Symmetry, Stereochemistry and Applications
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Lecture - 37
Oxidizing Agents in Organic Chemistry and Organometallic Compounds

Welcome to the course entitled Symmetry, Stereochemistry and Applications. In the previous lecture, we have been discussing about various organic reactions. And in those lectures we have talked about the different reducing agents and their effects on various carbonyl compounds.

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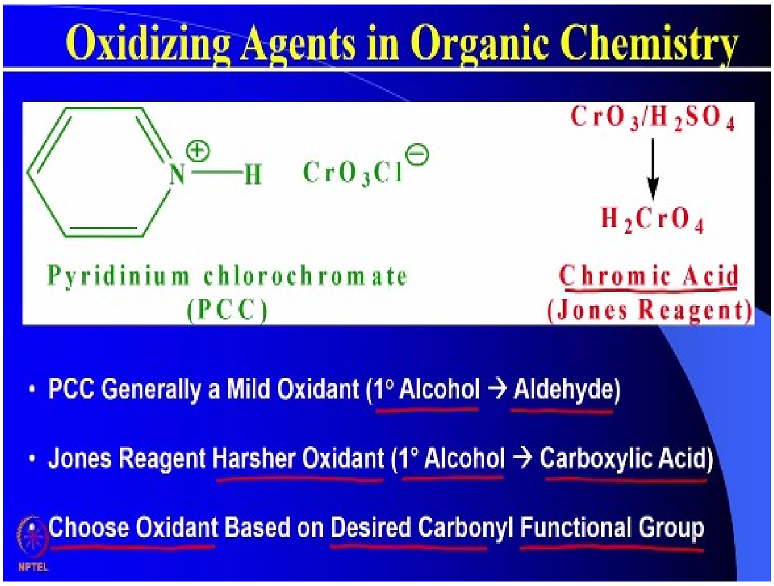

Oxidizing Agents in Organic Chemistry

- PCC Generally a Mild Oxidant (1° Alcohol → Aldehyde)
- Jones Reagent Harsher Oxidant (1° Alcohol → Carboxylic Acid)
- Choose Oxidant Based on Desired Carbonyl Functional Group

So in today’s lecture we will start with the discussion on the oxidizing agents in organic chemistry. Some of you may have studied in your 10 plus 2, different oxidizing agents in organic chemistry and those are chromic acid, pyridinium chlorochromate or in abbreviation written as PCC or potassium permanganate, which are routinely used in organic synthesis for oxidizing various compounds.

PCC is generally considered as a mild oxidizing agent. And it oxidizes 1 degree alcohol or primarily alcohol to aldehyde. Jones reagent, which is chromic acid is a harsher oxidizing agent and it oxidizes 1 degree alcohol to a carboxylic acid. This Jones reagent can be easily prepared in the lab using potassium dichromate and concentrated sulfuric acid. So what we do is we choose the oxidant based on the desired carbonyl functional group that we want upon oxidation.

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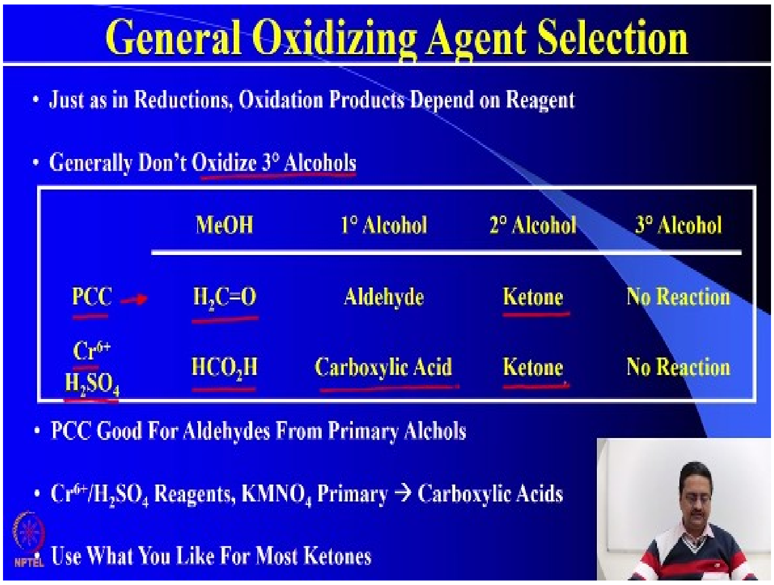

General Oxidizing Agent Selection

- Just as in Reductions, Oxidation Products Depend on Reagent
- Generally Don't Oxidize 3° Alcohols

