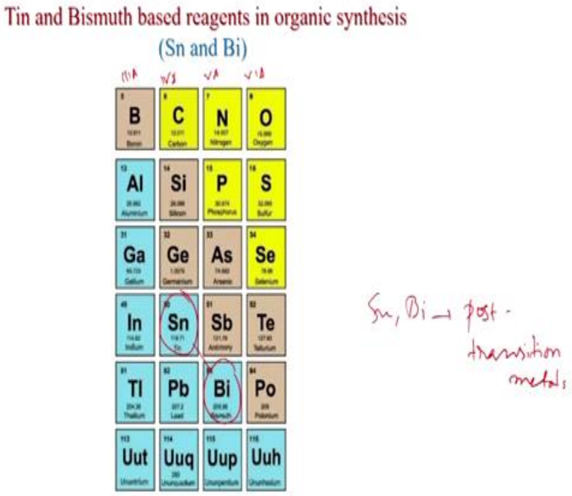
Reagents in Organic Synthesis
Professor Subhash Ch. Pan
Department of Chemistry
Indian Institute of Technology Guwahati
Lecture No 19

(Refer Slide Time: 0:37)

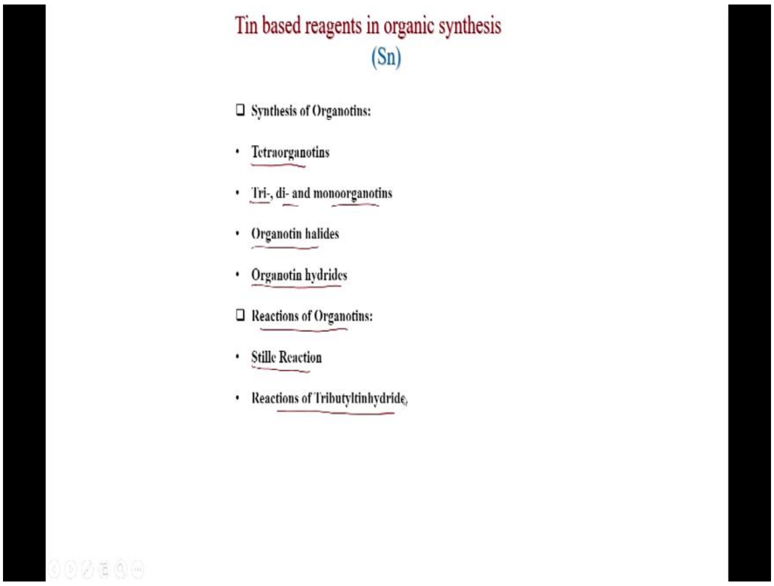


Tin and Bismuth based reagents in organic synthesis

(Sn and Bi)

Welcome again, today we will discuss Tin and Bismuth based reagents in Organic Synthesis. So if you see the periodic table again, three A, four A, five A, six A. So tin is here tin is in the same group with carbon and bismuth is the same group with phosphorous and they are post-transition metals and also they have diagonal relationships. So we will see the chemistry of these two reagents today.

(Refer Slide Time: 1:11)



Tin based reagents in organic synthesis

(Sn)

❑ Synthesis of Organotins:

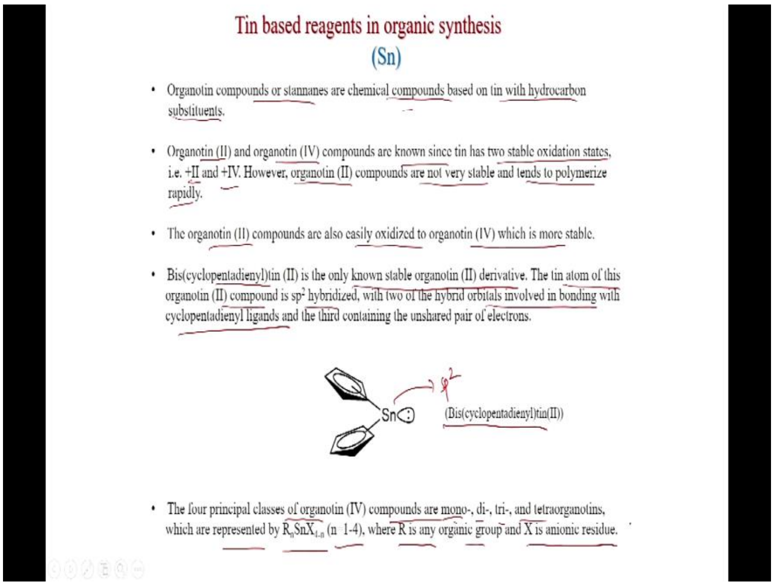
- Tetraorganotins
- Tri-, di- and monoorganotins
- Organotin halides
- Organotin hydrides

❑ Reactions of Organotins:

- Stille Reaction
- Reactions of Tributyltinhydride

So first we will discuss the tin based reagents in organic synthesis. First we will see synthesis of Organotins, Tetraorganotins, Tri-, di- and monoorganotins, Organotin halides also then Organotin hydrides which are useful hydride agents, reactions of Organotins, Stille reactions that is the coupling reactions we discussed and reactions of Tributyltinhydride we will discuss.

(Refer Slide Time: 1:38)



Tin based reagents in organic synthesis

(Sn)

- Organotin compounds or stannanes are chemical compounds based on tin with hydrocarbon substituents.
- Organotin (II) and organotin (IV) compounds are known since tin has two stable oxidation states, i.e. +II and +IV. However, organotin (II) compounds are not very stable and tends to polymerize rapidly.
- The organotin (II) compounds are also easily oxidized to organotin (IV) which is more stable.
- Bis(cyclopentadienyl)tin (II) is the only known stable organotin (II) derivative. The tin atom of this organotin (II) compound is sp^2 hybridized, with two of the hybrid orbitals involved in bonding with cyclopentadienyl ligands and the third containing the unshared pair of electrons.

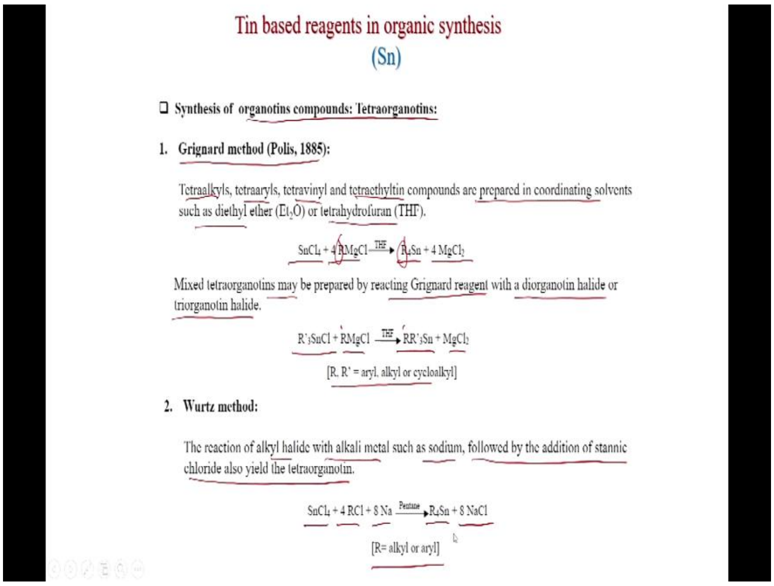
(Bis(cyclopentadienyl)tin(II))

- The four principal classes of organotin (IV) compounds are mono-, di-, tri-, and tetraorganotins, which are represented by R_nSnX_{4-n} (n 1-4), where R is any organic group and X is anionic residue.

So Organotin compounds or stannanes are chemical compounds based on tin with hydrocarbon substituents this is the Organotin compounds. And Organotin plus two and plus four compounds are known since tin has two stable oxidation states that is plus two and plus four. However organotin (II) compounds are not very stable and tends to polymerize rapidly. So organotin (IV) is the most stable and organotin two convert to organotin four. The organotin compounds are also easily oxidized to organotin which is more stable.

Bis(cyclopentadienyle)tin two is the only known stable organotin derivative. The tin atom of this organotin compound is sp 2 hybridized so this is the structure, with two of the hybrid orbitals involved in bonding with cyclopentadienyle ligands. So this is sp 2 hybridized and two sp 2 are engaged in this bonding and another sp 2 accommodate this lone pair . So this is the structure of bis(cyclopentadienyle)tin two and the four principle classes of organotin four compounds are mono, di-, tri-, and Tetraorganotins which are represented by RnSnX(4 -n), n is equal to 1 to 4 where R is any organic group and X is anionic residue like halide.

(Refer Slide Time: 3:05)



Tin based reagents in organic synthesis

(Sn)

❑ **Synthesis of organotins compounds: Tetraorganotins:**

1. **Grignard method (Polis, 1885):**

Tetraalkyls, tetraaryls, tetravinyl and tetraethyltin compounds are prepared in coordinating solvents such as diethyl ether (Et_2O) or tetrahydrofuran (THF).

$$SnCl_4 + 4\,RMgCl \xrightarrow{THF} R_4Sn + 4\,MgCl_2$$

Mixed tetraorganotins may be prepared by reacting Grignard reagent with a diorganotin halide or triorganotin halide.

$$R'_3SnCl + RMgCl \xrightarrow{THF} RR'_3Sn + MgCl_2$$

[R, R' = aryl, alkyl or cycloalkyl]

2. **Wurtz method:**

The reaction of alkyl halide with alkali metal such as sodium, followed by the addition of stannic chloride also yield the tetraorganotin.

$$SnCl_4 + 4\,RCl + 8\,Na \xrightarrow{Pentane} R_4Sn + 8\,NaCl$$

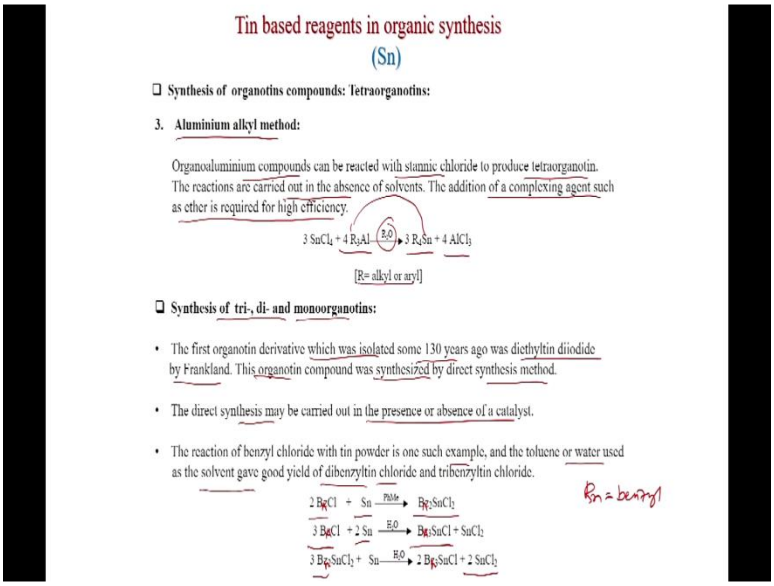
[R= alkyl or aryl]

So first we will discuss synthesis of organotin compounds and Tetraorganotins. The first report is Grignard method which is reported by Polis in 1885, so tetraalkyls, tetraaryls, tetravinyl and tetraethyltin compounds are prepared in coordinating solvents such as diethyl ether or tetrahydrofuran. Like here tetrachlorotin is there with Grignard reagent and this compound is formed tetraalkyl tin and you can see this R is coming here so four R groups have come and four molecule of Mg Cl 2 is produced.

Mixed tetraorganotins may be prepared by reacting Grignard reagent with a diorganotin halide or triorganotin halide, so mixed also is possible by this method. So what you have to start with is this one, instead of Sn Cl 4 you have to start with R dash three S n Cl plus R M g Cl one equivalent of Grignard and this R comes to here and Mg Cl is the byproduct. So R R dash can be aryl, alkyl or cycloalkyl.

Wurtz method, the reaction of alkyl halide with alkali metals such as sodium so instead of Grignard you can directly use alkali halide and that is the Wurtz method such as sodium, followed by the addition of stannic chloride also yield the tetraorganotins. So this is the equation you can see S n Cl 4, 4 R Cl, 8 sodium in pentane it produce tetraalkyl tin and eight molecule of sodium chloride is produced. So R is equal to alkyl or aryl.

