Principles of Organic Synthesis
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Lecture 27
Boron and Tin Containing Compounds

Welcome you all to Principles of Organic Synthesis. Presently, we study the reagents in organic synthesis. So far, we had two lectures in this topic. In the first lecture, we studied the preparation and application of phosphorus containing reagents, and in the second lecture, we covered the sulfur and silicon containing reagents. In this lecture, we will focus on boron and tin containing reagents.

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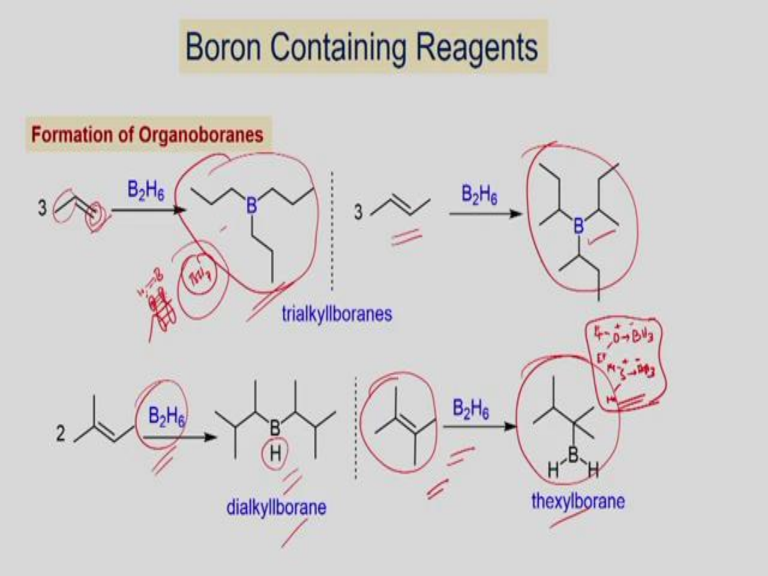

Boron Containing Reagents

Formation of Organoboranes

Let us begin with the preparation of alkylborane. Alkene inserts into the B-H bond of borane in *syn* mode with anti-Markovnikov addition, which is known as hydroboration and the process is stereospecific.

For example, three equiv of propene reacts with borane to produce tripropylborane. Similarly, three equiv of 2-butene reacts to give tri-*sec*-butylborane. On other hand, only two equiv of 2-methylbutene reacts to produce disiamylborane, while one equiv of 2,3-dimethyl-2-butene reacts to yield thexylborane, which is due to the steric hindrance of the substituted alkenes.

The C-B bond has less polarity (electronegativity of carbon is 2.55 and boron is 2.04), and therefore, alkyl boron compounds are stable under normal conditions though oxidized.

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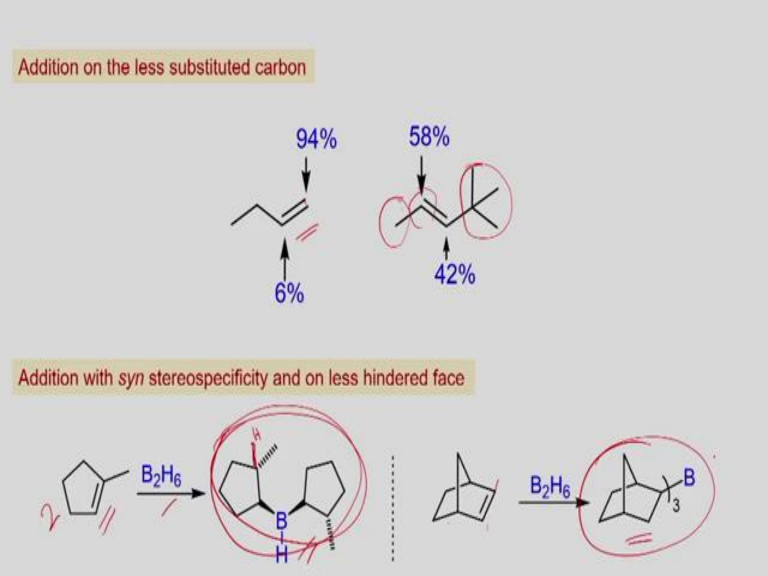

Addition on the less substituted carbon

Addition with *syn* stereospecificity and on less hindered face

Now, let us look at the selectivity in the reaction of the substituted linear and cyclic alkenes. 1-Butene with borane gives 94% anti-Markovnikov product, whereas, in case of 4,4-dimethylpent-2-ene, the selectivity is dropped to 58%. Further, borane approaches on the less hindered face. For example, the reaction of 1-methylcyclopentene gives *bis*(2-methylcyclopentyl)borane, while norbornene reacts to give the *exo*-tris(norbornyl)borane.

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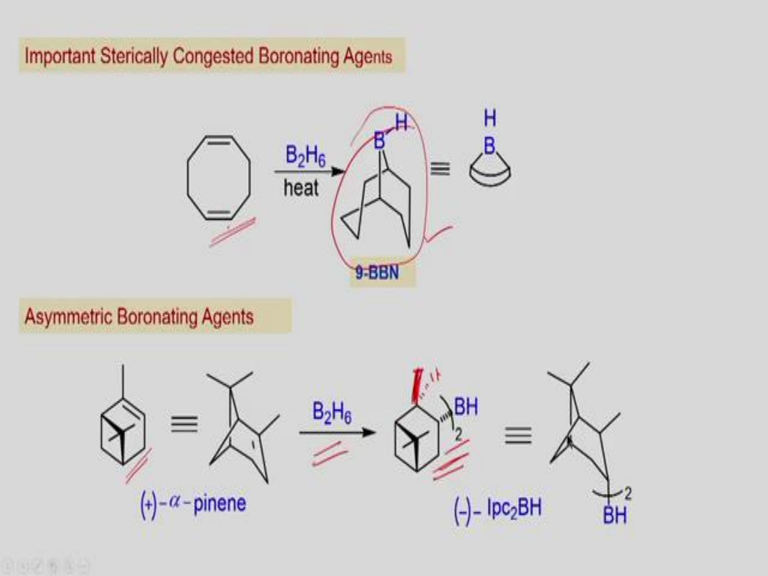

Important Sterically Congested Boronating Agents

Asymmetric Boronating Agents

Further, 1,5-cyclooctadiene with borane produces 9-borabicyclo[3.3.1]nonane (9-BBN). This is a stable and crystalline compound. The hydroboration of α-pinene also gives a nice example of steric controlled reaction. For example, two equiv of (+)–α-pinene reacts with borane to yield diisopinocampheylborane, (-)-Ipc_2BH, which finds broad utilities in asymmetric synthesis. It is mainly utilized for the preparation of chiral secondary alcohol.

