Principles of Organic synthesis
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Lecture 8
Organometallic Reagents

Welcome you all to principles of organic synthesis. At present, we study the organometallic reagents. So far, in this topic, we had one lecture where we studied the principles of reactions of organometallic reagents for the carbon-carbon bond formation. Then, we studied the preparation and reactions of Grignard reagents. In this lecture, we will study the organolithium reagents.

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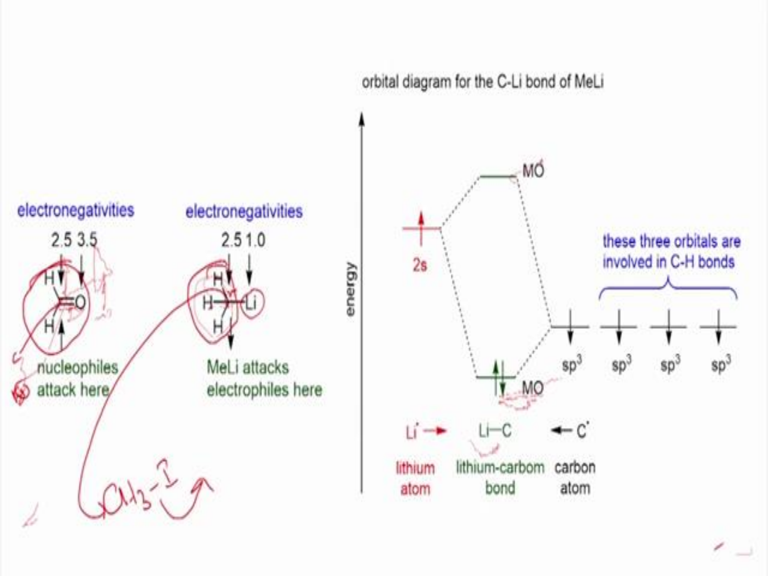

As you can see in this slide, if you look at the structure of methyllithium as an example, the electronegativity of lithium is 1 and carbon is 2.5. Thus, the sigma bond pair is polarized towards the carbon. In other words, carbon is nucleophilic.

If you remember in the beginning of the last lecture, where we studied the principles of the reaction of organometallic reagents. As you know, for example, in this case, the methyl group can act as a nucleophile. For example, if we react with methyl iodide, as we have seen earlier, it can undergo substitution reaction to give ethane. On the other hand, for example, if you react with formaldehyde, it can lead to addition reaction to produce ethanol.

Here you can see the energy level diagram of the molecular orbital of Cu-Li bond. The energy level of the bonding molecular orbital is very close to the sp^3 hybridized orbital of carbon compared to the 2s orbital lithium. Thus, the contribution of the sp^3 hybridized orbital in the Cu-Li bond formation is higher compared to the 2s orbital. Therefore, the electron density in the carbon is greater and acts as a base or nucleophile.

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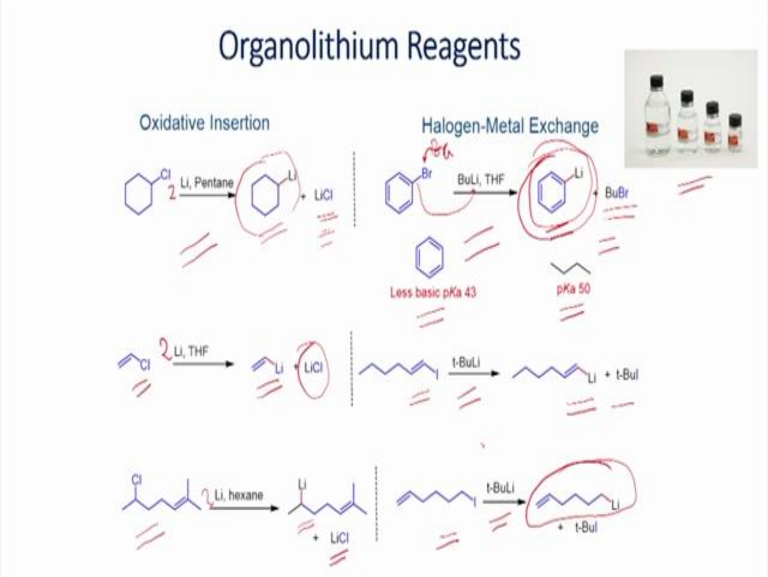

Organolithium Reagents

Oxidative Insertion

Halogen-Metal Exchange

Now let us see the preparation of the organolithium reagents and the application for the carbon carbon bond formation. If you look at here, you can find there are two methods are shown for the preparation of the organolithium reagents. The first one involves the reaction of halosubstrates with lithium metal to give the organolithium reagent where you generate one equiv of lithium salt as by product.

Let us look at the first example. One equiv of Li is converted to cyclohexyllithium and the other equiv of Li is converted to lithium chloride. Similarly, vinyl chloride with two equiv of Li gives vinyllithium and lithium chloride. You can also react alkyl chloride bearing the double bond, which can give the alkyllithium along with one equiv of lithium chloride.

This is an example for the oxidative addition. If you remember the Grignard reagent, where you react alkyl halide with magnesium to generate organomagnesium chloride. Similarly, here, alkyl halide undergoes addition reaction with Li via oxidative addition to give the organolithium reagent.

The other method involves the preparation of the organolithium reagent via the halogen metal exchange. The first example involves the reaction of bromobenzene with butyllithium to give phenyllithium where you generate bromobutane as a byproduct. The reason is because if you look at here this hydrogen is less acidic, therefore, you can form this product.

Similarly, vinyl iodide with tertiary butyllithium provides vinyl lithium. The third example involves the alkyl halide where you have the double bond, which can be reacted with tertiary-butyllithium to give the alkyllithium as the reagent.