(Refer Slide Time: 4:47)



Tin based reagents in organic synthesis

(Sn)

❑ **Synthesis of organotins compounds: Tetraorganotins:**

3. **Aluminium alkyl method:**

Organoaluminium compounds can be reacted with stannic chloride to produce tetraorganotin. The reactions are carried out in the absence of solvents. The addition of a complexing agent such as ether is required for high efficiency.

$$3\,SnCl_4 + 4\,R_3Al \xrightarrow{\boxed{R_2O}} 3\,R_4Sn + 4\,AlCl_3$$

[R= alkyl or aryl]

❑ **Synthesis of tri-, di- and monoorganotins:**

- The first organotin derivative which was isolated some 130 years ago was diethyltin diiodide by Frankland. This organotin compound was synthesized by direct synthesis method.
- The direct synthesis may be carried out in the presence or absence of a catalyst.
- The reaction of benzyl chloride with tin powder is one such example, and the toluene or water used as the solvent gave good yield of dibenzyltin chloride and tribenzyltin chloride.

$$2\,BzCl + Sn \xrightarrow{PhMe} Bz_2SnCl_2$$
$$3\,BzCl + 2\,Sn \xrightarrow{H_2O} Bz_3SnCl + SnCl_2$$
$$3\,Bz_2SnCl_2 + Sn \xrightarrow{H_2O} 2\,Bz_3SnCl + 2\,SnCl_2$$

Bn = benzyl

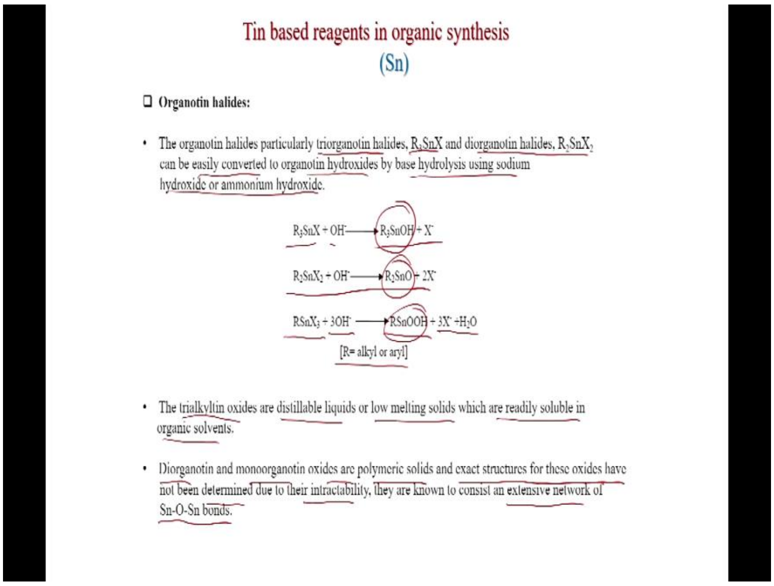
Some more methods are there Aluminium alkyl methods is there so organoaluminium compounds can be reacted with stannic chloride to produce tetraorganotin. The reactions are carried out in the absence of solvents. The addition of a complexing agent such as ether is required for high efficiency. Here ether is the solvent and this is the organoaluminium so this R then goes to the tin so you can see that tetraalkyl tin is produced and this R coming from the aluminium and four equivalent of aluminium chloride is produced. Here also R will be alkyl aryl.

Synthesis of tri-, di- and monoorganotins can be synthesized so the first organotin derivative which was isolated some 130 years ago was diethyltin diiodide by Frankland. This organotin compound was synthesized by direct synthesis method that we will see. The direct synthesis may be carried out in the presence or absence of a catalyst.

So the reaction of benzyl chloride with tin powder is one such example and the toluene or water used as the solvent gave good yield of dibenzyltin chloride so this is the dibenzyltin chloride also you can get tribenzyl also if you use three equivalent of benzyl chloride and two equivalent of tin then this benzyl three SnCl plus SnCl2 will be produced and this will be actually I think Bn, Bn is equal to benzyl. And three equivalent of Bn two Sn Cl 2 will produce two equivalent of Bn 3 SnCl plus 2 SnCl 2.

So tri-, di- and monoorganotins can be produced by this method.

(Refer Slide Time: 6:51)



Tin based reagents in organic synthesis

(Sn)

❑ **Organotin halides:**

- The organotin halides particularly triorganotin halides, R_3SnX and diorganotin halides, R_2SnX_2 can be easily converted to organotin hydroxides by base hydrolysis using sodium hydroxide or ammonium hydroxide.

$$R_3SnX + OH^- \longrightarrow R_3SnOH + X^-$$

$$R_2SnX_2 + OH^- \longrightarrow R_2SnO + 2X^-$$

$$RSnX_3 + 3OH^- \longrightarrow RSnOOH + 3X^- + H_2O$$

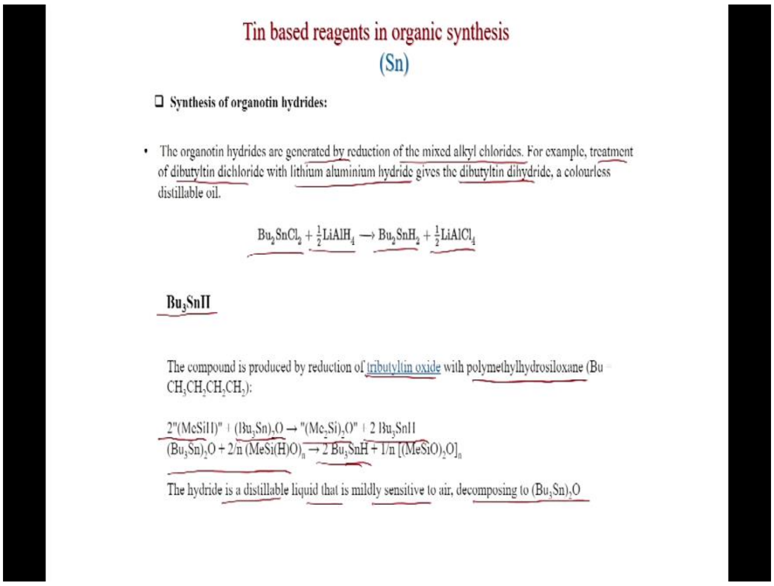
[R= alkyl or aryl]

- The trialkyltin oxides are distillable liquids or low melting solids which are readily soluble in organic solvents.
- Diorganotin and monoorganotin oxides are polymeric solids and exact structures for these oxides have not been determined due to their intractability, they are known to consist an extensive network of Sn-O-Sn bonds.

Now organotin halides, the organotin halides particularly triorganotin halides , R3 Sn X and diorganotin halides R2 Sn X 2 can be easily converted to organotin hydroxides by base hydrolysis using sodium hydroxide or ammonium hydroxide. So these are examples you can see these halides if we treated with hydroxides then the oxide or hydroxide are produced like hydroxide you get this displacement reaction X is displaced by hydroxide. Here also the oxide is forming here two equivalent of X minus is liberated when R Sn X 3 is used and three equivalent of hydroxide then tin peroxide plus 3 X minus plus H 2 O.

Here also R can be alkyl or aryl. The trialkyltin oxides are distillable liquids or low melting solids which are readily soluble in organic solvents. Di-organotin and mono-organotin oxides are polymeric solids and exact structures for these oxides have not been determined due to their intractability. So trialkyltin oxide this one is distillable liquids or low melting solids but other one diorganotin and mono-organotin are polymeric solids and exacts structures for these oxides have not been determined. They are known to consist an extensive network of Sn-O- Sn bonds.

(Refer Slide Time: 8:29)



Tin based reagents in organic synthesis

(Sn)

☐ **Synthesis of organotin hydrides:**

- The organotin hydrides are generated by reduction of the mixed alkyl chlorides. For example, treatment of dibutyltin dichloride with lithium aluminium hydride gives the dibutyltin dihydride, a colourless distillable oil.

$$Bu_2SnCl_2 + \frac{1}{2}LiAlH_4 \longrightarrow Bu_2SnH_2 + \frac{1}{2}LiAlCl_4$$

Bu_3SnH

The compound is produced by reduction of tributyltin oxide with polymethylhydrosiloxane (Bu = $CH_3CH_2CH_2CH_2$):

$2"(MeSiH)" + (Bu_3Sn)_2O \rightarrow "(Me_2Si)_2O" + 2\ Bu_3SnH$

$(Bu_3Sn)_2O + 2/n\ (MeSi(H)O)_n \rightarrow 2\ Bu_3SnH + 1/n\ [(MeSiO)_2O]_n$

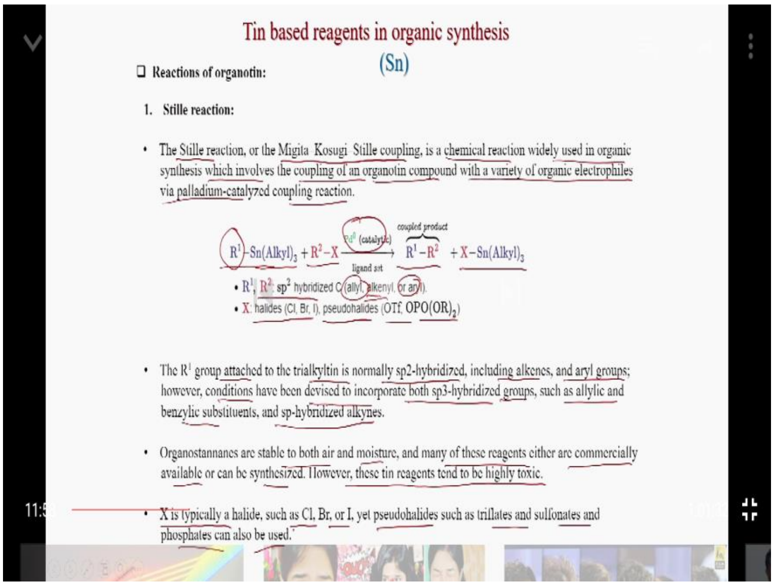
The hydride is a distillable liquid that is mildly sensitive to air, decomposing to $(Bu_3Sn)_2O$

Now we will see the hydride the organotin hydrides, organotin hydrides are generated by reduction of the mixed alkyl chlorides. For example treatment of dibutyltin dichloride with lithium aluminium hydride gives the dibutyltin dihydride, so you can see this is the colorless oil. So this is the reaction dibutyltin chloride with half equivalent lithium aluminium hydride which generates this dibutyltin dihydride and this is the byproduct.

Now this is very popular we know that dibutyltin hydride but this is produced in different method, this was produced by reduction of tributyltin oxide with polymethylhydrosiloxane. So this is the equation this is the hydrosiloxane and this is the tributyltin oxide then this is produced byproduct and this is the tributyltin hydride. Also this can be another equation you can shift oxide and this one n Bu 3 Sn H this is the tributyltin hydride which is produced. And the hydride is the distillable liquid that is mildly sensitive to air decomposing to the oxide tributyltin oxide.

So this is important that we have to store in an air-free condition so if it is coming in the air then its hydride can be oxidized to oxide.

(Refer Slide Time: 9:55)



Tin based reagents in organic synthesis

(Sn)

❑ **Reactions of organotin:**

1. **Stille reaction:**

- The Stille reaction, or the Migita Kosugi Stille coupling, is a chemical reaction widely used in organic synthesis which involves the coupling of an organotin compound with a variety of organic electrophiles via palladium-catalyzed coupling reaction.

$$R^1\text{-}Sn(Alkyl)_3 + R^2\text{-}X \xrightarrow[\text{ligand set}]{Pd^0\ (\text{catalytic})} \overbrace{R^1\text{-}R^2}^{\text{coupled product}} + X\text{-}Sn(Alkyl)_3$$

  - R^1, R^2: sp^2 hybridized C (allyl, alkenyl, or aryl).
  - X: halides (Cl, Br, I), pseudohalides (OTf, $OPO(OR)_2$)

- The R^1 group attached to the trialkyltin is normally sp2-hybridized, including alkenes, and aryl groups; however, conditions have been devised to incorporate both sp3-hybridized groups, such as allylic and benzylic substituents, and sp-hybridized alkynes.

- Organostannanes are stable to both air and moisture, and many of these reagents either are commercially available or can be synthesized. However, these tin reagents tend to be highly toxic.

- X is typically a halide, such as Cl, Br, or I, yet pseudohalides such as triflates and sulfonates and phosphates can also be used.

Now we will discuss reactions of organotins, so first we will discuss Stille reaction. So stille reaction or the Migita Kosugi Stille coupling is a chemical reaction widely used in organic synthesis which involves the coupling of an organotin compound with a variety of organic electrophiles via palladium-catalyzed coupling reaction. So this is palladium-catalyzed reaction as you can see here and these are the reactants so a tin compound R^1 will be actually the coupled and these are the tin components tin alkyl whole three plus R 2 X. So R 2 can be generally sp2 hybridized like, aryl or alkenyl but later we will see the allyls can also be used allyls and alkenyls also.

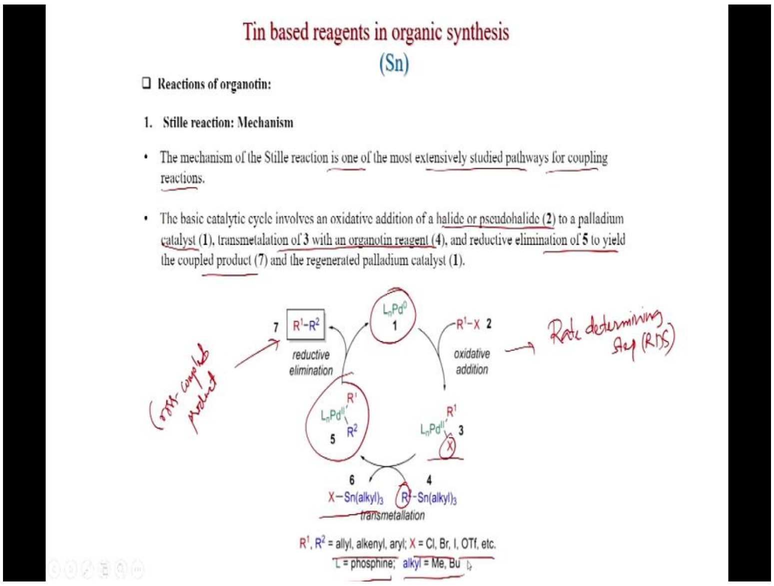
And this is the coupled product and this is the byproduct X Sn alkyl whole 3. X are halides chlorides, bromine or iodine also pseudohalides OTf, OPO(OR)2, so these are the X component.