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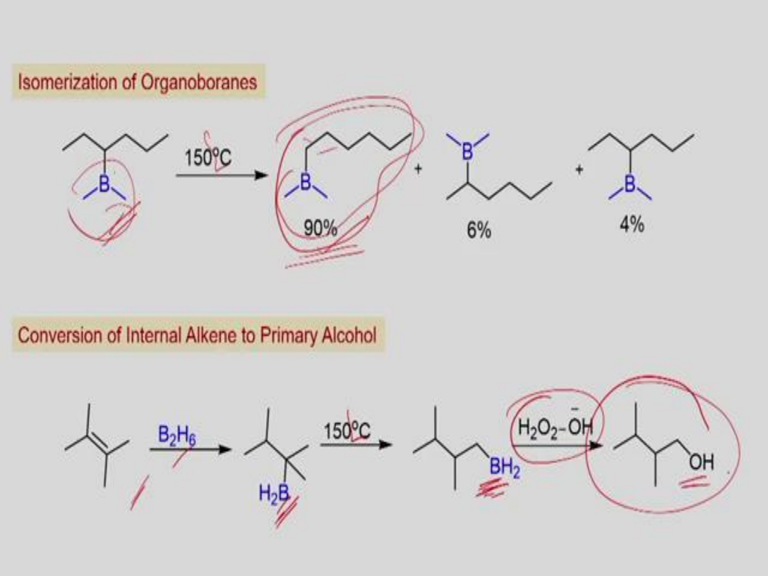

Isomerization of Organoboranes

Conversion of Internal Alkene to Primary Alcohol

Secondary and tertiary alkylboranes can isomerize on heating to give the less sterically hindered primary alkylborane. For example, the secondary alkylborane undergoes isomerization to give the primary alkylborane as the major compound. Similarly, thexylborane isomerizes to primary alkylborane. These reactions involve elimination followed by addition to give the less substituted compounds.

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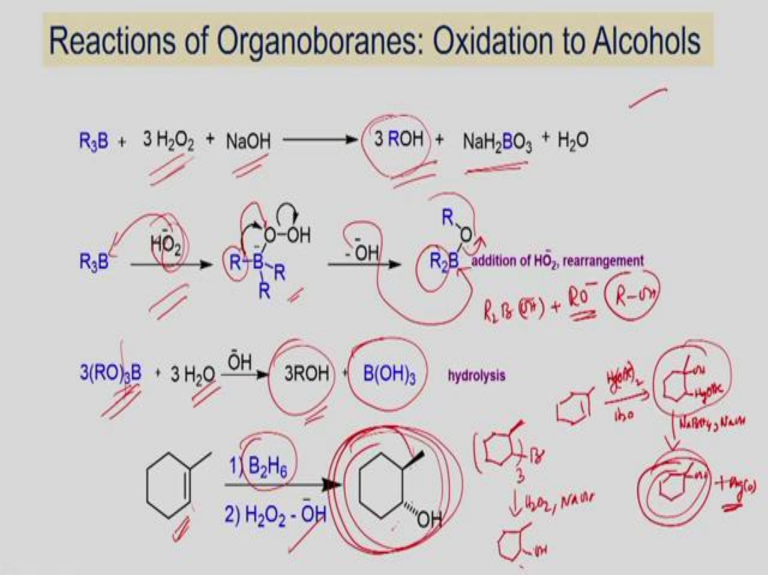

Reactions of Organoboranes: Oxidation to Alcohols

$R_3B + 3\,H_2O_2 + NaOH \longrightarrow 3\,ROH + NaH_2BO_3 + H_2O$

$3(RO)_3B + 3\,H_2O \xrightarrow{\bar{O}H} 3ROH + B(OH)_3$ hydrolysis

Now let us look at the oxidation of organoboranes to alcohols. The nucleophilic hydroperoxide ion attacks the boron atom. Migration of the alkyl group from boron to oxygen atom occurs with retention of the stereochemistry. The resultant trialkylborate on hydrolysis gives an alcohol. The hydroboration and oxidation is thus two-step reaction that transforms alkene to alcohol. The reaction involves *syn* addition of the hydrogen and the hydroxyl group, which is complimentary to the oxymercuration-demercuration reaction of alkene to alcohol.

Thus, hydroboration-oxidation of 1-methylcyclohexene gives *anti*-2-methylcyclohexanol, while the oxymercuration-demercuration yields 1-methylcyclohexanol.

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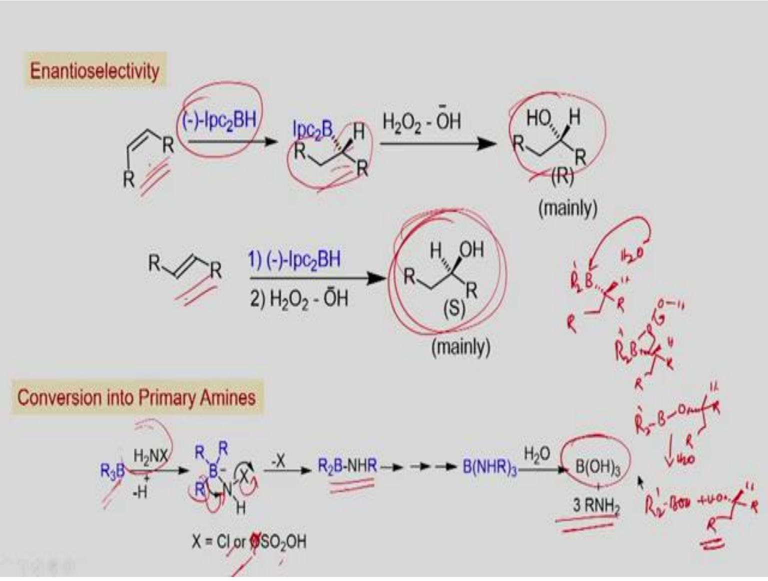

Enantioselectivity

Conversion into Primary Amines

Here the reaction of optically active borane with alkene produces optically active alkylborane, which on oxidation yields an optically active alcohol with retention configuration. By changing the stereochemistry of alkene, we can access both the enantiomers of the alcohol.