There are also commercial available organolithium reagents. You can also make organolithium reagent from alkyl halide as shown where you have to use two equiv of lithium. Alternatively, you can also try to react with butyllithium or tert-butyllithium by halogen metal exchange to make organolithium reagent.

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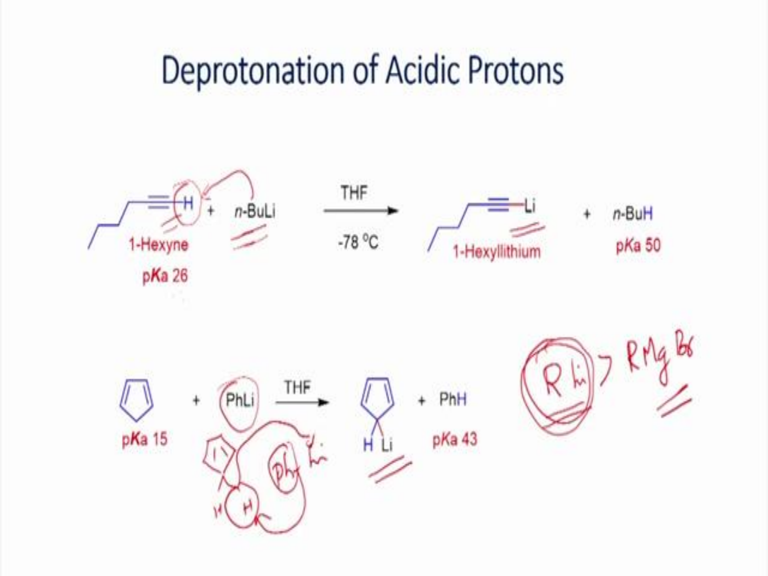

Deprotonation of Acidic Protons

In addition, if you have the substrate with acidic hydrogen, that can also react. For example, you have the terminal alkyne where you have the acidic hydrogen (pka 26), which can react with n-butyllithium to give the alkynyllithium reagent. Similarly, let us look at cyclopentadiene, which can react with phenyllithium to give the cyclopentadienyllithium reagent.

As we have seen the Grignard reagent, lithium reagent is also very sensitive to moisture and air. Therefore, we have to keep the reagent under inner atmosphere. Further, if you remember the principles of the reaction of organometallic reagents that we studied for the carbon carbon bond formation, the reactivity of the organolithium is greater compared to organomagnesium reagent. Particularly if we have alkyllithium, which are very reactive, and thus we have to store at low temperature. Otherwise, it may undergo self-coupling.

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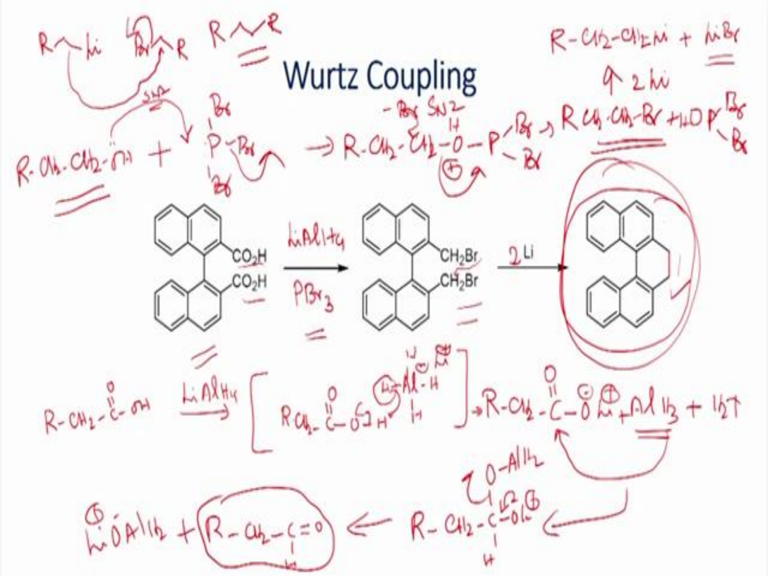

Wurtz Coupling

Now let us look at one example for the Wurtz coupling. If you look at the reaction, first the carboxylic acid is reduced to alcohol that can be done using lithium aluminum hydride. Which is further converted to the corresponding alkyl bromide. This can be reacted with lithium to give the C-C coupled product.

All of you know the reduction of carboxylic acid to alcohol. For example, you have the carboxylic acid, which can be reduced using lithium aluminum hydride. When you react with lithium aluminum hydride, first it acts as a base and deprotonate the carboxylic acid hydrogen. You will be able to form the lithium carboxylate intermediate, which reacts with aluminum hydride or lithium aluminum hydride to generate the intermediate. This can be converted to aldehyde, which can be further reacted with aluminum hydride to give the corresponding alcohol as the product.

The primary alcohol can undergo reaction with PBr_3 to form the intermediate, which can lead to S_N2 reaction with bromide anion to give the alkyl bromide. Therefore, if you have carboxylic acid, you can try to reduce using lithium aluminum hydride, and the resultant primary alcohol can react with PBr_3 to give the corresponding alkyl bromide.

Once you have the alkyl bromide, it can be reacted with lithium that can lead to the C-C coupled product. In this way, you can try to couple if you have the dihalo compound.

In summary, if you have the alkyl halide you can convert to alkyl lithium, which can react with another alkyl halide and you can make the carbon-carbon bond.