The R 1 group attached to the trialkyltin is normally Sp2- hybridized as we have said earlier including alkenes and aryl groups. However conditions have been devised to incorporate both Sp3-hybridized groups such as allylic and benzylic substituents and Sp-hybridized alkynes.

Organostannanes are stable to both air and moisture and many of these reagents either are commercially available or can be synthesized. However these tin reagents tend to be highly toxic so they are highly toxic tin reagents and you have to handle carefully.

X is typically halide such as Cl, Br or I yet pseudohalides such as triflates and sulfonates and phosphates can also be used.

(Refer Slide Time: 12:01)



Tin based reagents in organic synthesis
(Sn)

☐ **Reactions of organotin:**

1. **Stille reaction: Mechanism**

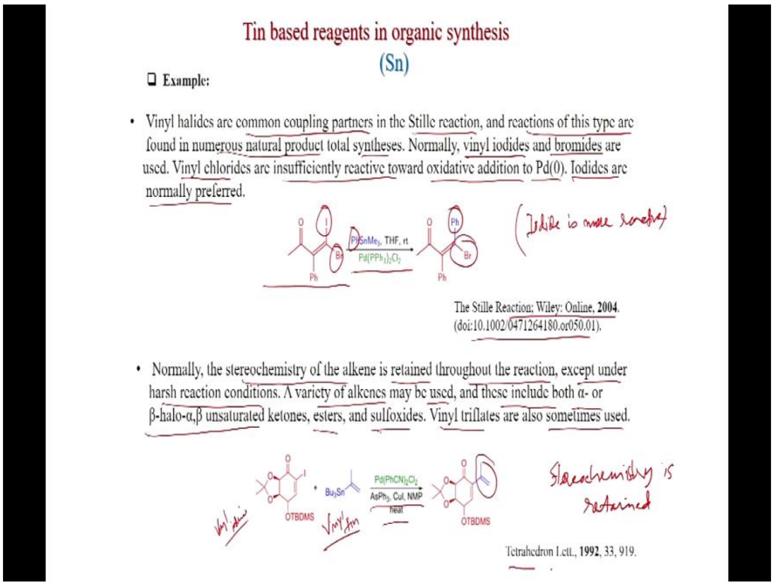
- The mechanism of the Stille reaction is one of the most extensively studied pathways for coupling reactions.
- The basic catalytic cycle involves an oxidative addition of a halide or pseudohalide (**2**) to a palladium catalyst (**1**), transmetalation of **3** with an organotin reagent (**4**), and reductive elimination of **5** to yield the coupled product (**7**) and the regenerated palladium catalyst (**1**).

R^1, R^2 = allyl, alkenyl, aryl; X = Cl, Br, I, OTf, etc.
L = phosphine; alkyl = Me, Bu

So what is the mechanism? The mechanism of the Stille reaction is one of the extensively studied pathways for coupling reactions. The basic catalytic cycle involves an oxidative addition of a halide or pseudo halide palladium catalyst. So this like other coupling reactions this oxidative addition happens here and this is the rate determined step RDS the oxidative addition will happen first and this intermediate will form and now the transmetalation of 3 with an organotin reagent will happen and so this step is important.

The R 2 is coming from the tin and this X will be displaced by the R 2 and X Sn alkyl 3 is formed and R 2 adds to the palladium and organotin reagent is formed and reductive elimination of 5 to yield the coupled product so this we know in other coupling reactions also this intermediate is formed and after the reductive elimination the cross coupled product, so this is the cross coupled product is formed and this is the catalyst which is generated again. So R 1, R 2, allyl, alkenyl, aryl, X is equal to Chlorine, Bromine, Iodine, OTf et cetera. L is equal to phosphate ligands alkyl is equal to methyl butyl.

(Refer Slide Time: 13:49)



Tin based reagents in organic synthesis
(Sn)

❑ **Example:**

- Vinyl halides are common coupling partners in the Stille reaction, and reactions of this type are found in numerous natural product total syntheses. Normally, vinyl iodides and bromides are used. Vinyl chlorides are insufficiently reactive toward oxidative addition to Pd(0). Iodides are normally preferred.

(Iodide is more reactive)

The Stille Reaction; Wiley: Online, **2004**. (doi:10.1002/0471264180.or050.01).

- Normally, the stereochemistry of the alkene is retained throughout the reaction, except under harsh reaction conditions. A variety of alkenes may be used, and these include both α- or β-halo-α,β unsaturated ketones, esters, and sulfoxides. Vinyl triflates are also sometimes used.

Stereochemistry is retained

Tetrahedron Lett., **1992**, 33, 919.

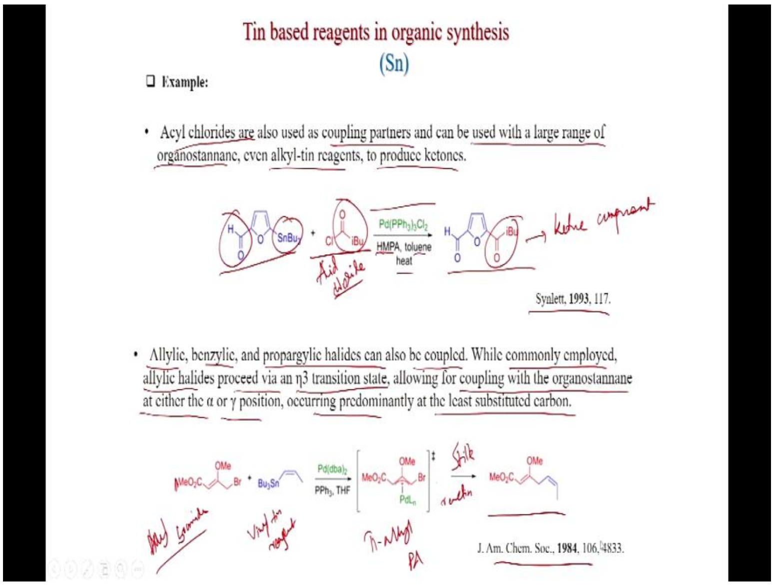
Now examples so in general the Vinyl halides are common coupling partners in the Stille reaction and reactions of this type are found in numerous natural product total synthesis. Normally vinyl iodides and bromides are used. Vinyl chlorides are insufficiently reactive towards oxidative addition to palladium 0. Iodides are normally preferred. So this is important when you chose the vinyl halide you have to choose either the iodide or the bromide because vinyl chlorides are less reactive.

Like here if you see this enone with iodide and bromide is there and with this Stille reagent and Pd(PPh3)2Cl 2 the Stille reaction happens with only iodide because here iodide is more reactive so this is important. And this Br bond is untouched so Stille coupling happens and this vinyl migrated to here. This is the review Stille Reaction, Wiley: online, 2004.

And also the stereochemistry of alkene is retained throughout the reaction except under harsh reaction conditions. A variety of alkenes may be used and this includes both alpha and beta-halo-alpha, beta unsaturated ketones, esters and sulfoxides. Vinyl triflates are also sometimes used.

So the stereochemistry is important, if you see this vinyl iodide so this is vinyl iodide and this is vinyl tin reagent and with this palladium catalyst Pd Ph CN whole 2 Cl 2 and these are the other co-catalysts and additives and then you get the Stille reaction. So if you see this double bond geometry this is intact, so you get this product. So stereochemistry is retained so this is very important, in the stereochemistry the reaction will be retained, if you have a particular stereochemistry of the alkene iodide or the tin that the stereochemistry will be intact. This was published in Tetrahedron Letters.

(Refer Slide Time: 16:26)



Tin based reagents in organic synthesis
(Sn)

☐ **Example:**

- Acyl chlorides are also used as coupling partners and can be used with a large range of organostannane, even alkyl-tin reagents, to produce ketones.

Synlett, **1993**, 117.

- Allylic, benzylic, and propargylic halides can also be coupled. While commonly employed, allylic halides proceed via an η3 transition state, allowing for coupling with the organostannane at either the α or γ position, occurring predominantly at the least substituted carbon.

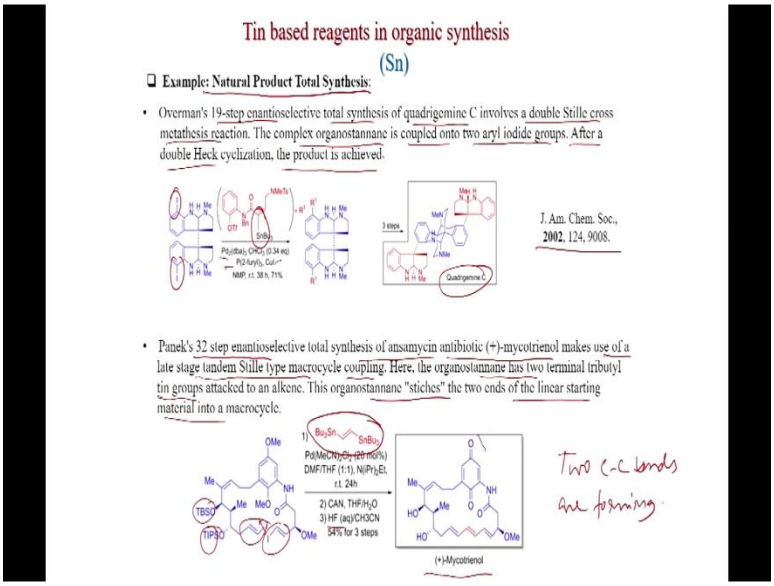
J. Am. Chem. Soc., **1984**, 106, 4833.

Some more examples, Acyl chlorides are also used as coupling partners and can be used with a large range of organostannane, even alkyl-tin reagents to produce ketones. So this is an efficient method to generate ketones from acyl chloride. You can see this is the acyl chloride, acid chloride and this is the tin compound where the furan motif also aldehyde motif is there. And when you mix them with this catalyst and HMPA, toluene heat you get this product this is the ketone. You can see this is the ketone component which is generated. So ketone component will be coming from the acid chloride, so Sn Bu3 is displaced by this group. This was published by Synlett in 1993.

So allylic, benzylic and propargylic halides can also be coupled. While commonly employed, allylic halides proceed via eta 3 transitional state allowing for coupling with the organostannane as either the alpha or gamma position, occurring predominantly at the least substituted carbon.

So if you see this is the allyl bromide and this is the vinyl tin reagent and when you mix them with palladium first this palladium will form π-allyl palladium, these are important intermediates in palladium chemistry. π-Allyl palladium will form because this is allylic bromide and then the Stille reaction will happen so this is the Stille reaction and this is very important the least substituted carbon, so the Stille reaction will happen at the least substituted carbon. You can see this carbon is substituted but this one is unsubstituted so here the reaction will happen and the olefin geometry will be irritant. This was published in Jacks 1984.

(Refer Slide Time: 18:40)



Tin based reagents in organic synthesis

(Sn)

☐ **Example: Natural Product Total Synthesis:**

- Overman's 19-step enantioselective total synthesis of quadrigemine C involves a double Stille cross metathesis reaction. The complex organostannane is coupled onto two aryl iodide groups. After a double Heck cyclization, the product is achieved.

J. Am. Chem. Soc., **2002**, 124, 9008.

- Panek's 32 step enantioselective total synthesis of ansamycin antibiotic (+)-mycotrienol makes use of a late stage tandem Stille type macrocycle coupling. Here, the organostannane has two terminal tributyl tin groups attacked to an alkene. This organostannane "stiches" the two ends of the linear starting material into a macrocycle.

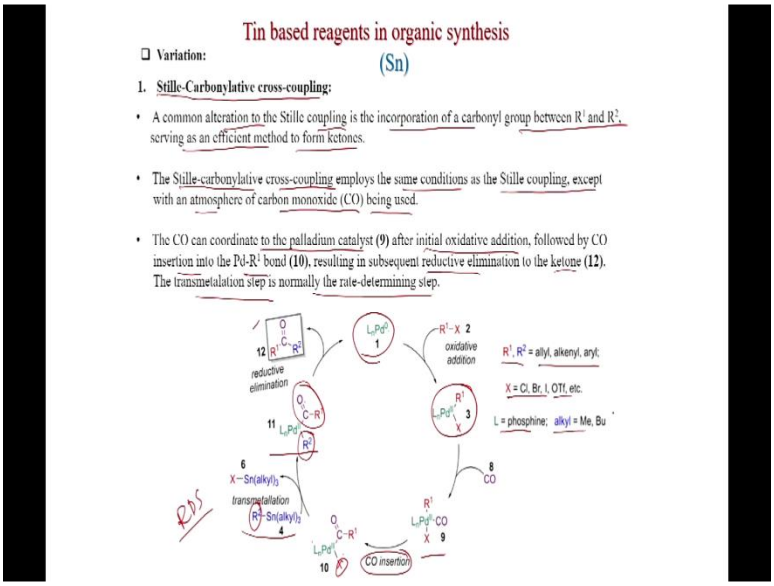
Two C-C bonds are forming.

