Reagents in Organic Synthesis
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Lecture 12
Lithium Based Reagents in Organic Synthesis

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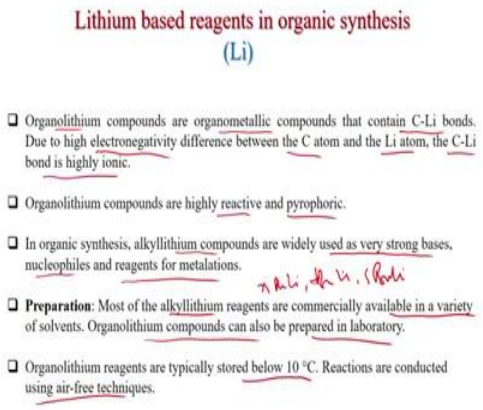

Welcome again, today we will discuss Lithium Based Reagents in Organic Synthesis. So organolithium compounds are organometallic compounds that contain carbon-lithium bonds and due to high electronegativity difference between the carbon atom and the lithium atom the C-Li bond is highly ionic. Organolithium compounds are highly reactive and pyrophoric that means they are moisture sensitive. In organic synthesis alkyllithium compounds are widely used as a very strong bases, nucleophiles and reagents for metalations.

Preparation, most of the alkyllithium reagents like n-butyllithium, secondary butyllithium, they are commercially available in a variety of solvents. Organolithium compounds can also be prepared in the laboratory. Organolithium reagents are typically stored below 10 degree centigrade; reactions are conducted using air-free techniques.

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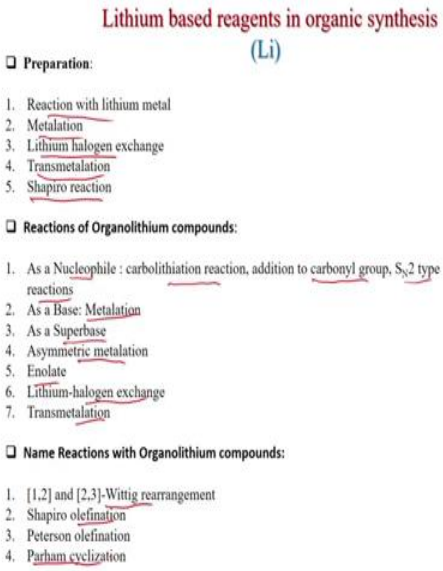

So, today in the class we will first discuss preparation it constitutes reactions with lithium metal, then we will discuss metalation, then lithium halogen exchange, then transmetalation and Shapiro reaction. Also reactions of organolithium compounds, variety of reactions are possible as a nucleophile, carbolithiation reaction, addition to carbonyl group, S_N2 type reactions we will discuss.

At a base metalation reaction, as a super base we will discuss some reactions. Asymmetric metalation also is possible we will discuss with chiral ligands and enolate chemistry, also lithium-halogen exchange reactions and transmetalation reactions. Also some name reactions with organolithium compounds like 1 to 2-3 sigma Witting rearrangement. Shapiro olefination and Peterson olefination and lastly Parham cyclization we will discuss.

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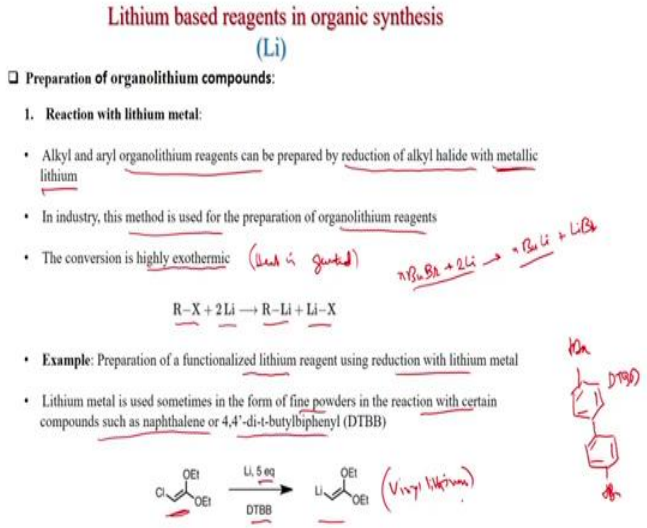

So, first discuss preparation of organolithium compounds and reaction with lithium metal. Alkyl and aryl organolithium reagents can be prepared by reduction of alkyl halide with metallic lithium. In industry generally this method is used for the preparation of organolithium reagents and the conversion is highly exothermic, so lot of heat is generated, heat is generated. Suppose, if the alkyl halide reacted with 2 equivalent of lithium metal then you get the RLi and lithium X and in industry n-butyllithium, suppose n-butyl bromide plus 2 lithium it will generate n-butyllithium plus lithium bromide.

So, butyllithium is prepared in this way, you have to react with 2 equivalent of metallic lithium. Preparation of functionalized lithium reagent using reduction lithium metal, lithium metal is used sometimes in the form of fine powders in the reactions with certain compounds such as naphthalene or 4-4 di-t-butylbiphenyl. So, this is di-t-butyl this is DTPB and when this vinyl chloride is treated with lithium 5 equivalent with DTPB then the vinyl lithium species is formed.

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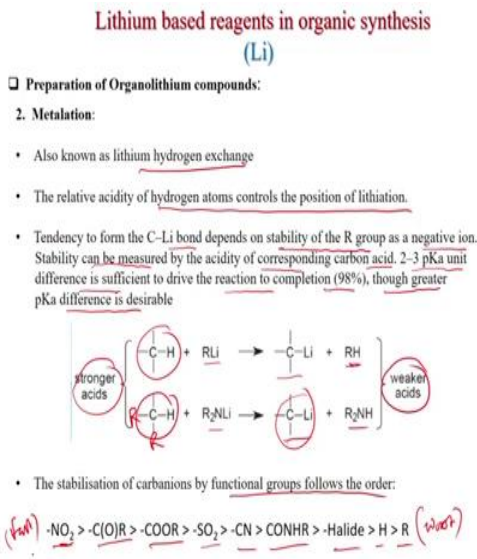

Some more preparation that is the metalation as known as lithium hydrogen exchange, so the CH bond is converted to C- lithium. The relative acidity of hydrogen atom controls the position of lithiation and tendency to form the C-lithium bond depends on stability of the R group as a negative ion, because ultimately the R group will carry a negative charge. So, stability can be measured by the acidity of corresponding carbon acid. 2-3 pKa unit difference is sufficient to drive the reaction to completion up to 98 percent though greater pKa difference is desirable.

Like here the alkane CH they are stronger acids and when R- lithium or R2 N- lithium they are converted to the lithiated compounds and RH and R2NH they should be weaker acids compared to the CH because so that the reaction will go to the forward direction. The stabilization of carbonions with functional group allows the orders, so you can put here some functional group and if there is a nitro group then the stabilization will, would be much better of this species, lithium species, then the ketone then ester, then sulfonyl, cyano, CONHR halide H and R. So, normal alkyl halide is the worst and this is will be very fast process.

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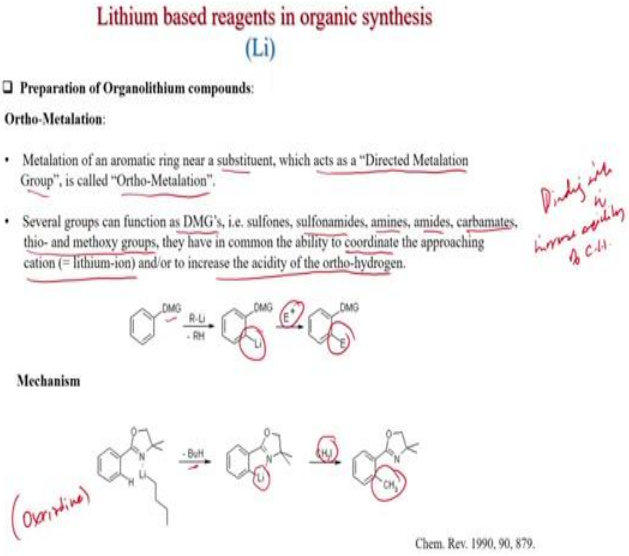

Preparation of ortho-metalation: Metalation of an aromatic ring near a substituent which act as Directed Metalation group is called Ortho-Metalation, so this very popular method and several group can function as DMG – Directed Metalation Group like sulfones, sulfonamides, amines, amides, carbamates, thio- and methoxy groups, they have in common the ability to coordinate the approaching cation; that is the lithium ion and/or to increase the acidity of the ortho-hydrogen.

So both they do, the binding with, binding with lithium and increase acidity of CH, so they also increase the acidity, like if a DMG group is present in the phenyl ring then the R- lithium if is used in the ortho-lithiation will happen and then this phenyl- lithium compound we can treat with different electrophiles to incorporate the electrophile group here.

What is the mechanism? So suppose this is the oxazoline, oxazoline what is present at the acting as a DMG group. Now butyllithium is treated to get the butane back and then this lithium which is stabilize also by this nitrogen and then methyl-iodide treatment provide this compound with a methyl group at the aromatic ring.

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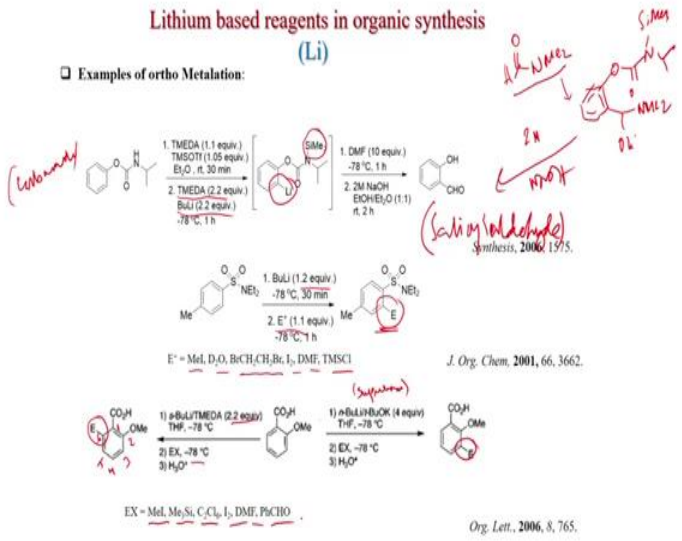

Also this carbamate, so this is carbamate when treated with TMEDA, TMSOTf ether, you get the first the cyclization here because this is quite acidic and now if you treat again TMEDA 2 equivalent butyllithium, 2 equivalent you get the ortho-lithiation and after that if you treat with DMF so DMF is this H O NMe2 and after treated with DMF you get, so you get this intermediate and after treatment with 2 molar NaOH you get this salicylaldehyde also this sulphonamide can act as a directing group, here also treatment with butyllithium 1.2 equivalent followed by electrophile, you get the electrophile incorporated at the ortho-position and different electrophile can be used like methyl iodide, D20-BrCH2CH2BrI, DMF, TMS chloride etc.

