Reagents in Organic Synthesis
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Lecture 15:
Boron Based Reagents in Organic Synthesis

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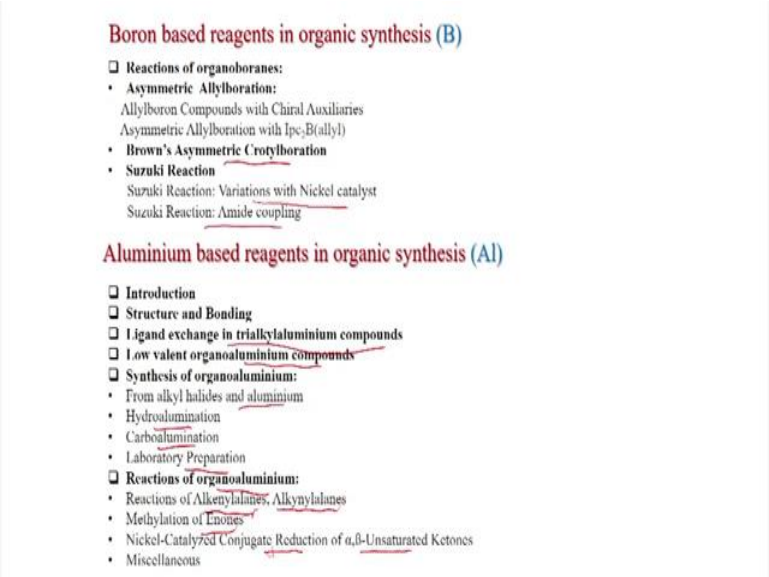

Welcome again. Today we will discuss boron and aluminum based organic reagents, so boron based reagents in organic synthesis, reactions of organoboranes, asymmetric allylboration, allylboron compounds with chiral auxiliaries first we will discuss and asymmetric allylboration with Ipc2 B allyl. Also Brown's asymmetric crotylboration we will discuss. This is the crotyl group you can incorporate. Suzuki reaction also we will discuss, Suzuki reactions variation also with nickel catalyst and amide coupling.

Then we will discuss aluminum based reagents in organic synthesis, introduction first we will discuss, then structure and bonding, ligand exchange in trialkylaluminum compounds, low valent organo aluminum compounds where the aluminum-aluminium bond is there, synthesis or organo aluminum from alkyl halides and aluminum. Hydro alumination, carbo alumination also we will discuss and laboratory preparation from aluminum chloride we will see and reactions of organoaluminum also we will discuss.

Reactions of alkenyl alanes, alkynyl alanes, methylation of enones that is the conjugate addition also conjugate reduction also we will discuss, and nickel catalyst conjugate reduction of alpha beta unsaturated ketones and miscellaneous examples.

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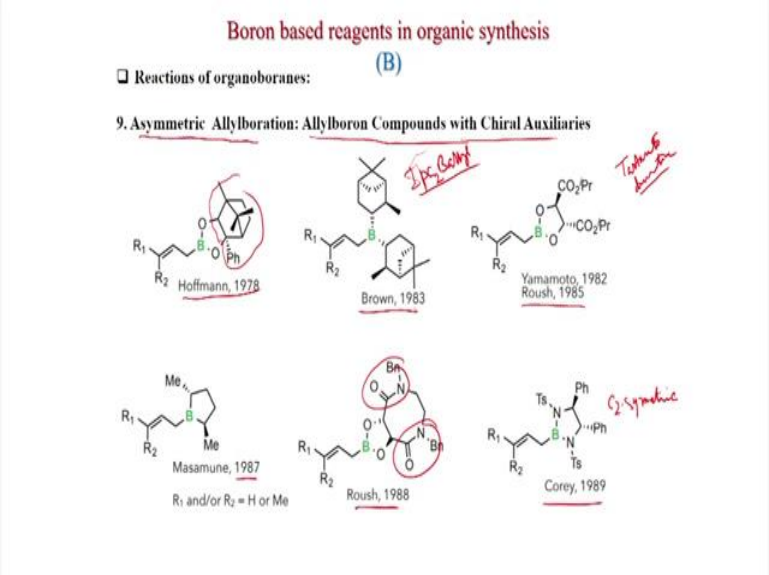

So, first we will discuss. Boron based reagents in organic synthesis, and asymmetric allylboration. We will form ester in this class so different carbon bond formation, here we will discuss, the allylboron compounds with chiral auxiliaries, and first a chiral auxiliary was discovered by Hoffmann in 1978 where this diol, chiral diol that was reacted with the boronic acid derivative and these chiral auxiliaries was incorporated into the allyl system.

Also Brown came up with this Pinene system and this is the very popular this called Ipc2 B allyl so isopinocamphenyl boron allyl compounds and these are the powerful chiral auxiliary that we will see in the next slide also. And this is the tartrate derivatives that incorporated with the allyl boron system and was employed by Yamamoto and Roush. Also this chiral borane, the C2 symmetric chiral borane was incorporated by Masamune in 1987 and this was a useful allylating reagent.

Roush came up with another moiety here the cyclic this amide is there and this was incorporated in the allyl boronic acid system. this also an useful allylating reagent. And Corey came up with this N-tosyl 1, 2 diphenyl amine and this C2 symmetric, this also C2 symmetric this is also and useful allyl boron reagent.

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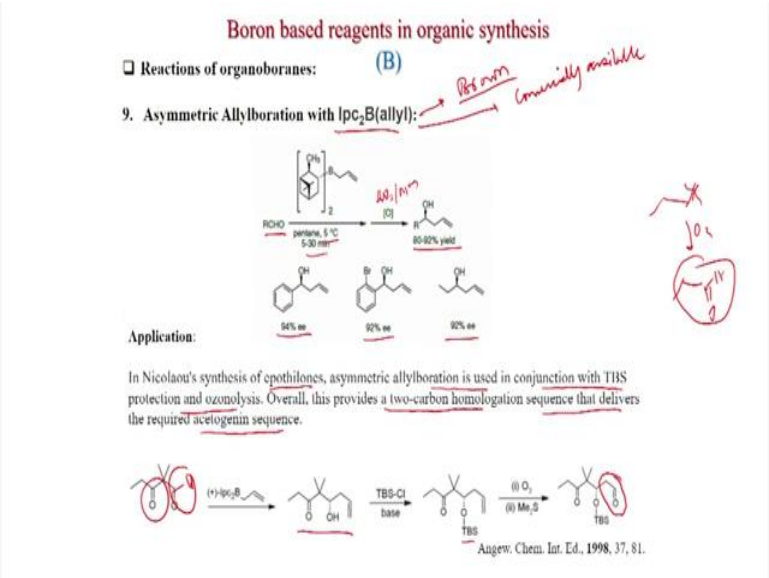

So, this is the most popular Ipc2B allyl that was developed by Brown, and this is also commercially available and this reagent if you treat with aldehyde in pentane 5 degree centigrade for very short time 5 to 30 minutes, after that if you treat with oxidation it is the H2O2/OH minus treatment you get this alcohol, secondary alcohol with the allyl motive and this reaction is quite general different aromatic as well as aliphatic you can see here, phenyl gives 94 percent ee and orthobromo derivative give 92 percent ee and this is the aliphatic aldehyde derived product this is the secondary alcohol you get 92 percent ee.

And this has many applications in natural product synthesis, for example, Nicolaou"s synthesis of epothilones, asymmetric allylboration is used in conjugation with TBS protection and ozonolysis, overall this provides the two carbon homologation sequence that delivers the required acetogenim sequence. Because this allyl motif we can easily cleave with ozonolysis and you get the aldehyde so that is the two carbon homologation that is the term used here.

Suppose, if you have this keto aldehyde and if treat this asymmetric allylboration with this isopinocamphenyl boron and species, allyl species then you get this asymmetric allylation and this product you get in high here, selectively this aldehyde is reacting so this is aldehyde, this is ketone and aldehyde is more reactive here and after TBS protection you get this secondary alcohol protection and after that if you do the ozonolysis followed by deductive work up with dimethyl sulfide you get this aldehyde.

So, ultimately this is the two carbon homologation, initially three carbons but, after ozonolysis you remove one carbon and you get this two carbon homologation. Now, this aldehyde can be further used for the nasal product.

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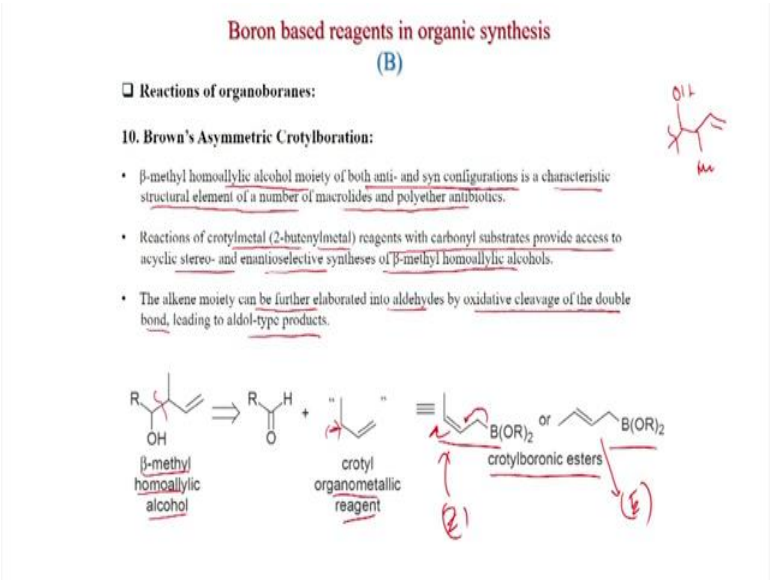

Brown's asymmetric crotylboration, beta methyl homoallylic alcohol moiety of both anti and syn configuration is a characteristic structural element of a number of macrolides and polyether antibiotics. So OH, Me like the system, this system is present in many macrolides and polyether and antibiotics. Reaction of crotyl metal (2 butenyl metal) reagents with carbonyl substrates provide access to acyclic stereo and enantioselective synthesis of beta methyl homoallylic alcohols. The alkyl moiety can be further elaborated into aldehydes by oxidative cleavage of the double bond leading to aldol type products that we have seen already.

So this is the homoallylic alcohol, beta methyl homoallylic alcohols just we have written here, here also we can write like this, beta methyl homoallylic alcohols and this can be form from aldehyde and an crotyl organo metallic reagents, so if a negative charge is here, then you can generate this, and this organo metallic reagent is possible that this similar compounds, so this crotylation is possible from boronic acid derivative, this is called crotylboronic ester and this in the Z conformer and this is in the E conformer. Because they can react like this and you get the desired product beta methyl homoallylic alcohol that we will see.