Now we will see some examples of the Stille reactions in the natural product synthesis because stille reaction is a powerful cross coupling reaction and has been applied in many natural product synthesis. So Overman’s 19-step enantioselective total synthesis of quadrigemine C involves a double Stille cross metathesis reaction. The complex organostannane is coupled onto two aryl iodide groups. After a double Heck cyclization, the product is achieved.

Like this one you can see two iodide motifs is present here and this is the tin attached to the double bond so what happens this R 1 is this the stille reaction happens with this catalyst this is a ligand co-catalyst and after three steps you can get this natural product. So these are some process is there and after double heck cyclizations the product will be formed and this was published in Jacks, 2002.

Also Panek group reported a 32- step enantioselective total synthesis of ansamycin antibiotic mycotrienole makes use of a tandem Stille type macrocycle coupling. Here the organostannane has two terminal tributyl tin groups attacked to an alkene. So organostannane so you can see this is the structure of organostannane, two terminal tributyl tin groups are present here and this organostannane stitches the two ends of the linear starting material So this is the linear starting material and here two vinyl iodide groups are present so iodide here and you get this product. So this is the trans-geometric it is retained because vinyl iodides are trans and with this after some CAN oxidation and HF that is the TIPS group TIPS group deprotection you get this natural product Mycotrienol. So this is very important the two C-C bonds are forming in a single reaction because two tin components are there so two C-C bonds are forming. This was published in Jacks, 1998.

(Refer Slide Time: 21:03)



Tin based reagents in organic synthesis

(Sn)

❑ Variation:

1. Stille-Carbonylative cross-coupling:

- A common alteration to the Stille coupling is the incorporation of a carbonyl group between R^1 and R^2, serving as an efficient method to form ketones.
- The Stille-carbonylative cross-coupling employs the same conditions as the Stille coupling, except with an atmosphere of carbon monoxide (CO) being used.
- The CO can coordinate to the palladium catalyst (**9**) after initial oxidative addition, followed by CO insertion into the Pd-R^1 bond (**10**), resulting in subsequent reductive elimination to the ketone (**12**). The transmetalation step is normally the rate-determining step.

R^1, R^2 = allyl, alkenyl, aryl;

X = Cl, Br, I, OTf, etc.

L = phosphine; alkyl = Me, Bu

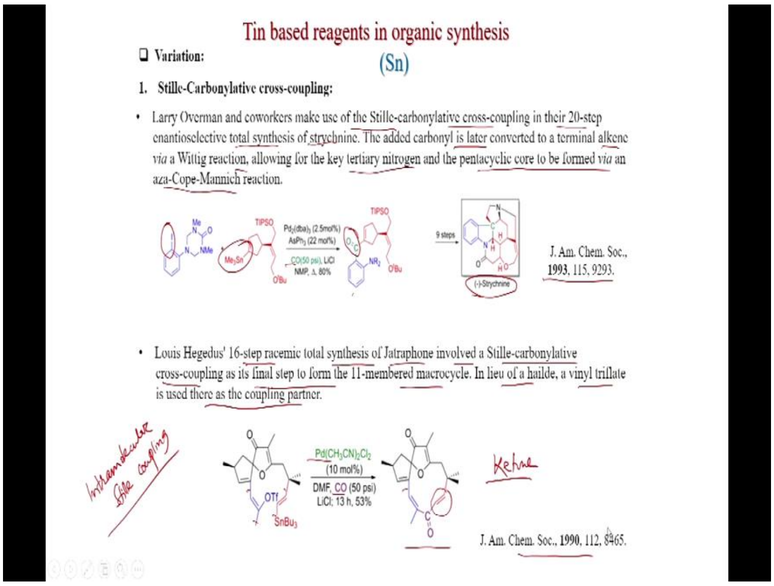
Some more variations are there, Stille Carbonylative cross-coupling. So we have seen the synthesis of ketones from acid chloride now we will see the synthesis of ketones from carbon monoxide. A common alteration to the Stille coupling is the incorporation of a carbonyl group between R 1 and R 2 serving as an efficient method to form ketones.

The Stille Carbonylative cross-coupling employs the same conditions as the Stille coupling, except with an atmosphere of carbon monoxide being used. So the carbonyl group is coming from the carbon monoxide here. And the carbon monoxide can coordinate to the palladium catalyst after initial oxidative addition. So this is the mechanism actually, so oxidative addition will happen as usual and now at this stage the carbon monoxide will add so the carbon monoxide is added to the oxidative addition complex and here also another oxidative addition followed by carbon monoxide insertion into the palladium R bond, so this will complex will form and then the insertion will happen.

So this is the insertion this is a very important step carbon monoxide insertion into the palladium and R 1. After that transmetalation will happen with this tin compound so X will be displaced by the R 2 and this intermediate will form and palladium is attached to R 2 and CO R 1, this is the main intermediate here and after reductive elimination you get this ketone and the catalyst ligand is regenerated. The transmetalation step is normally the rate determining step. So here this is the rate determining step, transmetalation step.

So you can see palladium R is from here this resulting in subsequent reductive elimination to the ketone. And R 1, R 2 is allyl, alkenyl, aryl. X is equal to Cl, Br, I, OTf. L is equal to phosphine, alkyl is equal to methyl butyl.

(Refer Slide Time: 23:15)



Tin based reagents in organic synthesis

(Sn)

❑ Variation:

1. **Stille-Carbonylative cross-coupling:**

- Larry Overman and coworkers make use of the Stille-carbonylative cross-coupling in their 20-step enantioselective total synthesis of strychnine. The added carbonyl is later converted to a terminal alkene *via* a Wittig reaction, allowing for the key tertiary nitrogen and the pentacyclic core to be formed *via* an aza-Cope-Mannich reaction.

J. Am. Chem. Soc., **1993**, 115, 9293.

- Louis Hegedus' 16-step racemic total synthesis of Jatraphone involved a Stille-carbonylative cross-coupling as its final step to form the 11-membered macrocycle. In lieu of a hailde, a vinyl triflate is used there as the coupling partner.

J. Am. Chem. Soc., **1990**, 112, 8465.

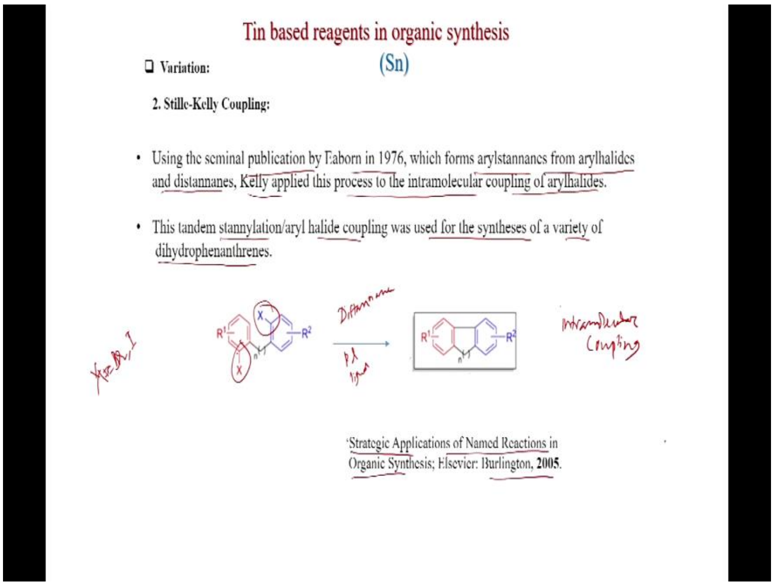
So Stille Carbonylative cross coupling, now we will see some examples. Larry Overman and coworkers make use of the Stille-carbonylative cross-coupling in their 20-step enantioselective total synthesis of strychnine. So this is the carbonylative stille cross-coupling so this is the vinyl aryl iodide and this is the vinyl tin and this carbonyl group is coming from the carbon monoxide and you can see this is the reaction is happening. And the added carbonyl is later converted to a terminal alkene via a Wittig reaction, allowing for the key tertiary nitrogen and the pentacyclic core to be formed via an aza-Cope Mannich reaction.

So this is the final product but this reaction is very important because this is the carbonyl group is formed via carbonyl group is attached to an aryl and a vinyl component. So this intermediate is formed as stille reaction and this work was published in Jacks, 1993.

Lewis Hegedus' 16-step racemic total synthesis of Jatraphone involved a Stille-carbonylative cross-coupling as its final step to form the 11-membered macrocycle. In lieu of a halide, a vinyl triflate is used there as the coupling partner. So this is important so this is intra-molecular Stille coupling because you vinyl triflate or vinyl tin, both are in the same compound. And now also they have particular geometry you can see here that this is the trans these two groups and this is also trans and this carbon monoxide is used here and with palladium catalyst DMF you get this ketone.

And this geometry is intact so this is also trans and this is also trans so geometry is important that the it is retained and carbon monoxide is inserted so ketone is formed. This is very important reaction and was published in Jacks, 1990.

(Refer Slide Time: 25:33)



Tin based reagents in organic synthesis

(Sn)

❑ Variation:

2. Stille-Kelly Coupling:

- Using the seminal publication by Eaborn in 1976, which forms arylstannanes from arylhalides and distannanes, Kelly applied this process to the intramolecular coupling of arylhalides.
- This tandem stannylation/aryl halide coupling was used for the syntheses of a variety of dihydrophenanthrenes.

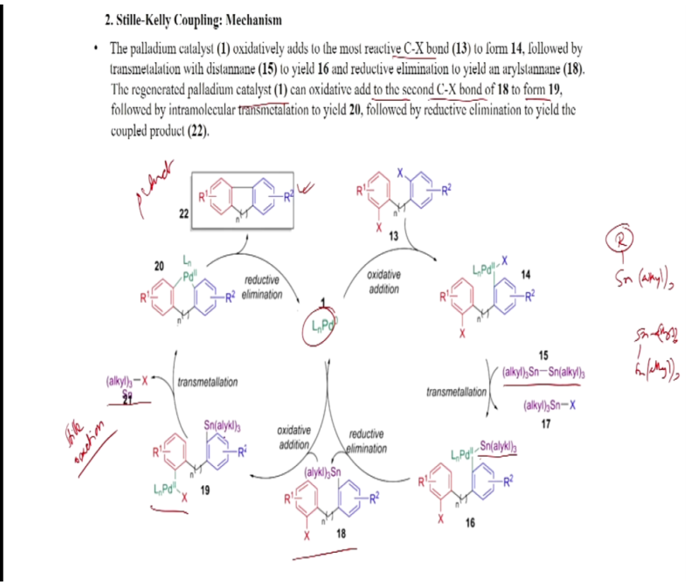
'Strategic Applications of Named Reactions in Organic Synthesis; Elsevier: Burlington, **2005**.

Now we will discuss another reaction Stille-Kelly coupling reaction. So in this reaction we will see that dibromide is converted into a cyclic product. So using the seminal publication by Eaborn in 1976, which forms arylstannanes from arylhalides and the distannanes. So this is important the distannanes and arylhalides will generate arylstannanes and Kelly applied this process to the intramolecular coupling of arylhalides, so this is also intramolecular reactions.

This tandem stannylation aryl halide coupling was used for the syntheses of a variety of dihydrophenanthrenes.

So this is the reaction you can see two halides are there, generally X is equal to bromine, iodine et cetera and if you put this distannane and palladium ligand et cetera then you get this cyclization. So intramolecular coupling you can say this carbon and added to this carbon, so intramolecular coupling. So this reaction was reviewed in this book Strategic Applications of Named Reactions in Organic Synthesis, 2005.

(Refer Slide Time: 27:03)



2. Stille-Kelly Coupling: Mechanism

- The palladium catalyst (**1**) oxidatively adds to the most reactive C-X bond (**13**) to form **14**, followed by transmetalation with distannane (**15**) to yield **16** and reductive elimination to yield an arylstannane (**18**). The regenerated palladium catalyst (**1**) can oxidative add to the second C-X bond of **18** to form **19**, followed by intramolecular transmetalation to yield **20**, followed by reductive elimination to yield the coupled product (**22**).

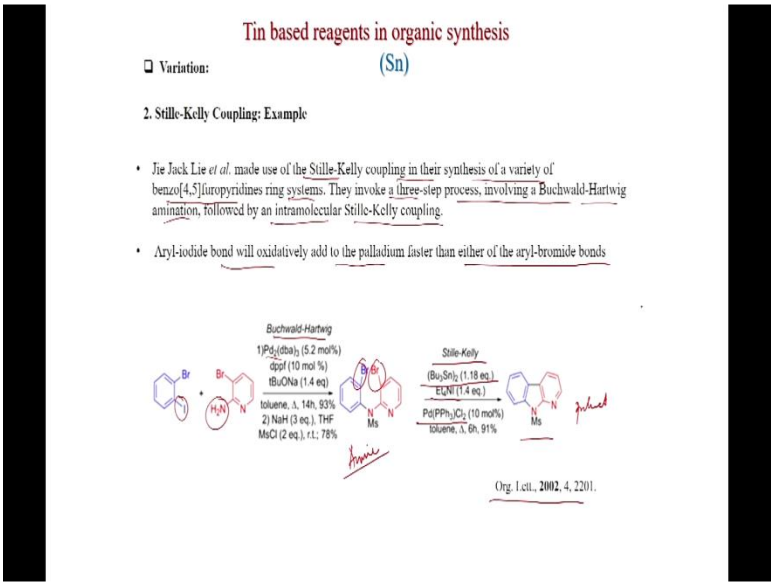
Now we will see the mechanism? What is happening here the palladium catalyst oxidatively adds to the most reactive C-X bond like this to most reactive one to form 14, so this is the 14 that is the oxidative addition, followed by transmetalation with distannane. So this is the important reaction that transmetalation will happen and you get this X is displaced by this tin alkyl whole three.