So different groups can be incorporate there, are at the ortho-position of this sulfonamide using just butyllithium. Also this carboxylic acid derivative 2 methoxy benzoic acid when treated with S butyllithium, secondary butyllithium TMEDA 2.2 equivalent is THF, followed by treatment to it electrophilic reagent, you get the electrophile at the 6^{th} position, so this is 6^{th} position. On the other hand treatment with n-butyllithium potassium tertiary-butoxide, so this is super base so will discuss later also, with super base you get the lithiation at the 3 position and the electrophile comes at the 3 position. And different electrophiles can be incorporated with methyl iodide, tri methyl silane, C2Cl6 iodine, DMF benzyl halide etc.

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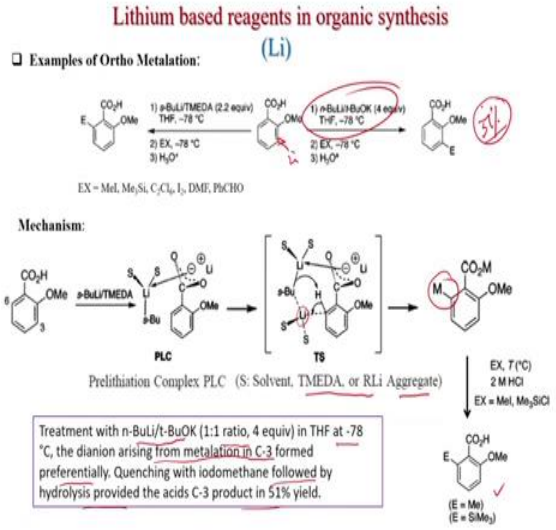

So this is the overall reaction, now what could be the mechanism of this reaction? So when secondary butyllithium and TMEDA is used then this kind of PLC is formed, prelithiation complex, here the carboxylate anion is generated and this is coordinated with the secondary butyllithium which is also connected with solvent or TMEDA, is means solvent of TMEDA or RLi aggregate, and then this is the proposed transition state where another molecule of lithium is here which attributes this CH and now this secondary butyl group attacks this hydrogen and lithium comes here and you get this 6 position metalation.

After the treatment with the electrophile reagent you get this compound. On the other hand treatment with n-butyl, tertiary-butyl, potassium tertiary-butoxide in one is to one ratio four equivalent, in THF at minus 78 degree centigrade the dianion from the metalation is C-3 formed preferentially. So, the metalation happens here under this condition and quenching with iodomethane followed by hydrolysis provided the acids C-3 product in 51 percent yield, so this is 51 percent, remaining other products are also forming.

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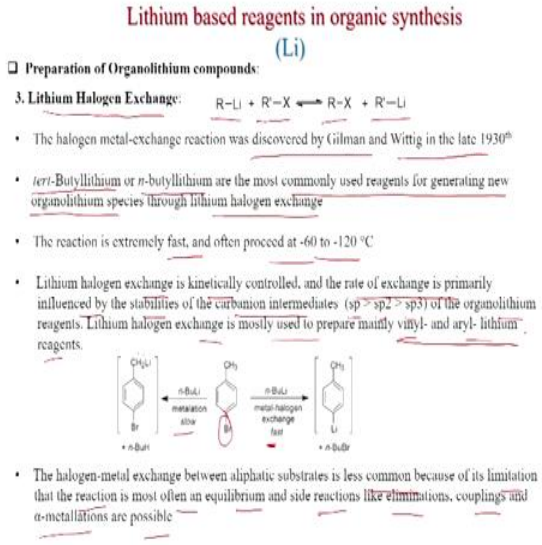

So, in the preparation of organolithium compounds the lithium halogen exchange is a popular method, however, you have to use and commercially available alkyl lithium and you have to react with an halide and you get RX and this is the newly generated lithium compounds. The halogen metal-exchange reaction was discovered by Gilman and Wittig in the late 1930s and tertiary-butyllithium, so it was that commercially available like tertiary-butyllithium or n-butyllithium are the most commonly used reagents for generating new organolithium species through lithium halogen exchange.

The reaction is extremely fast and often proceed at minus 60 to minus 120 degree centigrade and lithium halogen exchange is kinetically controlled and the rate of exchange is primarily induced, influenced by the stabilities of the carbanion intermediates sp, sp2, sp3 of the organolithium reagents. Lithium halogen exchange is mostly used to prepare mainly vinyl and aryl lithium reagents. Like if you treat p-bromotoluene and n-butyllithium the reaction at the CH3 that is the CH2 Li generation will be very much slow.

On the other hand the metal halogen exchange that is the this one is bromine will be replaced by lithium and this process is very fast so you can easily generate this newly generated organolithium compound. The halogen metal exchange between aliphatic substrate is less common because of its limitation that the reaction is most of it and equilibrium and side reaction

like eliminations, couplings, alpha metallations are possible. So this method is mainly useful for the generation of vinyl and aryl lithium reagents.

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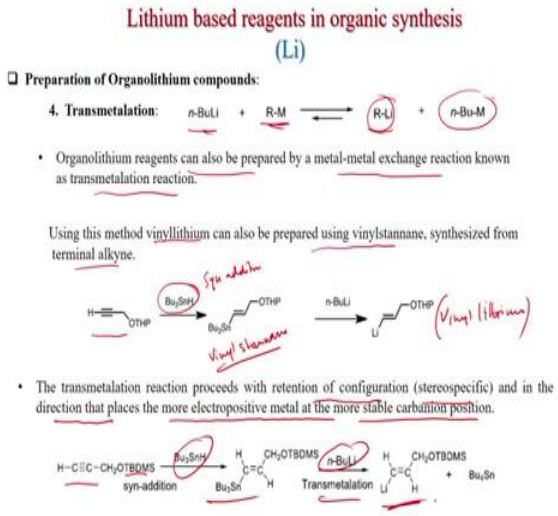

Transmetalation here another metal is reacted with a n-butyllithium so this exchange happens this are metal exchange with the lithium and n-butyl becomes n-butyl metal, organolithium reagents can be prepared by a metal-metal exchange reaction known as transmetalation reaction. Using this method vinyl lithium can be prepared using vinylstannane, synthesized from terminal alkyne. So, if you treat this terminal alkyne with tributyltin hydride then this vinylstannane, vinylstannane is formed and this is the syn addition and now treatment with n-butyllithium you get this vinyl lithium species.

Also this transmetalation reaction proceeds with retention of configuration that so it goes stereospecific and in the direction that places the more electropositive metal in the more stable carbanion position. So, similarly this terminal alkyne which OTBDMS group, syn addition happens of tributyltin hydride to generate this species and then n-butylllithium transmetalation you get this vinyl lithium.

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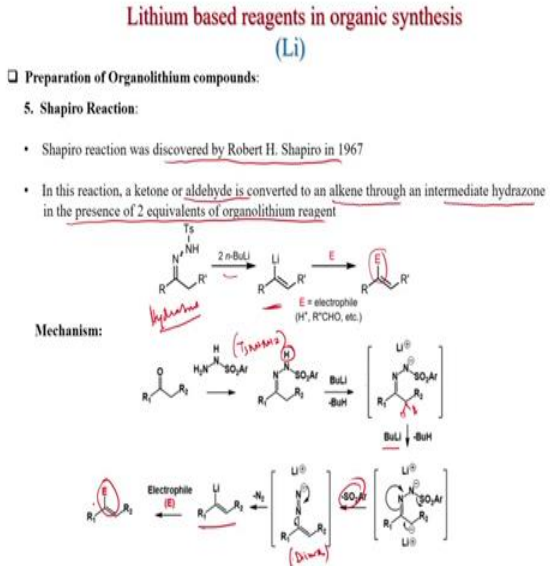

Shapiro reaction is also a popular method, Shapiro reaction was discovered by Robert H. Shapiro in 1967. In this reaction a ketone or aldehyde is converted to an alkene through an intermediate hydrazone, in the presence of 2 equivalents of organolithium reagents. So, this is the hydrazone when treated with 2 equivalent of n-butyllithium this vinyl lithium is formed, when it is treated with electrophile this electrophile is incorporated in this double bond.

What is the mechanism? So, the carbonyl compound first reacted with tosyl-hydrazine, so this is the tosyl-hydrazine to get the hydrazone and after that one agent of butyllithium will deprotonate this NH because this is quite acidic to generate this lithiated species and after that second equivalent of butyllithium will deprotonate this hydrogen to join this lithiated species and after that rearrangement will happen followed by elimination of SO2-Ar to generate this diimide and now the nitrogen elimination, we generate this vinyl lithium which on treatment with electrophile will generate the electrophilic incorporated olefins.

