Principles of Organic Synthesis
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Lecture 14
Electrophilic Aromatic Substitution

Welcome you all to Principles of Organic Synthesis. Presently, we study the electrophilic aromatic substitution. So far, we covered the principles of the electrophilic aromatic substitution and Friedel-Crafts reactions. In this lecture, we will study the formylation and related reactions.

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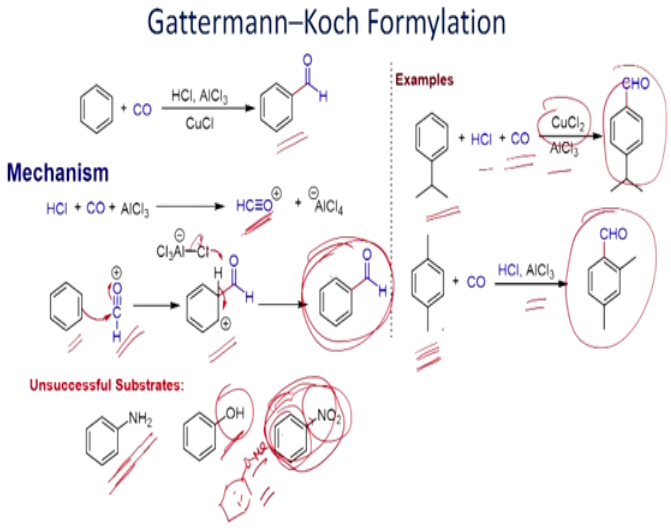

This slide shows the Gattermann-Koch formylation. Benzene reacts with carbon monoxide in the presence of HCl and $AlCl_3$ to give benzaldehyde. The reaction is usually carried out under high pressure. Alternatively, you can also use CuCl. As you can see, CuCl helps to undergo the reaction of the carbon monoxide with HCl to form the acylium cation. Once you form the acylium cation, which is the electrophile, and undergoes reaction with benzene to produce the carbocation intermediate. Removal of proton gives benzaldehyde.

You can see here the reaction of isopropylbenzene with carbon monoxide in the presence of $AlCl_3$, HCl and $CuCl_2$ to give 4-isopropylbenzaldehyde. The next example shows the reaction of *para*-xylene with carbon monoxide in the presence of $AlCl_3$ and HCl to produce 2,4-dimethylbenzaldehyde.

However, these reactions have some limitations. For example, if the substrate has functional group like amino, hydroxyl, ether and nitro, the reaction does not work. This is because when you have the amino or hydroxy group, it makes chelation with the Lewis acid. Similarly, ether can make chelation with the Lewis acid and the reaction can be slowed, while nitro is an electron withdrawing group and, thus, the nucleophilicity of the aryl ring is considerably reduced.

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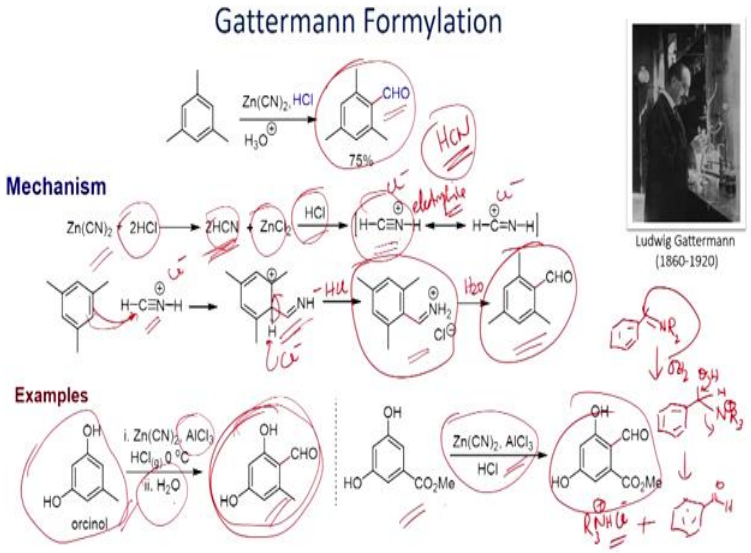

Just we have seen the Gattermann-Koch reaction where you use the combination of carbon monoxide, HCl and Lewis acid for the formylation. In place of carbon monoxide, you can also use hydrogen cyanide. This is known as the Gattermann formylation. Since hydrogen cyanide is toxic what you can do, you can start with zinc cyanide and hydrochloric acid to generate hydrogen cyanide in situ, which protonates and acts as the electrophile. Reaction with aromatic system gives the carbocation. Removal of proton by chloride ion followed by hydrolysis of the imine gives the aldehyde.