So earlier we have seen the tin alkyl whole three and vinyl which was group was transferred but here Sn alkyl whole three and Sn alkyl whole three is used. So what happened? One, this Sn alkyl three is migrated to palladium and now the reductive elimination will happen from this one to generate 18, so here what happened, the aryl tin component is generated. Now this palladium will be generated again and this palladium will do the oxidative addition to generate this one 19.

So the regenerated palladium oxidatively add to second C-X bond of 18 to form 19 and followed by transmetalation you get this transmetalation you get this palladium comes to this. Actually this is the Stille reaction is happening here this is the Stille reaction because we have the tin component and you have the oxidative palladium component so the Stille reaction happens and you get this intermediate followed by this reductive elimination you get this compound, this the product.

And catalysis is generated, this step is very important that distannane is used and distannane is generating this tin component aryl Stille component then this is reacting with aryl halide with palladium catalyst.

(Refer Slide Time: 29:19)



Tin based reagents in organic synthesis

(Sn)

❑ **Variation:**

2. Stille-Kelly Coupling: Example

- Jie Jack Lie *et al.* made use of the Stille-Kelly coupling in their synthesis of a variety of benzo[4,5]furopyridines ring systems. They invoke a three-step process, involving a Buchwald-Hartwig amination, followed by an intramolecular Stille-Kelly coupling.
- Aryl-iodide bond will oxidatively add to the palladium faster than either of the aryl-bromide bonds

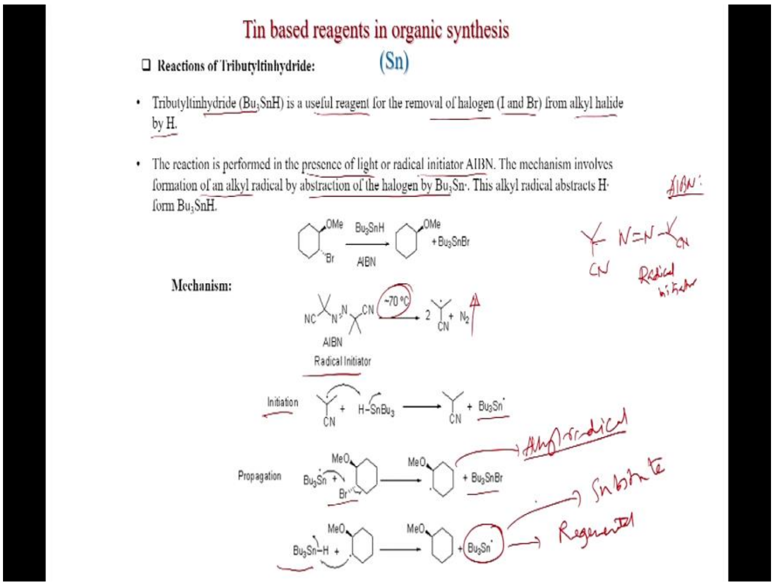
Org. Lett., **2002**, 4, 2201.

Some examples Jie Jack Lie et. al. made use of the Stille-Kelly coupling in their synthesis of a variety of benzo four five furopyridines ring systems. They invoke a three-step process involving a Buchwald-Hartwig amination followed by an intramolecular Stille-Kelly coupling

So this is the reaction so first what happened Buchwald-Hartwig coupling happens here with palladium catalyst so this NH2 add to this aryl iodide bond and you get this amine, so amination happens. And then this Stille-Kelly coupling reaction because you can see two aryl bromide is there now distannane you have to add and these are the additives these are the catalysts Pd PPh 2 Cl 2 and then you get this compound, so here they are telling the aryl iodide bond will oxidatively added to the palladium faster than either of the aryl-bromide bonds.

So this selective amination is happening in the aryl iodide so two aryl bromide is formed now here, Stille-Kelly coupling will give this product. This was published in Organic Letters, 2002.

(Refer Slide Time: 30:41)



Tin based reagents in organic synthesis

❑ **Reactions of Tributyltinhydride:** (Sn)

- Tributyltinhydride (Bu_3SnH) is a useful reagent for the removal of halogen (I and Br) from alkyl halide by H.
- The reaction is performed in the presence of light or radical initiator AIBN. The mechanism involves formation of an alkyl radical by abstraction of the halogen by $Bu_3Sn\cdot$. This alkyl radical abstracts H· form Bu_3SnH.

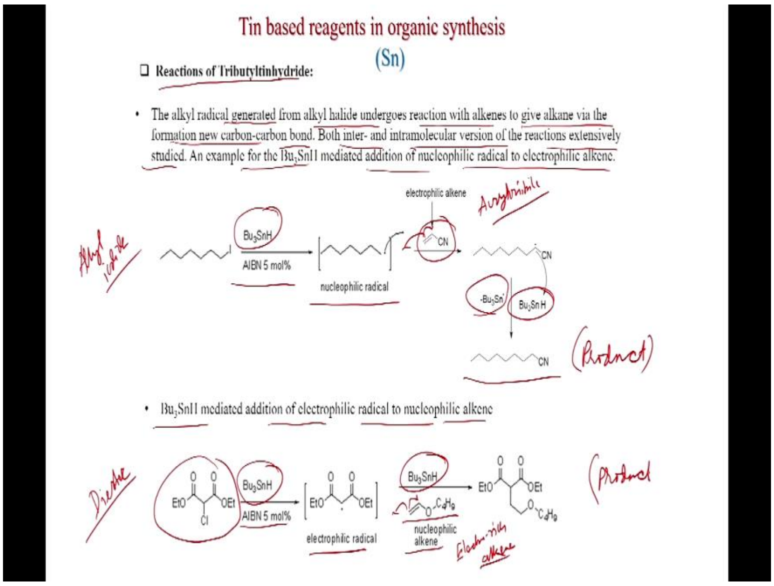
Mechanism:

Now we will discuss tributyltinhydride this is very popular reagent in Radical Chemistry. Tributyltinhydride is a useful reagent for the removal of halogen I and BR from alkyl halide by hydrogen. The reaction is performed in the presence of light or radical initiator AIBN. The mechanism involves formation of an alkyl radical by abstraction of the halogen by Bu 3 Sn dot.

So this is the reaction suppose example this is the alkyl bromide AIBN so this is structure of AIBN. This is the radical initiator this AIBN radical initiator because it generates nitrogen it generates a radical so that is the here. This is the radical initiator and around 70 degree centigrade the nitrogen will be eliminated as gas and this radical will be formed. So this radical is stabilized by cyano group also.

And now the initiation will happen in this radical generates the tributyltin radical. So this is very important. This radical generates the tributyltin radical by this way the hydrogen dot H dot is taken up by this radical. Now Bu 3 Sn dot will react this bromide to generate this alkyl radical. So this is the alkyl radical and Bu 3 Sn Br will form. So this alkyl radical again will react with tributyltinhydride so it will take H dot from tributyltinhydride and this will be regenerated so this is regenerated because this again will react with the substrate. So these are the propagation, so this method is very useful for dehydrohalogenation of aryls, chlorides, bromides or iodides et cetera.

(Refer Slide Time: 32:59)



Tin based reagents in organic synthesis

(Sn)

☐ **Reactions of Tributyltinhydride:**

- The alkyl radical generated from alkyl halide undergoes reaction with alkenes to give alkane via the formation new carbon-carbon bond. Both inter- and intramolecular version of the reactions extensively studied. An example for the Bu_3SnH mediated addition of nucleophilic radical to electrophilic alkene.

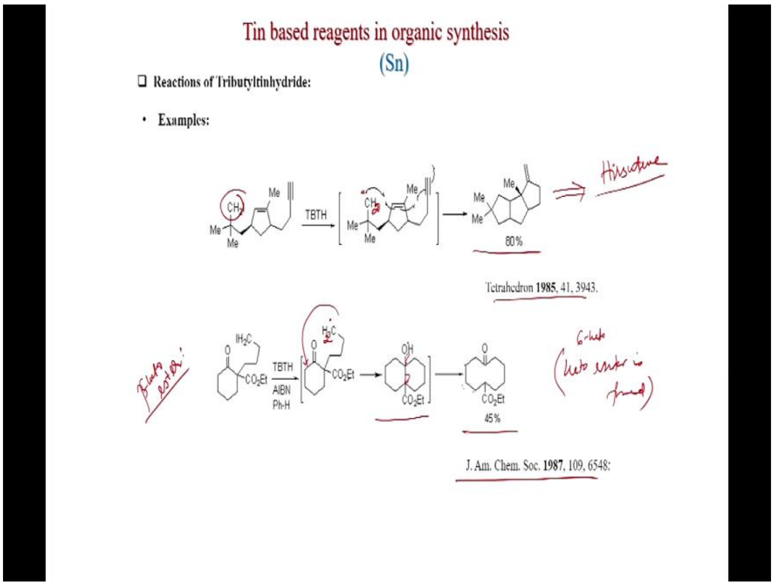
- Bu_3SnH mediated addition of electrophilic radical to nucleophilic alkene

So in the reactions of Tributyl tin hydrides the alkyl radical generated from alkyl halide undergoes reaction with alkenes to give alkane via the formation of new carbon-carbon bond. Both inter- and intra-molecular version of the reactions extensively studies. An example for the Tributyl tin mediated addition of nucleophile radical to electrophilic alkene.

So this is an alkyl iodide and we have seen that with tributyl tin hydride AIBN 5 mol percent you get this radical so this is nucleophilic radical and this is an electrophilic alkene. So this is Acrylonitrile and one electron goes there and there so you get a here and this radical of course stabilize by cyano group and then this radical will react with tributyl tin hydride to generate the neutral compound that is the product. And tributyl tin hydride again will generate so that the cycle will start again.

Also with tributyl tin hydride mediated addition of electrophilic radical to nucleophilic alkene also is possible like this one. This is the diester and with tributyl tin hydride you can add this electrophilic radical AIBN 5 mol percent to generate the electrophilic radical and now if you put a nucleophilic alkene. So this is electron rich alkene, electron rich alkene and here also electron goes like this so you get a radical here and that radical again will react with tributyl tin hydride like earlier you get this product.

(Refer Slide Time: 35:17)



Tin based reagents in organic synthesis

(Sn)

☐ **Reactions of Tributyltinhydride:**

- **Examples:**

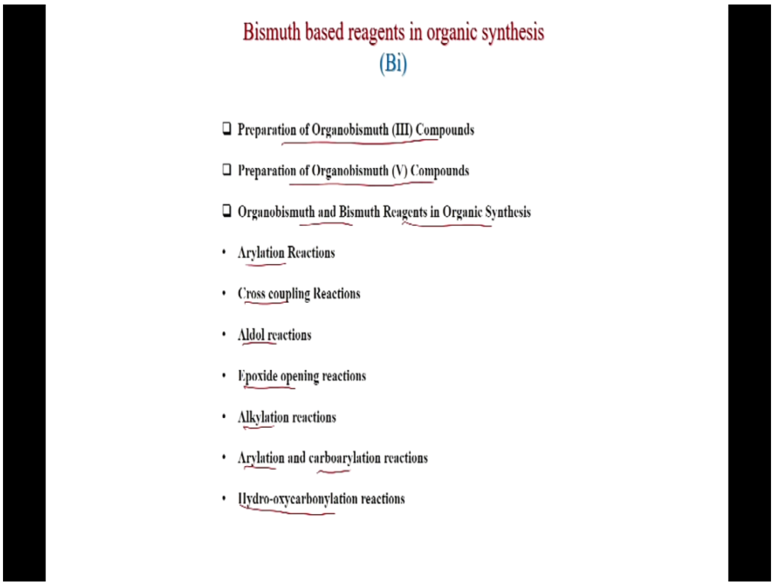
Tetrahedron **1985**, 41, 3943.

J. Am. Chem. Soc. **1987**, 109, 6548:

Examples here the radical which is formed is cyclizing actually so you can see this CH 2 I is generated a, this will be CH 2, a radical here and now this radical will migrate. So this radical will add to this double bond and there another radical will form and that will add to the triple bond. So you get this tricycle compound. These are actually very important because many natural product this motif is here like Hirsutine, Hirsutine compound this structure is present. And this was published in Tetrahedron, 1985.

Also if you have a beta keto ester then again this will be CH 2 and you generate a radical here, that radical will add to the carbonyl group to generate this one product. And this will this bond will break to generate this compound keto ester so keto ester. So 1, 2, 3, 4, 5, 6; 6 keto ester is formed. So this is very important that the radical can do many reactions. This was published in JACS, 1987.