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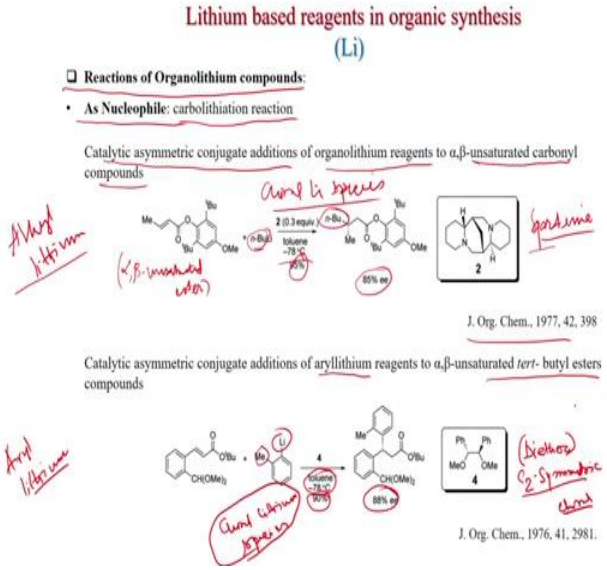

As nucleophile now we will discuss different reactions of organolithium compounds, so they are used as a nucleophile in various reaction, so first we will discuss carbolithiation reaction. Catalytic asymmetric conjugate additions of organolithium reagents to alpha-beta unsaturated carbonyl compounds is possible. Like here you can this is an ester, alpha-beta unsaturated ester, and when it is treated with n-butyllithium and this is sparteine, this is the chiral amine, so what happens this chiral amine binds with lithium and generate a chiral lithium species.

So, chiral lithium species is formed and this chiral lithium species that is the n-butyllithium, now the butyl group, this is butyl group is coming from this n-butyllithium which adds selectively to give this product conjugate addition product in 85 percent enantiomeric excess in at minus 78 degree centigrade with 95 percent yield, thus probably seen JOC.

Catalytic asymmetric conjugate addition of aryl-lithium reagents also is possible, this is alkyl lithium so this is alkyl lithium and this is aryl lithium, so here also this is the alpha-beta unsaturated the tertiary butyl ester, lithium at the ortho position of this methyl group and now this diether, when this diether, this is C2 symmetric diether, C2 symmetric, this is chiral, so this diether coordinates with this lithium and now the chiral lithium, chiral lithium species is generated.

This chiral lithium species adds selectively to this alpha-beta unsaturated ester to give this product in 88 percent enantiomeric excess in toluene solvent minus 78 degree centigrade and the

yield is also very good, 90 percent yield. So, these methods are very efficient, you can get the product in high yield when alkyl lithium and aryl lithium are added to alpha-beta unsaturated ester with a ligand, suitable ligand like sparteine or this kind of diether.

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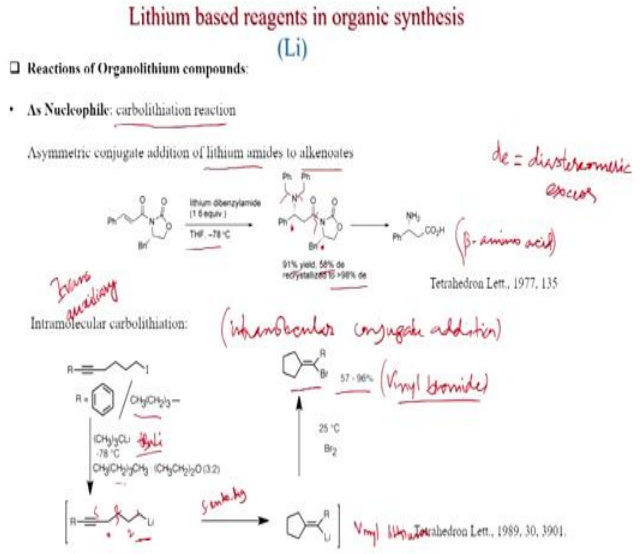

Reactions of organolithium compounds, so as nucleophile carbolithiation reaction also is very well known. Asymmetric conjugate addition of lithium amides to alkenoates. This is an example, here this one is Evan's auxiliary and when you treat this compound lithium dibenzyl amide in THF solvent and minus 70 degree centigrade the conjugate addition happen and two a new generate chiral center is formed here.

Now of because of this two chiral center the diastereomeric excess will be observed DE, DE is diastereomeric excess, so you get 91 percent yield and 58 percent diastereomeric excess and if you recrystallized then you get, had the 98 percent diastereomeric excess and after cleavage and deportation so this can be cleaved and this can be deported then you get beta amino acid.

And these are very useful amino acid, so here also you get the enantioselectivity will be preserved. This was published in Tetrahedron Letter. Now, intramolecular carbolithiation that is the intramolecular conjugate addition, so if you use this alkyl iodide with a triple bond present, however the substance can be phenyl or tertiary butyl and now if you use tertiary butyl lithium as this lithium reactant and minus 78 degree centigrade with the solvent you get this metal halogen exchange and you get this lithium.

Now, the intramolecular so if you see this 1, 2, 3, 4, 5 so 5 endo dig, 5 endo dig cyclisation will happen and you get this vinyl lithium and after treatment with bromine this lithium will be replaced by (bromo) and you get this vinyl bromide and these compounds are obtained in 57 to 96 percent yield. So, both intramolecular as well as intramolecular conjugate addition is possible to generate newly functionalized compound.

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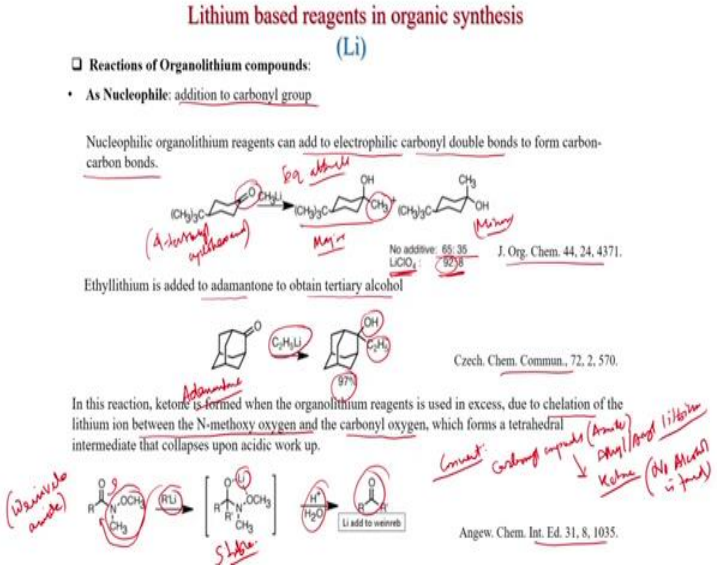

Now, we will discuss addition to carbonyl group, so earlier we discussed to the double bond, now we discussed the carbonyl group and nucleophilic organolithium reagents can add to electrophilic carbonyl double bonds to form carbon-carbon bonds, 4 tertiary-butyl cyclohexanone, so 4 tert-butyl cyclohexanone when treated with methyl lithium then this product is the major, so this is the major, this is minor. So, methyl wants to stay in the equatorial position that is the equatorial atom, so equatorial atom is favorable.

Interestingly when no additive is there then this selectivity is 65 is to 35, alternatively when lithium chloride is used as an additive then the selectivity increases to 92 is to 8, this is very remarkable that this product can be form in 92 percent selectivity when lithium chloride is used, this was published in JOC, lithium is added to adamentonone to obtain tertiary alcohol, so this process is generally different substances can be used like here adamentonone, adamentonone is treated with ethyl lithium, ethyl group is incorporated, a quaternary alcohol is formed in 97 percent yield, this was published in this journal.

In this reaction ketone is formed when the organolithium reagents used in excess, due to chelation of the lithium ion between the N-methaoxy oxygen and the carbonyl oxygen. So, this is called weinreb amide, so this very special reaction of weinreb amide, this is weinreb amide, this group is present N-methoxy methyl and now when it is treated with alkyl lithium what will happen?

This alkyl lithium will add here and now this compound will be stable, this lithiated compound because this lithium will have coordinated with this methoxy group, also it gives alkoxy group, so that this compound is stable and that is the ketone is not from in C2 only after acidic work of you get the ketone is formed, this was published in Angew, this is very important method to convert carbonyl compounds or the amides to ketone, alkyl or aryl lithium. So, this is very important, you get an Weinreb amide, the alkyl addition happens, so here have no alcohol is formed, so this is very important, no alcohol is formed because this complex is stable and after aqueous workup only if the ketone is liberated.

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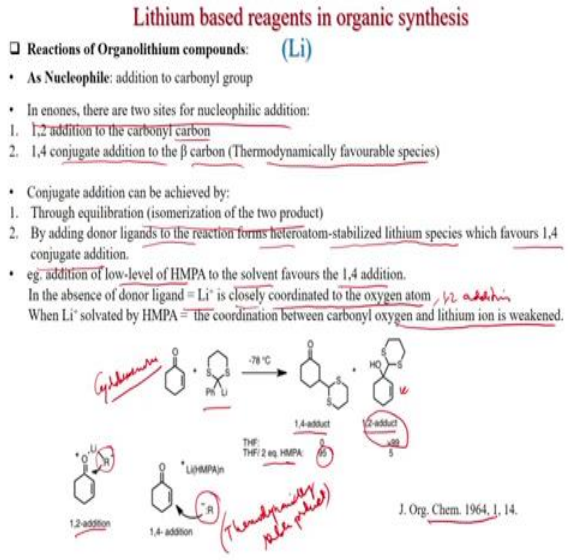

More example, addition to carbonyl groups, so we will discuss now enones. So, in enones there are two sites for nucleophilic addition, one to addition to the carbonyl compound, carbonyl carbon on the other hand one for conjugate addition to the beta carbon that is thermodynamically favorable species. Conjugate addition can be achieved by through equilibration, isomerization of

the two product, by adding donor ligands to the reaction, forms hetero-atom stabilized lithium species which favors 1, 4 conjugate addition.

As, for example, addition of low level of HMPA to the solvent favors 1,4 addition. In the absence of donor ligands lithium plus is closely coordinated to the oxygen atom and in the absence of donor ligand you get the 1, 2 addition. When lithium plus solvated by HMPA, their coordination between carbonyl oxygen and lithium ion is weakened. Suppose, this is cyclohexenone, cyclohexenone is treated with this diethyl lithiated species, at minus 78 degree centigrade there are possibilities of two product, this is 1, 4 addition product, this is 1, 2 product.