Let us see the application of Gattermann formylation for the functionalized aromatic systems. For example, orcinol undergoes formylation. Similarly, 3,5-dihydroxymethylbenzoate can be readily reacted to give the aldehyde. These reactions utilize the combination of zinc cyanide, HCl and $AlCl_3$. These results suggest that phenol derivatives can be formylated.

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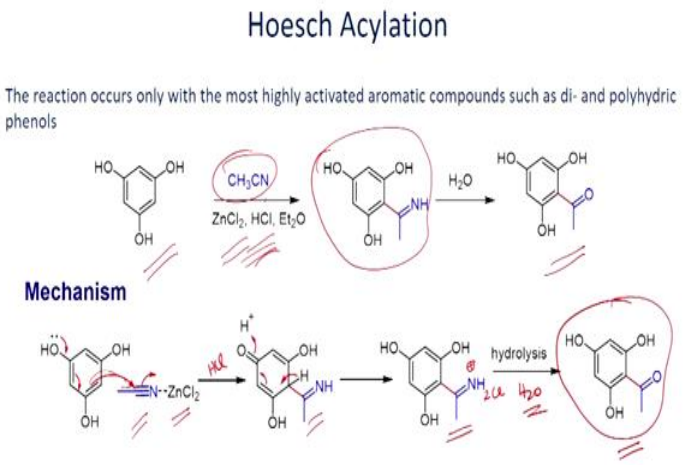

Just we have seen two examples for the formylation. First one involves the combination of carbon monoxide, HCl and Lewis acid, while the second example involves the combination of hydrogen cyanide, HCl and Lewis acid. Now, let us look at here the acylation using the combination of acetonitrile, zinc(II) chloride and HCl to give imine that can be hydrolyzed.

For example, polyhydroxy phenol can be readily reacted to give polyhydroxyacetophenone. Acetonitrile is activated by zinc(II) chloride via chelation that reacts as the electrophile with the polyhydroxy phenol to produce the imine derivative. Chloride ion from HCl helps to convert the cyclohexadienone to aromatic system. Aqueous hydrolysis of the imine produces the acetyl derivative.

If you compare all these reactions, the Gattermann-Koch formylation of arene involves the combination of carbon monoxide, HCl and Lewis acid, while the Gattermann reaction focuses on the formylation of phenol using hydrogen cyanide, HCl and Lewis acid, whereas the Hoesch acylation of polyhydroxy phenol utilizes acetonitrile, zinc(II) chloride and HCl to give the ketone as the product. In the Gattermann and Hoesch reactions imines are produced, which on hydrolysis give the carbonyl compounds.

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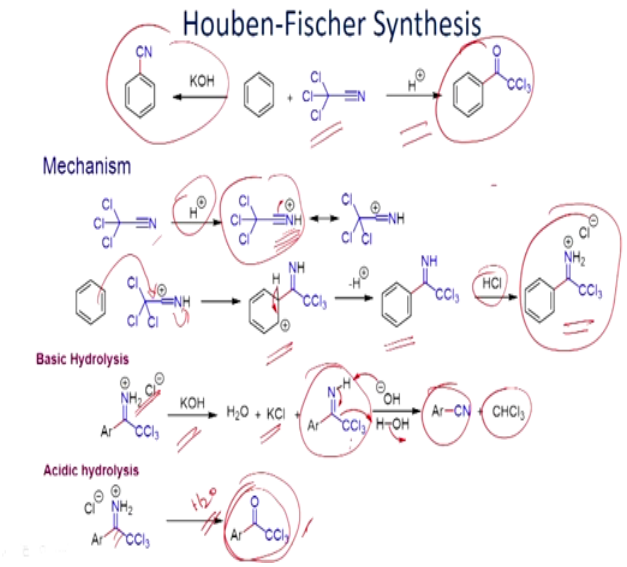