(Refer Slide Time: 36:53)

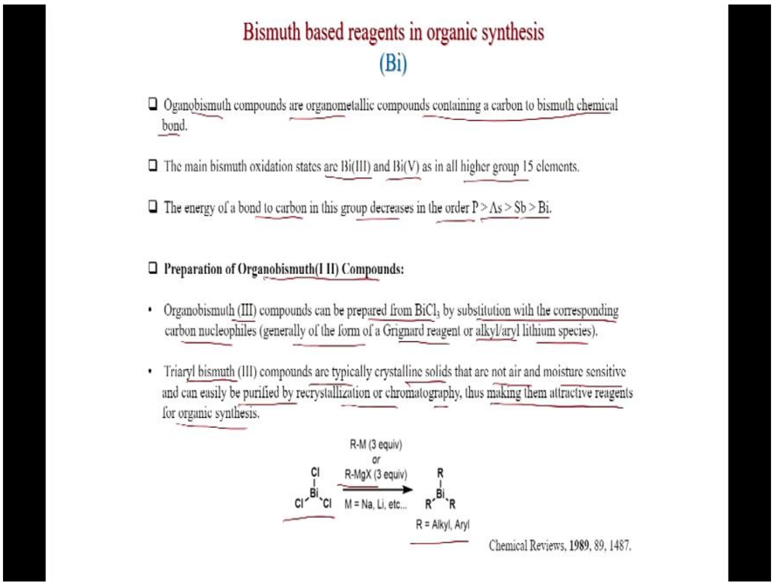


Bismuth based reagents in organic synthesis
(Bi)

- ☐ Preparation of Organobismuth (III) Compounds
- ☐ Preparation of Organobismuth (V) Compounds
- ☐ Organobismuth and Bismuth Reagents in Organic Synthesis
  - Arylation Reactions
  - Cross coupling Reactions
  - Aldol reactions
  - Epoxide opening reactions
  - Alkylation reactions
  - Arylation and carboarylation reactions
  - Hydro-oxycarbonylation reactions

Now we will discuss bismuth, bismuth based reagents in organic synthesis and here we will see bismuth plus three and plus five are the main oxidation states. So first we will discuss the preparation of Organobismuth compounds and then preparation of organobismuth five compounds, organobismuth and bismuth reagents in Organic Synthesis, Arylation Reactions Cross Coupling Reactions, Aldol, Epoxide opening, Alkylation, Arylation and carboarylation reactions and Hydro-oxycarbonylation reactions.

(Refer Slide Time: 37:29)



Bismuth based reagents in organic synthesis
(Bi)

- ☐ Oganobismuth compounds are organometallic compounds containing a carbon to bismuth chemical bond.
- ☐ The main bismuth oxidation states are Bi(III) and Bi(V) as in all higher group 15 elements.
- ☐ The energy of a bond to carbon in this group decreases in the order P > As > Sb > Bi.

- ☐ **Preparation of Organobismuth(I II) Compounds:**
  - Organobismuth (III) compounds can be prepared from $BiCl_3$ by substitution with the corresponding carbon nucleophiles (generally of the form of a Grignard reagent or alkyl/aryl lithium species).
  - Triaryl bismuth (III) compounds are typically crystalline solids that are not air and moisture sensitive and can easily be purified by recrystallization or chromatography, thus making them attractive reagents for organic synthesis.

Chemical Reviews, 1989, 89, 1487.

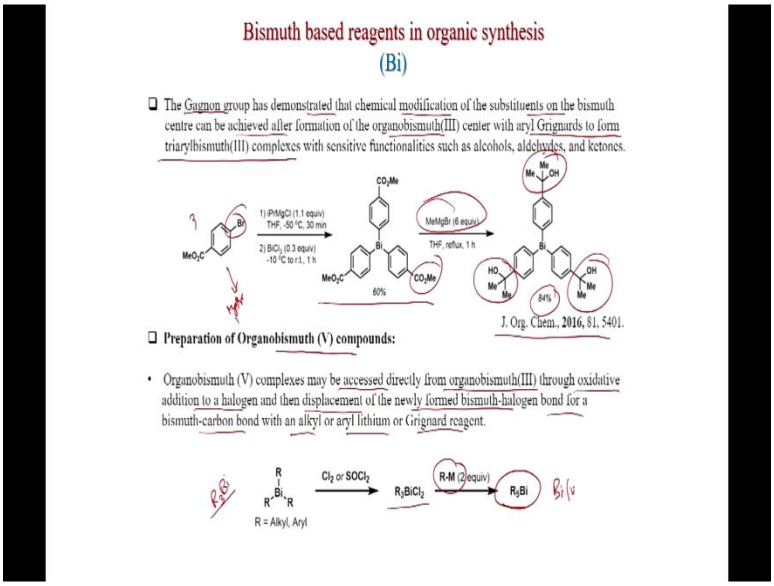
So first we will discuss general about Organobismuth, so organobismuth compounds are organometallic compounds containing a carbon to bismuth chemical bond. The main bismuth oxidation states are bismuth plus three and plus five as in all higher group 15 elements. And the energy of a bond to carbon in this group decreases in the order Phosphorous higher than Arsenic then Antimony then bismuth because bismuth is in large in size so the bismuth-carbon bond must be weak.

Preparation of organobismuth compounds was first three compounds; organobismuth three compounds can be prepared from bismuth trichloride by substitution with the corresponding carbon nucleophiles generally of the form of a Grignard reagent or alkyl aryl lithium species.

Triaryl bismuth three compounds are typically crystalline solids that are not air and moisture sensitive and can easily be purified by recrystallization or chromatography, thus making them attractive reagents for organic synthesis.

So they are not, bismuth three compounds are not moisture and air sensitive they are very useful in that way and with bismuth trichloride you can generate this trialkyl bismuth trialkyl and aryl bismuth for appropriate Grignard reagents three equivalent. This was reviewed in Chemical Reviews, 1989.

(Refer Slide Time: 38:57)



Bismuth based reagents in organic synthesis

(Bi)

☐ The Gagnon group has demonstrated that chemical modification of the substituents on the bismuth centre can be achieved after formation of the organobismuth(III) center with aryl Grignards to form triarylbismuth(III) complexes with sensitive functionalities such as alcohols, aldehydes, and ketones.

J. Org. Chem., 2016, 81, 5401.

☐ **Preparation of Organobismuth (V) compounds:**

- Organobismuth (V) complexes may be accessed directly from organobismuth(III) through oxidative addition to a halogen and then displacement of the newly formed bismuth-halogen bond for a bismuth-carbon bond with an alkyl or aryl lithium or Grignard reagent.

Now we will see the example of bismuth three compound syntheses, the Gagnon group has demonstrated that the chemical modification of the substituents on the bismuth centre can be achieved after formation of the organobismuth three with aryl Grignards to form triarylbismuth three complexes with sensitive functionalities such as alcohols, aldehydes and ketones.

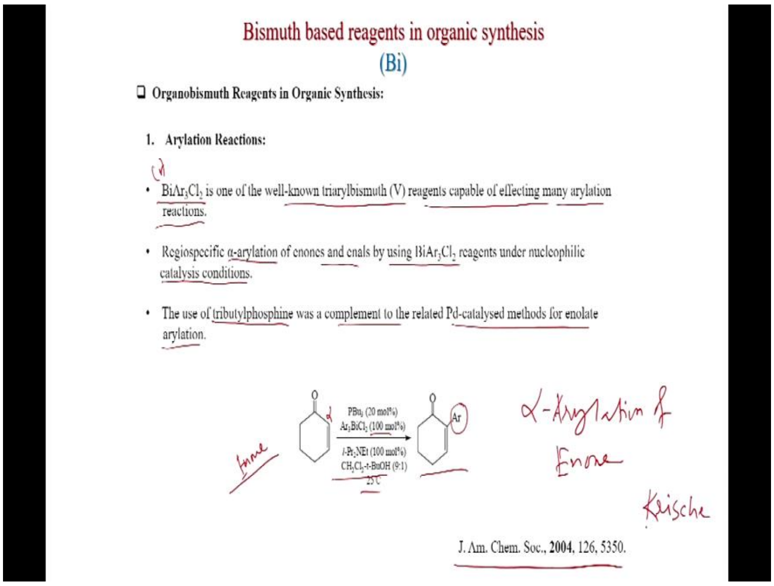
So this you can see aryl bromide is present and with this isopropyl magnesium chloride this is converted to Grignard, Aryl magnesium bromide. And then this of course three equivalent is present then this will react with bismuth chloride to generate this triarylbismuth.

And now again you can do this Grignard at this ester with methyl magnesium bromide six equivalent and you get this tertiary alcohol in 84 percent yield. This was published in J.O.C, 2016.

Now we will discuss preparation of organobismuth (V) compounds so far we have seen bismuth three. Now (V) complexes may be accessed directly from organobismuth three through oxidative addition to a halogen and then displacement of the newly formed bismuth-halogen bond for bismuth-carbon bond with an alkyl or aryl lithium or Grignard reagent.

So this is the reaction so whatever we have generated the trialkyl bismuth or triaryl bismuth that we have to react again with chlorine or SO Cl 2 to generate this one R 3 Bi Cl 2. Then further Grignard reagent RM or R dash M then you can get R 5 bismuth. So here bismuth in five oxidation state.

(Refer Slide Time: 40:55)



Bismuth based reagents in organic synthesis

(Bi)

❑ **Organobismuth Reagents in Organic Synthesis:**

1. **Arylation Reactions:**

(α)

- $BiAr_3Cl_2$ is one of the well-known triarylbismuth (V) reagents capable of effecting many arylation reactions.
- Regiospecific α-arylation of enones and enals by using $BiAr_3Cl_2$ reagents under nucleophilic catalysis conditions.
- The use of tributylphosphine was a complement to the related Pd-catalysed methods for enolate arylation.

α-Arylation of Enone

Krische

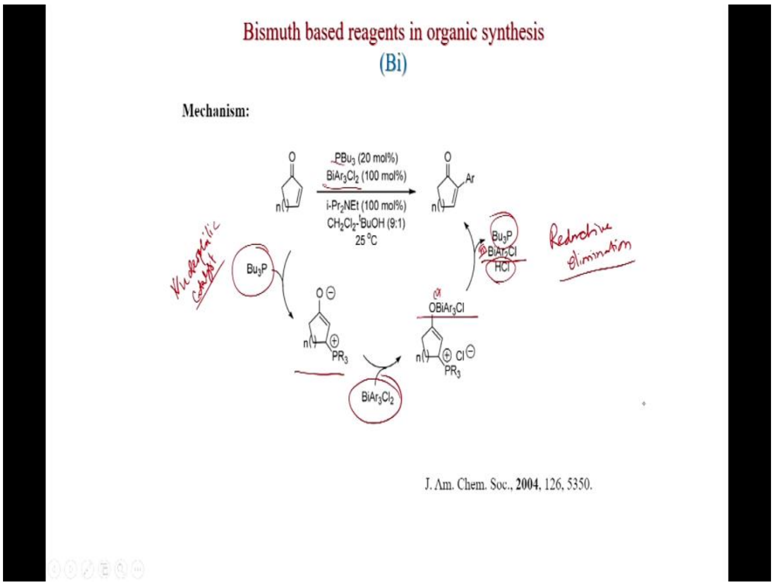
J. Am. Chem. Soc., **2004**, 126, 5350.

Now we will discuss some examples of the reactions, Organobismuth reagents. So this is the Bi Ar 3 Cl 2, so this is in bismuth in five oxidation state. So this is triaryl dichloride bismuth is one of the well know triarylbismuth (V) reagents capable of effecting many Arylation reactions.

Regiospecific alpha- Arylation of enones and enals by using Bi Ar 3 Cl 2 reagents under nucleophilic catalysis conditions. So this is very important, alpha-arylation of enones and enals, the use of tributylphosphine was a compliment to the related palladium-catalyzed methods for enolate arylation.

So this is the reaction, this is cyclohexenone, so this is an enone and if you put tributylphosphine 20 mol percent Ar3BiCl2 100 mol percent because one aryl group will come from this reagent and this unique base you need one equivalent and this is the solvent 25 degree centigrade then you get this product. So this is very useful reaction, arylation happen selectively at the alpha position, so alpha arylation of enone, alpha arylation of enone, it is a very useful reaction. And this was published by Krische, a well-known organic chemist from USA in JACS, 2004.