And interestingly when THF is used this 1, 2 product is formed in 99 percent selectivity, so this product is major, on the other hand when 2 equivalent of HMPA is there then this 1, 4 addition product that is the conjugate addition product is formed the major product. So, what could be the possible mechanism? So, this is the 1, 2 addition mechanism that the lithium is binding with the oxygen, carbonyl oxygen that is what here closely coordinated to the oxygen atom and now this 1, 2 addition because this is close to the carbonyl that 1, 2 attack will be possible.

On the other hand when HMPA is there then this oxygen lithium bond is not there, that bond is weakened because HMPA binds with the lithium and now this R minus is naked and there this is the thermodynamically stable product. Because there is no coordination of the lithium with the carbonyl oxygen so only the 1, 4 addition product will be possible this was published in JOC.

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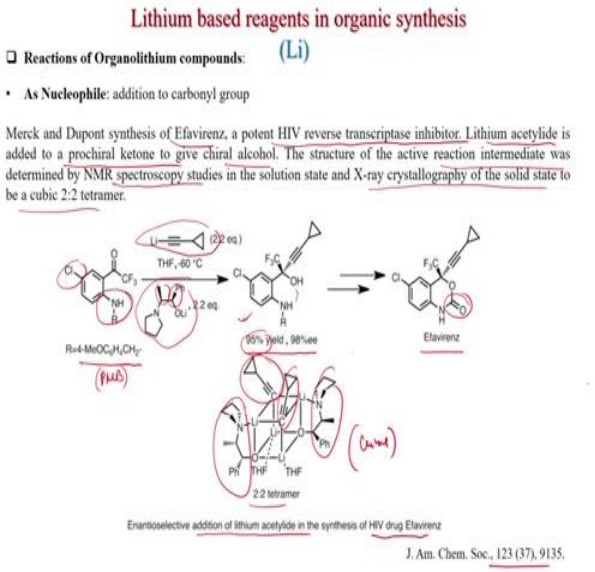

More examples, so Merck and Dupont synthesis of Efavirenz, a potent HIV reverse transriptase inhibitor, here lithium acetylide is added to a prochiral ketone to give chiral alcohol. So, this is the reaction that lithium species here lithium actylide is added to this ketone, here some functional group are present, amine group is there and R is equal to paramethoxy benzyl group, so PMB, and this is the ligand and this is also lithiated alkoxy lithium compound, which is secondary amine and 2 chiral centers are present and this compound is formed that is the addition product is formed in 98 percent enantiomeric excess.

So, this is a very important reacting you can get this compound in 98 percent enantiomeric excess, I mean 95 percent yield and after that this can be cyclized with a carbonyl activated carbonyl compound like fossil, you can get this compound Elfavirenz and this is the tetramer that is the active reaction intermediate was determined by NMR spectroscopy studied in the solution state and X-ray crystallography of the solid state to be a cubic 2 is to 2 dimer.

So, here 2 equivalent of ligand is present and 2 equivalent of this lithium acetylide and this makes the tetramer compound, you can see here lithium, oxygen lithium, carbon lithium, carbon lithium, lithium oxygen. So, like this tetramer is formed and which gives so this is chiral, so this chiral lithium species adding selectively to the carbonyl compound, this is the enantioselective addition of lithium acetylide in the synthesis of HIV drug, this was published in JACS.

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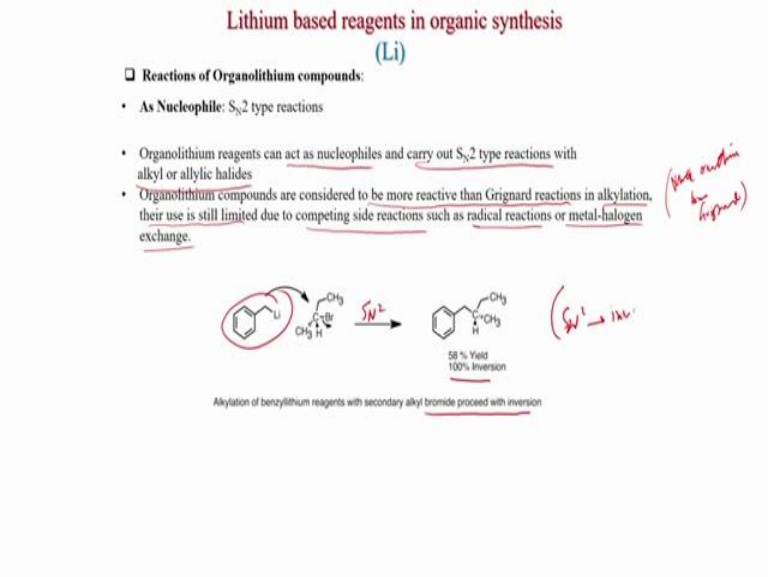

S_N 2 type reactions also possible, organolithium reagents can act as nucleophiles and carry out S_N 2 type reaction with alkyl or allylic halides. Organolithium compounds are considered to be more reactive than Grignard reactions in alkylation, however their use is still limited due to competing side reactions such as radical reactions, metal-halogen exchange because many side reactions are there, so they are more reactive, more reactive than Grignard.

So when Grignard addition may not take place due to steric reason you can use this lithium compound, and this is the SN 2 substitution reaction, SN 2 reaction here and this benzyllithium species is added to this group, here 100 percent inversion is possible. Secondary centre will proceed with inversion because this is SN 2 mechanism, SN 2 mechanism with inversion of stereochemistry will be there.

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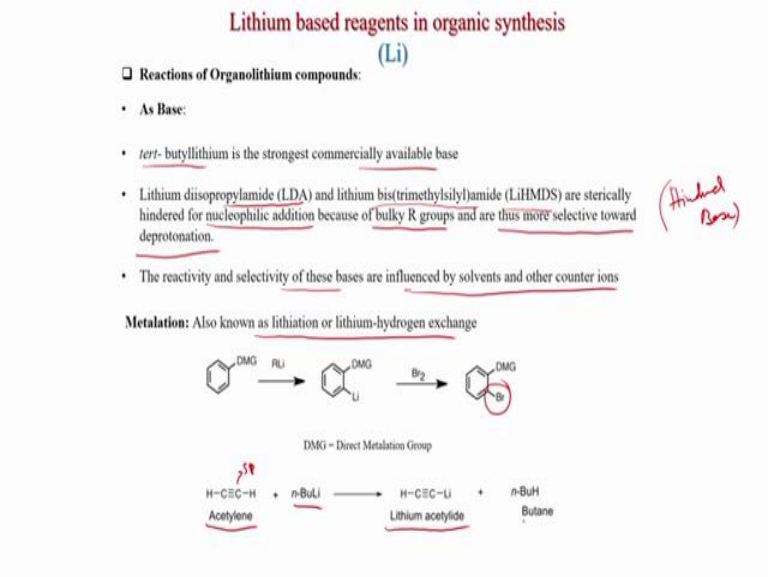

As base also it is thus many reaction, tertiary-butyllithium is strongest commercially available base and LDA – Lithium diisopropylamide, this we already discussed earlier, lithium bis trimethylsilyl amide LiHMDS are sterically hindered for nucleophilic addition because of bulky R groups and are thus more selective toward deprotonation, so they are hindered base not as a nucleophile.

The reactivity and selectivity of these bases are influenced by solvents and other counter ions and this already we discussed metalation reaction known as lithiation or lithium-hydrogen exchange like DMG RLi you get this lithium species, after treatment with bromine you get this bromide compound, DMG Directed Metallated Group, also and triple bound we already discussed this is SP hybridized so they are more stable you can deprotonate n-butyllithium and lithium acetylide is formed and butane is the side product.

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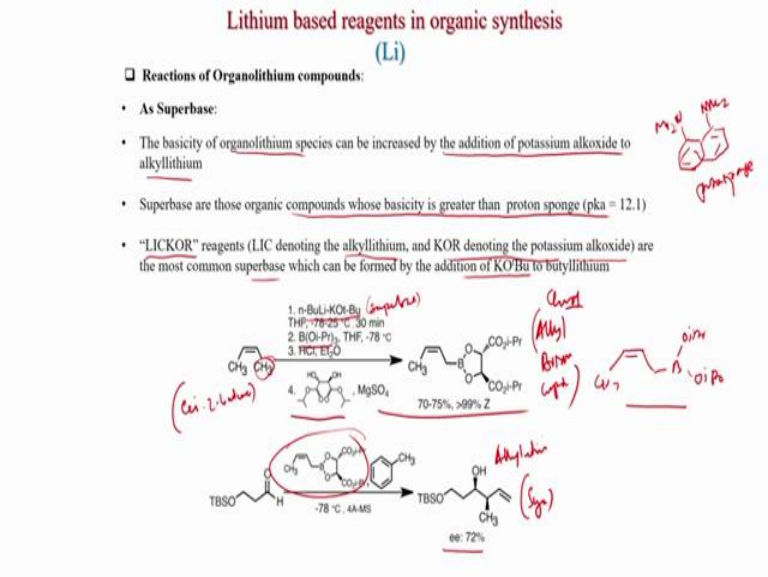

As superbase the basicity of oraganolithium species can be increased by addition of potassium alkoxide to alkyllithium and superbase are those organic compounds which basicity is greater than proton sponge, so this is proton sponge, LICKOR, LIC denoting the alkyllithium and KOR denoting the potassium alkoxide are the most common superbase which can be formed by addition of potassium tertiary-butoxide to butyllithium.

Like this reaction you can see this is Cis 2 Butene, Cis 2 Butene when treated with the superbase, so this is superbase is there and you get the deprotonation here and after that you get this treatment with this triisopropylborate you get this compound, Cis 3 Cis 2B O isopropyle O isopropyle, this intermediate is formed after that HCl you get this deprotection and after that reacted with tartrate diisopropyl tartrate.

You get this allyl boronate species, so this is allyl boron compound. This formed and this is chiral, chiral allyl boron because this is now tartrate is there, so this is C2 symmetric and 99 percent Z so this stereochemistry is not disturbed, it is retained and this compound, this compound when treated with this normal aliphatic aldehyde, then this reaction, allylation reaction happens and you get the product in 72 percent, so this is a syn. So this is the reagent which we added to the aldehyde and you get this allylation, so allylation happens.