Further, alkyborane reacts with chloroamine or sulfamic acid to produce primary amine. Migration of alkyl group from boron atom to nitrogen atom takes place via substitution.

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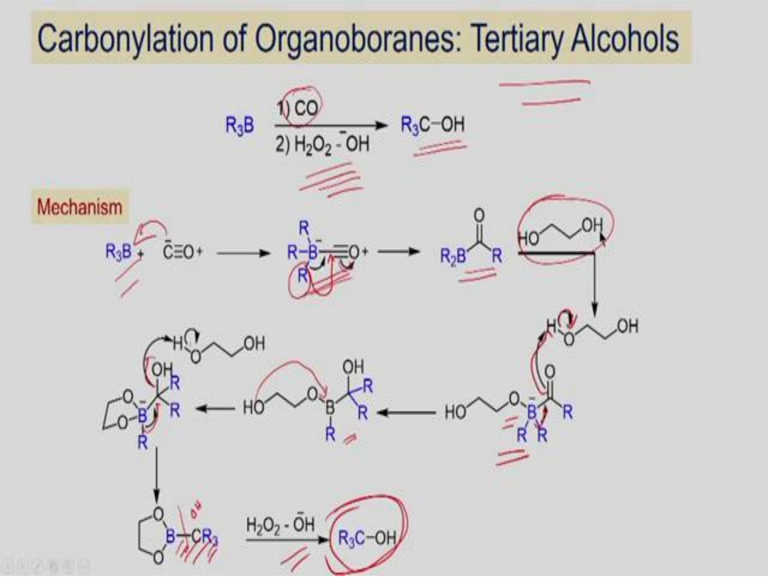

Carbonylation of Organoboranes: Tertiary Alcohols

Mechanism

Carbonylation of alkylborane and subsequent alkyl group transfer to carbonyl carbon produces acylborane, which can be reacted with ethylene glycol to give the cyclic ester. Oxidation using alkaline hydrogen peroxide produces a tertiary alcohol.

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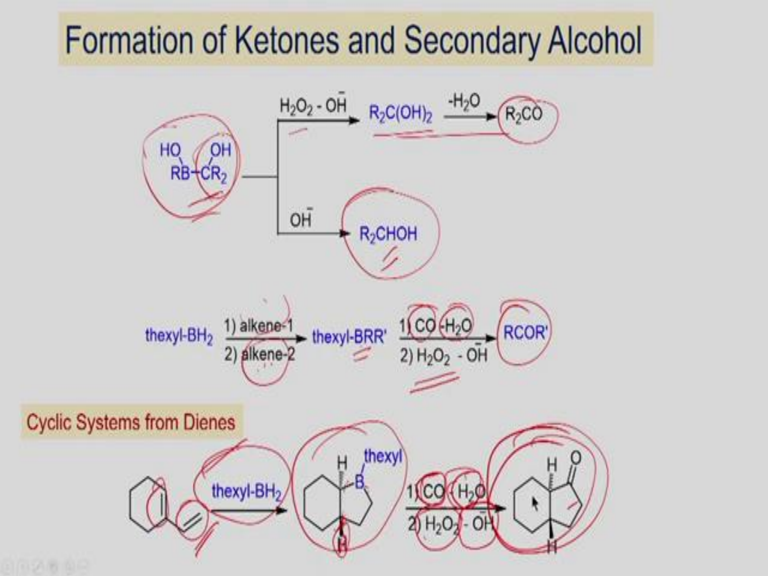

Formation of Ketones and Secondary Alcohol

Cyclic Systems from Dienes

The above reaction using water instead of ethylene glycol gives the intermediate with hydroxyl group, which can be hydrolyzed to a secondary alcohol or oxidized using alkaline hydrogen peroxide to produce a ketone. For example, thexyl-BH$_2$ reacts with two different alkenes. The resultant alkylborane on carbonylation followed by migration of the alkyl group and oxidation using alkaline hydrogen peroxide gives an unsymmetrical ketone. Thus, 1-vinylcyclohexene reacts with thexyl-BH$_2$ and the resultant borane by carbonylation and oxidation gives a bicyclic ketone.

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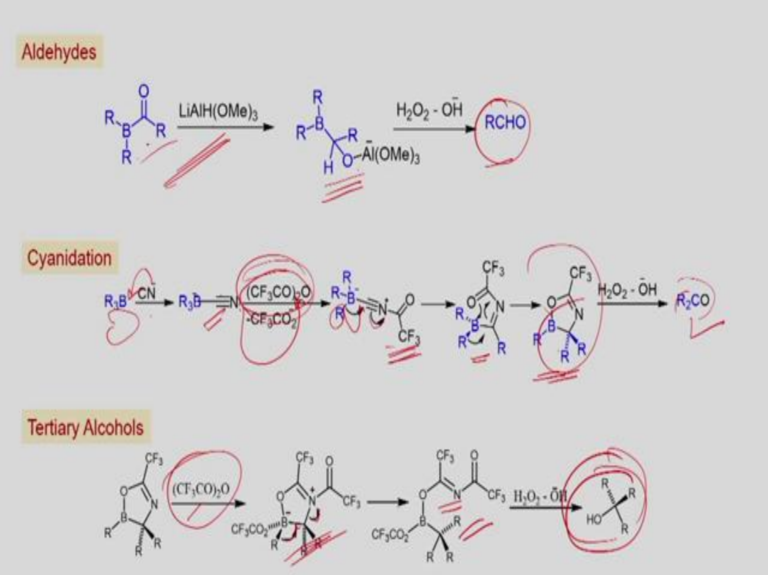

The acylborane can be reacted with lithium trimethoxyaluminum hydride to give the alkoxy derivative, which can be oxidized using alkaline hydrogen peroxide to yield aldehyde.