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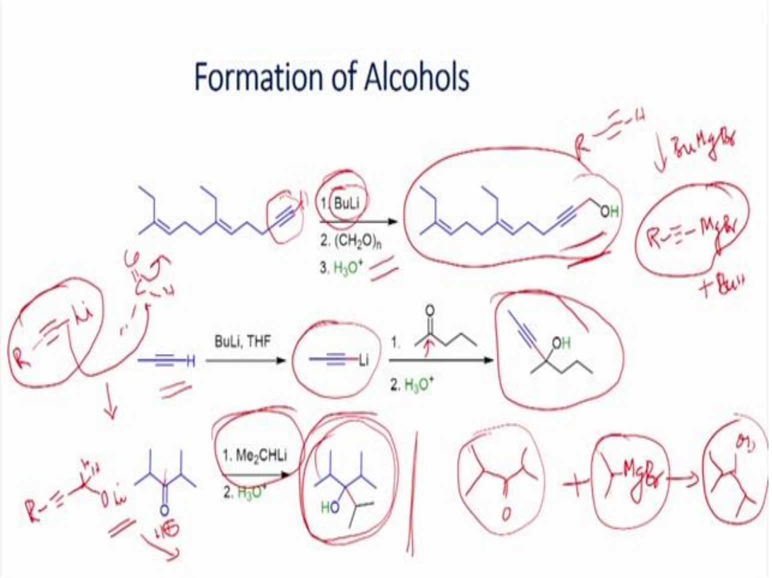

Formation of Alcohols

Now let us look at the reaction the alkyne with n-butyllithium to give the alkynyllithiuim that reacts with paraformaldehyde to give the primary alcohol.

The next example involves the reaction of alkyne with n-nutyllithium where you can generate the corresponding alkynyllithium that can undergo addition reaction with ketone to produce tertiary alcohol.

The third example involves the reaction of diisopropyl ketone with isopropyllithium, which can undergo addition reaction to give the tertiary alcohol as the product. This is an important example because the reaction using Grignard reagent does not give the additional product. Instead, it reduces the carbonyl group to secondary alcohol due to the bulkiness of the isopropyl group. On the other hand, isopropyl lithium readily undergoes addition reaction to generate the tertiary alcohol as the product.

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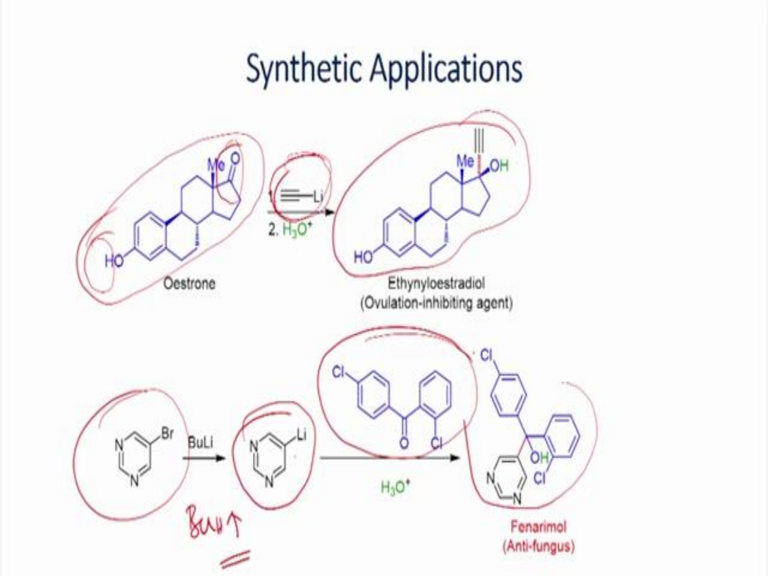

Synthetic Applications

This slide shows some more examples. The first example involves the reaction of the cyclic ketone with alkynyllithium, which undergoes addition reaction to give alcohol as the product. Here you have to use an excess of the reagent because you have the OH group. Once the reaction is over, when you do the work up, you can regenerate the OH group. The product is used as an ovulation-inhibiting agent.

The next example involves the reaction of heteroaryl bromide with n-butyllithium to generate heteroaryllithium, which undergoes addition reaction with ketone to give the tertiary alcohol as the product that is used as an anti-fungal agent.

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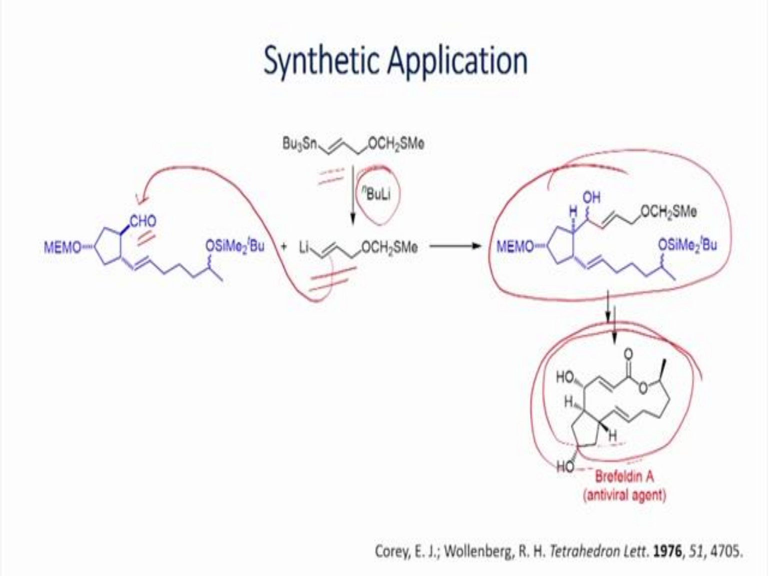

Synthetic Application

Brefeldin A
(antiviral agent)

Corey, E. J.; Wollenberg, R. H. *Tetrahedron Lett.* **1976**, *51*, 4705.