	MeOH	1° Alcohol	2° Alcohol	3° Alcohol
PCC	$H_2C=O$	Aldehyde	Ketone	No Reaction
Cr^{6+} H_2SO_4	HCO_2H	Carboxylic Acid	Ketone	No Reaction

- PCC Good For Aldehydes From Primary Alchols
- Cr^{6+}/H_2SO_4 Reagents, $KMNO_4$ Primary → Carboxylic Acids
- Use What You Like For Most Ketones

So just like the previous lecture where we talked about the effect of different reducing agent on various organocarbonyl compounds, here I am tabulating the effects of these two oxidizing agents on various alcohols and the corresponding products. We generally do not try to oxidize 3 degree alcohols. We only try to oxidize methanol, 1 degree alcohol or 2 degree alcohol.

So if you use PCC, pyridinium chlorochromate, it can oxidize methanol to formaldehyde, 1 degree alcohol to any other higher aldehyde, 2 degree alcohol to a ketone. And it does not have any effect on a 3 degree alcohol. You see that this oxidation using PCC is restricted up to aldehyde and ketone and it does not oxidize the alcohol to the highest oxidation state, that is carboxylic acid.

If you want to do that, if you want to oxidize a compound to its carboxylic acid, then we should use this chromic acid or Jones reagent which oxidizes methanol to formic acid, 1 degree alcohol to a corresponding carboxylic acid. And of course, a 2 degree alcohol can only be oxidized up to ketone and not to a carboxylic acid. So depending on what kind of product you are trying to form, we should choose appropriate oxidizing agent and the reaction conditions.

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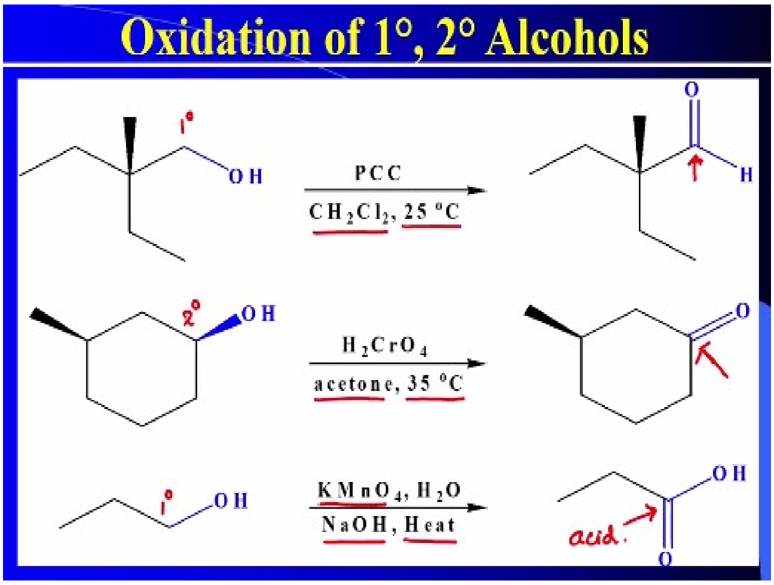

Oxidation of 1°, 2° Alcohols

So let us see a few examples here. So in this particular first example, this alcohol is a 1 degree alcohol. And when you are using PCC in presence of dichloromethane at room temperature, we are getting an aldehyde prepared. When we have a 2 degree alcohol which is shown here as a cyclic alcohol, a cyclohexanol derivative and in presence of acetone as a solvent at about room temperature, the reaction yields a ketone.

And on the other hand, if you just use 1 degree alcohol and use potassium permanganate in alkaline medium and heat it where this aqueous KMnO4 heated with sodium hydroxide solution, this 1 degree alcohol is then converted to the corresponding carboxylic acid. So depending on what kind of reagent you are choosing the product is different. In the first case, we have seen the formation of aldehyde.

Second case it has formed a ketone. And in the third case, when we have changed the reagent from chromic acid to a potassium permanganate then we are getting a carboxylic acid as the product.