Further, cyanide ion, which is isoelectronic with carbon monoxide, undergoes similar reaction. Reaction with alkylborane produces an adduct that is not sufficiently electron attracting to induce the rearrangement. Thus, reaction with trifluoroacetic anhydride gives N-acetyl derivative, which leads to rearrangement of the two alkyl group from boron to carbon. Oxidation using alkaline hydrogen peroxide gives the ketone. The third substituent can migrate from boron to carbon on heating, which can be oxidized using alkaline hydrogen peroxide to give a tertiary alcohol. These methods superior compared to the above described carbonlyation approach as the cyanide ion based reactions are effective at low temperatures.

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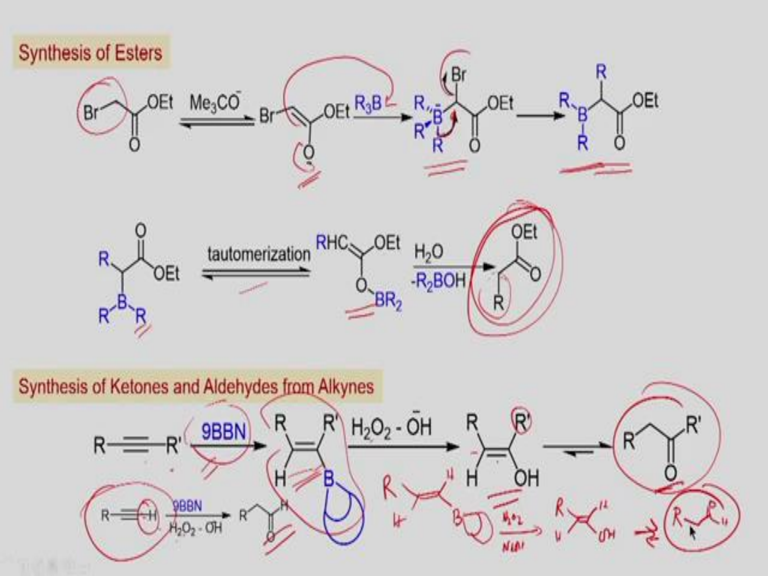

Synthesis of Esters

Synthesis of Ketones and Aldehydes from Alkynes

Enolate of α-haloester reacts with borane to produce an anion that rearranges to a borate, which on hydrolysis yields an ester. 9-BBN is often used to give two of the alkyl groups in the borane.

Alkyne can be boronated employing 9-BBN or Sia2BH, and the resultant adduct can be oxidized using alkaline hydrogen peroxide. In this way, internal alkyne can be converted to ketone, while the reaction of terminal alkyne yields an aldehyde. These reactions are complimentary to the hydration of alkyne using mercury(II) sulfate.

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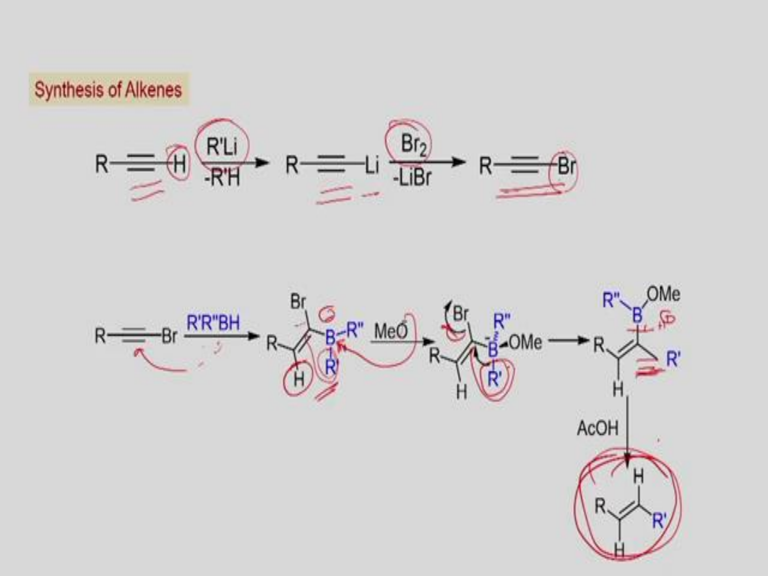

Synthesis of Alkenes

Terminal alkynes can be converted to (*E*) or (*Z*)-alkene by controlling the reaction conditions. Thexylborane is generally employed to give one of the alkyl groups. For example, reaction of alkyne with lithium reagent gives alkynyllithium, which can react with bromine followed by borane to give the hydroboration product. Methoxide induced rearrangement leads to elimination of the halide, which can be protonated to yield (*E*)-alkene.

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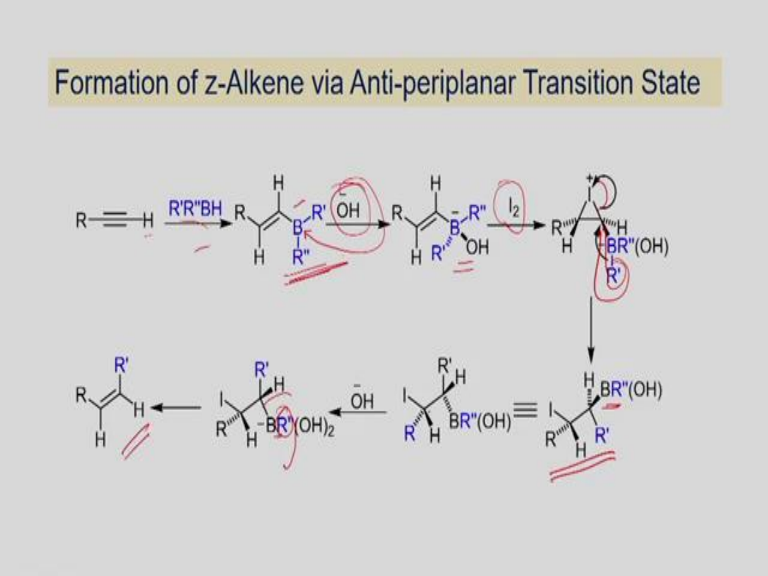

Formation of z-Alkene via Anti-periplanar Transition State

While the hydroboration of terminal alkyne gives a vinylborane, which reacts with hydroxide ion followed by iodine to yield iodinium ion. It converts to (*Z*)-alkene via the rearrangement of the iodonium ion and elimination using an antiperiplanar transition state.