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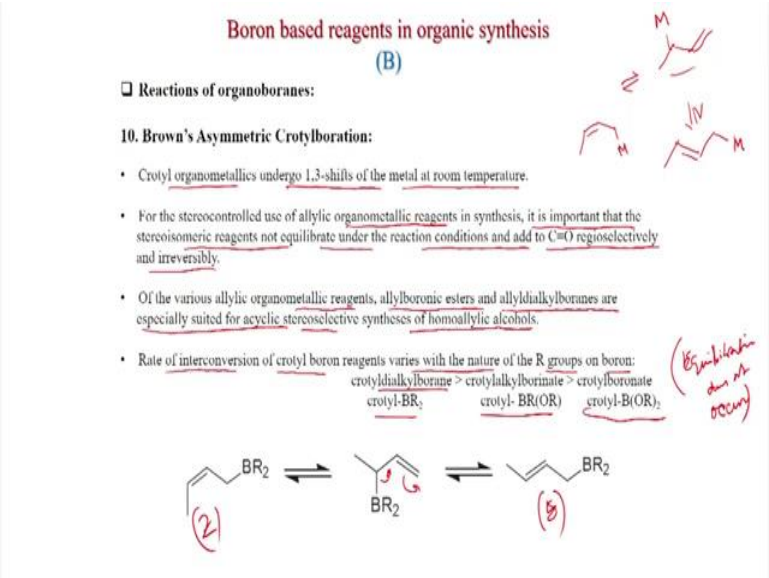

Brown's asymmetric crotylboration so crotyl organo metallics undergo 1, 3 shifts to the metal at room temperature so this also important there is a possibility of 1, 3 shifts for the stereo controlled use of allylic oregano metallic reagent in synthesis it is important that the stereo isometric reagents not equilibrate under the reaction conditions and add to carbon oxygen double bond regioselectively and irreversibly.

So, what happen suppose if you have a trans this one then this can equilibrate and can give this and this can again equilibrate to the syn derivative so, here it was *E*, then this and then this so, this equilibration is possible and if this equilibration is fast and you get a mixture of the products, of the various allyl oregano metallic reagents, allylboronic easters and allyl dialkyl boranes are specifically suited for acyclic stereo selective synthesis of homoallylic alcohol.

For allylboronic esters this equilibration will not occur so that you can get the selectivity so here it is the story. The rate of interconversion of crotyl boron reagents varies with the nature of the R groups and boron crotyl dialkyl borane then crotyl alkylboronate so when you put the OR group then the actually B on the OR group on the boron then you get the more stable so crotylboronate with two OR group on the boron that is the more stable and equilibrium or equilibration does not occur.

So that is why when this boronate esters are used then this equilibration does not occur. And you get high selectivity, so here this is the equilibration so this is Z goes to this with terminal

olefin and now, this again equilibrate and it can go to E so if this equilibration is faster and equilibration occur, then you do not get selectivity.

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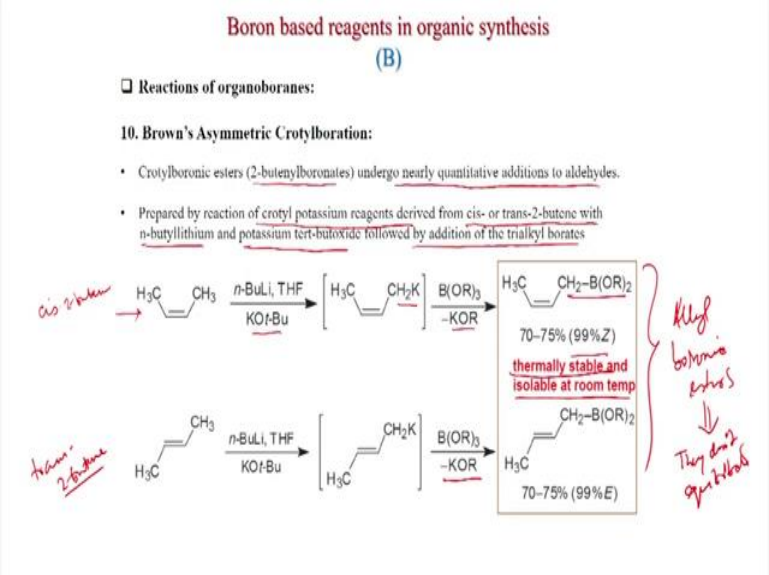

Crotylboronic esters to butenylboronates undergo nearly quantitative addition to aldehydes prepared by reaction of crotyl potassium reagents derive from cis or trans 2 butene with n butylithium and potassium tert butoxide followed by addition of the trialkylborates. So this is the preparation so, you start with here cis 2 butene and now you treat with n butylithium and potassium tertiary butoxide this very strong base you get the CH2K here, after that trialkylborates eliminate and KOR then you get this boronate ester.

So, this is the gent similarly from the trans 2 butene you can get the E so this is the reaction is similar n butylithium and potassium tertiary butoxide you get this one and after that trialkylborates reaction you get minus KOR and this is the E boronic esters. So this is the allyl boronic esters, and the useful here, they do not equilibrate. They are thermally stable and isolable at room temperature. So, then do not equilibrate they are thermally stable and they do stereo selective addition to aldehydes.

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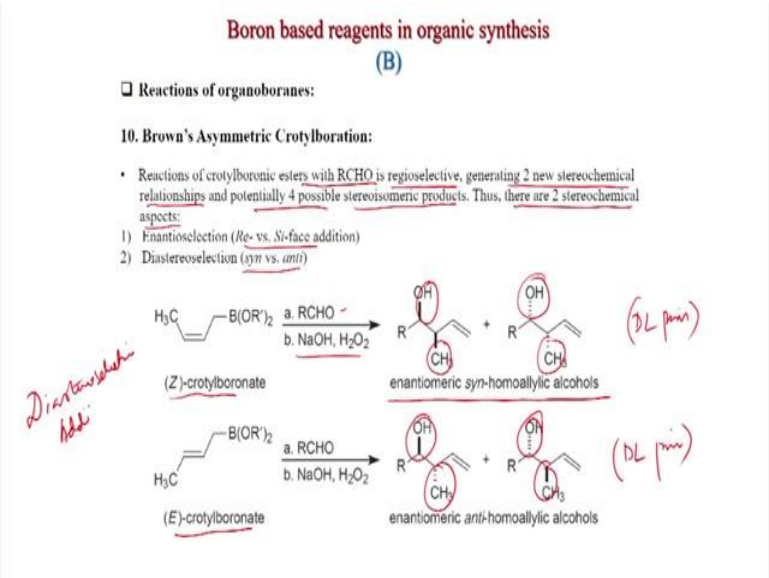

That we will see now, reaction of crotylboronic esters with RCHO is regioselective generating 2 new stereo chemical relationships and potentially 4 possible stereoisomeric products. Thus, there are 2 stereo chemical aspects, enantioselection that is *Re* versus *Si* face addition and diastoselection syn versus anti.

Suppose if you add Z crotylboronate with RCHO followed by NaOH/ H2O2 treatment you get syn homoallylic alcohols, so with Z get the syn these two groups on the same side and here also same side only their enantiomeric relation and with *E* crotyl boronate also with RCHO NaOH treatment you get now, the anti. So they are dl pair, that you will see with chiral catalyst you get the only one enantiomer but, simple boronic esters give the diastereoselective so here diastereoselective addition.

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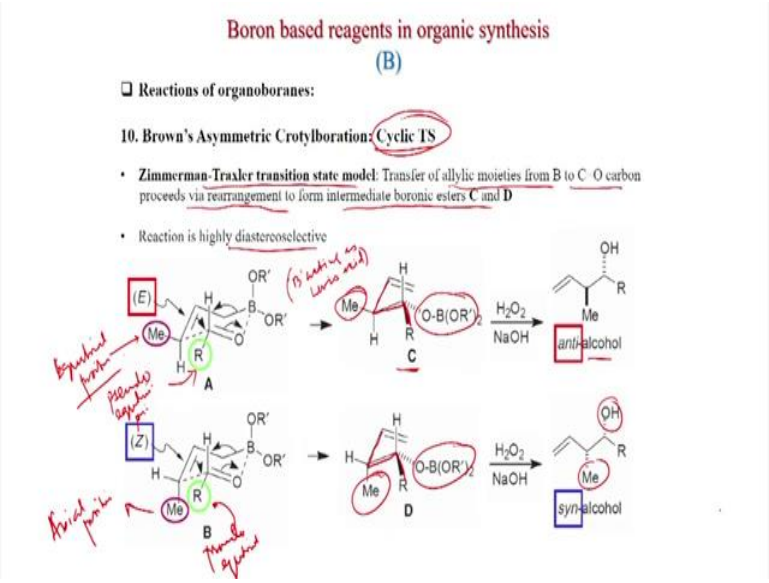

And for this di stereo selective addition the cyclic transition state 6 member is proposed which tells that the reaction is highly di stereo selective or stereo selective and Zimmerman trasler transition settle model has been proposed, transfer of allyl moieties from boron to C double bond O carbon proceeds via rearrangement to form intermediate boronic esters C and D reaction is highly di stereo selective so for E systems E allyl or E crotyl boronate system here methyl is in the equilateral position.

And this is the E you can see the double bond and this R takes pseudo equilateral position also in the cyclic transition state you can see that the carbonyl group is activated by the boron. So boron is acting as a Luis acid so boron is acting as Luis acid. And that is why no external Luis acid catalyst is required. Simple boron is acting as Luis acid also the allyl group here that is the crotyl group will add.

And because of this cyclic transition state after addition you get this intermediate C boronic acid C after that H2O2 NaOH you get this anti-alcohol. So, here in the zigzag you can see that this group, this is the we have written in the plane and now, this methyl and O BR which is ultimately getting to OHR in the trans so that is the anti. So when E crotyloboronate is used, you get the anti-alcohol.

And now, Z crotylboronate what will happen, in Z olefin this methyl and this substitution will be in the same side that is why methyl should be in the axial position. And this again in pseudo equilateral so this does not change because this is the most stable position of R and

now, after addition you get this intermediate after H2O2 in which you get the syn alcohol. Here again this is the we are writing in the plane this bonds and now this methyl and OH will be in the same side so you are getting the syn alcohol.

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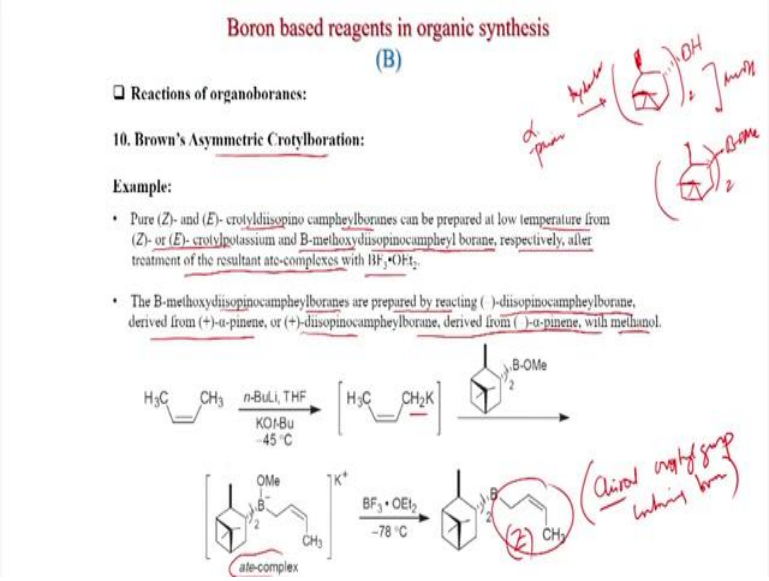

Pure E and Z crotyldiisopino campheylboranes can be prepared, so now we are discussing the asymmetric variant can be prepared a low temperature from Z or E crotyl potassium boron methoxi diisopino campheylboranes respectively after treatment of resultant ate complex with BF3 ether. The boron methoxy diisopino campheylboranes are prepared by reacting minus diisopino campheylboranes derived from alpha pinnene or diisopino campheylboranes derived from minus alpha pinnene with methanol.