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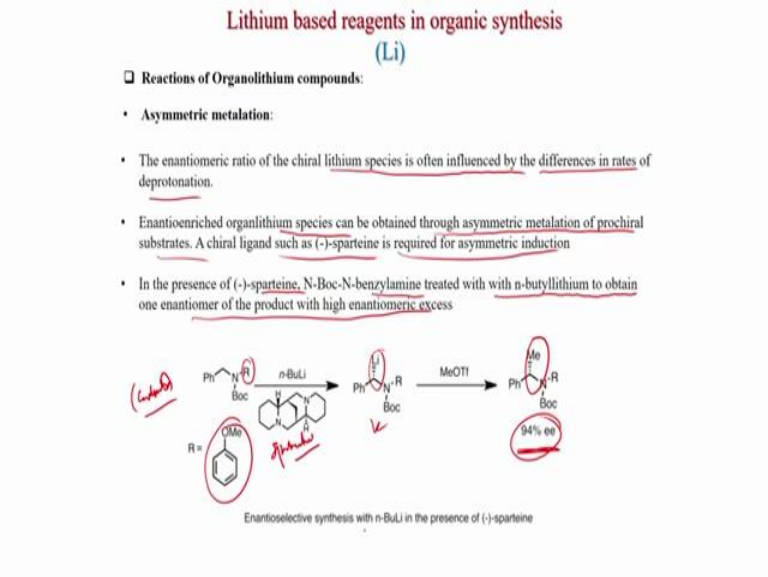

Asymmetric metalation is possible the enantiomeric ratio of chiral lithium species is often influenced by the difference in rate of deprotonation. Enantio enriched organolithium species can be obtained through asymmetric metalation of prochiral substrate; a chiral ligand such as sparteine is used for the asymmetric induction, this already we have seen. In the presence of sparteine N-Boc-N-benzyleamine treated with n-butyllithium to obtain one enantiomer for the product with high enantiomeric excess, suppose this N-Boc compound when treated with this butyllithium and sparteine and this is the para methoxyphenyl compound, this is the substance, para methoxyphenyl substance and then this lithium species is chiral because this sparteine is chiral so lithium species form is chiral.

And after treatment with methyl triflate you get the methylation and 94 percent enantiomeric excess is formed, so this is very useful or this is the carbamate, so this is carbamate compound and this is the chiral center, chiral lithium is formed, very good enantioselectivity after methylation a product is formed in 94 percent enantiomeric excess, so enantioselective synthesis with n-butyllithium in the presence of sparteine.

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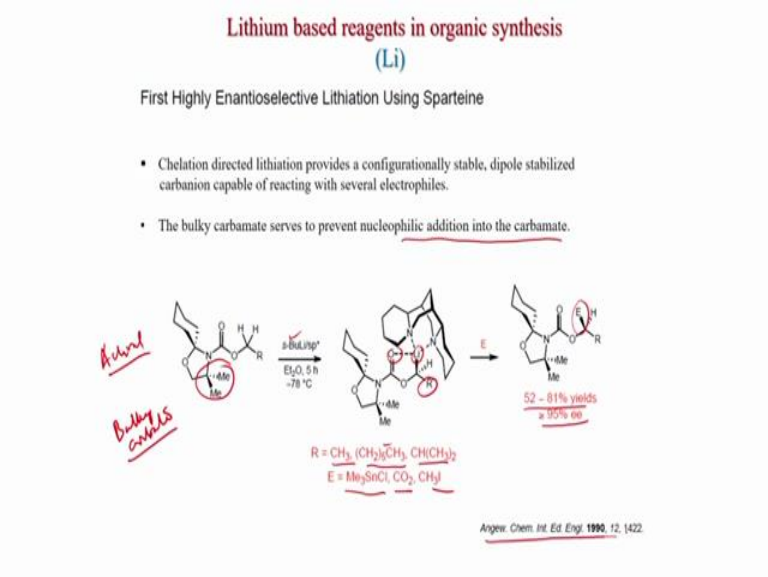

However the first highly enantioselective lithiation was reported by Hoppe. So, we will discuss now the bulky carbamate serves to prevent nucleophilic addition into the carbamate, so this is bulky carbamate and this also is achiral, so this carbamate is achiral where this is not chiral center to both groups are same, this compound went into the secondary butyllithium and sparteine, earlier we have seen N-butyllithium, here secondary butyllithium is used and this species is formed.

So lithium as selectively form a side and this lithium is quarternate with this carbamate oxygen to give intermediate like this and after that electrophilic treatment with different eletrophiles will give this product, higher than 95 percent enantiomeric excess in 52 to 81 percent yield and different R group is possible here, this R can be methyl, isopropyl, this is isopropyl and this is normal hexyl group. Also trimethyltin compound can be incorporated here, carboxylic acid group after treatment with carbon dioxide and methyl group from the methyl iodide, you can get different compounds here, electrophilic compounds and Angew Chem was the published journal.

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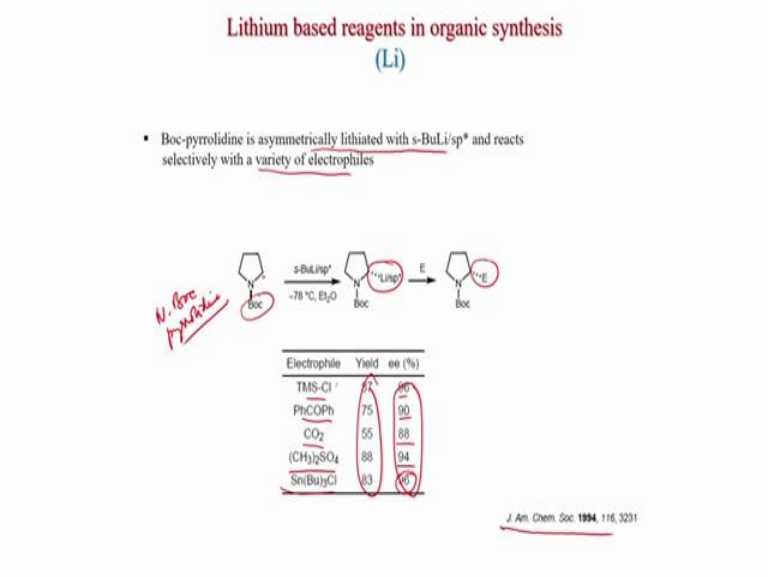

Boc-pyrrolidine also is asymmetrically lithiated with secondary butyllithium sparteine and reacts selectively with a variety of eletrophiles, so this is the N Boc pyrrolidine, so this is important the Boc group that oxygen will bind with the lithium that we have seen here so that Boc group, agents of Boc group is important and after secondary butyllithium sparteine you get this lithium species and after treatment with eletrophile, the eletrophile is incorporated here and different eletrophile you can see moderate to high yields and high enantiomeric excess like TMS chloride 96 percent yield, PHCOPh it is ketone, you can get an alcohol here 90 percent.

CO2 carboxylic acid group will come 88 percent enantiomeric excess, dimethyl sulphate methyl group will come 94 percent and tributyl tin chloride, a tin compound will be generated 96 percent enantiomeric excess, and this was published in JACS. So this is very useful method to do alpha functionization of the pyrrolidine, N Boc pyrrolidine, just like treatment with secondary butyllithium sparteine followed by different electrophile and you can get a different type of compounds.

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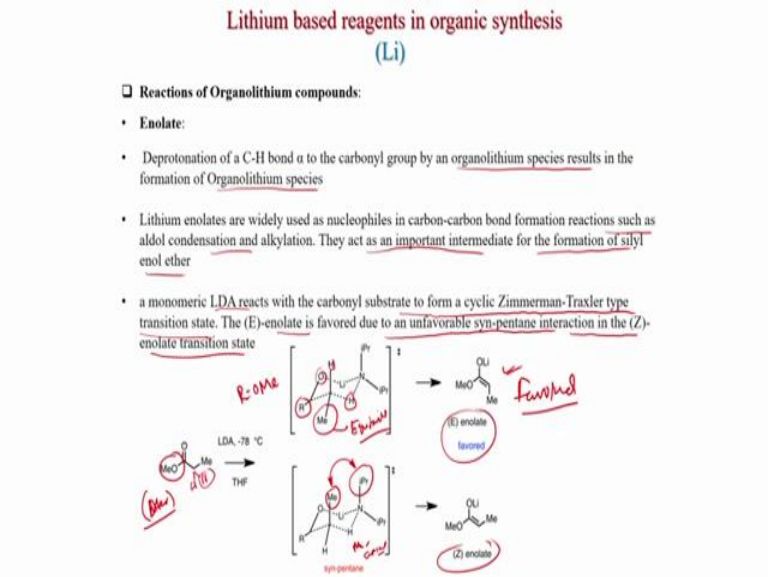

Enolate chemistry is also very popular, deprotonation of CH bond alpha to carbonyl group by an organolithium species results in the formation of organolithium species. Lithium enolates are widely used as nucleophiles in carbon-carbon bond formation reaction such as aldol condensation and alkylation, they act as an important intermediate for the formation of silyl enol ether.

And a monomeric LDA reacts with carbonyl substrate to form a cyclic Zimmerman-Traxler type transition state, this we will discuss and E-enolate is favored due to an unfavorable syn-pentane interaction in the Z enolate transition state. So, this is an ester, when treated with LDA what will happen, the enolate will form and here R is equal to methoxy, so this methoxy is here and now the deprotonation will happen from this hydrogen and you get enolate so this is this oxygen, this oxygen here and this one will bind with the lithium and this hydrogen, one hydrogen is here and another hydrogen is here, this one hydrogen will bind with the amine nitrogen.

And this is the Zimmerman-Traxler transition state and you can see this methyl group in the equatorial, so this is equatorial, this is stable and you get the E enolate that is favored. On the other hand when methyl group is in the axial, so methyl is in axial then this syn-pentane interaction is there with this isopropyl group and this Z enolate is not favorable, so this is favored and this only form E enolate when you treat an ester a carbonyl compound with LDA.