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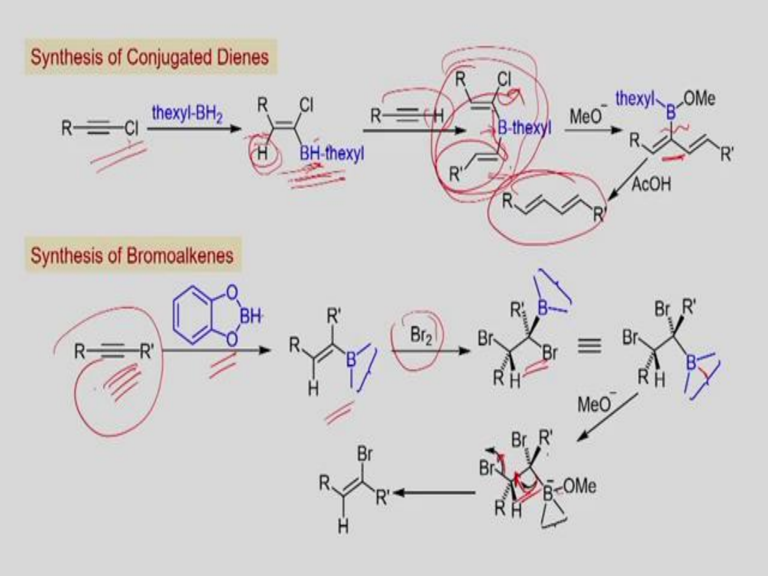

Here is an application for the synthesis of conjugated alkene. For example, hydroboration of chloroalkyne with thexyl-BH_2 give the vinylborane, which can be further reacted with terminal alkyne to yield divinylborane. Treatment with methoxide induces alkenyl rearrangement to give the conjugated adduct, which on protonalysis gives the conjugated 1,3-diene.

When we react internal alkyne with catecholborane, we will end up with a vinylborane, which can be reacted with bromine. The 1,2-dibromo compound with methoxide yields vinylbromide via anti-elimination.

So far, we have seen the use of classical borane for the organic transformations. All of you know very well the use of boronic acid for the Suzuki C-C coupling. Recently, efforts are made on the use of boronic acid for the C-H arylation, which are important in synthetic chemistry. Here we will see two representative examples.

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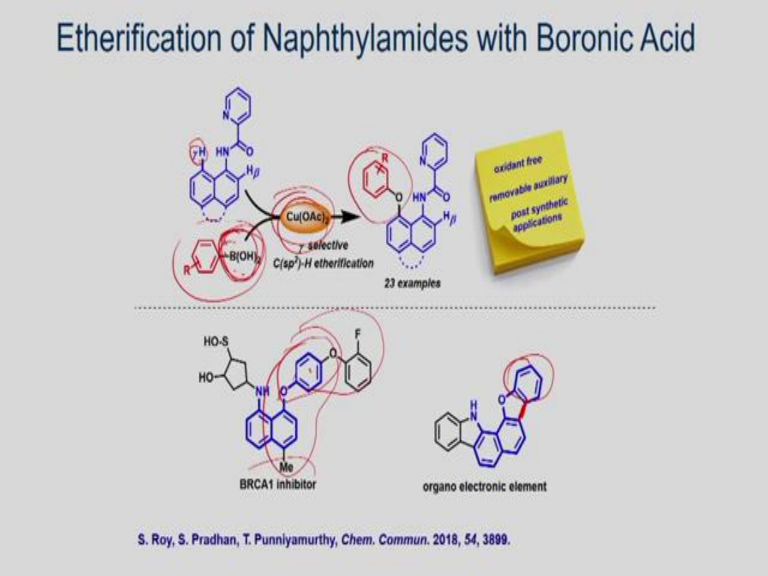

Etherification of Naphthylamides with Boronic Acid

oxidant free
removable auxiliary
post synthetic applications

BRCA1 inhibitor

organo electronic element

S. Roy, S. Pradhan, T. Punniyamurthy, *Chem. Commun.* 2018, *54*, 3899.

Here is naphthyl based biologically active compounds. If you look at them, their γ–position has aryl ether substituent. This can be accomplished using arylboronic acid as the arylating agent in the presence of water. The selectivity of the C-H bond can be controlled using the chelating group. The catalyst makes chelation with picolinamide and activates the γ-C-H bond through cyclometalation. The carbon-metal bond then reacts with boronic acid in the presence of water to give the aryl ether derivative.

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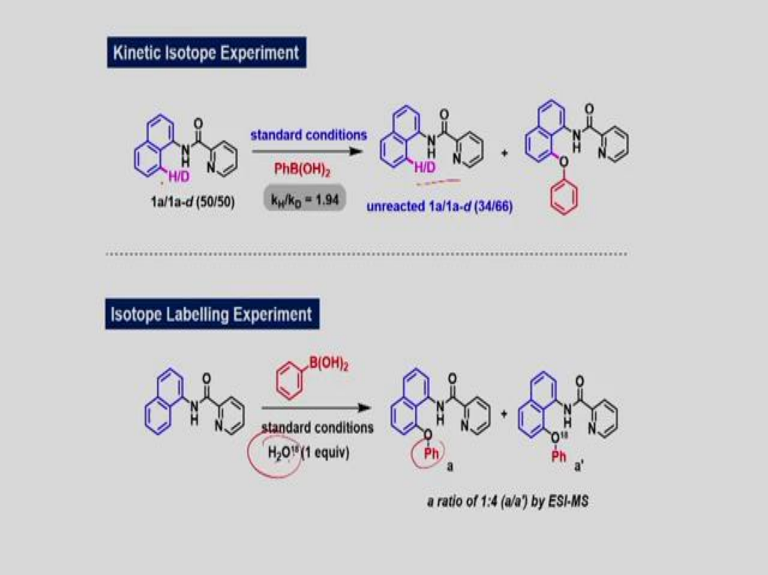

Kinetic Isotope Experiment

1a/1a-*d* (50/50)

k_H/k_D = 1.94

unreacted 1a/1a-*d* (34/66)

Isotope Labelling Experiment

a ratio of 1:4 (a/a') by ESI-MS

Kinetic isotope experiment shows $K_H/K_D = 1.94$, which suggests that C-H bond cleavage may be the rate determining step. In addition, the experiment using H_2O^{18} showed 80% of ether has O^{18} oxygen that suggests that water is the oxygen source.