So, here the starting material is same sys 2 butene and after n butyl potassium tertiary butyl side you get this one and after that you have to use the chiral boron reagent so this is derived from the alpha pinene and alpha pinene hydroboration followed by treatment with methanol, so this you can get from alpha pinene that hydroboration you get this after that methanol you get this, methoxy compound.

After that this can be reacted with methoxy compound and you get this ate complex, here the boron is coordinated with 4 so it has a negative charge and after BF3 treatment that methoxy group can be removed and you get now, chiral crotyl group containing boron so here the chiral crotyl group is present and this is the Z geometry.

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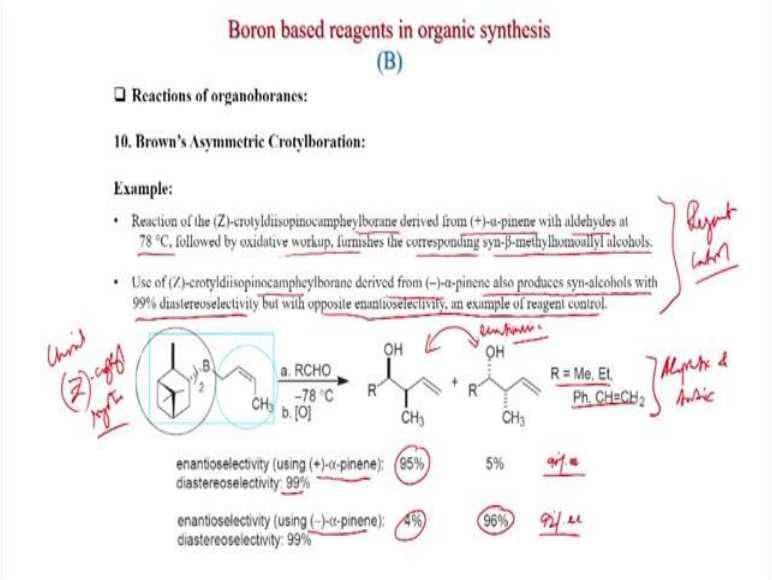

Similarly, from the trans you can get the trans geometric reaction of the Z crotyldiisopino campheylboranes derived from plus alpha pinene aldehydes at minus 78 degree centigrade followed by oxidative work up furnished the corresponding syn beta methyl homoallylic alcohols.

Use of Z crotyldi-isopino campheylboranes derived from minus alpha pinene also produces syn these with 99 percent di stereo selectivity but, with opposite enantioselectivity and this is an example of reagents control, so reagents control, so if you change the reagent then you get defferent product. So, here with Z system with chiral Z crotyl system, you get this homoallylation and homoallylic alcohols with RCHO minus 78 degree centigrade and this reaction can be used with aliphatic aldehydes as well as aromatic, aliphatic and aromatic.

And when you use the plus alpha pinene then you get 95 percent so they are enantiomeric relation, enantiomeric or DL pair and with plus alpha pinene you get only this enantiomer measure 95 percent, so 90 percent ee. And diastereoselectivity 99 percent and enantioselectivity is minus alpha pinene then you get the other enantiomer 96 percent 4 percent, so 92 percent ee. So these are very useful that you get not only di stereo selectivity but also enantioselective when use this isopenocamphenyl crotyl boron system.

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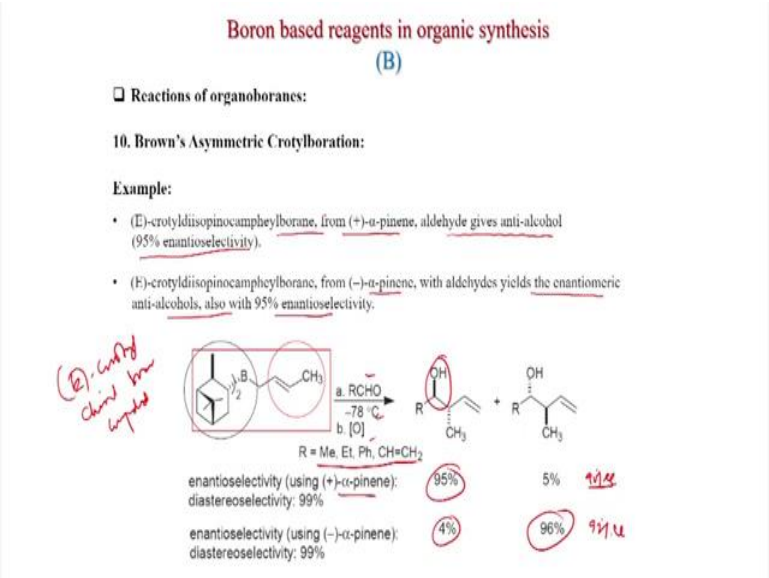

Similarly, from the E system, E crotyl di-isopino campheylboranes from alpha pinene you can generate and aldehyde gives anti-alcohol products 95 percent enantioselectivity and minus alpha pinene with aldehyde the enantiomeric anti alcohols also with 95 percent enantioselectivity so this is the E crotyl chiral boron compound and this one when treated with aldehyde minus 78 followed by oxidation you get this 2 enantiomer.

And here also the reaction is generating the aliphatic aromatic and when plus alpha pinene is used, this alcohol geometry is same for both cases Z and E when it is treated with plus alpha pinene system alpha pinnene derive boron compound then 95 percent this one, 5 percent this one, 90 percent ee and when minus alpha pinene this is the measure 96 percent 4 percent and you get 92 percent ee.

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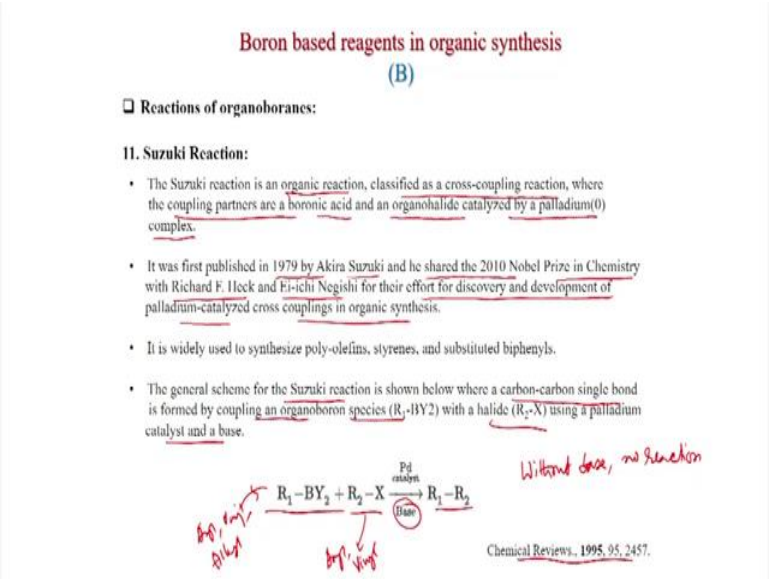

Now, we will discuss Suzuki reaction so Suzuki reaction is an organic reaction classified as a cross coupling reaction where the coupling partners are a boronic acid and an organohalide catalyzed by a palladium complex. So this is palladium catalyzed reaction but, also we will see nickel also, can be used. It was first published in 1979 by Akira Suzuki and shared the 2010 noble prize in chemistry with Richard F. Heck and Ei-ichi Negishi for their effort for discovery and development of palladium catalyzed cross coupling in organic synthesis.

It is widely used to synthesize poly olefins styrenes and substituted biphenyls general scheme for the Suzuki reaction is shown below where a carbon carbon single bond is formed by coupling of an organoboron species R_1BY2 with halide R_2X using a palladium catalyst and a base. So this R_1BY2 and R_2 X this can be both aryl, vinyl, even alkyl and this generally is the aryl and vinyl system.

Then you get this R_1-R_2 single bond is forming and in Suzuki reaction the base is required, without base no reaction so base is very much required and we will see the mechanism, there is a chemical reviews also.

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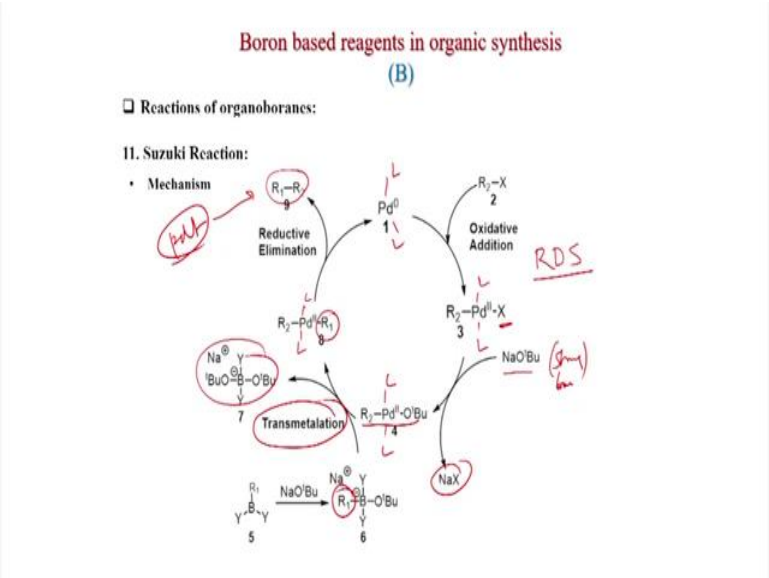

And the in the mechanism the palladium 0 is the active catalyst here, and here ligand can be there neutral legend you can put and first it will react with the alkyl halide the activates oxidative addition will happen and you get this intermediate palladium 0 become palladium 2 now, oxidative addition and this is the rate determine step RDS.

After that the strong base is there which displaced X minus so NaX is formed and the O tertiarybutoxide come with palladium now, after that what will happen the boronic acid derivative also reacting with sodium tertiary butoxide so base has two roles, one is the displacement of X here to make this species and also make the boron tetra coordinated so then only after boron has a negative charge then only this R_1 group will migrate to palladium and that is called trans metalation.

So palladium gets R_1 and this O tertiary butoxide come to the boron so you get this boronate species and finally reductive elimination will happen. So after reductive elimination palladium 2 becomes palladium 0 and R_2 - R_1 they make a bond and you get this compound this is the product. So a boronic acid and alkyl halide reacts in presence of a palladium catalyst and base to generate them.

