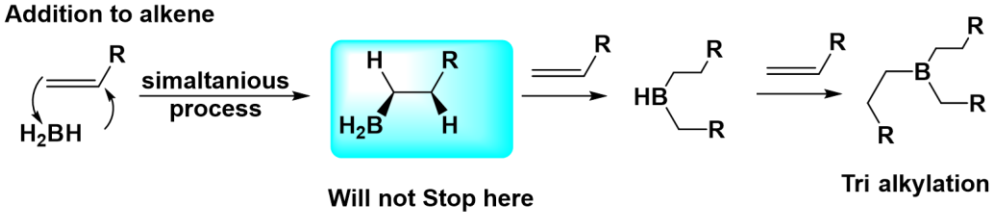


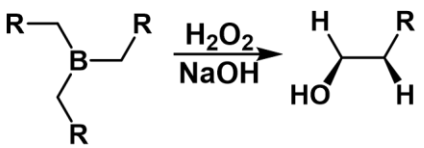
Using more vigorous oxidants such as Cr(VI) reagent ($K_2Cr_2O_7$) not only stop to alcohol but also ended up with acid.



So, now we are going to talk about the polyhydro potassium that means, I think the thing I am telling you again and again that after the addition first addition first this concentrated addition it will not stop here it will add with another one another one it will go to the corresponding trialkyl boron ok.

So, and then this trialkyl boron oxidized to the corresponding alcohol. So, the question arises that can this is going to happen always or can you able to stop to a mono after the first hydroboration can you able to design some sort of reagents? why this is happening? Because you are designing after the first hydroboration, you are designing a compound you have two boron with two hydrogens. Because of that reason that can also participate in another hydroboration and still it is new all the hydrogen to form this trialkyl boron. So, the question comes can we able to develop some sort of a reagent which can only have a one boron with a one hydrogen. So, now those type of reagent can be used as a monohydroborating agent.

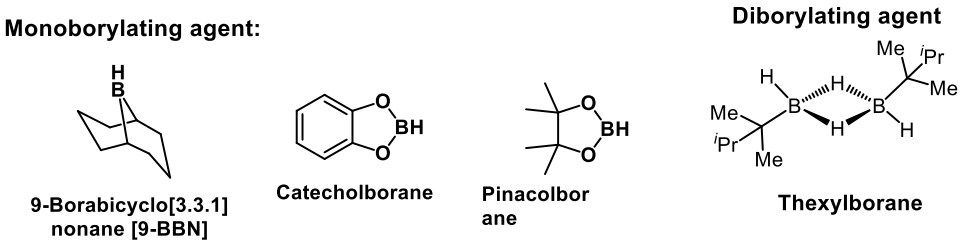


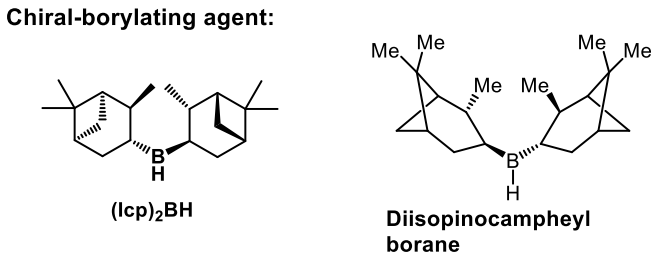


How to perform the selective and mono hydroboration?

So, we are going to talk about some of these. Again, I think there are several different variations was developed one of the things is the in the catechol boron which is very reactive one ok. Then there are the 9-BBN. So, I you might be thinking that how this type of reagent was getting developed of course, you know they are developed from the corresponding olefin ok. So, from there they can this type of reagent was developed I am going to come back to that discussion also. So, there are different type of variation like the pinnacol borane ok.

So, you can see then the in the 9-BBN, then thexylborane. So, this is the structure of that corresponding diborane and then in the $(ICP)_2$ I think we are going to talk about this with this pinene part because this can be used for the asymmetric synthesis and we are going to talk about some of the di-isopropanol the campyl borane.