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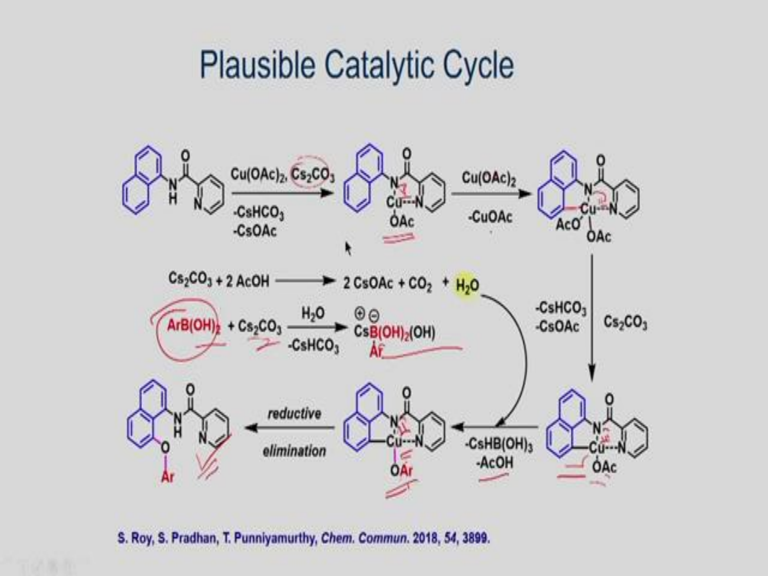

Plausible Catalytic Cycle

S. Roy, S. Pradhan, T. Punniyamurthy, *Chem. Commun.* 2018, *54*, 3899.

These experimental results suggest that chelation of copper(II) salt with substrate may give the copper(II) intermediate, which can be converted to copper(III) by redox process. Activation of the γ-C-H bond through cyclometalation followed by reaction of the phenoxide that can be generated from boronic acid and water can give the copper(III) phenoxy derivative. Reductive elimination can produce the ether.

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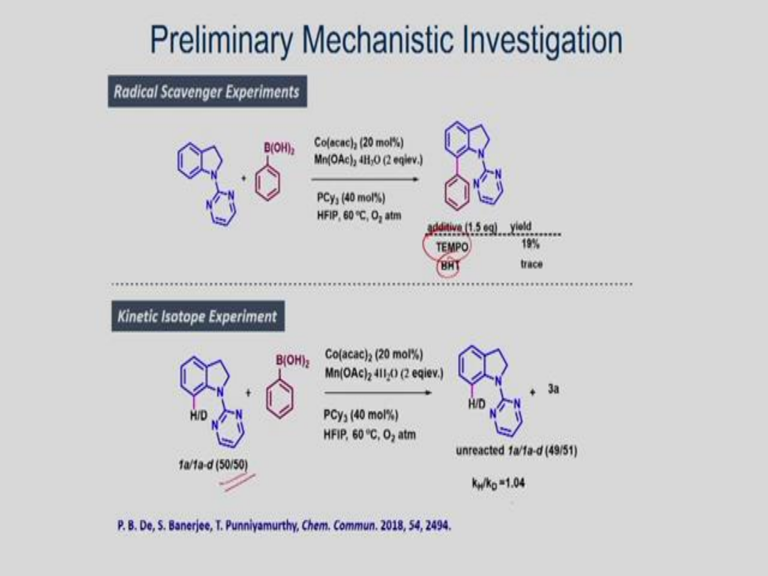

Preliminary Mechanistic Investigation

Radical Scavenger Experiments

additive (1.5 eq)	yield
TEMPO	19%
BHT	trace

Kinetic Isotope Experiment

$k_H/k_D = 1.04$

P. B. De, S. Banerjee, T. Punniyamurthy, *Chem. Commun.* 2018, 54, 2494.

Here is an another example for the regioselective C7 C-H arylation of indoline with boronic acid. This reaction effective using the combination of Co(acac)$_2$ and Mn(OAc)$_2$ catalytic system. The reaction is less effective in the presence of radical scavenger TEMPO/BHT, which suggests that the reaction involves a radical intermediate. In addition, the kinetic isotope experiment shows K_H/K_D=1.04, which suggests that the C-H bond cleavage may not be involved in the rate determining step.

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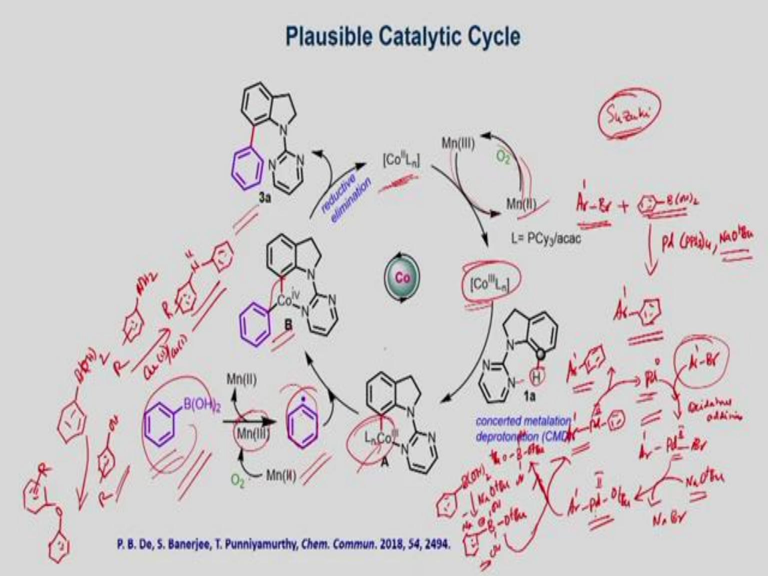

Plausible Catalytic Cycle

P. B. De, S. Banerjee, T. Punniyamurthy, *Chem. Commun.* 2018, 54, 2494.

Oxidation of cobalt(II) to cobalt(III) can be facilitated using Mn(III). Oxidation of Mn(II) using molecular oxygen can regenerate Mn(III). Chelation of Co(III) with the substrate followed by C-H activation can give Co(III) intermediate. The aryl radical that can be generated from boronic acid using Mn(III) can react with cobalt(III) to give cobalt(IV) species, which gives the product by the reductive elimination.