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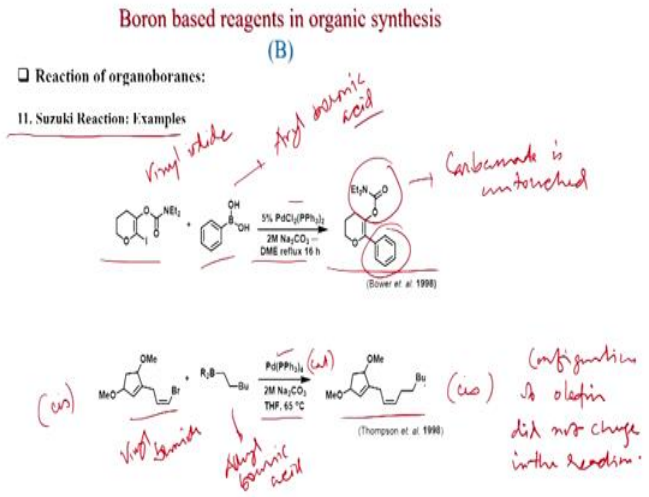

So reactions of organoboranes and the examples are like here if you see this is vinyl iodized and this is aryl boronic acid with 5 percent Pd/C to PPh3 with 2 molar sodium carbonate DME reflux 16 hours, you get this product and you see this is the cross coupling happened here and this carbamate moiety is untouched, also this is you can see this is vinyl bromide and this is alkyl boronic acid.

Here tetra cis triphenyl phosphate palladium also catalytic amount and 2 molar sodium carbonate THF 65 degree centigrade you get this product and as you can see here, the olefin geometry is cis. Here also the vinyl bromide geometric was cis so the configuration of olefin did not change. In the reaction, so it is important that both aryl as well as aliphatic boronic acid can be used and you can get cross coupled product.

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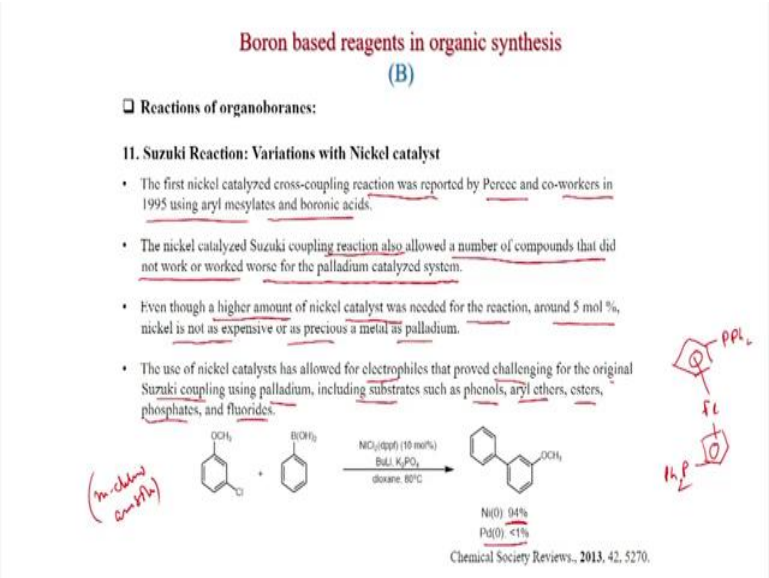

Now, we will see the variation with nickel catalyst so the first nickel catalyst cross coupling reaction was reported by Parcec and Co-worker in 1995 using aryl mesylates and boronic acids. The nickel catalyst Suzuki coupling reaction also allowed a number of compounds that did not work or worked for the palladium catalyst system. So this is very important because wherever palladium catalyst did not work you can use the nickel catalysis.

Even though a higher amount of nickel catalyst was needed for this reaction around 5 more percent nickel is not as expensive or precious a metal as palladium. The use of nickel catalyst has allowed for electrophiles that proved challenging for the original Suzuki coupling using palladium including subtracts such as phenol, aryl, ethers, esters, phosphates and fluorides.

So this is a coupling reaction this is meta chloroanisole when reacting with phenol boronic acid with NiCl2 (dppf) and butylithium is the base so DPPF is, this is DPPF this is the legend butyl lithium and potassium phosphate both are base here and dioxin 80 degree centigrade you get this product. Nickel 0 you get 94 percent yield on the other palladium catalyst you get only less that 1 percent so, this is a usefulness of nickel catalysis because palladium system does not work here.

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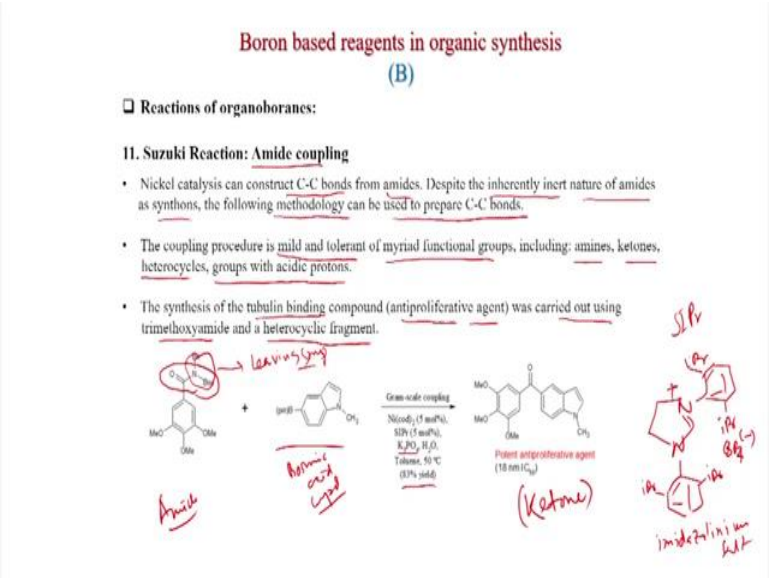

Also we will see another example nickel catalyst amide coupling nickel catalyst can construct C-C bonds from amides despite the inherently inert nature of amides as synthons, the following methodology can be used to prepare the carbon-carbon bonds. The coupling procedure is mild and tolerant of myriad functional groups including amines, ketones, heterocycles groups with acidic protons the synthesis of the tubulin binding compound anti proliferative agent was carried out using tri methoxy amide and heterocyclic fragment.

So, this is the boronic acid derivatives, boronic acid compound this is the pinnacle boronate and this is the amide so this is the amide also a bock group is there and now, what happen when you do this nickel COD is the catalyst and this is an imidazolinium salt SIPR, this is the structure isopropyl is present and here also isopropyl. So this imidazolinium salt and with potassium phosphate is the base H2O toluene 50 degree centigrade you get 83 percent yield of this product so what happen this group as leaved this is the leaving group.

So you get a ketone here so is ketone is formed from an amide generally amide group cannot be eliminated so easily but, here with this a nickel catalyst condition you can this amide coupling possible.

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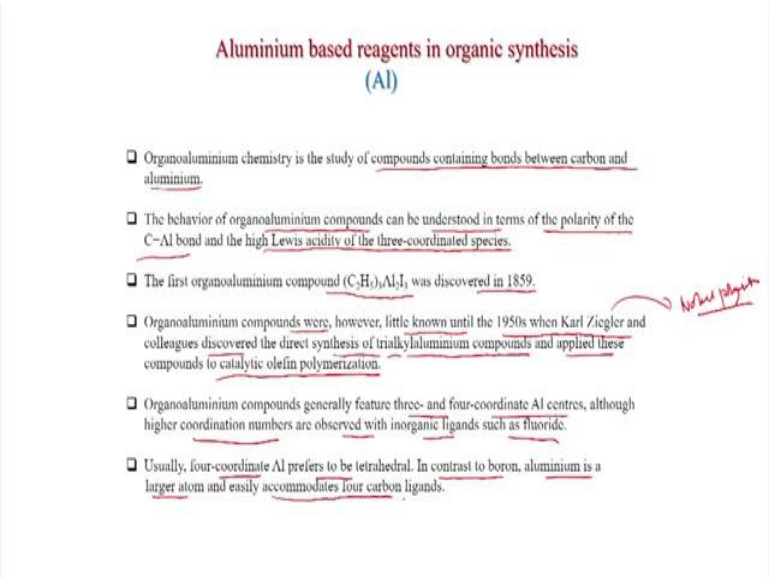

Now, we will discuss aluminum based reagents in organic synthesis. Organo aluminum chemistry is the study of compounds containing bonds between carbon and aluminum, the behavior of organo aluminum compounds can be understood in terms of the polarity of the C Al bond and the high Lewis acidity of the three coordinated species. The first organo aluminum compound (C2H5)3 Al2I3 was discovered in 1859.

And organo aluminum compound were however little known until the 1950s when Karl Ziegler and colleagues discovered the direct synthesis of tri alkyl aluminum compounds and applied these compounds to catalytic olefin polymerization. So, Karl Ziegler got noble prize because of this polymerization and here tri alkyl aluminum compounds are used. Oregano aluminum compounds generally feature three and four coordinate aluminum centers although higher coordination numbers are observed with in organic ligands such as fluoride.

Usually four coordinated aluminum prefers to be tetrahedral. In contrast to boron, aluminum is larger atom and can easily accommodate four carbon ligands.

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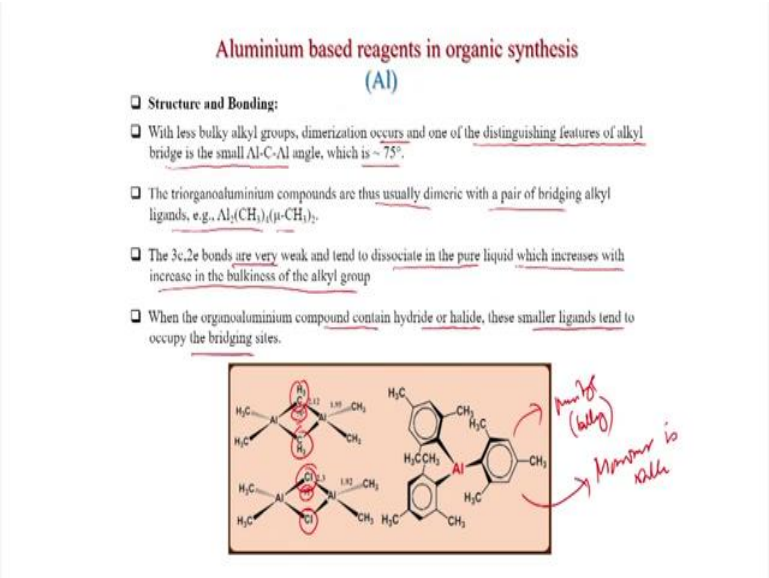

So structure and bonding with less bulky alkyl groups dimerization occurs and one of the distinguish features of alkyl bridge is the small aluminum C aluminum angle which is 75 degree. So with less bulky alkyl groups the dimerization will happen that we will see the tri organo aluminum compounds are thus, usually dimeric with the pair of bridging alkyl ligands, for example, Al2(CH3)4 (µ-CH3)2 so this is the bridging methyl group. The three carbon three electron bonds are very weak and tend to dissociate in the pure liquid which increases with increase in the bulkiness of the alkyl group.