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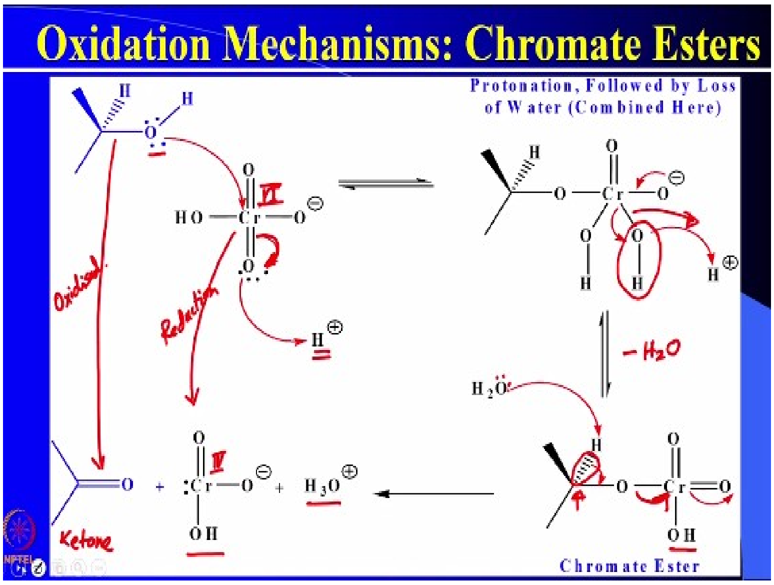

Oxidation Mechanisms: Chromate Esters

Protonation, Followed by Loss of Water (Combined Here)

Chromate Ester

Let us see how this reaction proceeds, how the oxidation reaction happens using the chromic acid oxidizing agent. So when you take an alcohol, which has lone pair of electrons, so that lone pair of electrons attacks the chromium center and the carbon oxygen bond opens up as is shown here and it forms a chromate ester.

And as the reaction is happening in acidic medium so immediately the chromium oxygen bond opens and OH bond is formed. So you have two OH groups and one anionic O minus in the molecule. So this compound then further rearranges by the formation of a fresh carbon oxygen double bond and elimination of this OH as water molecule and this forms this compound which is called the chromate ester.

This chromate ester then further reacts with the water molecule which takes up the proton from the carbon adjacent to the oxygen and double bond forms with the electrons that are present in the carbon hydrogen bond with the oxygen and oxygen chromium bond gets broken. As a result, H3O+ that is the acid is released and a ketone is formed along with the reduced form of the chromium reagent.

If you see here the oxidation state of chromium here is 6. And in this case, the oxidation state of chromium is 4. So there is a reduction of the chromium reagent. Whereas the substrate is oxidized. So hope this reaction mechanism is clear to you.

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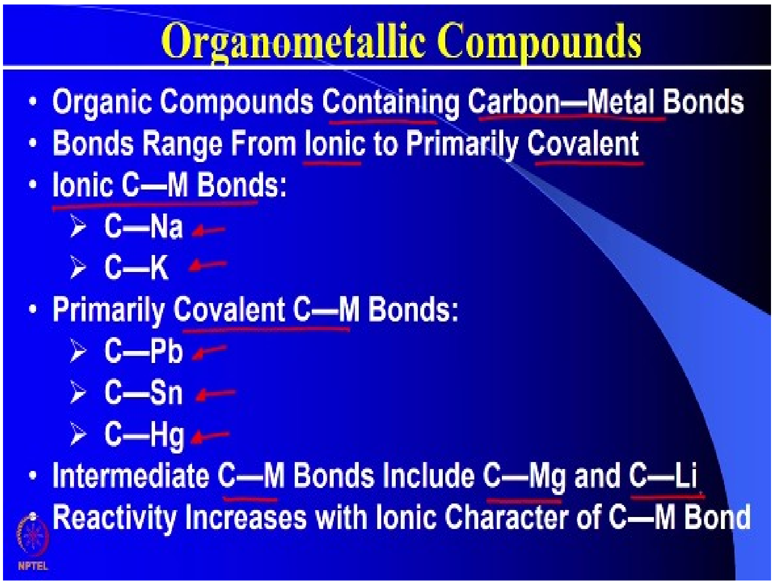

Organometallic Compounds

- Organic Compounds Containing Carbon—Metal Bonds
- Bonds Range From Ionic to Primarily Covalent
- Ionic C—M Bonds:
  - C—Na
  - C—K
- Primarily Covalent C—M Bonds:
  - C—Pb
  - C—Sn
  - C—Hg
- Intermediate C—M Bonds Include C—Mg and C—Li
- Reactivity Increases with Ionic Character of C—M Bond

Let us try to then see other different organic reagents that are used in various organic reactions. So let us start discussing about organometallic compounds. As you can understand, this course is a very basic course and we will just discuss a few organometallic reagents and their reactions and the products that they form and the reaction mechanisms will not be discussed at this point.

This organometallic compounds are those compounds which contains a carbon-metal bond. This bond, carbon-metal bond ranges from ionic to covalent. So some of the carbon-metal bond may be ionic in nature, some may be purely covalent in nature and some may be intermediate, that is between ionic and covalent in nature. So examples of carbon-metal bonds which are ionic are carbon-sodium bond, carbon-potassium bond.