Here the Houben-Fischer Synthesis is shown, where you can see benzene readily undergoes reaction with trichloroacetonitrile in the presence of acid to give the ketone. On the other hand, base hydrolysis produces benzonitrile as the product. In case of acid based reaction, acid protonates the nitrile, which acts as the electrophile, and reacts with benzene to give the imine. It is hydrolyzed by aq HCl to produce the ketone. On other hand, in base hydrolysis, base facilities the elimination of chloroform to generate the benzonitrile.

If you compare with Hoesch reaction where we have seen the reaction of acetonitrile, which can be readily reacted in the presence of Lewis acid and HCl to give acetophenone. While the present Houben-Fischer reaction utilizes trichloroacetonitrile that depends on the reaction condition gives either tirchloroacetphenone or benzonitrile.

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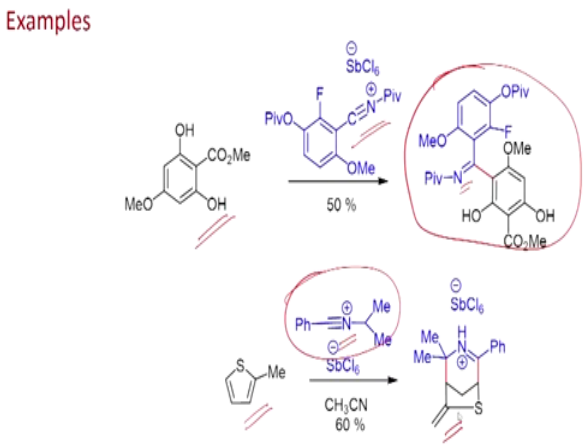

Here some examples are shown. Functionalized phenol reacts with functionalized aryl nitrile to produce the imine, which depends on the reaction conditions can further be converted to the valuable compounds. For example, using acid hydrolysis, it can be converted to ketone. Similarly, the reaction of 2-methylthiophene with activated benzonitrile gives the bicyclic heterocyclic scaffold.

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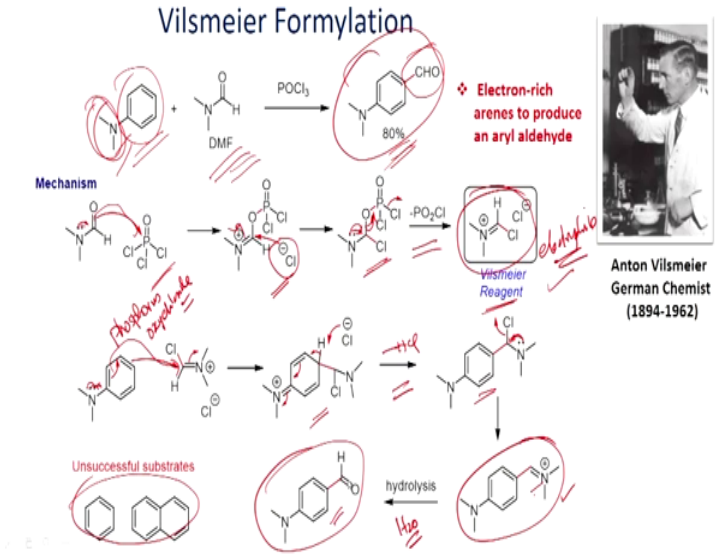

So far we have seen four types of reactions for the acylation of aromatic systems. The first two types involve the formylation, whereas the third and fourth focus on the ketone formation. Here we will see the Vilsmeier formylation, which involves the reaction of aromatic system with DMF in the presence of $POCl_3$ to produce the aldehyde. The reaction

works well when you have the electron rich aromatic system. If you have the electron donating group, the reaction is facilitated. DMF reacts with $POCl_3$ to produce an chloroiminiun ion, which acts as the electrophile. The lone pair in the nitrogen of *N,N*-dimethylaminebenzene assist the aromatic ring to undergo addition reaction with the imine salt to give the aminobenzene. Elimination of HCl gives imine, which on hydrolysis produces the aldehyde. Thus, the reaction is effective with aromatic system having electron donating group. On the other hand, the reaction is less effective when you have the simple benzene or naphthalene, which does not undergo reaction.