So, when the alkyl groups are bulky then you get the monomeric otherwise the dimeric is possible, when the organo aluminum compound contain hydride or halide, these smaller ligands tend to occupy the bridging sites. These are examples suppose here the methyl group is bridging here methyl group is bridging and here chloride is bridging, here the angle is 75, here 91 degree and when this mesityl group is present, so these are mesityl groups they are bulky then the monomeric, so here monomeric is stable because dimerization is not possible because of the bulkiness of the substituent, here mesityl group is present.

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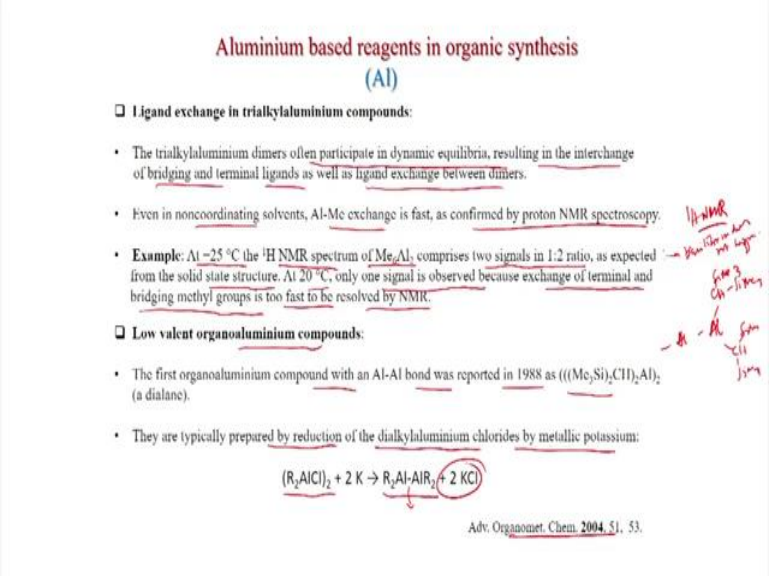

Ligands exchange in tri alkyl aluminum compounds, the tri alkyl aluminum dimers often participate in dynamic equilibria resulting in the interchange of bridging and terminal ligands as well as ligands exchange between dimers. Even in non-coordinating solvents aluminum methyl exchange is fast as confirmed by proton NMR spectroscopy. So by proton NMR one is NMR you can determine that how many kinds of methyl group is present, for example, at minus 25 degree centigrade the one is NMR spectrum of Me6Al2 comprises two signals in 1:2 ratio as expected from the solid state structure.

So this tells that the equilibrium is not happening so equilibrium does not happen that is why is showing in the NMR spectrum, from the solid state 20 degree centigrade only one signal is observed because exchange of terminal and bridging methyl group is too fast to be resolved by NMR. So at high temperature the equilibration is happening.

Now, low variant organo aluminum compounds, the first organo aluminum compound with aluminum aluminum bond was reported in 1988 as (Me3Si)2 (CH)2 aluminum whole 2. So here aluminum aluminum is there, now CH Si Me3, Si Me 3 similarly, here CH Si Me3, Si Me 3 so here aluminum aluminum bond is present and this was the discovered in 1988. They are typically prepared by reduction of the di alkyl aluminum chlorides by metallic potassium like here, R2 AlCl whole 2 plus 2 potassium, you get R2 Al Al R2 so this is the aluminum aluminum bond plus 2KCl. This was reported in advanced oregano metallic chemistry.

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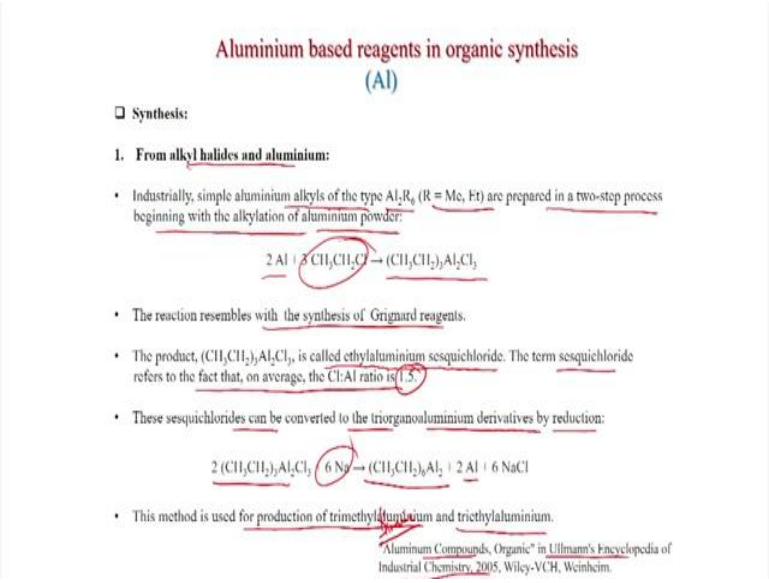

Synthesis from alkyl halide and aluminum industrially simple aluminum, alkyls of the type Al2R6, R is equal to methyl are prepared in a twostep process beginning with the alkylation of aluminum powder. So, aluminum powder you can react with alkyl chloride and then you get this intermediate CH 3 CH2 whole 3 Al 2 Cl3 and the reaction reassembles with the synthesis of Grignard reagents. Now, this product is called ethyl aluminum sesquichloride. The term sesquichloride refers to the fact that on average the Cl to aluminum ratio is 1.5. Suppose here 3 chlorine, 2 aluminum, so the ratio is 1.5.

These sesquicholorides can be converted to the tri organo aluminum derivatives by reduction so, this intermediate if you react with sodium then you get this dimeric aluminum compound plus 2 Al so this is dimeric, 2 Al plus 6 NaCl. So, what is this possibly tells us that first Al2 react with an alkyl halide and then this intermediate can react with sodium then you get this alkylated aluminum compound. This method is used for the production of tri methyl aluminum and tri ethyl aluminum. This is the review aluminum compounds organic in Ulmanns cyclopedia of industrial chemistry 2005.

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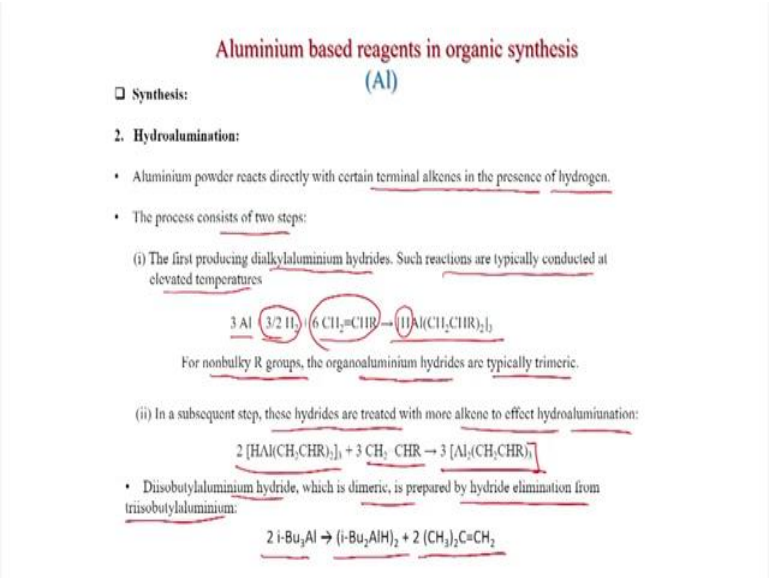

Synthesis some more synthesis the hydroalumination, aluminum powder reacts directly with certain terminal alkenes in the presence of hydrogen. The process consists of two steps, so here first producing di alkyl aluminum hydrides such reactions are typically conducted at elevated temperatures. So here an aluminum in presence of hydrogen, is reacted with an olefin and then you get this HAl CH2 CHR2 whole 3. So here an aluminum hydride is present and now if you react for non-bulky alkyl groups the organo aluminum hydrides are typically trimeric.

So if R group is not bulky then you can get another addition in a subsequent step these hydrides are treated with more alkene to effect hydroalumination so, this hydride HAl CH2 CHR at this one can be reacted with further olefin you get this species so, here 3 alkyl groups are coordinated to aluminum. Di iso butyl aluminum hydride which is dimeric is prepared by hydride elimination from tri iso butyl aluminum so, tri iso butyl aluminum can go to this hydride species and this olefin is generated. This is the iso butene.

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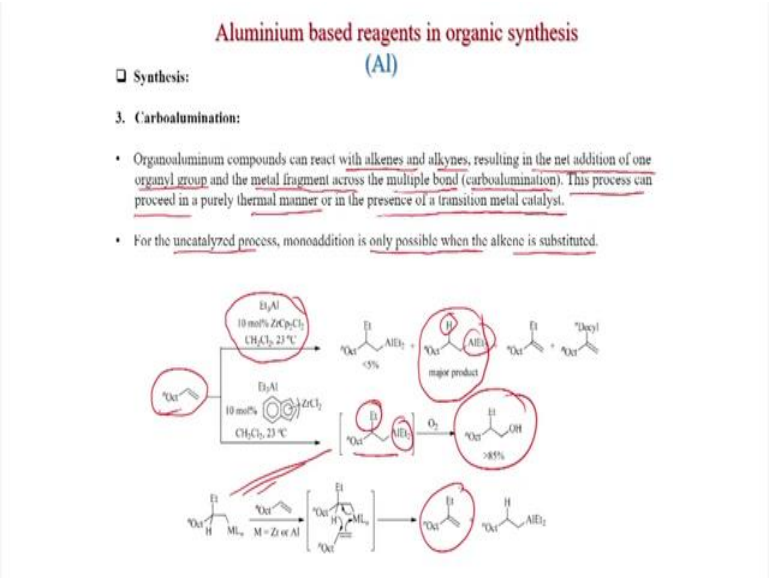

Corbo alumination, organo aluminum compounds can react with alkyls and alkynes resulting in the net addition of one organyl group and the metal fragment across the multiple bond carbo alumination. This process can proceed in a purely thermal manner or in the presence of transition metal catalyst. Further uncatalyzed process mono addition is only possible when the alkyl is substituted. Like here the olefin with n-octyl group that is one shown here, when it is treated with this one tri ethyl aluminum 10 mole percent zirconium CP2 Cl2 you get this product as the major so, here what happen the AlEt2 and hydrogen has been added, this is the major product.

This case when, this catalyst is used, then you get this intermediate with ethyl group so this ethyl group is added now. Ethyl and di ethyl aluminum, here hydrogen di ethyl aluminum with this catalyst ethyl, di ethyl aluminum and after oxygen treatment you get this alcohol with the ethyl group incorporated. Further if you have a more olefin then this species can react like this way and you get this olefin, so ethyl group contain olefin can be also update.