Whereas the primarily covalent bonds are carbon-lead, carbon-tin and carbon-mercury compounds. The intermediate carbon-metal bonds are very important. Those are carbon-magnesium and carbon-lithium, which forms a character which is which has similarity between both of ionic and covalent bonds. And the reactivity increases with ionic character of carbon-metal bond.

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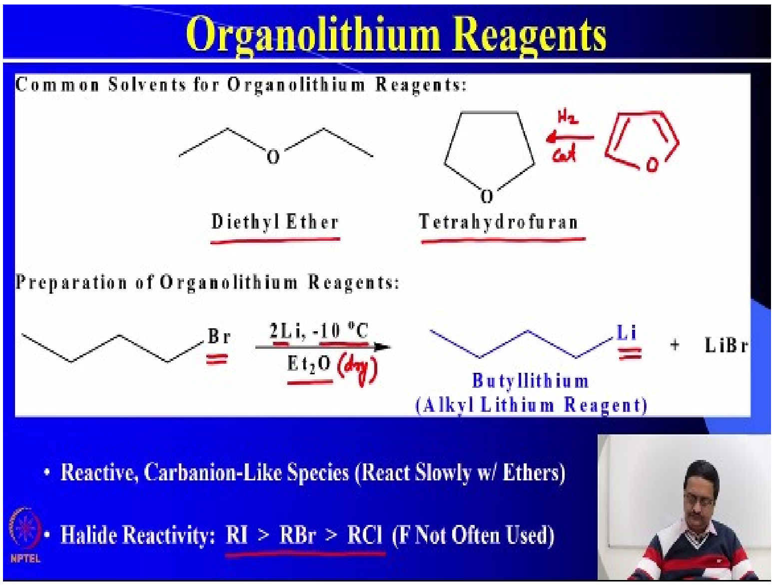

Organolithium Reagents

Common Solvents for Organolithium Reagents:

Diethyl Ether

Tetrahydrofuran

$\xleftarrow[\text{cat}]{H_2}$

Preparation of Organolithium Reagents:

Br $\xrightarrow[\text{Et}_2\text{O (dry)}]{\text{2Li, -10 °C}}$ Li + LiBr

Butyllithium
(Alkyl Lithium Reagent)

- Reactive, Carbanion-Like Species (React Slowly w/ Ethers)
- Halide Reactivity: RI > RBr > RCl (F Not Often Used)

So when we try to use this reagents which have carbon-metal bond, these reagents are always very highly moisture sensitive. That means, they are hygroscopic in nature. So the reactions would be done in a very dry condition and without any trace of moisture. So for those type of reactions we use two different types of solvents; two different solvents, both are ethers. One is diethyl ether and the other one is tetrahydrofuran.

Some of you may recall that this compound is called furan, which is then hydrogenated to give you the tetrahydrofuran. So normally what we do is we take these solvents and we dry those solvents on metallic sodium. As some of you may be aware that metallic sodium is highly reactive towards water.

The solvents are taken in a round bottom flask with sodium and then the mixture is boiled for a long period of time with a condenser on top of it. And then after few hours of boiling with sodium, the solvents are then distilled and collected in round bottom flask and used for further reaction. So this drying of solvent is very important in this particular case.

So when you use this dry solvent, the dry diethyl ether with lithium at -10 degree centigrade and alkyl halide gets converted to the corresponding alkyl lithium compound. Here it is butyllithium compound. Remember that this butyllithium compound is highly moisture sensitive. Therefore, the reaction has to be done under nitrogen atmosphere in a very dry condition.

The reactivity of halide is as usual that iodides are more reactive than bromides and bromides are more reactive than chloride. And the alkyl fluorides are not generally used because the carbon fluorine bond is very strong and it cannot be broken so easily at -10 degrees centigrade.

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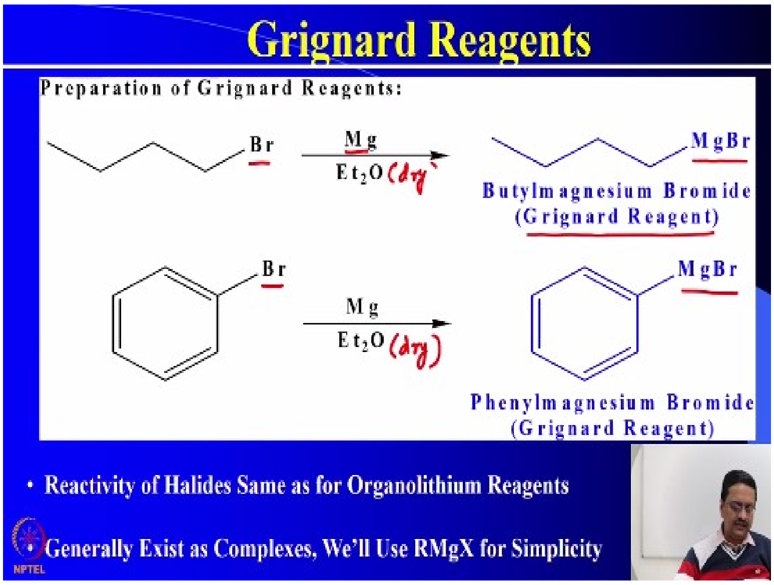