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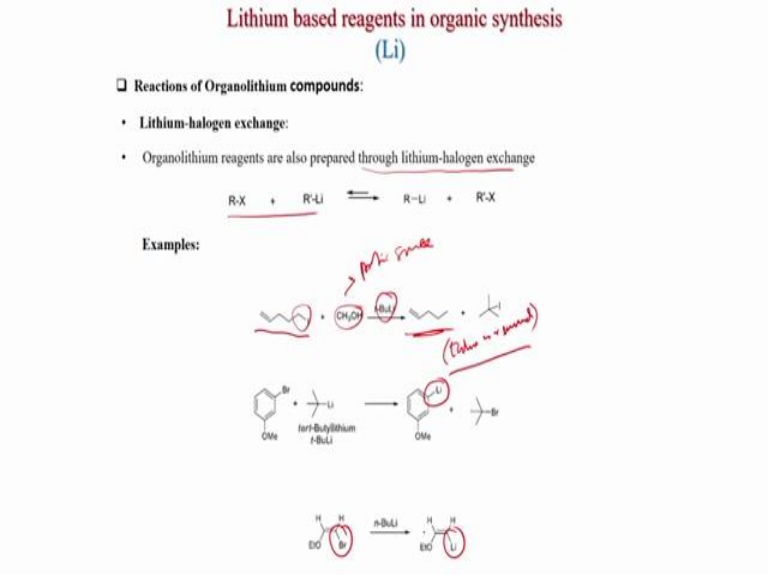

Lithium halogen exchange, organolithium reagents are also prepared through lithium halogen exchange, this is already we discussed and like this compound a double bond and alkyl iodide when treated with tertiary butyllithium, that lithium species will form, the exchange will happen and then this is the protic source then you get the removal, so iodine is removed, so this is very useful method to remove and halide group from a alkyl halide and only the olefin is formed here.

Also aromatic exchange also is possible here, tertiary butyllithium, metal halogen exchange you get the lithium here also vinyl bromide you can get the vinyl lithium, this already we discussed and different reactions now you can do with this reagent.

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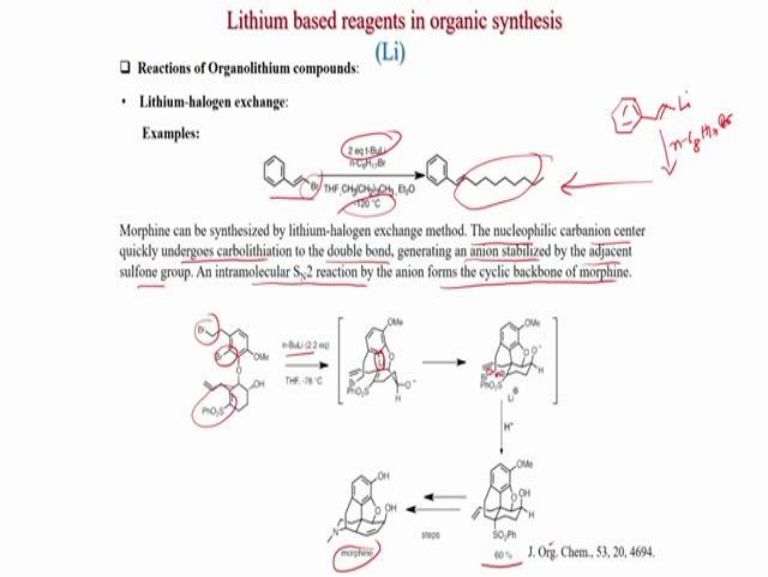

Like here this vinyl bromide when treated with 2 equivalent tertiary butyllithium and THF minus 120 degree centigrade and you get this lithium species and this lithium species when treated with n-octyl bromide and this n-octyl bromide is incorporated here, so this is n octyl group which is coming from this n-octyl bromide so lithium, vinyl lithium is formed and then after that reaction, so this is very useful method to increase the chain length so here nothing is there only bromine then you do the metal halogen exchange with tertiary butyllithium and after that quenching with this bromide.

Morphine can be synthesized by lithium halogen exchange method, the nucleophilic carbonion center quickly undergoes carbolithiation to the double bond, generating an anion stabilized by the adjacent sulfone group. An intramolecular S_N 2 reaction by the anion form the cyclic backbone so this is the reaction and here you can, this alpha beta unsaturated sulfonyl and this is the aromatic bromide and this is the alkyl bromide.

However, when you treat with n butyllithium then this is formed because this is stable and now it adds to this alpha beta unsaturated sulfone to generate this species, the negative charge, the alpha position of the sulfonyl group and now S_N 2 reaction will happen, so this will react and bromine will be eliminated, you get this product and this can be converted to morphine in few steps, so this is very important method that you generate an alkyl lithium species which does a conjugate

addition to alpha beta unsaturated sulfonyl and then again followed by second cyclization and you get this intermediate, this work was published in J Org Chem.

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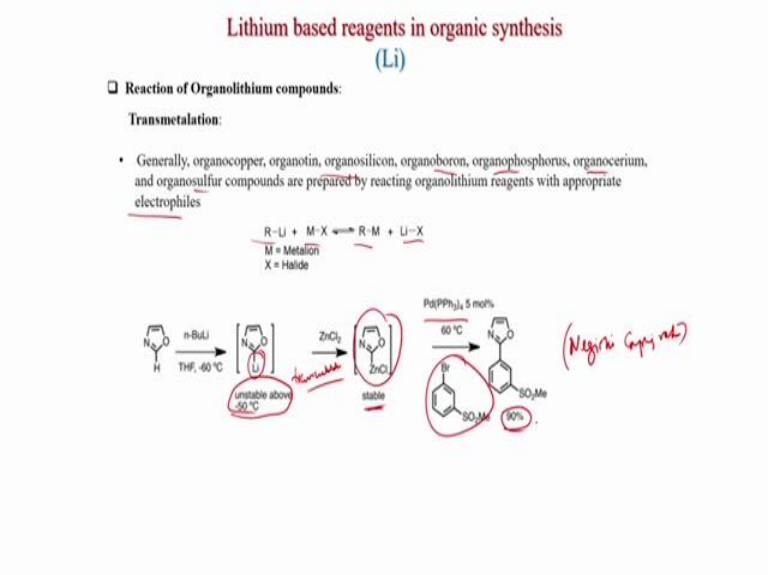

Transmetalation generally organocopper, organotin and organosilicon, organoboron, phosphorus, cerium, sulfur compounds are prepared by reacting organolithium reagents with appropriate electrophiles like R alkyl, MX RM lithium X, so this is the exchange transmetalation. Suppose, this oxazole when treated with the N butyllithium, this is formed, however this is unstable, minus 50 degree centigrade, how to make it stable and then you have to treat with zinc chloride so this zinc species is stable.

So, this is very important, this is the transmetalation, lithium becomes zinc and now this compound you can treat in Negishi coupling reaction, zinc and this aromatic bromide and with triphenylphosphine palladium as a catalyst you get this product in 90 percent yield.

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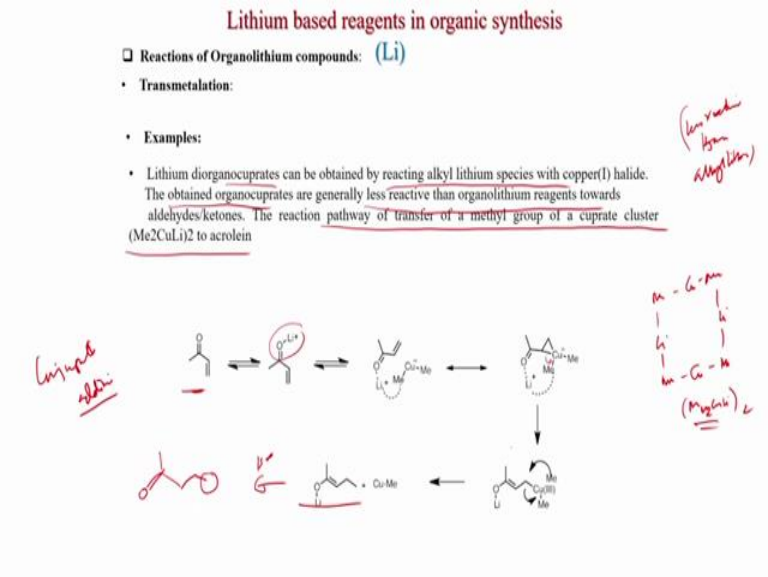

Some more examples, lithium diorganocuprates can be obtained by reacting alkyl lithium species with copper halide. The obtained organocuprates are generally less reactive than organolithium reagents towards aldehydes and ketones, the reaction pathway to transfer of a methyl group of a cuprate ester to acrolein. So this is very important, this is less reactive, this cuprate species less reactive than alkyl lithium and here we will discuss how a conjugate addition is happening.

So, this acrolein first reacted with this one, this coordination happens and after that this cuprate comes and cuprate adds to the double bond, so this species actually, Cu methyl- methyl-lithium methyl, this is the compound, (Me_2Cu Li)2 and after that that cuprate adds to the double bond and now this becomes, this bond cleavage here and you get a copper 3 and now this methyl group will be adding here to get this enolate and this enolate can be converted after acidic workup to the ketone.

So this ketone can be obtained after methyl group adds, so this is the extra methyl group that adds to this species, so this is very important, conjugate addition is happening when (Me 2 Cu Li)2 is added to acrolein.