(Refer Slide Time: 42:37)



Bismuth based reagents in organic synthesis

(Bi)

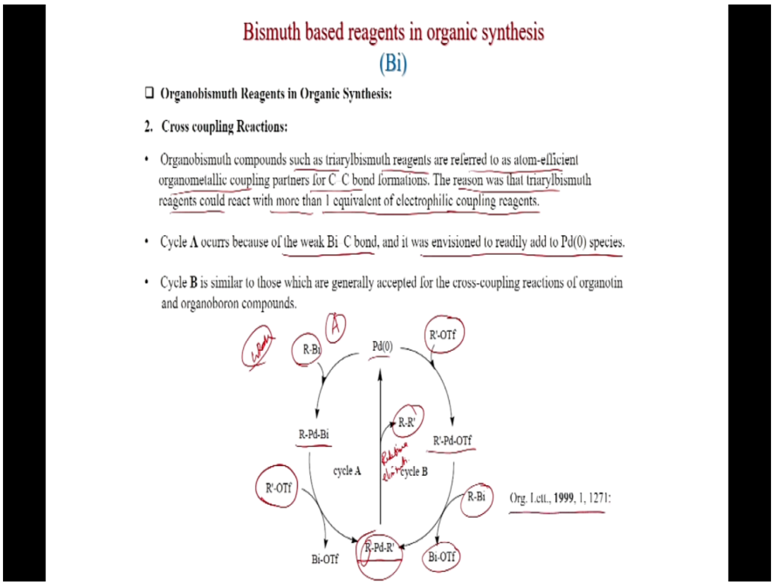
Mechanism:

J. Am. Chem. Soc., **2004**, 126, 5350.

So what will be the mechanism? So this is the reaction again we have drawn here the tributyl phosphine and this is the Bi Ar 3 Cl 2, so what could be the mechanism. So first we know that phosphine is a nucleophile so this nucleophilic catalyst, the tributyl phosphine that adds to the beta position and to generate this enolate and then the enolate reacts with this reagent so this enolate reacts with this and 1 Cl minus will displace so 2 chlorine was there now it is 1 chlorine bismuth still in (V) because bismuth connected with five component and now the reductive elimination will happen.

So this is important, reductive elimination will happen and the reductive elimination is happening in such a way that the aryl group is migrated to here so here this is the byproduct that is the bismuth species so here bismuth in three because it is connected to three component and regenerate tributyl phosphine also HCl is generated. So this is the mechanism that first the tributyl phosphine adds to the beta position generate the enolate and then the enolate reacts with this and this enolate is converted to the ketone with the aryl migration.

(Refer Slide Time: 44:13)



Bismuth based reagents in organic synthesis

(Bi)

☐ **Organobismuth Reagents in Organic Synthesis:**

2. Cross coupling Reactions:

- Organobismuth compounds such as triarylbismuth reagents are referred to as atom-efficient organometallic coupling partners for C C bond formations. The reason was that triarylbismuth reagents could react with more than 1 equivalent of electrophilic coupling reagents.
- Cycle **A** ocurrs because of the weak Bi C bond, and it was envisioned to readily add to Pd(0) species.
- Cycle **B** is similar to those which are generally accepted for the cross-coupling reactions of organotin and organoboron compounds.

Org. Lett., **1999**, 1, 1271:

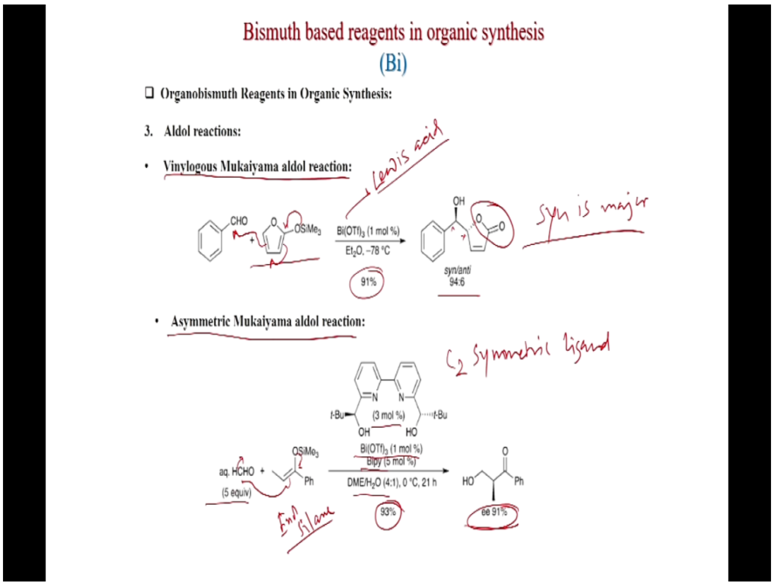
Now we will see the cross coupling reaction, organobismuth reagents can also be in cross coupling reactions like tin components. Organobismuths compound such as triarylbismuth reagents are referred to as an atom-efficient organometallic coupling partner for C-C bond formations. The reason was that triarylbismuth reagents could react with more than 1 equivalent of electrophilic coupling reagents. This is very important.

And this the proposed cycle that the cycle A, so this is the cycle A, so this is the addition first is happening in cycle A, palladium adds to R- Bi because this is very weak, we have already told that boron carbon bond is weak that is the explanation here the cycle A occurs because of the weak bismuth carbon Boron and it as envisioned to readily add o palladium 0 species to generate this.

Now other partner will come suppose R dash OTf, the bismuth O triflate will be generated and you get this. Now palladium is connected to both R and R dash and of course the reductive elimination will happen reductive elimination to generate the palladium zero and this is the product.

Now another cycle is possible also so that R dash OTf adds to palladium first to generate this and now the transmetalation will happen and R bismuth goes to bismuth triflate and the R group goes to the palladium to generate this same intermediate R palladium R dash after reductive elimination you get this. So this was published in Organic Letters is 1999.

(Refer Slide Time: 46:11)



Bismuth based reagents in organic synthesis

(Bi)

❑ Organobismuth Reagents in Organic Synthesis:

3. Aldol reactions:

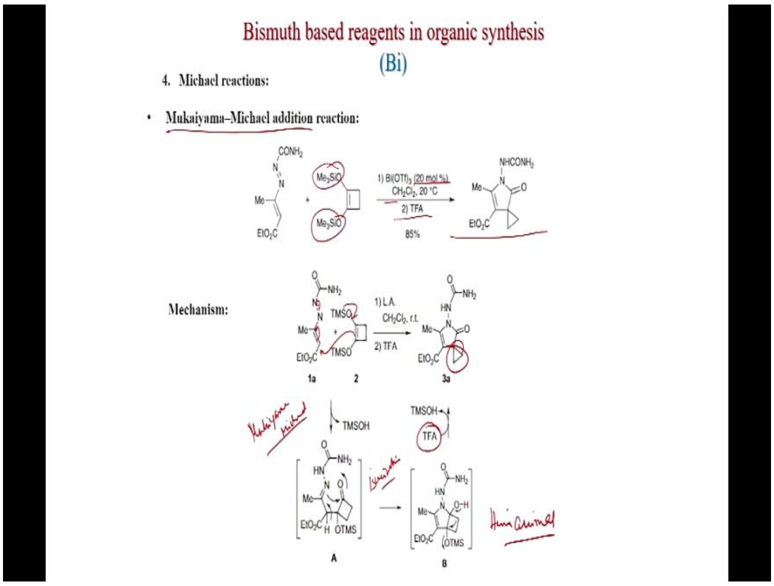
- Vinylogous Mukaiyama aldol reaction:

- Asymmetric Mukaiyama aldol reaction:

Now the Aldol reaction we will see and first one is Vinlylogous Mukaiyama aldol reactions. So bismuth triflate here, it is a Lewis acid, Lewis acid. So bismuth triflate is a Lewis acid and it can react with this furan OTMS and this is the Vinlylogous Mukaiyama aldol. What will happen? It will add here and you get this lactone motif here and the double bond generated here and you get this product, this is two chiral centers are present syn anti 94 is to 6, so syn is measured here. And in 91 percent yield and this is very efficient and only 1 mol percent of this bismuth triflate.

Now this reaction can be also possible with chiral ligand and you can develop an asymmetric version that is presented here with aqueous formaldehyde and this is the enol silane with this ligand this is C 2 symmetric ligand and with bismuth triflate again with 1 mol percent. So 3 mol percent ligand and 1 mol percent bismuth triflate so you have to make sure that bismuth binding with this ligand and becoming a chiral bismuth, this is another ligand piperidine with this solvent you get this product. It is 91 percent ee and 93 percent yield. So this is where the reaction is happening this adds to the formaldehyde. So this was published in Organic letters, 2005.

(Refer Slide Time: 48:07)



Bismuth based reagents in organic synthesis

(Bi)

4. Michael reactions:

- Mukaiyama–Michael addition reaction:

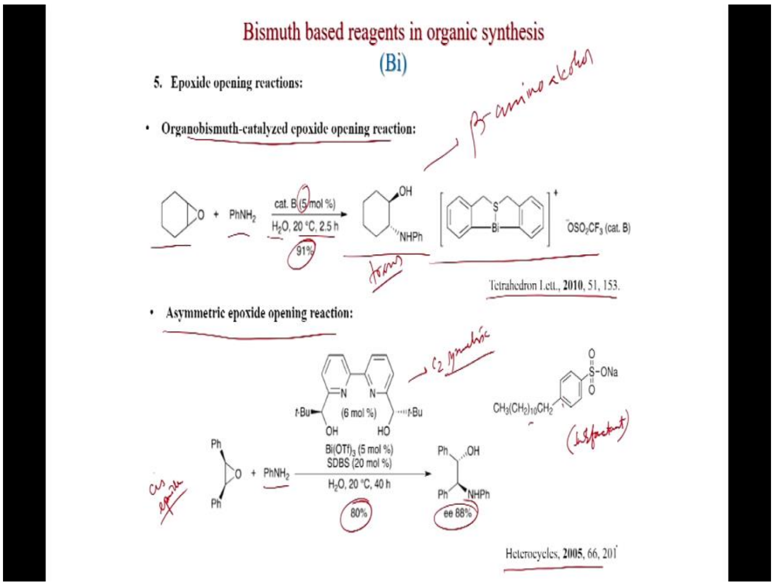
Mechanism:

Also Michael reaction is also possible, Mukaiyama-Michael addition reaction like this, this is disilane is there and with this bismuth triflate here 20 mol percent dichloromethane solvent followed by TFA addition you get this 5-member ring with a cyclopropane.

So what would be the mechanism of this reaction? And first thing is the Michael reaction is happening so this is the reaction again has been drawn so what happens this adds to this so this is first step is Mukaiyama Michael is happening here which added to the double bond and this double bond is migrated to here and again in the presence of acid this double bond isomerizes, so here this is isomerization is happening, isomerization and then this nitrogen is reacting to the carbonyl group to generate this hemi aminal, Hemi aminal is generated and that again rearranges to generate the ketone and these carbon attacks to this so that this cyclopropane is generated and this is only possible with TFA so that this OTMS will be a leaving group.

So this is a useful method with bismuth triflate that Mukaiyama Michael reaction followed by rearrangement cyclization you get this 5- member ring.

(Refer Slide Time: 50:00)



Bismuth based reagents in organic synthesis

(Bi)

5. Epoxide opening reactions:

- Organobismuth-catalyzed epoxide opening reaction:

Tetrahedron Lett., 2010, 51, 153.

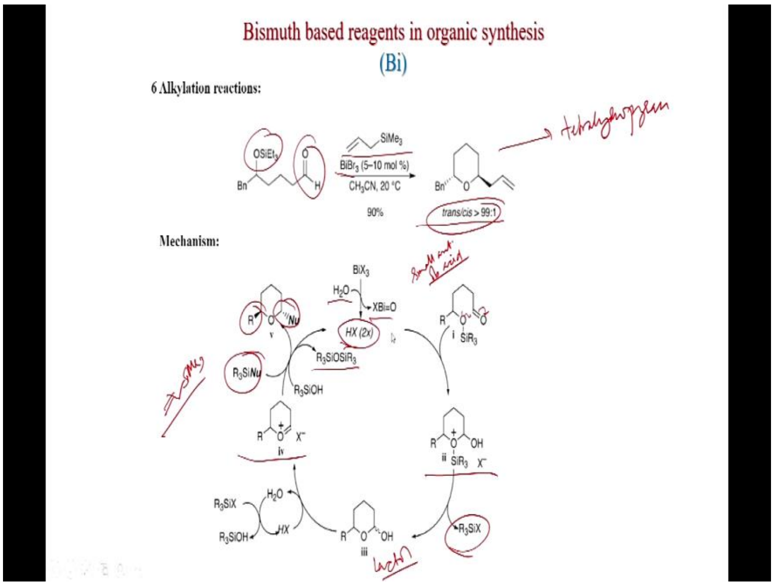
- Asymmetric epoxide opening reaction:

Heterocycles, 2005, 66, 201

Now Epoxide opening reactions we discussed, organobismuth –catalyzed epoxide opening reaction is possible like cyclohexane epoxide with aniline and catalyst b that is the bismuth reagent and here you can see aryl groups are attached also with sulfur and with this catalyst actually this catalyst is 5 mol percent only used and the water solvent 20 degree centigrade you get this beta amino alcohol, these are useful products. So this is a trans-geometry you get 91 percent yield. This was published in Tetrahedron Letter.

The reaction can also be possible in the asymmetric version and if you use the chiral ligand like earlier we used this ligand the same ligand so this is C 2 symmetric, the same ligand can be used for the Epoxide opening reaction with aniline and here this is the cis epoxide the cis epoxide and you get this product the beta aminalalcohol is formed in 80 percent yield with 88 percent enantiomeric excess and SDBS. This is the structure of SDBS this is surfactant which has been added in the reaction. This work was published in Heterocycles, 2005.