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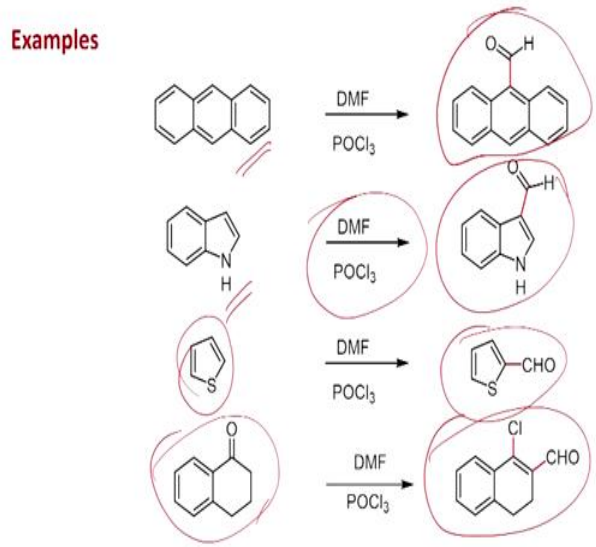

Here some examples are shown. Just I have shown to you in the previous slide that benzene and naphthalene do not undergo reaction, however, anthracene reacts to give anthracene-9-carboxaldehyde. Similarly, indole reacts at third position to yield indole-3-carboxaldehyde. Likewise, thiophene reacts at 2-position to give thiophene-2-carboxaldehdye. Further, 3,4-dihydronaphthalenone undergoes reaction to produce 1-chloro-3,4-dihydronaphthalene-2-carbaldehyde.

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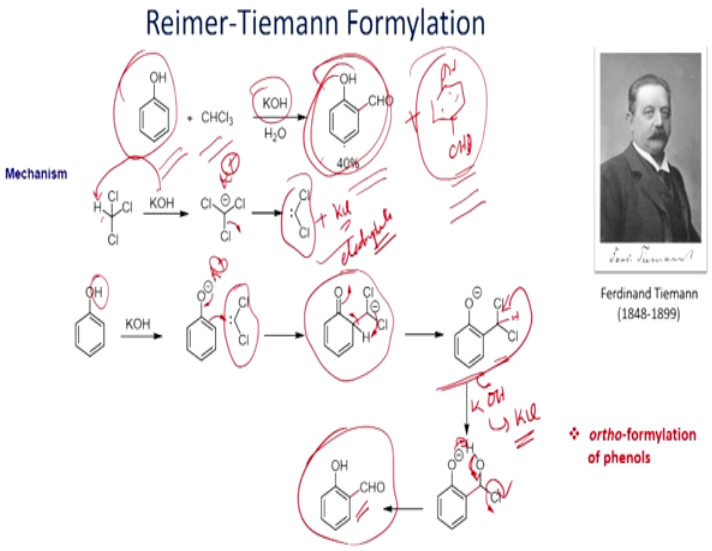

The next example is Reimer-Tiemann formylation. If you look at the previous reactions, they usually form the iminium ion as the electrophile, which undergoes reaction with the aromatic system to give the addition product that leads to hydrolysis to give the aldehyde. Here if you look, phenol reacts with chloroform in the presence of base to give salicylaldehyde. The reaction also gives a reasonable amount of 4-hydroxybenzaldehyde as the byproduct. Base deprotonates chloroform to give trichloromethyl carbanion, which loses Cl^- to produce the dichlorocarbene. It acts as the electrophile and undergoes reaction with phenoxide. Proton shift, nucleophilic substitution and elimination of HCl produces salicylaldehyde.