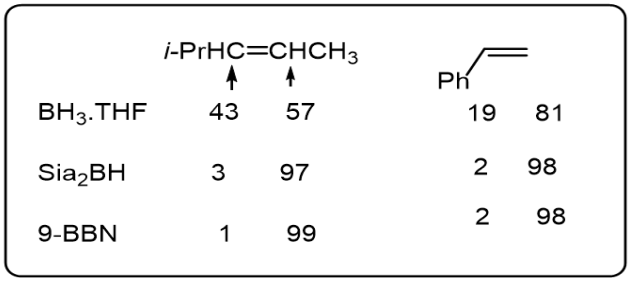


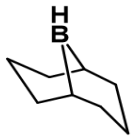


There are some other persons we are going to we are going to talk about like here in the next slide I think we talk about this one the diisopinacampheyl borane. So, this is called Si_2BH. So, diceyamylborane you can think you can think from the structure what is the difference we are bringing here.

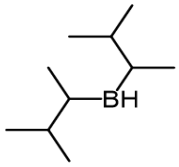
We are bringing some sort of a hydroxyl in a reagent which are bulky in the and also had only one BH group. So, what is the idea here? The problem is once you use BH_3,THF lot of times you do not find you know you know good selectivity of course, you know here we still see a very good selectivity for this particular compound, but in some other cases I have not you know collected all the example, but there are example where you going to see like you know hair particularly from styrene you can see you have like you know almost you know 80-20. There are also example we will see a 40-60 ratio or sometime even like you know just 55 and 45 because that because what is happening the BH_3 THF is a smaller region. So, that is why you do not find any selectable difference because here is a difference

you have a isopropyl one side you have a methyl another side. So, this is we are talking about olefin having isopropyl one side and methyl another side.





9-Borabicyclo[3.3.1] nonane [9-BBN]



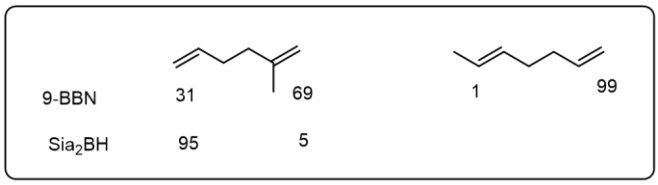
Disiamylborane

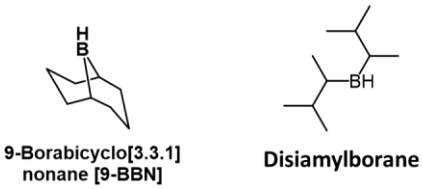
Now, we can see once you change the borane to the sea oil borane or the 9-BBN means that once you bring to this bulkier borane reagent. What is happening here? Now, you can see that that difference of isopropyl versus methyl. So, the difference of isopropyl versus methyl is now getting the predominate here ok. So, these factors are getting you know the interactions getting predominant because you are bringing a bulkier boron. So, that is why the advantage is there that is why this bulkier boron is developed for this type of purpose where you see the selectivity will be poor using DHTTHF.

Here you can see also like for the styrene this selectivity can be improved drastically very high ok. Of course, it is giving this terminal selectivity we are not changing the selectivity, but what we are showing here we can improv the selectivity to a very high level using this type of hydroboration reagent. Again, there is an important example here, I think why because you can see in this example, if you are using this diacium alboran here for this particular case you have a terminal olefin and you have a terminal olefin, but you have a methyl in the internal position. So, this will be a very challenging hydroboration correct. because you have to only rely on this interaction of this methyl group.

If you use 9-BBN what is happening in case of 9-BBN this one getting 31% here it is 69%. So, here the other important factor is the interaction of the 9-BBN with the olefin is the important factor here, but here in the other cases, we can see here this will be a you know 1% here because there is a methyl group here. versus the terminal is 99%. But once you come to like the CIL boron. So, you can see that that is the important of this di CML boron here because that can give you 95% selectivity in this position and can differentiate this group that can differentiate the if you have internal mythology.

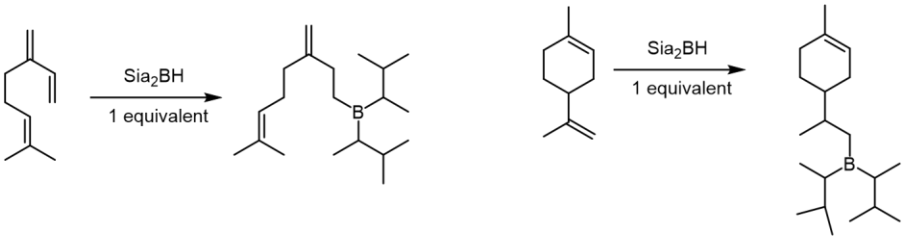
That is why once people try the if you have of course, some of the studies was done to understand through a computational. But the thing is if you try to do a hydroboration, you have to explore different region to find out the selectivity.