(Refer Slide Time: 51:35)



Bismuth based reagents in organic synthesis

(Bi)

6 Alkylation reactions:

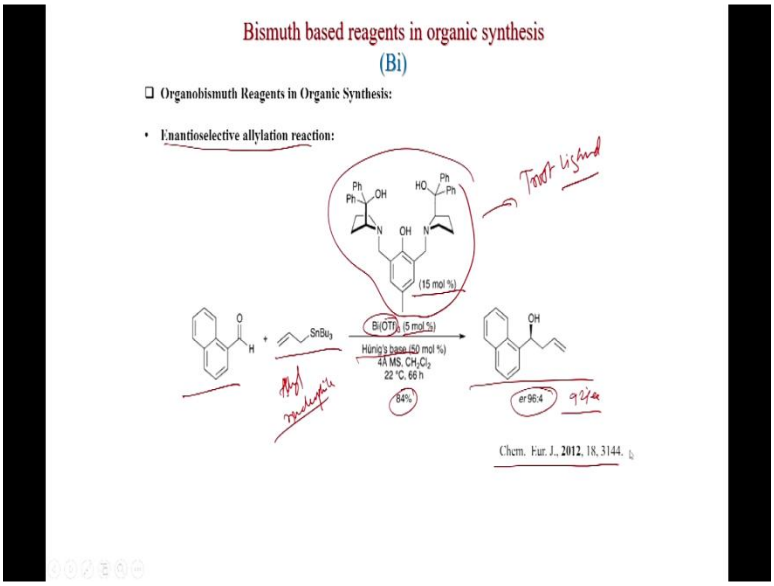
Mechanism:

Now we will discuss Alkylation reaction so if you see this structure here then aldehyde OSiEt3 group and allyl silane you have to add with bismuth bromide 5 to 10 mol percent then you get this tetrahydropyran, tetrahydropyran product in trans is to cis 99 is to 1. So this is very selective reaction so what is happening Bi Br3 H2 O it generates a small amount of acid so this is very important, small amount of acid is generateed. And that acid will generate the aldehyde of course and then addition will happen addition will happen, you get this intermediate then R 3 Si X will eliminate and you get this lactol.

So this lactol is formed and this lactol we know that the lactol in presence of acid generate the oxonium ion and once the oxonium ion is generated then the allyl nucleophile will react allyl silane will react to generate an allylation.

Now this product will be selective that the trans product will be formed exclusively and this R 3 Si O is regenerate this and regenerate HX. So this is the catalytic cycle and this work was published by JACS2003.

(Refer Slide Time: 53:07)


Bismuth based reagents in organic synthesis
(Bi)

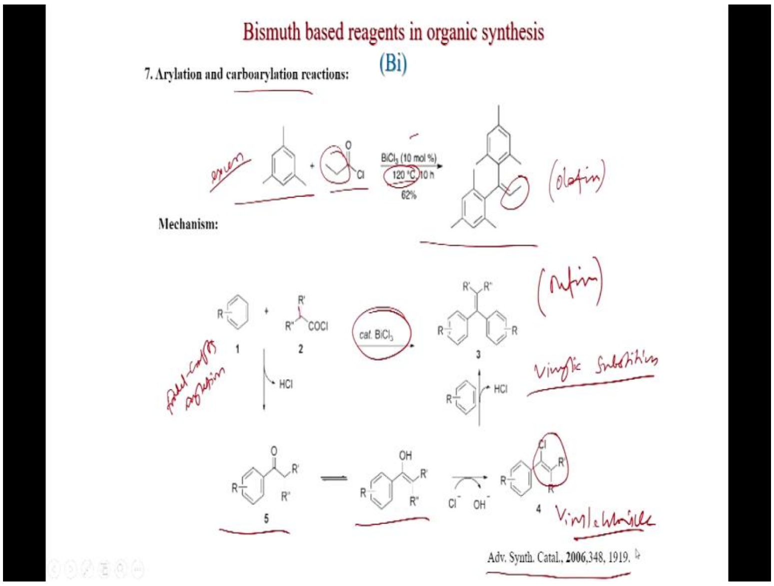
❑ Organobismuth Reagents in Organic Synthesis:

- Enantioselective allylation reaction:

Chem. Eur. J., 2012, 18, 3144.

Now we will see another reaction. Enantioselective allylation reaction, this was an allylation reaction instead of allyl syn here allyl tin is used tin allyl tributyl tin because allyl tributyl tin has a allyl nucleophile here and if you use naphthaldehyde then this allyl alcohol is formed, 84 percent yield 92 percent ee. So this reaction is very useful. And the ligand is used this is the Trost ligand and bismuth triflate is the catalyst here. So ligand we have to use 15 mol percent and bismuth triflate 5 mol percent, also you need Hunig base 15 mol percent and molecular sieves, so that the reaction will give high yield and high enantioselectivity. This was published in Chemistry European Journal in 2012.

(Refer Slide Time: 54:06)


Bismuth based reagents in organic synthesis
(Bi)

7. Arylation and carboarylation reactions:

Mechanism:

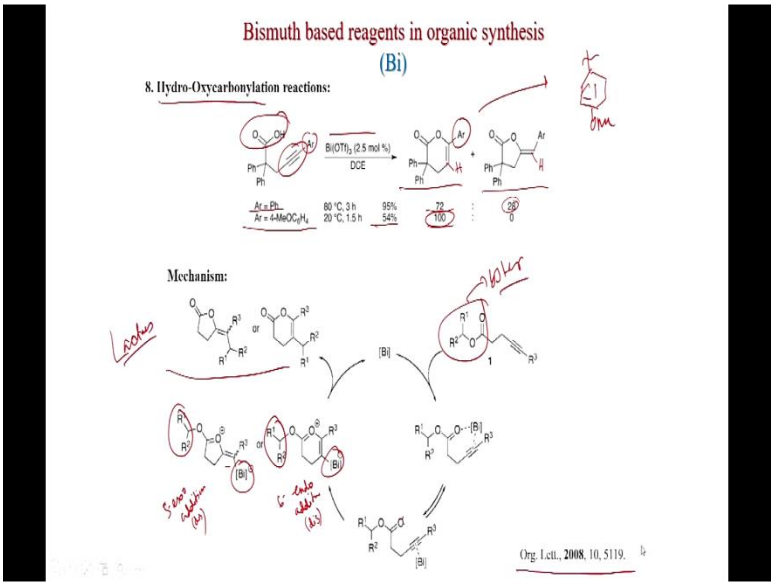
Adv. Synth. Catal., 2006, 348, 1919.

Now we will discuss the Arylation and carboarylation reactions so if you use mesityline with acid chloride bismuth chloride 10 mol percent, 120 degree centigrade, this of course you have to use excess and you get this Olefin. This is very interesting reaction, Olefin is formed here. With this group it is coming from this also upwards.

So what will be the mechanism of this reaction, the first this Friedel-Crafts Acylation will happen to generate this ketone and this ketone will be in the enol form and this enol will go to the vinyl chloride. So this is really important, vinyl chloride is formed here. Cl minus will displace OH minus and again the acid mediated vinylic substitutions so this is vinylic substitutions reaction is happening, vinylic substitutions that aryl group displaces the chloride and you get the olefin.

So this reaction was the Friedel-crafts acylation to generate the ketone then the arylation then the Cl minus will displace OH minus and then the vinylic substitutions will generate the Olefin. So this is the catalyst bismuth trichloride, of course this reaction is high temperature 120 degree centigrade, you have to do. This work was published in Advance Synthesis Catalysis, 2006.

(Refer Slide Time: 55:42)



Bismuth based reagents in organic synthesis

(Bi)

8. Hydro-Oxycarbonylation reactions:

Ar = Ph	80 °C, 3 h	95%	72	:	28
Ar = 4-MeOC$_6$H$_4$	20 °C, 1.5 h	54%	100	:	0

Mechanism:

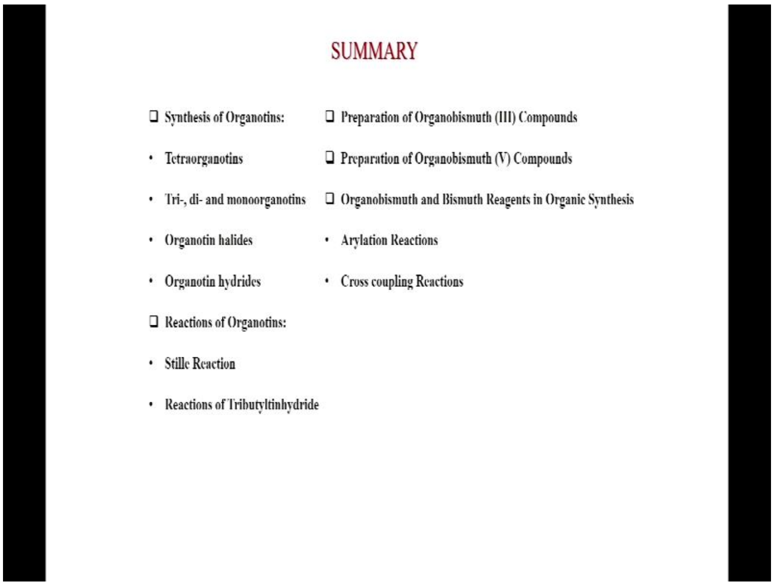
Org. Lett., **2008**, 10, 5119.

And lastly we will discuss hydro-oxyarbonylation reaction, so this is the reaction. There is the acid motif is there and alkyne is there, internal alkyne with aryl substituent, bismuth triflate 2.5 mol percent. You get this six-member and five-member ring and this six-member lactone and five-member lactone. And Ar is equal to Ph you get 72:28 and Ar is equal to 4 methoxyphenyl, in that 28 degree centigrade you get less yield but better selectivity 100 percent this product is formed.

So when Ar is equal to 4 methoxy because that is electron donating so we will see the mechanism, here this can be also ester because here this will be ester is used in the mechanism. So this carbonyl group of the ester or acid with (56:40) bismuth along with triple bond and the addition will happen because the triple bond is activated in this carbonyl group will add to the triple bond and this is the endo addition, this is six-endo addition and this is five-exo addition.

This is a dig, five-endo dig, six-endo dig because it is added to triple bonds and after that after that this will be carbonyl group and this R 1 and R 2 can migrate to here in the bismuth position but since we are using acid here so this is hydrogen so hydrogen comes here and you get these products, so this is hydrogen here you get these products. So this is an interesting reaction that with bismuth triflate if we have a carboxylic acid then alkyne then you can get the cyclization and you can get lactone, so these are lactones. So this was published in Organic letters, 2008.

(Refer Slide Time: 57:58)



SUMMARY

☐ Synthesis of Organotins:
- Tetraorganotins
- Tri-, di- and monoorganotins
- Organotin halides
- Organotin hydrides

☐ Reactions of Organotins:
- Stille Reaction
- Reactions of Tributyltinhydride

☐ Preparation of Organobismuth (III) Compounds

☐ Preparation of Organobismuth (V) Compounds

☐ Organobismuth and Bismuth Reagents in Organic Synthesis
- Arylation Reactions
- Cross coupling Reactions

So today we have discussed first organotin reagents and first we have discussed tetraorganotins then tri-, di- and monoorganotins. So in tetraorganotins we have seen they can be generated by Grignard reagent and tri-, di- and monoorganotins can be also be generated by Grignard reagent when you have used R 2 tin Cl 2 like this. Also by Wurtz method also you can generate this tetraalkyl tin that is the alkyl chloride, sodium and you have to use the tin reagent so then you can get this tetra aryl tin or tetraalkyl tin.

Also aluminium reagents can also be used to generate this. Then organotin halides we have seen and organotin hydrides we have seen the preparation and that with lithium aluminium hydride you can prepare this reagent the organotin reagent and Tributyltinhydride you can generate. Reactions of organotins, Stille reaction we have seen. Stille reaction is a powerful coupling reaction where the tin component will be added to the vinyl triplet or vinyl chloride or vinyl iodide or bromide and you can get this cross coupling product and Stille variant also is there Stille-Kelly coupling where the intramolecular dihalo component are coupled to give this product, cyclized product. And carbonylative Stille coupling is also a useful reaction where carbon monoxide is used and this reaction can also be used in natural product synthesis.

Reaction of Tributyltinhydride also you have seen this with AIBN can generate radical and this radical has can add to the alkyl bromide to further dehydrohalogenation also it can add cyclides, it can add to Olefin. Then this radical migrate to the triple bond that also causes and we have seen a three cycle is generated in a single operation.

And lastly we have seen the bismuth, the organic bismuth first we have seen the bismuth three compounds, then bismuth five compounds and their reactions we have seen, arylation reaction we have seen, the enone when it is treated with Ar 3 Bi Cl 2 the alpha arylation of enone is forming in this reaction is very efficient and also cross coupling reaction we have seen because the bismuth carbon bond is very weak so it can be useful for that coupling reaction and less than one equivalent can be used.

Also you have seen the Mukaiyama aldol reactions that can be performed in asymmetrically also with chiral C2-symmetric ligands. Then epoxide opening reaction we have seen with aniline and Alkylation reaction we have seen and we have seen arylation or carboarylation reaction also we have seen that when the tetrahydropyran can be generated. And lastly we have seen hydro oxy carbonylation reaction where acid and alkyne motif is there and the acid is adding to the triple bond and you generate the five-member or six-member lactone. Thank you!