Grignard Reagents

Preparation of Grignard Reagents:

Butylmagnesium Bromide
(Grignard Reagent)

Phenylmagnesium Bromide
(Grignard Reagent)

- Reactivity of Halides Same as for Organolithium Reagents
- Generally Exist as Complexes, We'll Use RMgX for Simplicity

The one of the most important organometallic reagent is Grignard reagent, which you must have heard about. So a Grignard reagent **is** can be formed if you treat an alkyl halide with metallic magnesium in dry ether. It forms this magnesium bromide which is here the butyl magnesium bromide called the Grignard reagent. This reagent is also highly moisture sensitive.

So we should use always the dry solvent to make this compound. So even with phenyl bromide or bromobenzene, you can generate phenyl magnesium bromide using the same reaction procedure. Again the reactivity of these halides are same for organolithium compounds. That is RI is most reactive and then RBr and then RCl.

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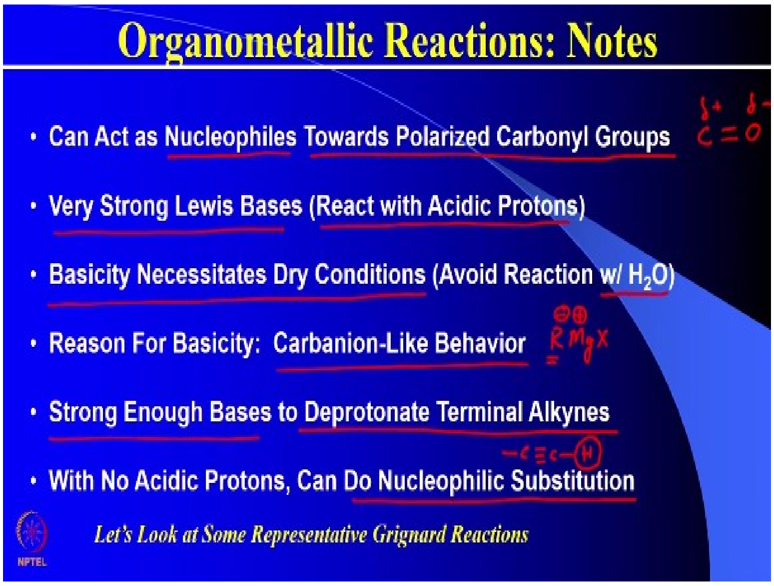

Organometallic Reactions: Notes

- Can Act as Nucleophiles Towards Polarized Carbonyl Groups $\overset{\delta+}{C}=\overset{\delta-}{O}$
- Very Strong Lewis Bases (React with Acidic Protons)
- Basicity Necessitates Dry Conditions (Avoid Reaction w/ H_2O)
- Reason For Basicity: Carbanion-Like Behavior $\overset{\ominus}{R}\overset{\oplus}{Mg}X$
- Strong Enough Bases to Deprotonate Terminal Alkynes $-C\equiv C-\textcircled{H}$
- With No Acidic Protons, Can Do Nucleophilic Substitution

Let's Look at Some Representative Grignard Reactions

So these organometallic reactions, organometallic reagents can act as nucleophiles towards polarized carbonyl groups that means, C double bond O group which is del plus and del minus, that is the polarized carbonyl group. They act as very strong Lewis bases. So they react with acidic protons. So they react with alcohol, they react with acid, they react with acetylene, where the acetylene proton is acidic.

This basicity requires a very high dry condition. So we always avoid contamination of water. The basicity, the reason for basicity is the carbon ion like behavior. RMgX can be considered as R- MgX+ and a polarized compound where the R is like a carbanion.

Therefore, it behaves as a strong base. So this is a strong enough base to deprotonate terminal alkyne, which I have already indicated, which means, if you have a C triple bond CH group, it can deprotonate that hydrogen from this compound. If there is no acidic proton, it can do nucleophilic substitution reaction as well. So in the next slide, let us see some of the representative Grignard reactions.