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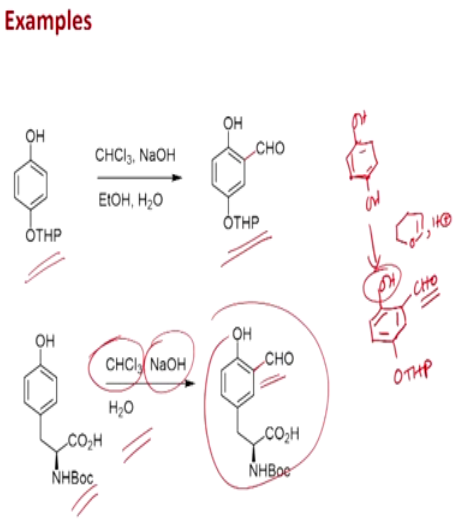

Here some examples are shown. So if you have 1,4-dihydroxy compound, you can protect on the OH groups with THP in the presence of acid. Now you can try to selectively react with

carbon next to the free OH group to introduce the aldehyde group. Similarly, the formylation of the amino acid can be carried out using chloroform and sodium hydroxide.

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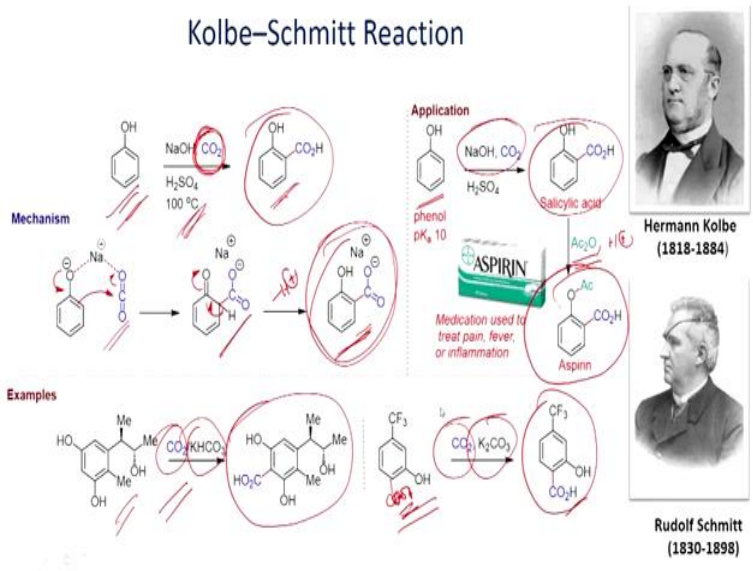

The next reaction is the Kolbe-Schmitt Reaction, which involves the reaction of phenol with carbon dioxide in the presence of NaOH to give salicylic acid.

If you look at the Reimer-Teimann reaction, where we have seen the reaction of phenol with chloroform in the presence of base. On the other hand, here in place of chloroform, we use carbon dioxide, which undergoes reaction to give the salicylic acid. The reaction is carried out under heating. Phenoxide undergoes addition reaction with carbon dioxide to give salicylic acid.

Here the reaction of the dihydroxy compound is shown, which reacts with the carbon dioxide using $KHCO_3$ to give the functionalized salicylic acid. Similarly, 3-(trifluoromethyl)phenol reacts to give the salicylic acid derivative. Let us see the preparation of asprin synthesis. Salicylic acid reacts with acetic anhydride to give asprin in the presence of catalytic amount of acid.

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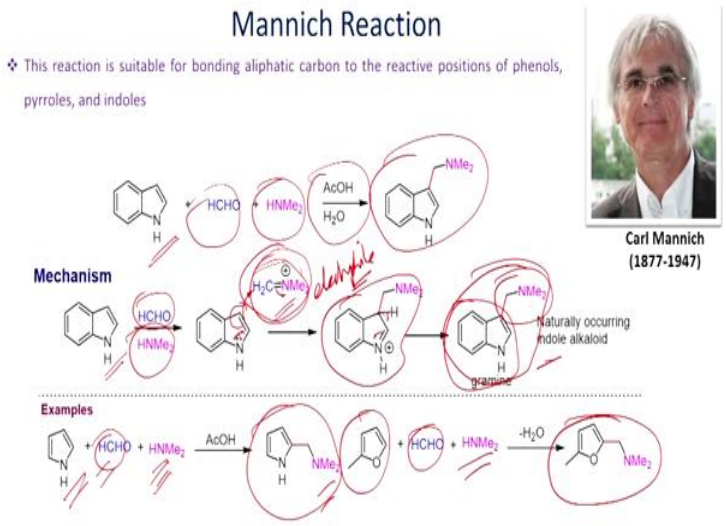