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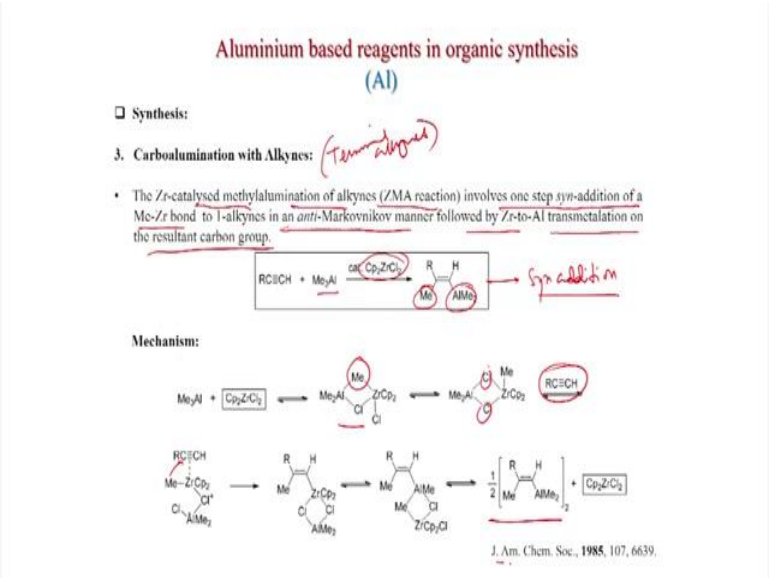

Carboalumination with alkynes also is possible, the Zirconium catalyst methyl alumination of alkynes ZMA reaction involves one step syn addition of a Me Zr bond to 1 alkyne in an anti Markovnikov manner followed by zirconium to aluminum transmetalation on the resultant carbon group. Like here the Me 3 Al catalytic Cp2 Zr Cl 2 at methyl and aluminum 2, so this is the syn addition. So, alkyne this is terminal alkynes. The addition will be syn.

Mechanism is the mechanism that Me 3 Al react with Cp2 Zr Cl 2 to generate this, there is a methyl bridge now, chloro bridge and methyl is connected to zirconium. So now, this aluminum alkyne will coordinate with zirconium and now this methyl group will go there. And because there is negative charge that will be stable or the terminal carbon so, that carbon will coordinate with zirconium and after that this exchange will happen, the carbon will bound to the aluminum species now, and you get this one plus Cp 2 Zr Cl2. This was published in JACS.

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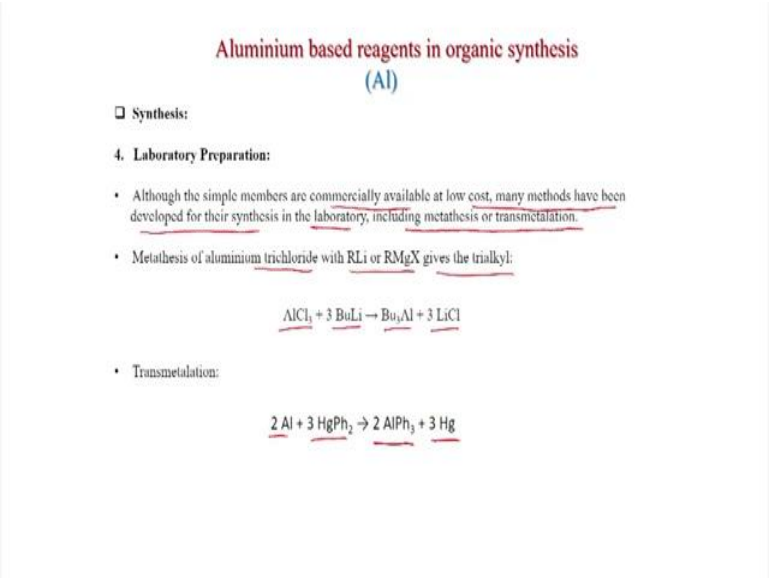

In the laboratory simple members are commercially available at low cost many methods have been developed for their synthesis in the laboratory, including metathesis or transmetalation. metathesis of aluminum tri chloride with RLi or RMgX gives the tri alkyl aluminum this is Al Cl3 plus 3 butyl Bu3 Al plus 3 lithium chloride. Transmetalation also is possible 2 aluminum plus 3 HgPh2 2Al Ph 3 plus 3 Hg. This is the trans metalation and this is the aluminum chloride with n butyl lithium reaction.

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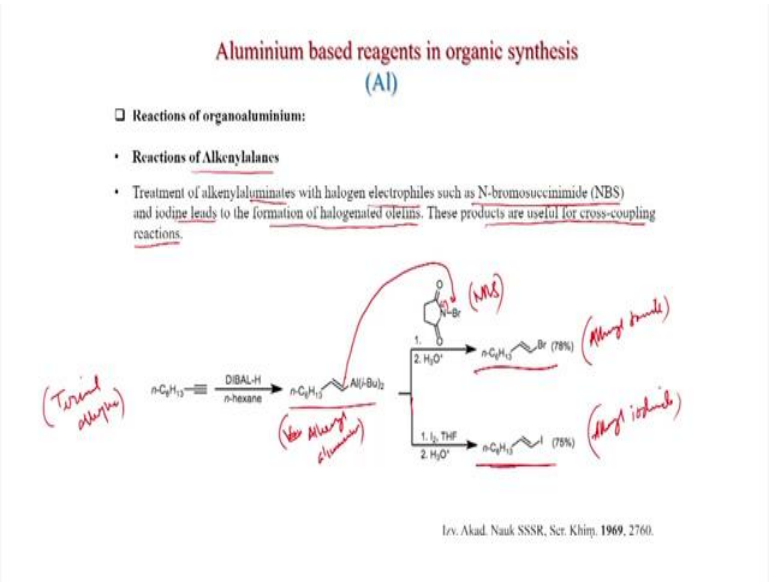

Now, we will discuss different reactions of organo aluminum. First we will discuss reactions of alkenylalanes. Treatment of alkenyl aluminates with halogen electrophiles such as N

bromosuccinimide and iodine leads to the formation of halogenated olefins. These products are useful for cross coupling reactions. Like here this terminal alkyne when treated with DIBAL-H you get this alkenyl aluminum compound so here, you can get very easily alkenyl aluminum compound and this alkenyl aluminum when reacting with N-bromosuccinimide with the NBS you get this alkenyl bromide.

So here, this acts as the nucleophile and you get the reaction bromide comes and with iodine THF toy get the alkenyl iodine. So these are very useful reaction that from alkyl you can get the alkenyl bromide or iodine. This was published in this journal.

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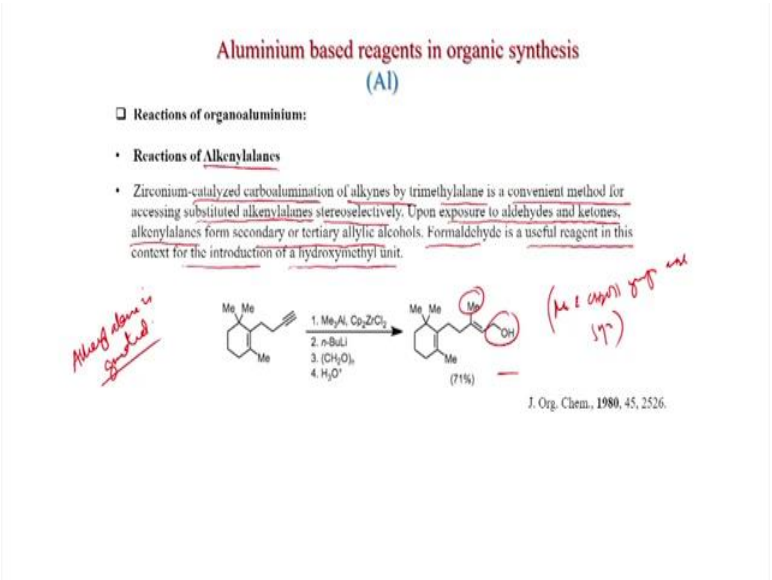

More reactions of alkenyl alanes zirconium catalyzed carbo elimination of alkynes by trimethylalane is a convenient method for accessing substituted alkenyl alanes stereoselectively. Upon exposure to aldehydes and ketones, alkenyl alanes from secondary or tertiary allylic alcohol, formaldehyde is a useful reagent in this context for the introduction of a hydroxymethyl unit.

So, this is a reaction of alkenylalanes so in situ the alkenylalane is generated, how first this trimethylaluminum Cp 2 Zr Cl2. You get this syn addition then n butyl lithium that is the metal transmetalation, the lithium will come then the hydroxymethylation is paraform aldehyde you get this one. And here methyl and CH2OH group are syn, so they are syn same side this was published in JOC 1980.

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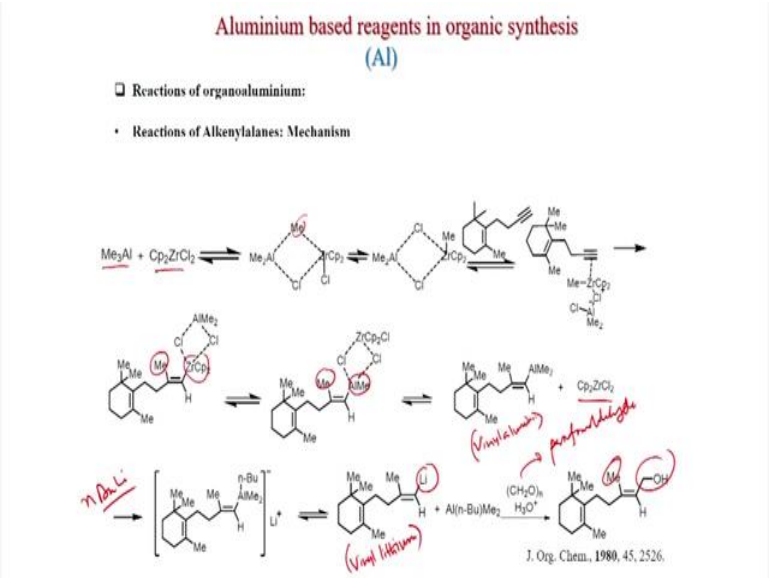

So, what is the mechanism of this reaction so trimethylaluminum first reaction with Cp2 Zr Cl 2 we have seen like this, the methyl bridge then the chloro bridge is now, this addition reaction will happen first the coordination of the terminal alkyne with this zirconium and after that this methyl will comes Zr and after that aluminum will be coordinated and after that butyl lithium with this will be catalyst will regenerate and after that n butyl lithium, so here n butyl lithium is added.

First the butyl group will coordinate with the aluminum and after that lithium will comes. So this is the Vinyl lithium species. So, this is important that the vinyl aluminum and so this is vinyl or alkenyl aluminum, vinyl aluminum is converted into vinyl lithium and after that hydroxymethylation will happen with paraformaldehyde. So, this is paraformaldehyde the hydroxyl methylation will happen and you get this one Me CH2 is on the same side of the double bond.