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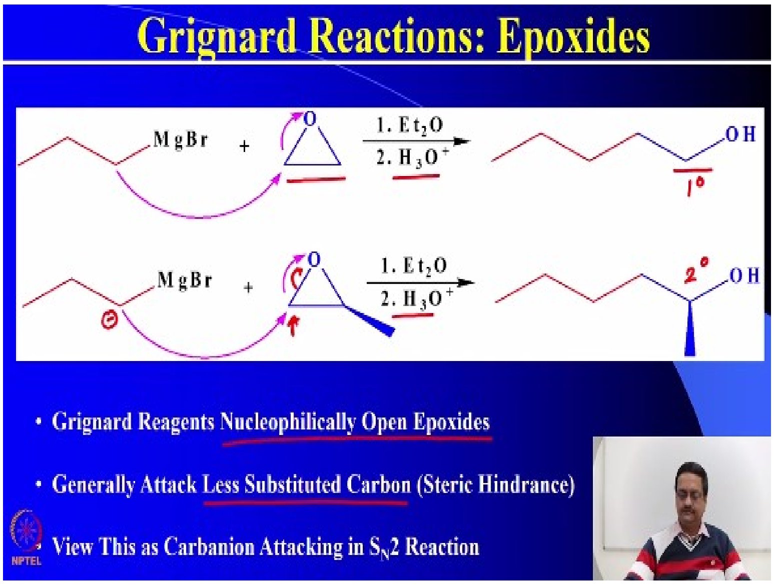

Grignard Reactions: Epoxides

- Grignard Reagents Nucleophilically Open Epoxides
- Generally Attack Less Substituted Carbon (Steric Hindrance)
- View This as Carbanion Attacking in S_N2 Reaction

So when you use a Grignard reagent with a cyclic ethyl like this, which reacts with the alkyl magnesium bromide and upon hydrolysis it forms a 1 degree alcohol. This cyclic ether which is substituted here react in the same manner to generate a 2 degree alcohol.

So Grignard reagent nucleophilically opens these epoxides and generally attacks less substituted carbon, which is here and view this reaction as a carbon ion atom in the form of SN2 reaction. This negatively charged or negatively polarized carbon attacks the less hindered site and simultaneously the carbon oxygen bond opens up to give you a reaction intermediate which upon hydrolysis gives you the product, 2 degree alcohol.

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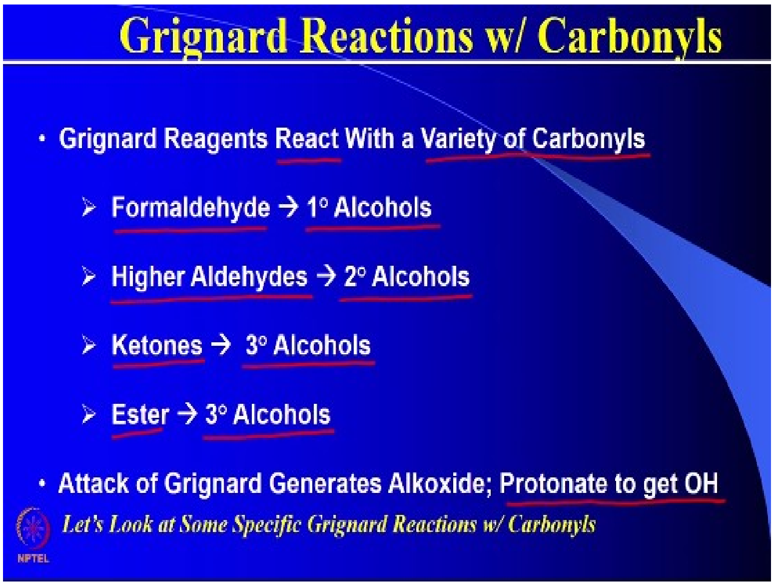

Grignard Reactions w/ Carbonyls

- Grignard Reagents React With a Variety of Carbonyls
  - Formaldehyde → 1° Alcohols
  - Higher Aldehydes → 2° Alcohols
  - Ketones → 3° Alcohols
  - Ester → 3° Alcohols
- Attack of Grignard Generates Alkoxide; Protonate to get OH

Let's Look at Some Specific Grignard Reactions w/ Carbonyls

So when you use this Grignard reagents with different carbonyls, you get different types of products. Grignard reagents react with a variety of carbonyl compounds. If you treat formaldehyde with a Grignard reagent, you will get a 1 degree alcohol. Any other aldehyde will lead to 2 degree alcohols. Ketones will form a 3 degree alcohol and esters also will form 3 degree alcohol.

So attack of Grignard reagent generates alkoxides and protonated to get the OH substituted in the compound.