This slide shows some more example for the addition reaction with aldehyde. In this case, vinyl tin undergoes reaction with butyllithium through transmetallation to give vinyllithium, which can undergo addition reaction with the aldehyde to produce the allylic alcohol as the product. This has been converted to anti-viral macrocyclic lactone by several steps. Here the crucial step is the addition reaction of the vinyllithium with aldehyde to give alcohol, which has been further converted to the microcyclic lactone.

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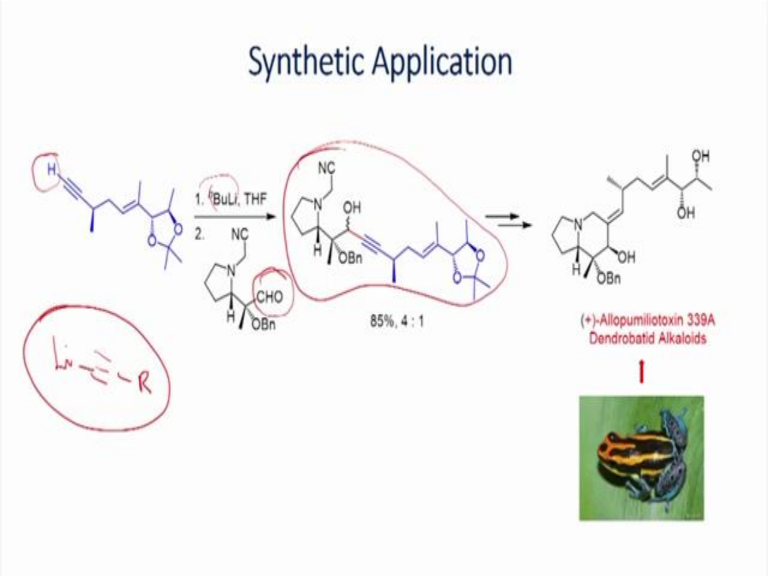

Synthetic Application

85%, 4 : 1

(+)-Allopumiliotoxin 339A
Dendrobatid Alkaloids

The other example involves the reaction of terminal alkyne bearing a double bond and ketal functional groups. It can be selectively reacted with n-butyllithium to produce the corresponding alkynyllithium, which undergoes addition reaction with the aldehyde functional group to give the addition product. The alcohol has been further converted to the alkaloid by several steps. As you can see here, organolithium plays a crucial role in the synthesis of complex molecule. We can use the reagent to undergo addition with carbonyl compound to give the alcohol that can be further converted into useful compounds.

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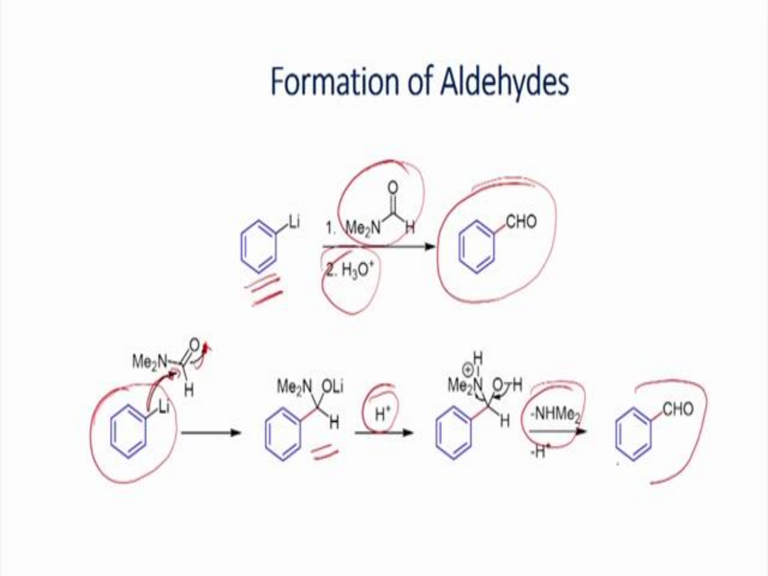

Formation of Aldehydes

This example involves the reaction of phenyllithium with DMF to produce benzaldehyde. Phenyllithium undergoes addition reaction with DMF to give lithiumalkoxide, which on acid work up converts to aldehyde. This is an important reaction if you want to convert aryl halide to the corresponding aryl aldehyde.

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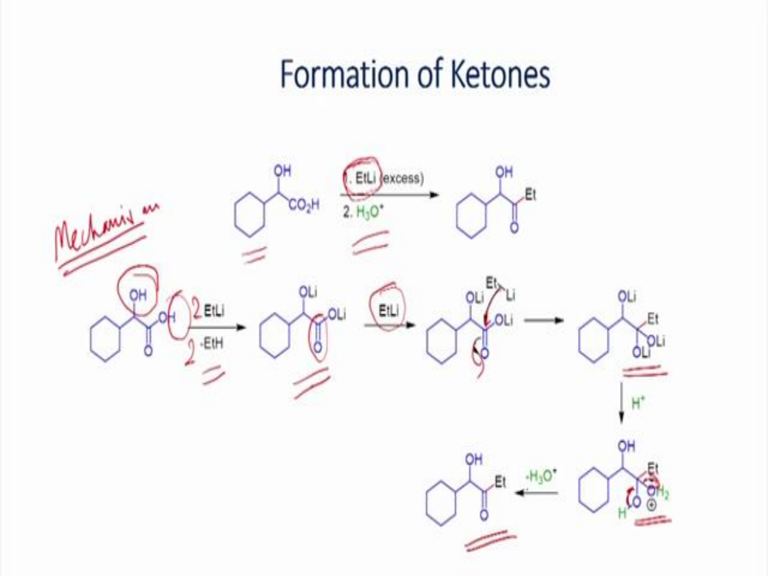

Formation of Ketones

The next example involves the reaction of carboxylic acid with an excess alkyllithium. If you try to remember the Grignard reaction, which can undergo addition to carbon dioxide to give the carboxylic acid. Here carboxylic acid can be readily reacted with an excess lithium to give ketone as a product. This is because as we have seen in the earlier lecture, organolithium is more reactive compared to Grignard reagent. Therefore, organolithium can undergo further reaction with lithium carboxylate to give ketone as the product.