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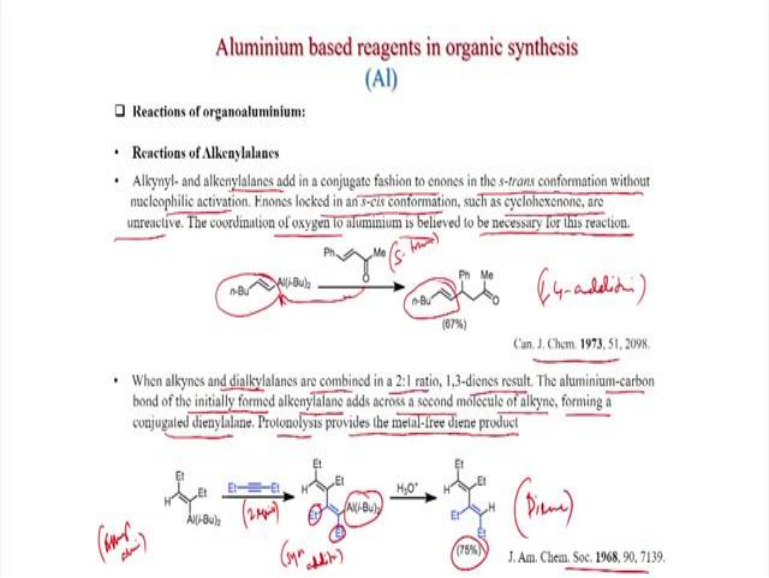

Alkenylalanes, alkynyl alanes add in a conjugate fashion to enones in the s-trans conformation without nucleophilic activation. Enones locked in an s-cis configuration, such as cyclohexanone are unreactive. The coordination of oxygen to aluminum is believed to be necessary for this reaction. So, here this oxygen is coordinated to aluminum and that is why, without catalyst you can get the conjugate addition.

So here, this is in the s trans confirmation and the s-trans confirmation only this reaction will happen and this group, alkynyl group is adding to the alpha beta unsaturated ketone and this is the 1, 4 addition. This was published in this time now. When dialkylalanes are combined in a 2 :1 ratio, 1, 3 dienes result. The aluminum carbon bond of the initially formed alkenylalane adds across a second molecule of the alkyne forming a conjugated dienylalane. Protonolysis provides the metal free diene product.

So, this is the first reaction this is the alkenyl aluminum and this is the alkyne and this is 2 equivalents. Then this addition will happen, this adds to here, and aluminum is coordinated to this carbon now, and this is you can see the syn addition, 2 ethyl group on the same side so, syn addition is happening, and after that if you do the protonolysis with aqueous acid then you get the H here and this diene is formed in 75 percent yield. This was published in JACs 1968.

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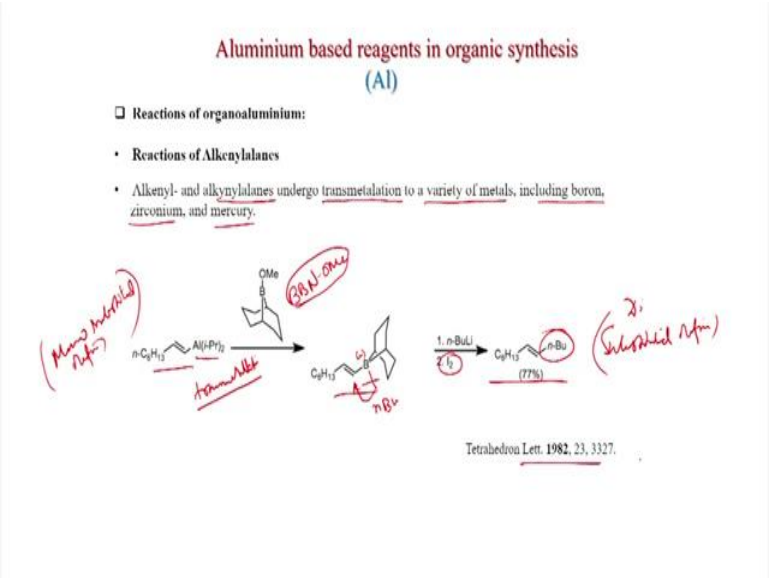

Reactions of the alkynylalanes, and alkynylalanes undergo transmetalation to a variety of metals including boron zirconium and mercury. Transmetalation here this is the BBN derivative BBN methoxy compound so this is the bulky boron compound and this does a transmetalation. Now, alkenyl boron compound is formed and after n butyl lithium iodine, you get this so what happens n-butyl lithium adds here and now boron, and now somehow with iodine you can get this addition at the vinyl species you get the substituted olefin so here, substituted, here di substituted olefin is forming and it is mono substituted starting material.

So this is the reaction that mono substituted, of course, with aluminum you can get, vinyl aluminum it can generate and then you can bring an alkyl group, n butyl this is the strategy, that first we treat with the boron BBN methoxy compound you get this one and after that n butyl lithium adding you get this, this was published in Tetrahedron Letters.

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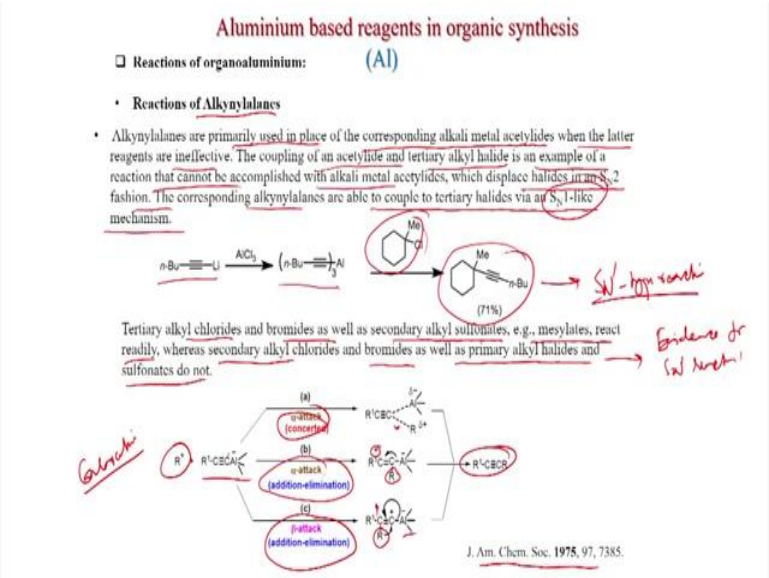

Alkynylalanes now we will discuss alkynylalanaes are primarily used in place of the corresponding alkali metal accetylides when the letter reagents are ineffective the coupling of an accetylide and tertiary alkyl halide is an example of a reaction that cannot be accomplish with the alkali metal accetylide which displace halides in an SN2 fashion the corresponding alkynylalanes are able to couple the tertiary halides via an SN 1 like mechanism. Sn 1 like mechanism.

So here this alkenyl lithium you van treat with aluminum chloride to generate this tri alkyl aluminum this is the laboratory preparation aluminum chloride and lithium species can generate the tri alkyl aluminum. Now, if you treat with this one, you get this so this is the SN 1 type reaction because you know the SN 2 reaction does not happen in quaternary system, tertiary alkyl chlorides and bromides as well as secondary alkyl sulfonates for example mesylates react readily whereas secondary alkyl chlorides and bromides as well as primary alkyl halides and sulfonates do not.

So this is an evidence for SN1 reaction because secondary alkyl chlorides and bromides as well as primary alkyl halides and sullfonates do not do the reaction. So these are the possible mechanisms that carbocation is formed, so carbocation is formed first from this species halide and now, this will be this Cl minus will be here, so the aluminum is tetra coordinated now, and first the alpha attack is possible, alpha attack concerted.

So this is the alpha attack carbon is connected to the R so this is the bond is forming and this bond is weekend, so this is the alpha attack concerted now, alpha attack addition elimination is also possible that here R is adding to this terminal carbon as well as the aluminum and here a carbocation is formed here, carbon gets a positive charge and after that this elimination you get this, alkyne.

Alternatively, beta attack is also possible the addition elimination so beta attack, this is the beta carbon here the R is added here the carbocation now, the migration will happen 1, 2 migration of R group also with that triple bond formation that this group will eliminate then you get the alkyne so, these are the possible mechanism that but the important thing is that this acts as SN 1 fashion, and with this tertiary chloride you can get this product. Tertiary alkyl halide this was JACS 1975, 97, 73885.

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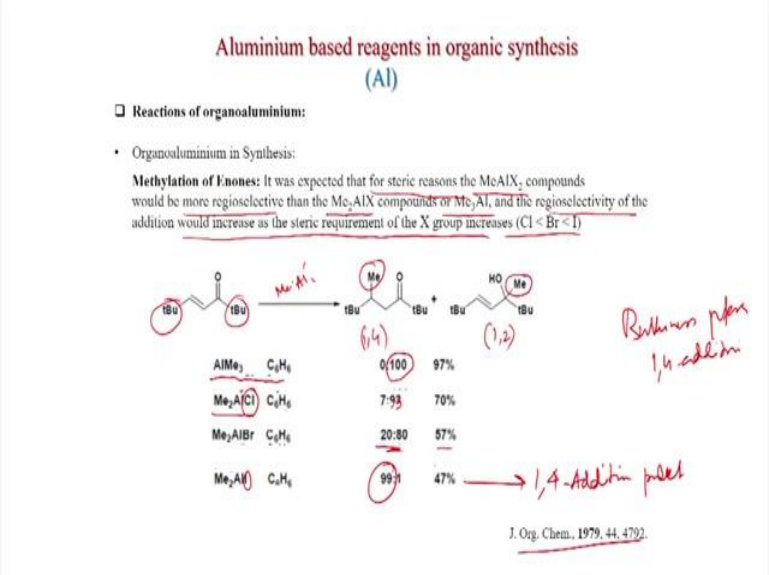

Methylation of enones it was expected that for steric reasons the MeAlX2 coumpounds would be more regioselective that the any Me2AlX compounds or Me3Al and the regioselectivity of the addition is increases as the steric requirement of the X group increases aldehyde greater than bromide generator than chloride. So this is the reaction conjugate reaction and if you add this methyl aluminum species methyl aluminum species, then you can get this one 1, 4 addition and this is the 1, 2 addition both case an methyl group is coming.

Now, we can see that with different methylating aluminum compounds you can get different products so Al Me 3 when Al Me 3 benzene you get this product (1,2) 100 percent. This is

93, 7 is to 93 when Me 2 Al Cl is there so, this is getting reduced now because a methyl group is replaced that chlorine so bulkiness has increased.

Me 2 Al Br is a 20 :80 you get 57 percent will also decrease and Me 2 Al R this is the bulky group now, you get 99 percent of this one so this is totally opposite now, here the tri methyl aluminum this is as the, so this selectively gives 1,4 addition product so this is very important that when the bulkiness increases. So, bulkiness provides 1,4 additions this was published in JOC.