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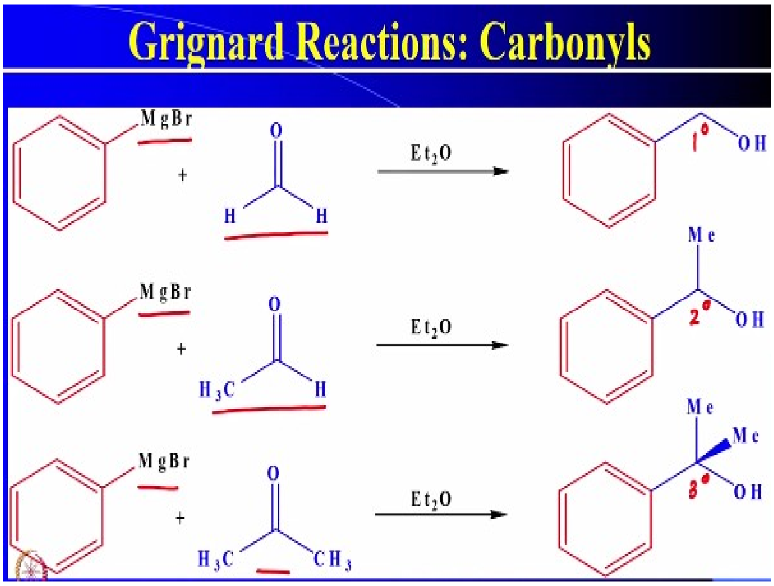

Grignard Reactions: Carbonyls

So let us see a couple of such examples. In case of phenylmagnesium bromide treated with formaldehyde, generates a 1 degree alcohol which is benzyl alcohol. This phenyl magnesium bromide when it is treated with the acetaldehyde that is 2 carbon aldehyde it generates a 2 degree alcohol. Phenyl magnesium bromide when treated with a ketone generates a 3 degree alcohol.

So depending on the substrate on which the same Grignard reagent is treated, you generate different alcohols of different degree.

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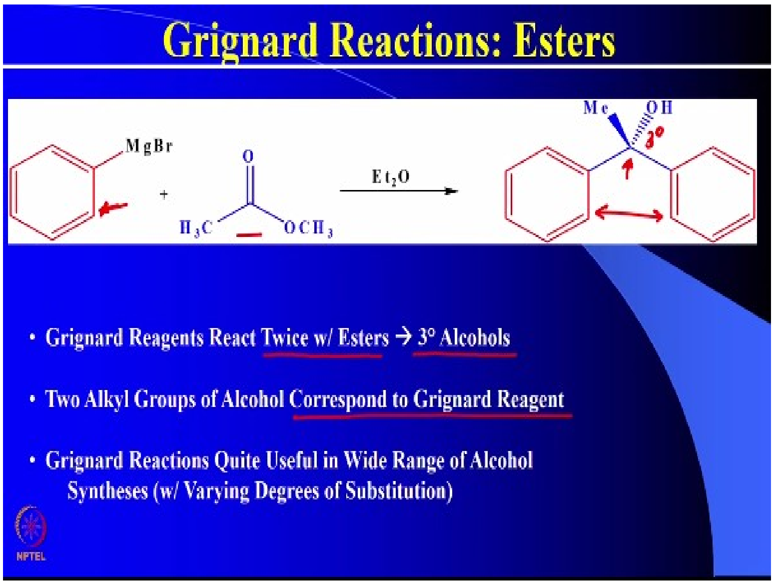

Grignard Reactions: Esters

- Grignard Reagents React Twice w/ Esters → 3° Alcohols
- Two Alkyl Groups of Alcohol Correspond to Grignard Reagent
- Grignard Reactions Quite Useful in Wide Range of Alcohol Syntheses (w/ Varying Degrees of Substitution)

When the same phenylmagnesium bromide is treated an ester, this reaction happens in two steps. It reacts two times with esters to form a 3 degree alcohol which contains the alkyl or allyl groups that are there in the Grignard reagent. So with one equivalent of the ester two equivalents of Grignard reagent reacts to form a three degree alcohol, right?