Let us see the mechanism. Since the compound has OH group, you have to use 2 equiv of ethyllithium to generate the lithium salt. Once you form the salt, the carbonyl group of the lithium carboxylate can undergo further reaction with an another equiv of ethyllithium via 1,2-addition as shown here to form the salt. Which on work up loses water molecule and produces the ketone as the product.

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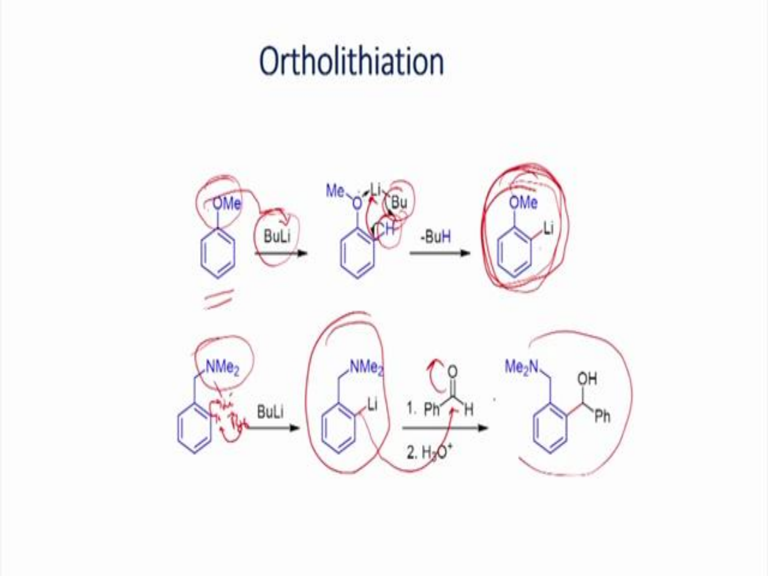

Ortholithiation

Now, let us look at the effect of chelating group in the formation of organolithium. For example, when you react anisole with n-butyllithium, you can selectively do ortholithiation. The lone pair of methoxy group makes chelation with alkyllithium and you will form the intermediate. The alkyl group can act as a base and deprotonate the *ortho* hydrogen of the aromatic ring to lead the *ortho*-lithiation.

The next example involves the chelation of the dimethylamino group with butyllithium, which facilitates the *ortho*-lithiation. This is further reacted with benzaldehyde to give the addition product.

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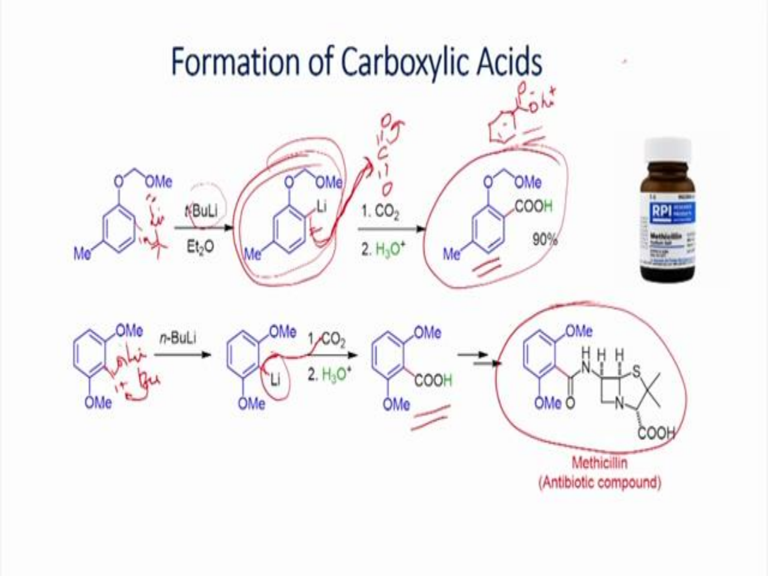
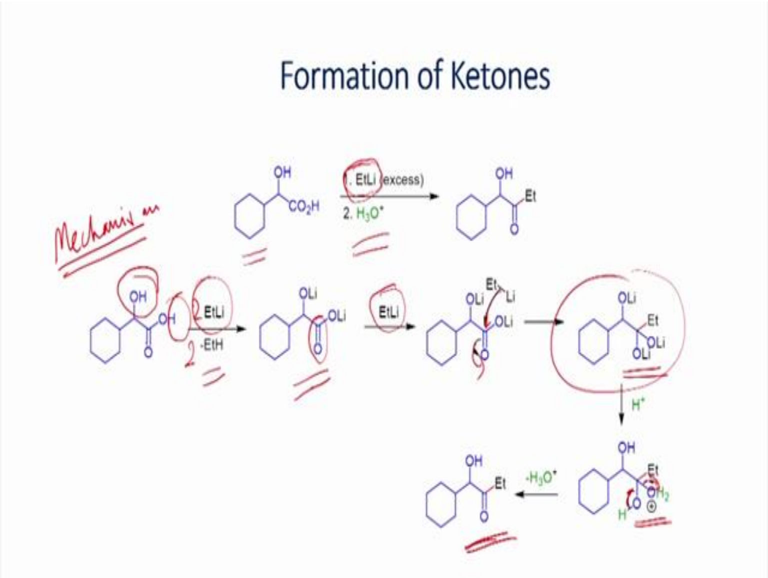

Formation of Carboxylic Acids

Let us see an application of chelating group assisted lithium in the synthesis of biologically active compound. Chelation of MOM ether with tertiary butyllithium facilitates the *ortho* lithiation of the aromatic ring. Which reacts with carbon dioxide to produce the carboxylic acid derivative.