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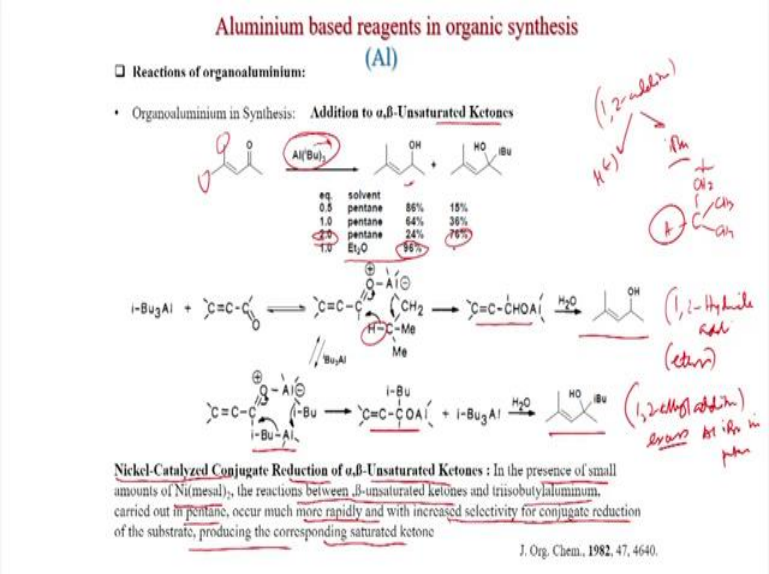

Addition to alpha beta unsaturated ketone now, the aluminum isobutyl is their so isobutyl group when is present then, you can get here the hydride addition this is very important the hydride here, conjugate because this is now di substituted so conjugate addition is not possible 1,2 additions only. At 1,2 additions only, one case is treated with the hydride minus and other case the isobutyl group and it has been found when you increase the equivalent of this 1,2 equivalent you get 76 percent of this one butyl group added.

On the other hand, methyl you get 96 percent of this one this is the hydride addition now, hydride is coming if you see the structure isobutyl group so this hydride, this hydrogen acting as a hydride and we will give this product. And ether only this 1,2 hydride addition is happening, so what to the possible mechanism so tri isobutyl aluminum makes this intermediate and this is the hydride addition is happening, you can see this hydride, is going to the activated carbonyl compound and you get this 1,2 addition and you get this alcohol so this is 1, 2 hydride addition and this preferably an ether.

Alternatively, if we have more equivalent of tri isobutyl aluminum then this one, this aluminum isobutyl negative will react with this another equivalent and then the isobutyl group will add to the carbonyl so this is also 6, 1,2,3,4,5,6 so 6 atoms are present and now you get this isobutyl group and after that this product. hydrolysis product. So this is 1,2 alkyl addition and this is preferring in excess Al isobutyl in pentane.

Now, nickel catalysis if we put in the system what happens, nickel catalysis is reaction in presence of small amount of Ni (Mesal)2 the reaction between alpha beta unsaturated ketones and tri isobutyl aluminum carried out in pentane, occur much more rapidly and with increased selectivity for conjugate reduction of the substrate producing the corresponding saturated ketone.

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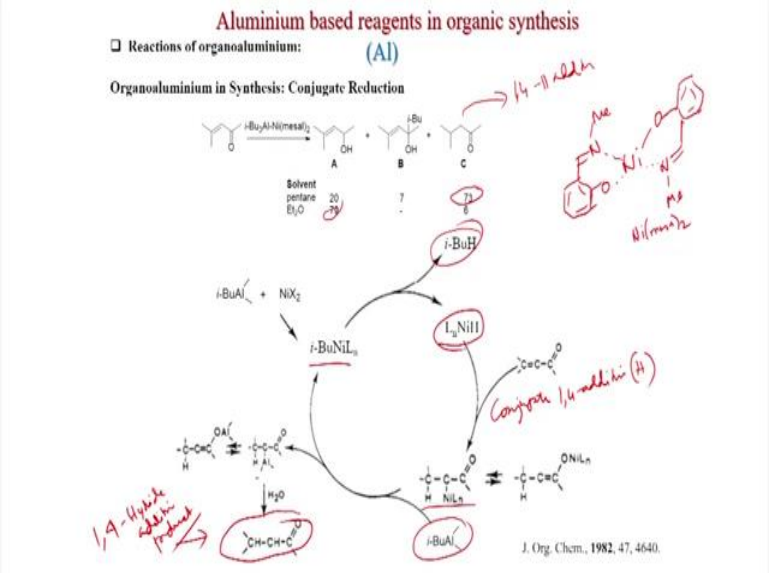

So, in presence of nickel what happens this is the hydride reduction and also 1, 4 this is the another product 1, 4 hydride addition is also forming and mesal is one, this is nickel mesial 2 so in pentane you get 73 percent yield of this 1,4 addition so this will discuss however in ether you get only this product as the major. The hydride addition but, in pentane you get this 1,4 addition so this mechanism we will see, this first react with nickel and you get this isobutyl nickel Ln.

Now, isobutyl will eliminate and this is formed. That is active hydride species and Ln nickel hydride reacts with this carbonyl compound and you can see this conjugate addition is happening, conjugate 1,4 addition of hydride and you get this, this can be equal with this now, this is coming and displace this nickel with aluminum and after that you get this, enolate

also hydrolysis gives the ketone so this is the product here, 1,4 hydride addition product. So this is the special about nickel when you put the nickel catalyst then the 1, 4 hydride addition is possible.

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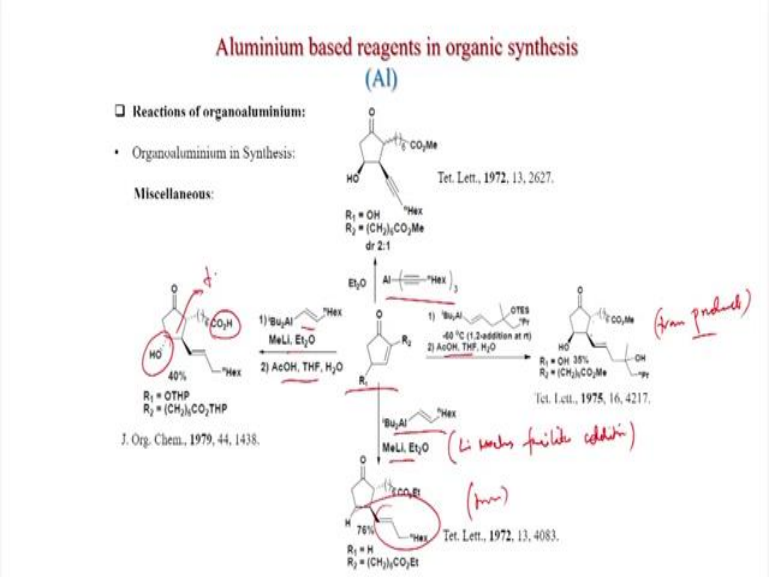

Some miscellaneous example here, this cyclic enone has been employed, here alkenyl aluminum can be reacted and this kind of system here, this alkenyl aluminum react and you get some product here OH group already there and this product were formed in dr 2:1 ratio also vinyl aluminum followed by acetic acid treatment you get this so, this is the trans product is forming, that is the more stable here this groups are trans and if you treat with methyl lithium then the alkenyl so earlier we have seen alkenyl does not add to cyclic olefins.

And lithium exchanges facilitate addition, you get this here also the trans product is formed. So alkenyl group is forming also here another alkenyl group with methyl lithium and acetic acid treatment you can get this compound the hydrolysis of the ester is happening, and you get the carbo oxalic acid derivative and you get this similar compound here the hydroxide group is their earlier. So, only thing is common that the trans geometry is forming in each case.

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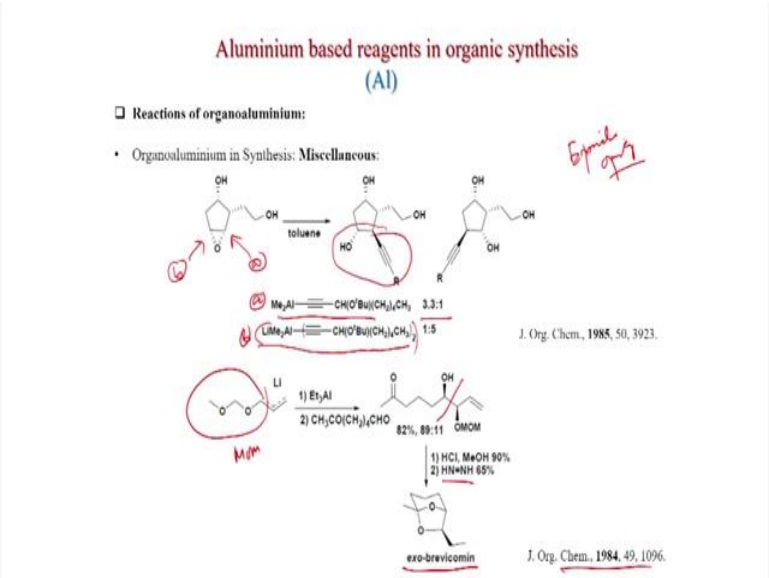

And this is another example of epoxide opening, with this aluminum species you get 3.3 is to 1, so this is the major, so the opening is happening from this side. On the other hand, if you use this one, the lithium Me2 Al then you get this product that is the attack from this side. So, this a b so a case attack from this side and this is the b case, also if you treat with this one, allylic lithium species with triethyl aluminum you get this allyl aluminum compound and that, this is coming from the aldehyde this is the MOM, and you get this, with the terminal double bond.

After that HCl methanol you can get this actual formation and after that you can reduce with dimyde, you can reduce the double bond to get the exo-brevicomin this was published in JOC 1984. So today we have seen first boron asymmetric allylation and asymmetric crotylation so asymmetric allylation we have seen the different chiral axillary can be employed and IPC2B allyl which is commercially available is most useful and also it has been used in Nicolaou's synthesis.

Where the double bond can we cleaved with ozonolysis session that is the 2 carbon homologation. Also crotylboration we have seen that with isopino camphenyl boron crotyl system you can get high diastereo as well as enantioselecctivity because it takes the 6-member cyclic transition state and in Z geometry we have seen that methyl takes an axial position and with E system methyl takes the equatorial position.

So, you can get with Z you can get the syn add with E system you can get the anti-product. And these products are forming high enantioselectivity up to 94 percent ee as well as high diastereoselectivity up to 99 percent. Then we have seen the aluminum reagents in organic synthesis, and aluminum can be prepared in very ways from reaction with alkyl halide, so first reaction with aluminum alkyl halide, then you get chloro compound, chloro di alkyl aluminum and that can be reacted with sodium to get a tri alkyl aluminum.

Also we have seen from olefin hydroalumination we have seen that through hydroalumination also we can do so, aluminum reacted with hydrogen and olefin generate the hydrated aluminum di alkyl species that can be reacted with further olefin to generate the tri alkyl aluminum. Also carboalumination we have seen that the aluminum can be find this way and lastly we were seen the general synthesis with aluminum chloride and n-butyl lithium, alkyl lithium it can generate the tri alkyl aluminum compound.

Also with trans metalation like mercury compound can give the phenyl or alkyl groups to aluminum and in this way you can generate the alkyl compound. So, next we have seen the reactions of, first we have seen that trans metalation alkenyl aluminum can be reacted with BBN o-methoxy to get the boron compound, also of it is reacted with alkylation that then you can get also the double bond can be more substituted.

And then we have seen the conjugate addition. And we have seen that if you increase the bulkiness of the aluminum iodide then the 1,4 addition is facile. So methyl group with tri methyl aluminum it gives 1,2 addition product on the other hand di methyl aluminum iodide it gives the 1, 4 addition product, so steric increases the 1,4 addition.

Also we have seen that without nickel catalyst with isobutyl system we have seen that it can give the hydride as well as donor also and you can get the 2 product, 1, 2 addition products only, but with nickel system we have seen that when nickel is added then the hydride addition product is the major product. I hope you have enjoyed the course. Thank You.