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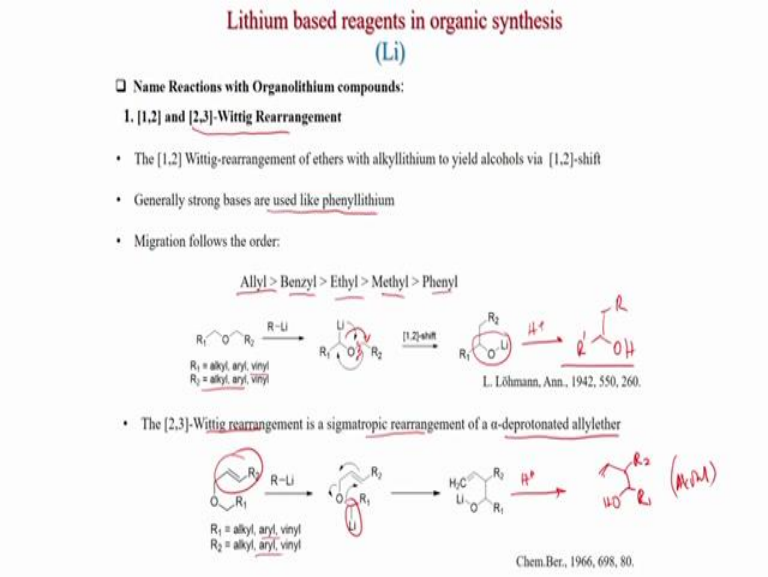

Name reactions – now we will discuss some name reactions of organolithiums, 1, 2 and 2,3 Wittig rearrangement, the 1,2 Wittig rearrangement of ethers with alkyllithium to yield alcohols via 1, 2 shift. Generally strong bases are used like phenyllithium. Migration follows the order: allyl, then benzyl, then ethyl, then methyl, phenyl, so this is the migration order, allyl better than benzyl than ethyl.

Suppose if you have this ether R1 is alkyl, aryl or vinyl, R2 also alkyl, aryl, vinyl then R lithium then what happen, one C-H will be deprotonated by this alkyl lithium species, this lithium is formed because this is stabilized with oxygen, now this carbon attacks here, this bond cleaves, so this one breaks and you get this one to shift that is why it is called one to shift and this is the form, this oxygen, carbon oxygen bond is cleaved and this become now you get a alcohol, so after treatment which aqueous workup you get the alcohol.

So alcohol is formed from an ether, also 2,3 Wittig rearrangement is a sigmatropic rearrangement of alpha deprotonated allylether so here is allyl group is present, so this is allyl group and R1 R2 can be alkyl aryl vinyl. Now alkyl lithium will deprotonate this one here this lithium species will form, this as to a double one and the migration will happen, now this carbon oxygen bond will cleave, here also after treatment with acidic workup you get this alcohol.

So what is the arrangements, here the allyl group is there, here also allyl is not there but the alcohol is formed from ether.

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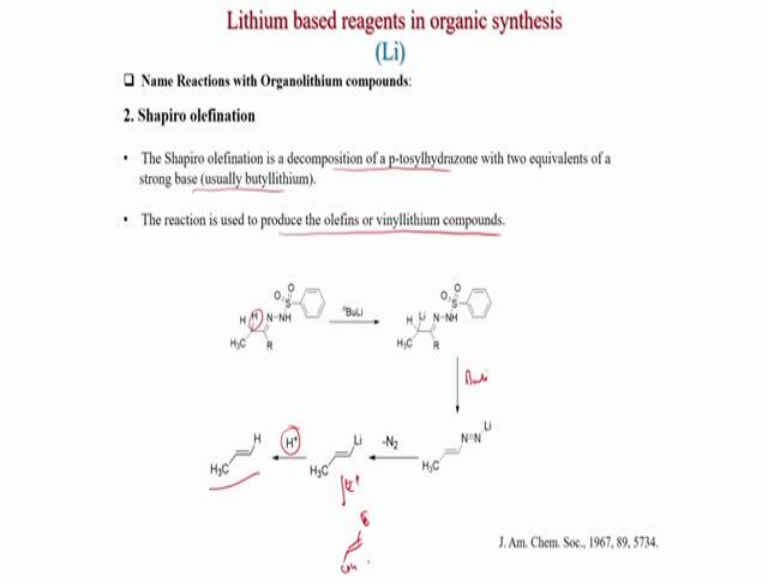

Shapiro olefination, Shapiro reaction already we discussed now it is a decomposition of para tosylhydrazone with two equivalents of strong base usually butyllithium, the reaction is to produce the olefins or vinyl lithium compounds so this is the hydrazone butyllithium, this proton getting deprotonated here, it is in both proton will get deprotonated, butyllithium this also will get deprotonated and after removal of sulfonyl group you generate this, after nitrogen elimination you get the vinyl lithium and if you treat with just aqueous workup then you get the alkene and if you treat with electrophile then the electrophile will come here.

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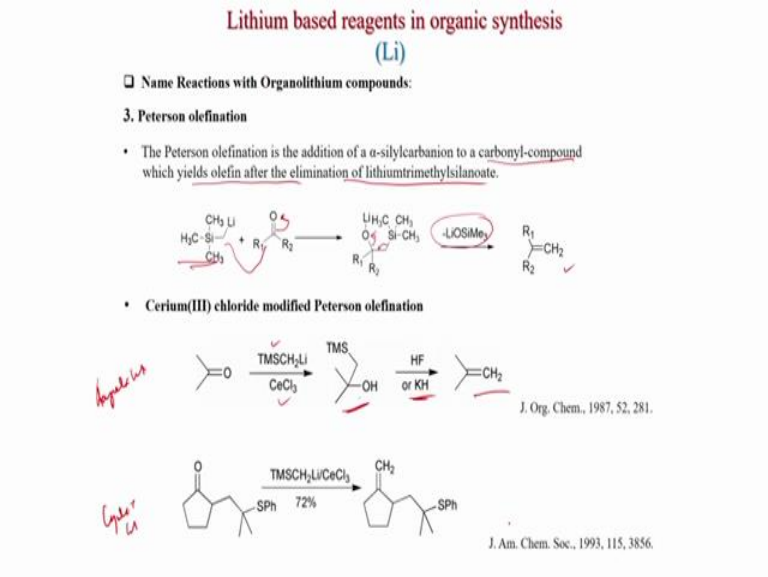

Peterson olefination, Peterson olefination is the addition of alpha silylcarbanion to carbonyl compound which yield olefin after the elimination of lithiumtrimethylsilanoate, this is the reagent that we have to add to the carbonyl compound, trimethylsilyles, lithiated species then this compound will form and now this we will eliminate that is the lithiumtrimethylsilanoate and you get an olefin, so like this you get a olefin here as the product.

Cerium chloride modified Peterson olefination like this reagent with cerium chloride give this intermediate, TMS and alcohol, now with treatment with HF or strong base KH you get the olefin, this method can be also used for cyclic ketones so this is acyclic ketone, this is cyclic ketone and you get this product.

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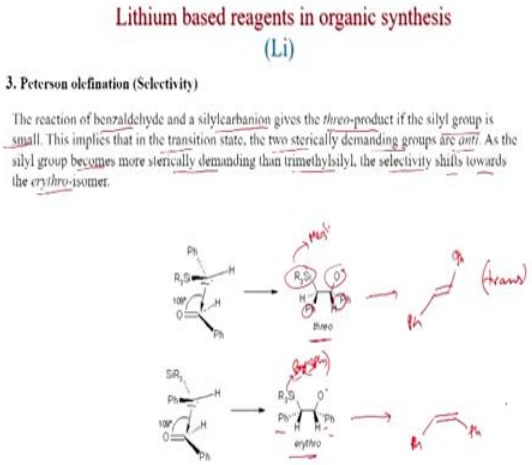

In the Peterson olefination the selectivity is very important like the reaction of benzaldehyde and silylcarbanion gives the threo product if the silyl group is small, this implies that in the transition state, the two sterically demanding groups are anti, as the silyl group becomes more sterically demanding than trimethylsilyl the selectivity shifts towards the erythro-isomer. Like here if you this silylated lithium compound, if you react with benzaldehyde then you get this threo isomer and in the threo isomer these two R3Si and O minus these are in the syn and these, if it is only small so like Me3Si then only this threo isomer will be stable.

And after elimination this threo isomer will give trans alkene because you can see these two phenyl groups are in the opposite side of each other, so you get trans alkene, also there is a possibility that if this phenyl is in the top then this erythro-isomer will form and in the erythro-isomer you can see this phenyl are in the syn to each other and this is only possible if this is big, big like Si Ph3 then this erythro will form and this erythro will generate the cis alkene, because you can see these two phenyls are in the same side so this will be cis.

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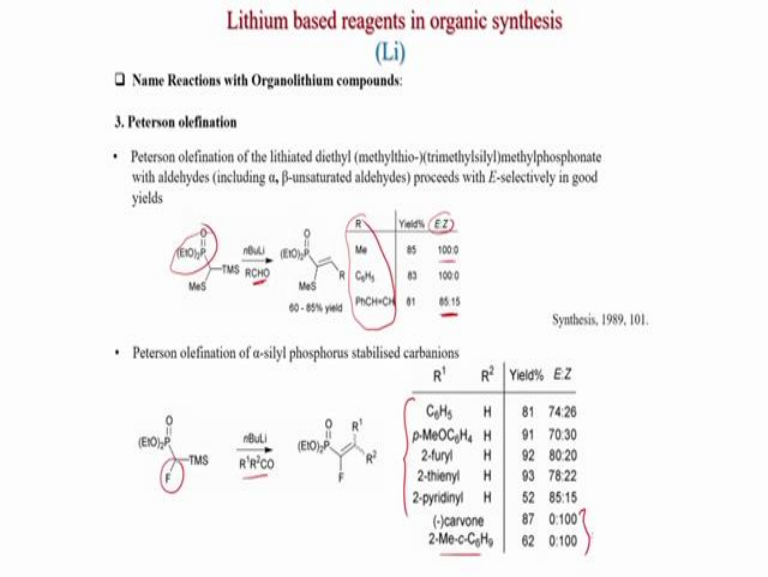

Now name reactions are Peterson olefination some more example of lithiated diethyl methylphosphonate with aldehydes including alpha beta unsaturated aldehydes proceeds with E selectivity in good yields. Like here this compound we treat it with n-butyllithium and different aldehyde, aldehyde is used and this will be the group here, bulky group here phosphonate and E is the major, here suppose 100 is to 0 so when R is equal to methyl then you get 100 percent E, then R is equal to phenyl you get 100 percent also.