Here the Mannich reaction is shown. As you can see here, in this example, indole reacts with iminium ion that is generated from the condensation of formaldehyde with dimethylamine. Formaldehyde undergoes condensation with dimethylamine to give dimethyliminium ion, which acts as the electrophile. Reaction of indoles with the iminium ion gives 1-(inol-3-yl)-*N*,*N*-dimethylmethanamine.

Similarly, pyrrole reacts with formaldehyde and dimethylamine to give *N*,*N*-dimethyl-1-(pyrrol-2-yl)methanamine, while 2-methylfuran with formaldehyde and dimethylamine yields *N*,*N*-dimethyl-1-(5-methylfuran-2yl)methanamine.

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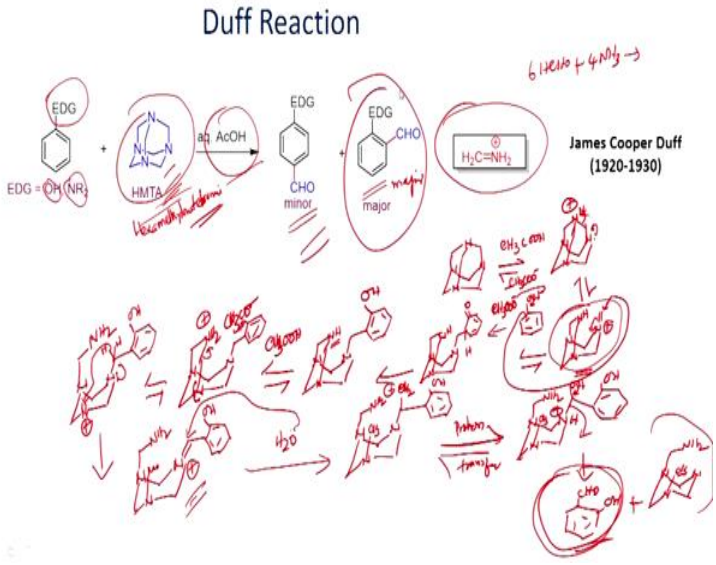

This slide shows the reaction of electron-rich aromatic system with hexamethylenetetramine using acid to give a mixture of aldehydes, which is known as Duff reaction. When you look at the ratio, *ortho* product is always major compared to *para* product.

If you remember, we have studied the formation of hexamethylenetetramine where six molecules of HCHO condense with four molecules of NH_3. So in this reaction, electron rich aromatic ring undergoes reaction with hexamethylenetetramine. This is one of the practical synthetic routes that we use for the formylation.

Let us see the mechanism. First, hexamethylenetetramine undergoes reaction with acid. For example, if you take acetic acid, the protonation of the nitrogen followed by cleavage of the C-N bond gives an iminium ion, which acts as the electrophile, and undergoes reaction with aromatic ring to give the addition product that on hydrolysis gives the aldehyde.