Now let us look at the next example, the chelation of methoxy group facilitates the regioselective lithium of the aromatic ring. Which undergoes reaction with carboxylic acid to give aryl carboxylic acid. This has been further converted into methicillin, which we use an antibiotic compound.


Formation of Ketones

If you remember the previous reaction, where we have seen the reaction of carboxylic acid with alkyllithium to give ketone as the product. Whereas here aryllithium undergoes reaction to give the lithium carboxylate, which does not undergo further reaction, because aryllithium is less reactive compared to alkyllithium. Thus, the carboxylate on work up generates the carboxylic acid as the product.

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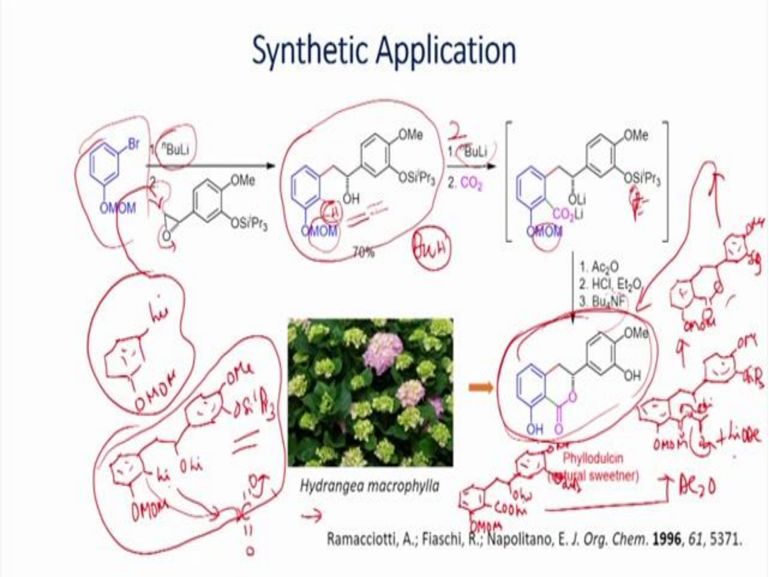

Synthetic Application

Hydrangea macrophylla

Ramacciotti, A.; Fiaschi, R.; Napolitano, E. *J. Org. Chem.* **1996**, *61*, 5371.

Now, let us look at the reaction with epoxide. In this case, the reaction of aryl bromide with n-butyllithium gives the aryllithium, which undergoes reaction at the less sterically hindered carbon of the epoxide to give the alcohol product. Which can be further reacted with excess n-butyllithium since you have the OH as well as MOM chelating group to give the aryllithium. Reaction with carbon dioxide will give the lithium carboxylate, which can be reacted in situ with acetic anhydride to give the lactone as the product. Reaction with HCl will cleave the MOM ether, while tetrabutylammonium fluoride can cleave the silyl ether to produce the target product.

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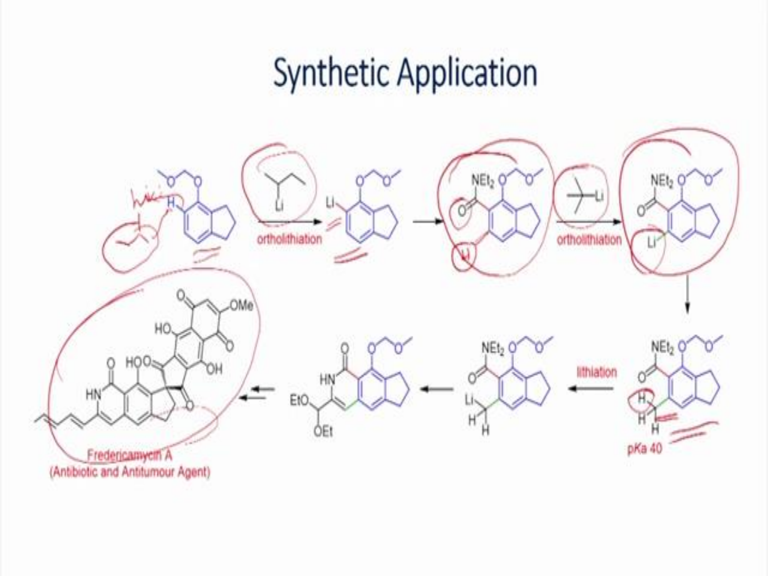

Synthetic Application

Fredericamycin A
(Antibiotic and Antitumour Agent)

Here an another example is shown for the chelation assisted lithiation. In this case as just we have seen, the MOM ether can make chelation with the secondary butyllithium, and facilitate the ortholithiation of the aryl ring. Conversion to amide and ortholithiation utilizing the amide carbonyl chelation can produce the aryllithium intermedate. Which is reacted with methyl iodide. Lithiation of the methyl C-H and acetal formation, and subsequent transformation gives the antibiotic polycyclic compound.