So far we have seen the recent developments in the use of boronic acid for the arylation of aryl C-H bonds.

Now let briefly look at the use of organotin reagents for the carbon-carbon bond formation.

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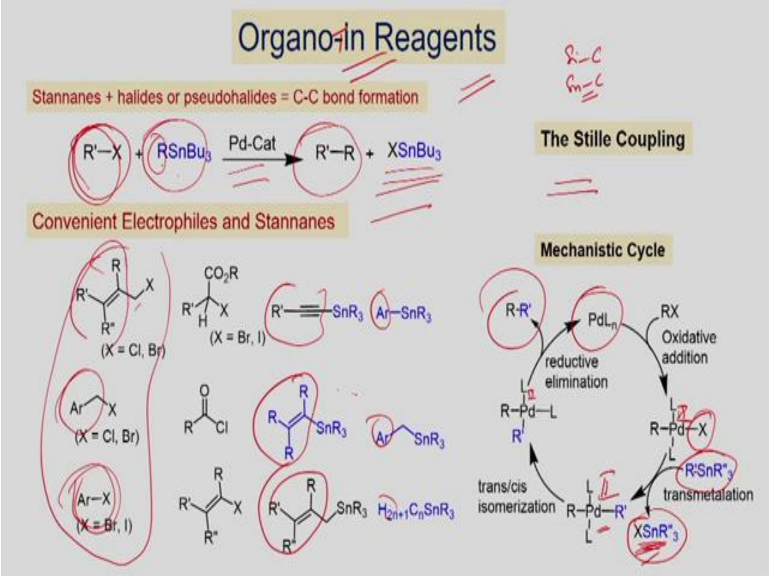

Organotin Reagents

Stannanes + halides or pseudohalides = C-C bond formation

The Stille Coupling

Convenient Electrophiles and Stannanes

Mechanistic Cycle

If you compare with an organosilicon, organotin is more reactive. This is because C-Sn bond is longer and more polarized. However, the toxicity of tin limits its potential applications. Here we will cover some of the important transformations.

Let us focus on the Stille coupling where alkyl/aryl/vinyl halides cross-couple with organotin in the presence of Pd-catalysis to produce the C-C coupled products. The convenient electrophiles and stannanes are here summarized. As you can see a variety of acyl, allyl, alkyl, aryl and vinyl halides can be coupled with alkynyl, vinyl, allyl, alkyl and aryltin. Oxidative addition of the halo substrate produces Pd(II), which undergoes transmetalation with organotin to give Pd(II) species. Reductive elimination gives the C-C coupled product to complete the catalytic cycle.

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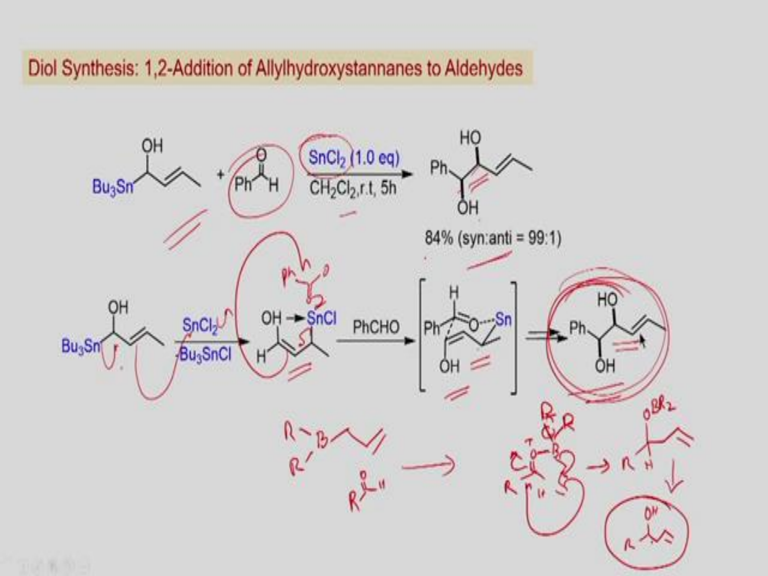

Diol Synthesis: 1,2-Addition of Allylhydroxystannanes to Aldehydes

Here is Lewis acid catalyzed allylation of aldehydes. This reaction has been well explored. The allyltin makes chelation with tin(II) chloride and reacts with benzaldehyde to give *syn*-diol. The stereochemistry can be understood by drawing the six-membered transition-state. Asymmetric version of the reaction has been well explored using chiral BINOL based ligands with excellent enantioselectivity.

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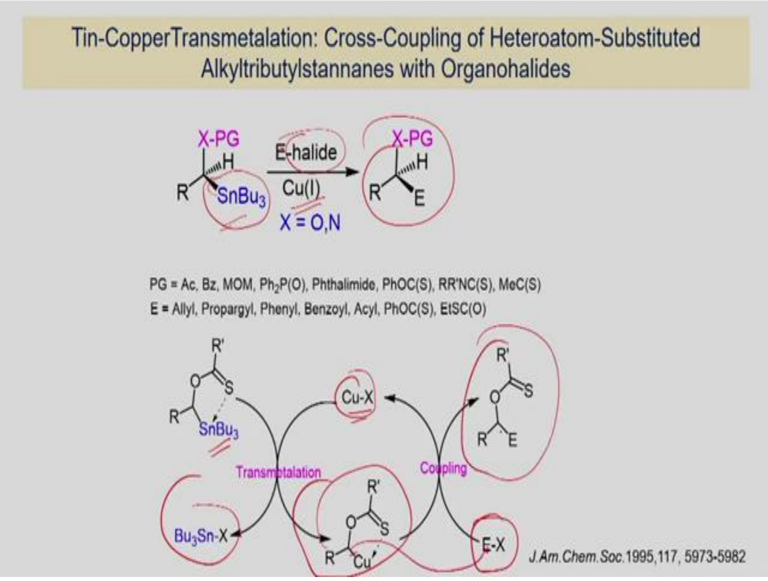