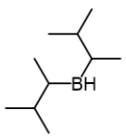




9-Borabicyclo[3.3.1] nonane [9-BBN] **Disiamylborane**

Another important, example here how this disiamylborane is important. Here you can see there are so many different olefins here of course, both are terminal you can talk about you can think about, but the substitution was mono versus di. Here you can see it is selectively happening only in this position to get to this product. Again, you have that here I think it is a this is a easier version because you have an internal versus terminal and the terminal is the winner.





Disiamylborane

There are some other cases I think we try to show you that there are some cases like if you use a 3-methyl cyclopentane, 3-methyl cyclopentane or 4-methyl cyclohexene. These are a difficult substrate to deal with ok. Some of the cases using the diborane the selectivity is poor, but of course, using the 9-BBN we can get some more selectivity. ok, but not not good, but every case we are seeing some like so.

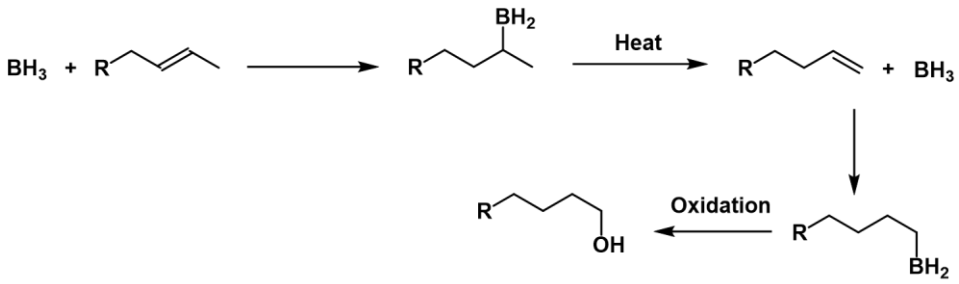
So, this type of cases once you have substrate like this. So, this is a 3-methyl cyclopentene or you have a 4-methyl cyclohexene. ok because the problem is like how to control the cis versus trans because once you go for a hydro potassium now there will be based on the methyl geometry you end up forming a cis versus trans. So, that is one factor so that means, now what I am going to talk about in the next that how the facial selectivity is important. That means, if you talk about the cyclohexane or the cyclopentane, then now the approach of the olive approach of the the hydroborating agent to a particular phase become very important. So, we are going to talk about some of this in the next lecture.

However the addition of borane to the less hindered olefin always result in the mixture of regioisomeric product formation. Because diborane itself is a relatively small molecule, the stereoselectivity is not high for unhindered alkenes.

	Product composition[b]								
	3-Methyl cyclopentene			4-Methyl cyclohexene				7,7-Dimethylbi-cyclo[2.2.1]heptene	
	trans-2	*cis*-3	*trans*-3	*cis*-2	*trans*-2	*cis*-3	*trans*-3	*exo*	*endo*
Diborane	45	55		16	34	18	32	22	78[c]
Disiamylborane	40	60		18	30	27	25	–	–
9-BBN	25	50	25	0	20	40	40	3	97

Here are some data comparing the direction of approach for three cyclic alkenes. The products in all cases result from *syn* addition, but the mixtures result from both the low regioselectivity and from addition to both faces of the double bond.

And then the other things what is happen sometime you find out that I think we are going to talk about also about this scenario that in case of heat sometime this hydro after the first hydroboration this can rearrange this can go for an elimination again hydroboration till it go to the terminal position. That means, you started from an internal olefin and then under heat there is process can happen that here it can first go for a hydroboration then it is going to get out through some sort of a elimination and then again hydroboration till it is going to the terminal position. So, this is saying this hydroboration is reversible and upon heating it can migrate to the to the less inner position and migration cannot occur past to a past to a quaternary carbon ok.



- Hydroboration is reversible in nature
- Upon heating the boron migrates to the less hindered position
- Migration cannot occur past a quaternary carbon.
- Migrations are more facile for *tetra*-substituted alkenes and occur at 50–60 C.
- Bulky substituents on boron facilitate the migration

So, we are going to talk about some of these some of the examples of this in the next class. Again, I think we talk about that the stability of different type of different type of the diol here we talk about we also talk about the mechanism of the hydroboration reaction and also, we talk about the different type of the mono hydroboration in this particular particular path.

So, and how that was important for selective hydroboration. Again, these are the textbooks and thank you so much for coming to the class. I am going to see you guys in the next class. Thank you.