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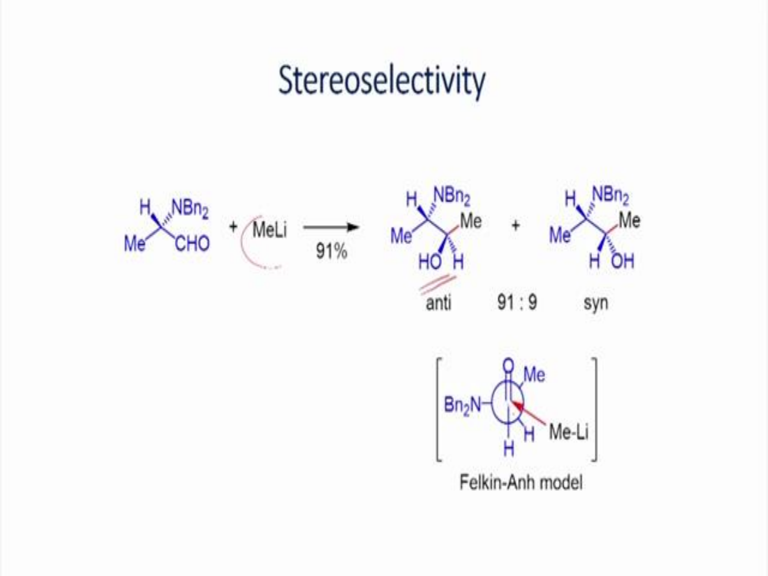

Stereoselectivity

Felkin-Anh model

Here an example is shown for the stereoselective addition of methyllithium with aldehyde bearing chiral center at the α–carbon. When you react with methyl lithium, as you can see here, methyllithium undergoes addition reaction with the carbonic group through the less sterically hindered side to give anti compound as a major product with the diastereomeric ratio 91:9. You have two face of the carbonyl group, and can try to selectively react with alkyllithium with good diastereoselectivity.

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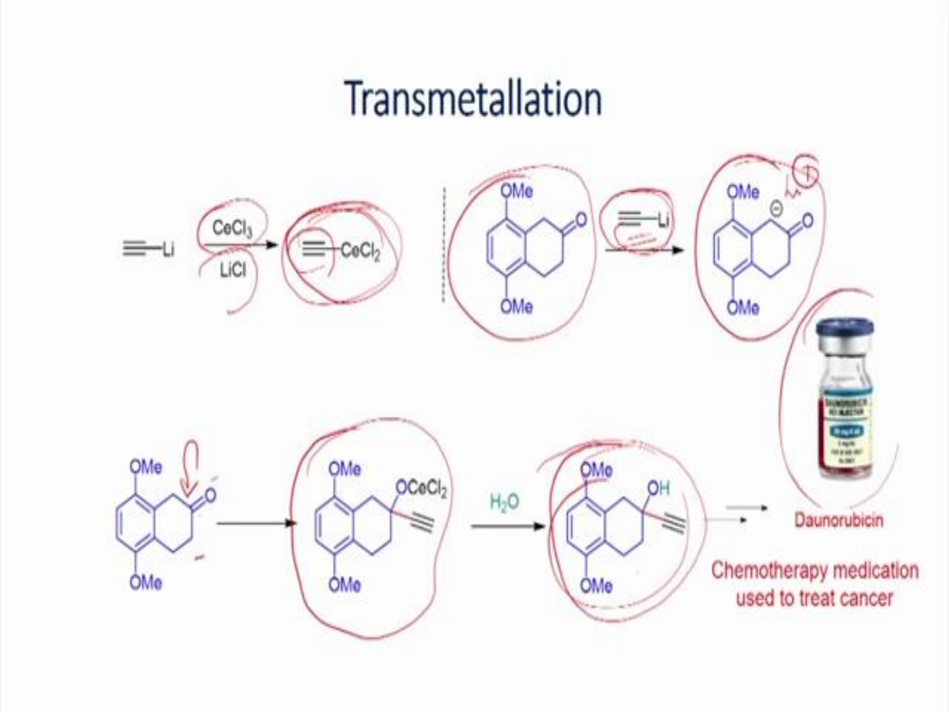

Transmetallation

Daunorubicin

Chemotherapy medication used to treat cancer

Organolithium reagents also widely find applications for the carbon-carbon bond formation via transmetallation. In this example, alkynyllithium with cerium(III) chloride gives the alkynylcerium reagent, which undergoes 1,2-addtion with the carbonyl group to give the alcohol, which has been further converted to daunorubicin. Instead, if the alkynyllithium is used, which will act as a base compared to nucleophile. Thus, it will deprotonate the benzylic C-H next to the carbonyl group instead of the addition reaction. Therefore, organolithium can be converted to more useful compound through transmetallation that can lead to very interesting carbon-carbon bond formation.

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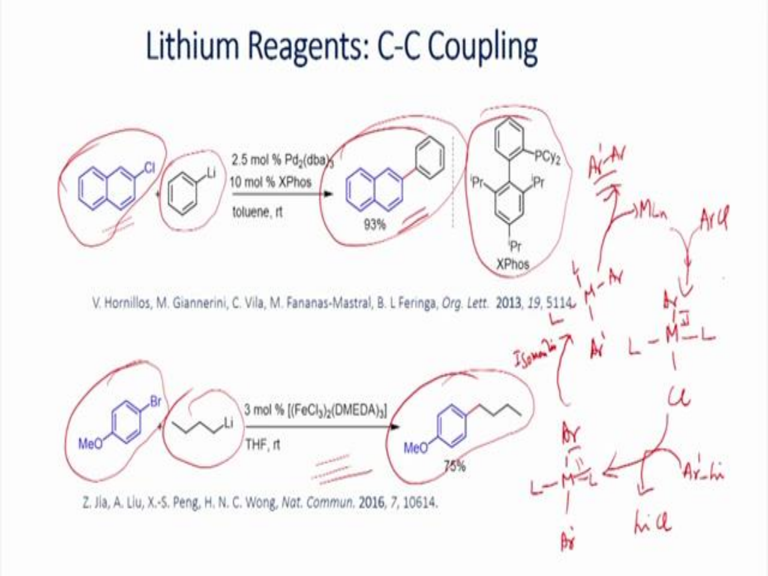

Lithium Reagents: C-C Coupling

V. Hornillos, M. Giannerini, C. Vila, M. Fananas-Mastral, B. L Feringa, *Org. Lett.* 2013, *19*, 5114.

Z. Jia, A. Liu, X.-S. Peng, H. N. C. Wong, *Nat. Commun.* 2016, *7*, 10614.

The next example involves the reaction of phenyllithium. Naphthyl chloride with phenyllithium can be coupled using palladium catalyst to give the biaryl system. Similarly, you can couple alkyl lithium with aryl halide to introduce alkyl chain via C-C coupling reaction.