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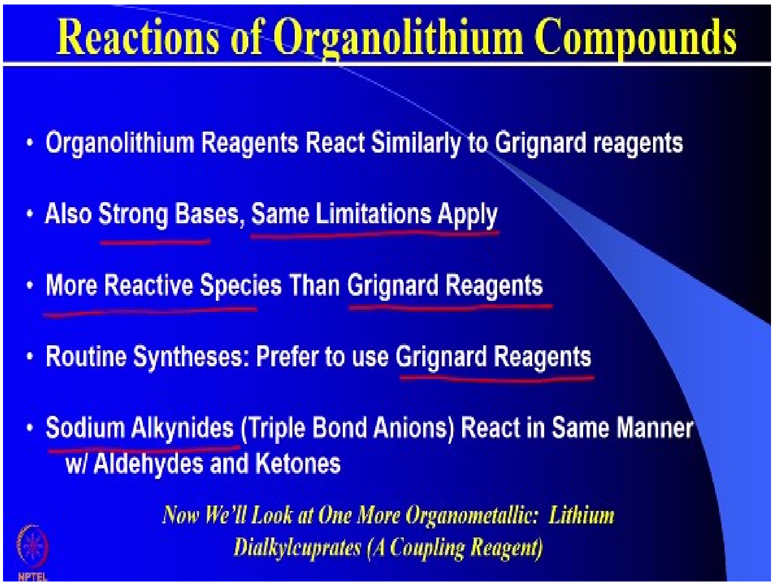

Reactions of Organolithium Compounds

- Organolithium Reagents React Similarly to Grignard reagents
- Also Strong Bases, Same Limitations Apply
- More Reactive Species Than Grignard Reagents
- Routine Syntheses: Prefer to use Grignard Reagents
- Sodium Alkynides (Triple Bond Anions) React in Same Manner w/ Aldehydes and Ketones

Now We'll Look at One More Organometallic: Lithium Dialkylcuprates (A Coupling Reagent)

Now let us see some of the reactions of organolithium compounds. Organolithium reagents react similarly to Grignard reagents. They are also strong bases and have same limitations like they are highly moisture sensitive. Therefore, one has to maintain the moisture free and oxygen free conditions and therefore, we should use the reagents under nitrogen atmosphere only.

These reagents are more reactive than Grignard reagents. So routine synthesis we always prefer to use Grignard reagents which are less reactive. And this alkynides like the triple bonded anions react in the same manner with aldehydes and ketones.

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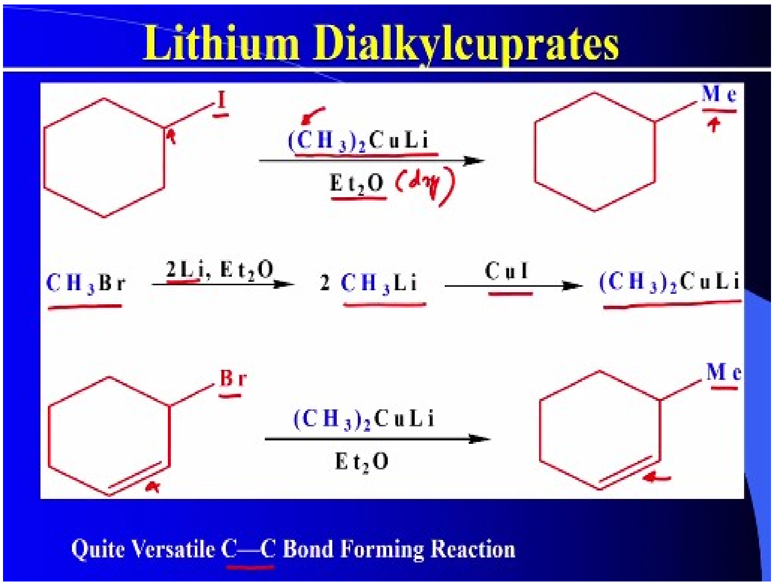

Lithium Dialkylcuprates

$$CH_3Br \xrightarrow{2Li,\ Et_2O} 2\ CH_3Li \xrightarrow{CuI} (CH_3)_2CuLi$$

Quite Versatile C—C Bond Forming Reaction

So when you try to understand some of these reactions, first we need to make the corresponding lithium dialkylcuprate reagent. So when you treat methyl bromide with two equivalents of lithium, you get the methyl lithium and then if you treat methyl lithium with copper iodide, you get dimethyl lithium cuprate.

So this dimethyl lithium cuprate is the corresponding organometallic compound that we use to convert a number of different organic compounds. So here the example is that iodocyclohexane is converted to methylcyclohexane using dimethyl lithium cuprate in dry ether medium. Or a bromo compound is converted to this methyl compound keeping this double bond unaltered in the reaction medium.

So this reaction is very useful in the formation of a new C-C bond. Here, this carbon is now bonded to another carbon which is coming from your reagent which has a methyl group. So there are many such reactions in which you will encounter these organic and organometallic reagents.

I would like to suggest that you please go through the textbook that are prescribed for this course and follow those reactions from the textbook. In the following lecture, in the coming next lecture, I will discuss about some of those reactions and give some examples. Thank you.