And R is equal to cinnamyl then 85 percent. Now if there is a fluorine is there then also this reaction works and with it different ketones, defined ketones the product can be obtained in different ratio like here EZ ratio is formed, on the other hand carvone and two methyl cyclohexanone the Z compound is measured, so here Z is measured.

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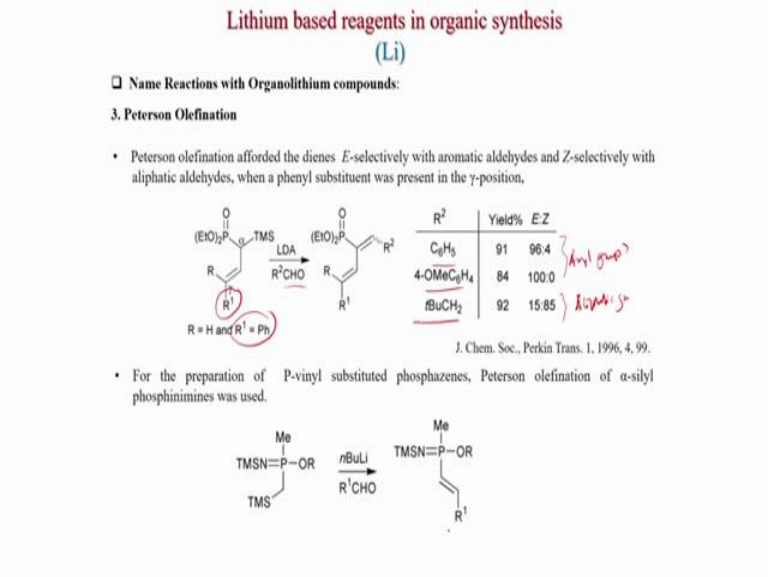

Some more example of Peterson olefination here also a phenyl substrate is here, R is 1 is equal to phenyl and double bond then with treatment with LDA and aldehyde you can get E selectivity is more, phenyl, for methoxyphenyl so this is aryl system, aryl group the E, on the other hand if aliphatic group is there then the Z is more, so aliphatic group when the Z is more, the selectivity getting reversed and also this para-vinyl substituted phosphazenes Peterson olefination is possible and you get these product.

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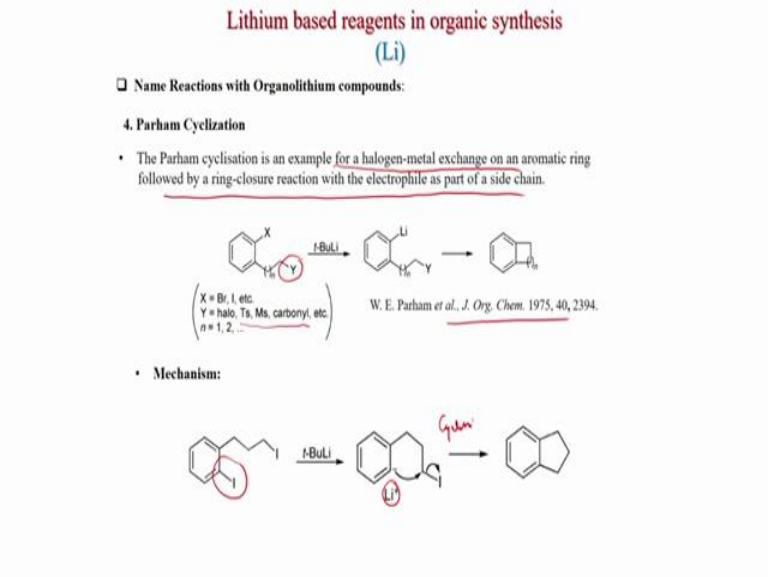

Now we will discuss lastly Parham cyclisation, Parham cyclisation is an example for halogen metal exchange of an aromatic ring followed by ring-closure reaction with the electrophile as part of side chain. So this is the side chain, this is leaving group, why is the leaving group halogen Ts, Ms mesityl carbonyl etc. now metal halogen exchange will happen and then the cyclisation. This was published first in JOC by Parham in 1975. What is the mechanism, now metal halogen exchange here and now this lithium will react here, cyclisation happens and you get this cyclic compound.

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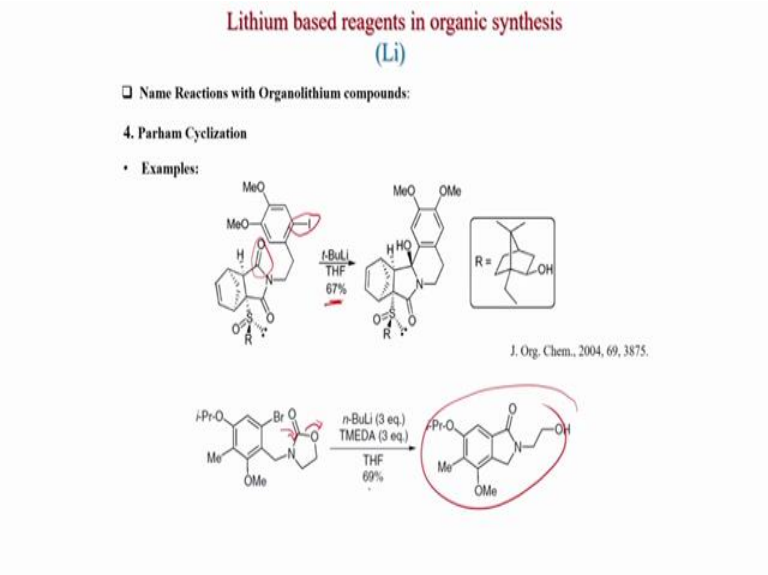

Some more examples here, the metal halogen exchange will happen and it adds to the this is the amide group and you get the cyclised product in 67 percent yield, also here metal halogen exchange will happen and then this will attack here and this will open so you get this product in 69 percent yield.

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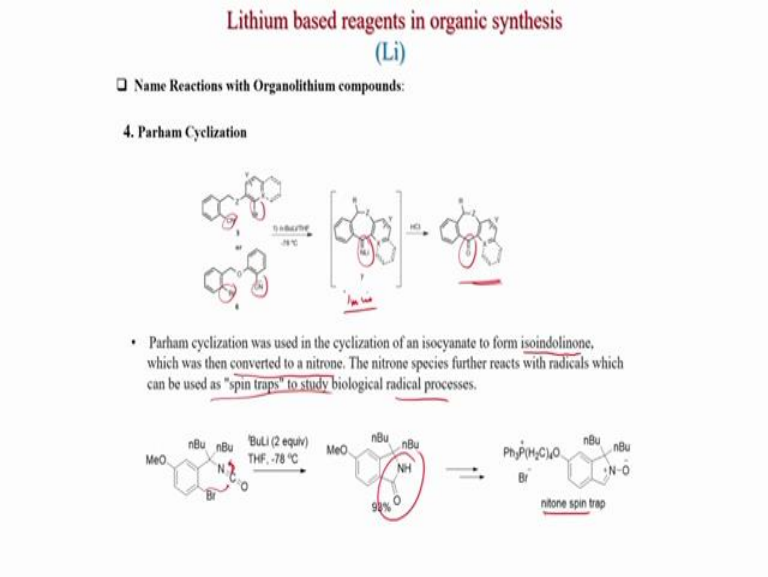

Also cyano group can be used as an electrophile species and when this bromo compound is exchanged with lithium, lithium compound is generated, then this can attack the cyano group to generate this imine species so this is imine species and this imine can be converted to carbonyl after acidic treatment so you can get this cyclic compound.

Also an isocyante to form isoindolinone which was then converted to nitrone, so this is the reaction here, here the lithium is formed and then this can react here, this double bond is moved here, so you get this amide here and the nitrone species further reacts with radicals which can be used as spin traps, so this can be compound converted to nitrone spin trap for the biological radical process.

So, today we have discussed lithium based reagents and first we have discussed defined procedure for preparation so we have first discussed that lithium treatment with alkyl bromide can generate N-butyllithium, then the CH proton that can be metalation that can be also possible, with N-butyllithium. You can and that is possibly mainly with aromatic system when a directed group is present then this metalation is very possible and also we have discussed the chiral metalation also is possible when sparteine and chiral lithium species is generated.

Then we have discussed the metal halogen exchange so metal halogen exchange also is possible and this is mainly useful for aryl system and aryl and vinyl species also this metal halogen exchange, if you have, halogen group is there then with N-butyllithium you can generate this

vinyl lithium or aryl lithium species which can be used for different reactions. Also transmetalation we have discussed like different metal like tin compound we have seen that it adds to the triple bond to generate the vinyl stannane and when it is treated with n-butyllithium then the tin is converted to the lithium species.

Then we have discussed different reactions of this alkyllithium species so different reactions like the metal halogen exchange we have seen that different electrophiles can be incorporated after metal halogen exchange, also the metalation reaction also we have seen the different electrophiles can be incorporated and we have seen the conjugate addition, this is also very useful reaction for alkyl as well as aryl lithium species, conjugate addition to alpha beta unsaturated ester and if a chiral ligand is present then you can control the selectivity.

Also carbonyl 1,2 addition also is possible and we have seen the selective 1 4 addition if you put some HMPA then the 1 4 addition that is thermodynamic stable is forming and with sparteine we have seen that chiral coordination that is the actually that is the N Boc pyrrolidine, even aliphatic also N Boc cases with sparteine you can generate the chiral lithium species and there chiral lithium you can treat with different electrophile to generate the chiral compound.

And lastly we have seen some name reaction like Shapiro reaction, the hydrazone, then the butyllithium is generated vinyl lithium and treatment with different electrophile you can get the substituted olefin, also Peterson olefination we have seen that if trimethylsilyl group is there then you can get the selectively E product and lastly we have seen the cyclisation, Parham cyclisation where a metal halogen exchange is first occurred and then followed by cyclisation reaction where a electrophile is already present in the molecule then the cyclisation will happen and this is very useful to get different cyclic product, thank you.