Now, let us look at the mechanism. Palladium undergoes oxidative addition with halo substrate. For example, if you take aryl chloride, oxidative addition gives the Pd(II) intermediate. Which can react with aryllithium via transmetallation to produce the Pd9II) intermediate. Trans-cis isomerization and reductive elimination can produce the C-C coupled product.

If you remember the Kumada coupling, where the reaction of alkyl/aryl halide with alkyl/aryl magnesium halide has been demonstrated using palladium as well as the nickel based catalytic systems. Where if you remember, the metal first undergoes oxidative addition with alkyl or aryl halide, which then reacts with the Grignard reagent through transmetallation. The latter undergoes isomerization and the reductive elimination to give the C C coupled product.

Similarly, here the metal undergoes oxidative addition with this alkyl or aryl halide, which then leads to transmetallation with alkyl aryllithium. Isomerization and reductive elimination give the C-C couple product to complete the catalyst cycle. In addition, organolithium also find wide applications to make soft nucleophile for example Gilman reagent, which we will study in the next lecture.

For example, if you have methyllithium, you can try to react it with copper(I) iodide to form organocopper, which can be further reacted with another equiv of methyllithium to furnish the Gilman reagent (lower order cuprate). If you compare the nucleophilicity, the methyl group of the Gilman reagent is less nucleophilic compared to methyl group of methyllithium. Therefore, Gilman reagent can be used for the conjugate addition reaction.

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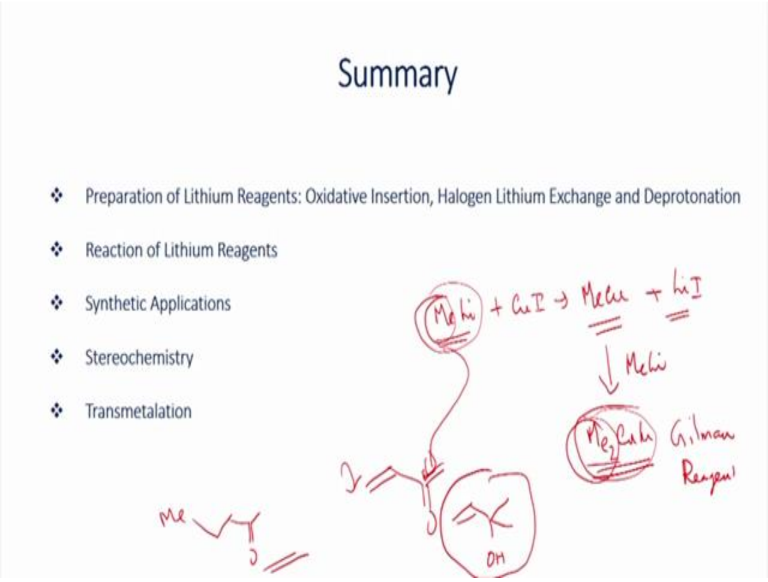

Summary

- Preparation of Lithium Reagents: Oxidative Insertion, Halogen Lithium Exchange and Deprotonation
- Reaction of Lithium Reagents
- Synthetic Applications
- Stereochemistry
- Transmetalation

In summary, we have seen the preparation and reactions of lithium reagents. In the preparation, we have seen three approaches. In the first approach, we have seen the reaction of halo substrate with the 2 equiv of lithium metals. In this reaction, you generate one equiv of lithium halide as a byproduct. In the second approach, we have seen the reaction of halo substrates with alkyl lithium, where the halogen metal exchange takes place to generate organolithium, in which, you generate alkyl halide as a byproduct.

In the third approach, if the substrate has acidic hydrogen, you can try to react those substrates with alkyllithium, where alkyllithium acts as a base and you can deprotonate the acidic hydrogen to generate organolithium. For example, if you take terminal alkyne or cyclopentadienyl substrate you can deprotonate using n-butyllithium, and will be able to form the corresponding organolithium compounds.

Then we have seen the reactions of organolithium. First we have seen the addition reaction to aldehydes and ketones to get the corresponding alcohol as the product. If you have phenyllithium, you can react with dimethylformamide to form benzaldehyde. Thus, if you aryl halide, you can convert to aryllithium reagent, which can react with dimethylformamide to give the aryl aldehyde as the product.

Next, we have seen the reactions of epoxides as well as alkyl halide. The nucleophilic ring opening of epoxide takes place at the less hindered carbon. Alkyl halide can be coupled via nucleophilic substitution, Then, we have seen the addition reaction of diisopropyl ketone with isopropyllithium to give the tertiary alcohol. Next, we have seen the addition to carbon dioxide to get carboxylic acid as the product. In case of alkyllithium, the lithium carboxylate can further undergo reaction to give the ketone as the product.

Then, we have ortholithiation using chelating group for the regioselective functionalization and their application for the construction of complex molecules. At the end, we have seen the transmetallation approach, for the carbon-carbon bond formation. There is also one example using iron based catalyst for the coupling of organolithium reagents with alkyl halide through transmetallation. With this we conclude this lecture, thank you very much.