Tin-CopperTransmetalation: Cross-Coupling of Heteroatom-Substituted Alkyltributylstannanes with Organohalides

PG = Ac, Bz, MOM, Ph$_2$P(O), Phthalimide, PhOC(S), RR'NC(S), MeC(S)
E = Allyl, Propargyl, Phenyl, Benzoyl, Acyl, PhOC(S), EtSC(O)

J.Am.Chem.Soc.1995,117, 5973-5982

Here is an example where heteroatom substituted alkyltributylstannane reacts with alkyl halide via tin-copper transmetalation. The copper(I) intermediate reacts with halo substrate to give the C-C coupled product. The reaction takes place with retention of stereochemistry.

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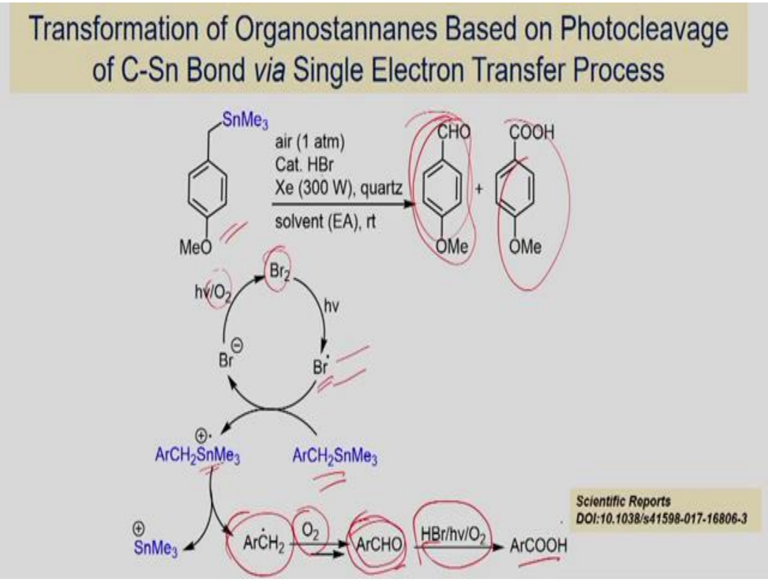

Transformation of Organostannanes Based on Photocleavage of C-Sn Bond *via* Single Electron Transfer Process

Scientific Reports
DOI:10.1038/s41598-017-16806-3

Here is an example where you can the use light for the cleavage of carbon-tin bond to produce a benzyl radical that can be converted to benzaldehyde with molecular oxygen. The aldehyde can be further oxidized to benzoic acid employing HBr.

We have seen few examples on the use of the organotin reagents for the organic transformations, which play important role in C-C bond formation.

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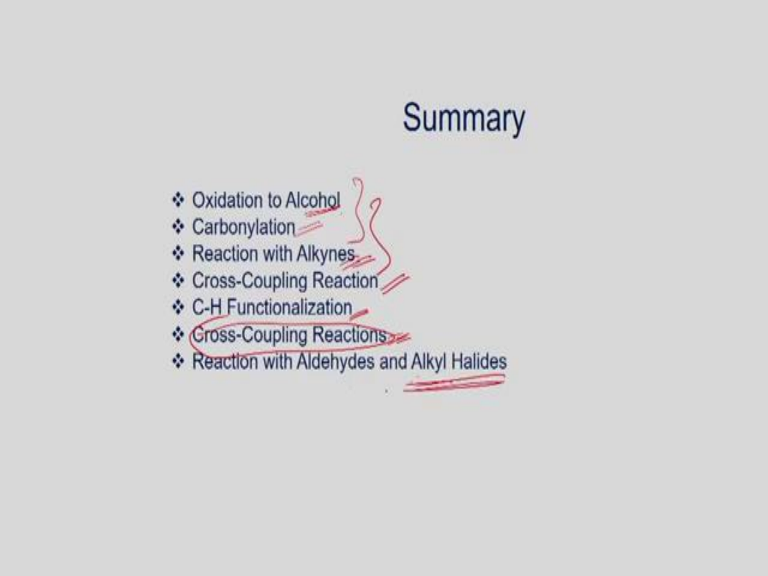

Summary

- Oxidation to Alcohol
- Carbonylation
- Reaction with Alkynes
- Cross-Coupling Reaction
- C-H Functionalization
- Cross-Coupling Reactions
- Reaction with Aldehydes and Alkyl Halides

In summary, in the first part, we have seen the preparation and reaction of organoboranes, which find broad utilities in synthetic chemistry.

We have seen the hydration of alkene via a two-step hydroboration and oxidation. The reaction is stereospecific, involving the *syn* addition at the less hindered face to give an anti-Markovnikov product.

We have seen the reaction of organoborane with carbon monoxide and cyanide ion. They provide potential route for the preparation for alcohol, aldehyde and ketone.

The reaction of borane with alkyne provides an effective synthetic tool for the preparation of aldehyde, ketone and cis/trans alkenes.

We know that boronic acid plays an important synthetic role for the C-C cross-coupling reaction. Recently, efforts are made for the arylation with C-H bond using boronic acid in the presence of transition-metal-catalysis. We have seen two example for the functionalization of naphthyl and indoline compounds.

In the second part, we have briefly seen the use of organotin for the C-C bond formation. We have seen the Stille coupling.

We have then seen the allylation of benzaldehyde using tin(II) chloride as a catalyst.

We have also seen the transmetalation of organotin with copper(I) halide for the C-C bond formation.

Effort is also made on the use of photocatalysis for the cleavage of C-Sn bond to form benzyl radical that has been converted to aldehyde and carboxylic acid. With these let us conclude this lecture. Thank you very much.