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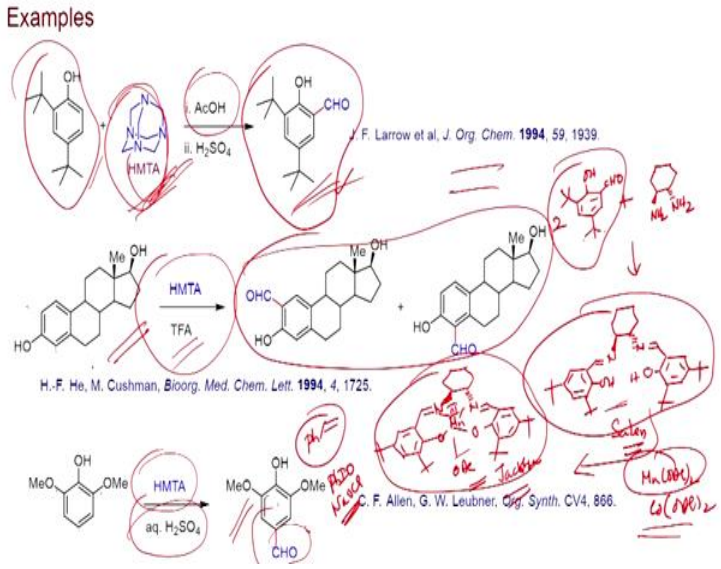

Now let us look at some of the recent literature examples. In the first example, substituted phenol reacts with hexamethylenetetramine in the presence of acetic acid and sulfuric acid to give functionalized aldehyde. This is an important aldehyde, which is used to make the salen ligand. Two equiv of the aldehyde with 1,2-diamine gives the salen ligand.

For example, optically active 1,2-diaminocyclohexane with two equiv of the aldehyde gives the salen, which can be reacted with $Mn(OAc)_2$ to produce the chiral Mn(III)salen complex. These are known as Jacobsen and Katsuki catalysts, are used for the asymmetric epoxidation of alkenes in the presence of oxidants such as PhIO and NaOCl. These reactions are popular

and find broad application. Subsequently, chiral Co(III)salen and Cr(III)salen have been prepared and used for several applications.

The next example involves the formylation of the aromatic ring of polycyclic compound using hexamethylenetetramine in the presence of TFA. Similarly, 2,5-dimethoxyphenol reacts with hexamethylenetetramine in the presence of aqueous sulfuric acid to give the *para* aldehyde.

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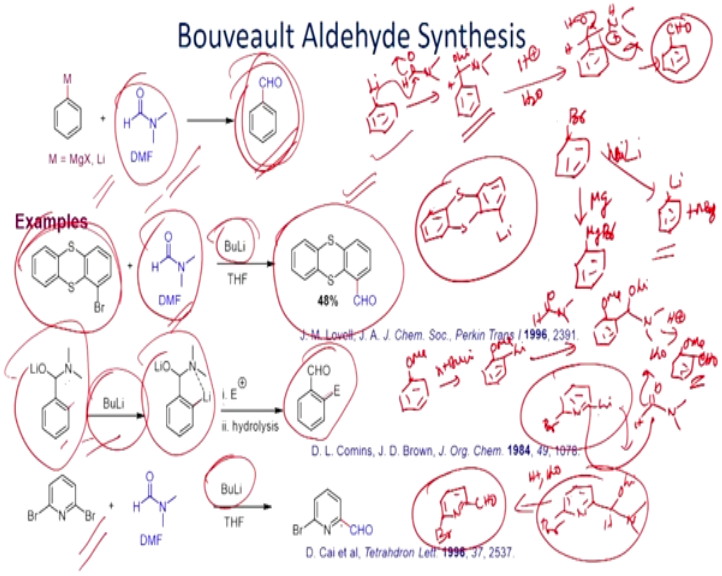

Now let us look at Bouveault aldehyde synthesis. Arylmagnesium halide/aryllithium undergoes addition reaction with DMF, which on work-up converts to aldehyde. Thus, aryl halides can be converted to aryllithium or arylmagenesum halide, which can be reacted with DMF to give the addition product that during work up converts to aldehyde.

Let us see some examples. The first one involves the reaction aryl bromide with n-BuLi to give the aryllithium, which undergoes addition reaction with DMF that on work up undergoes hydrolysis to give the aldehyde.

The next example involves the *N*-chelation assisted *ortho*-lithiation of arene, which reacts with electrophile to give the addition compound. If you react with DMF, you will be able to introduce aldehyde functional group.

The third example involves the reaction 2,6-dibromopyridine, which reacts with one equiv of BuLi to replace one of the bromo group with Li. Which reacts with DMF to give the addition product that on hydrolysis gives the aldehyde.

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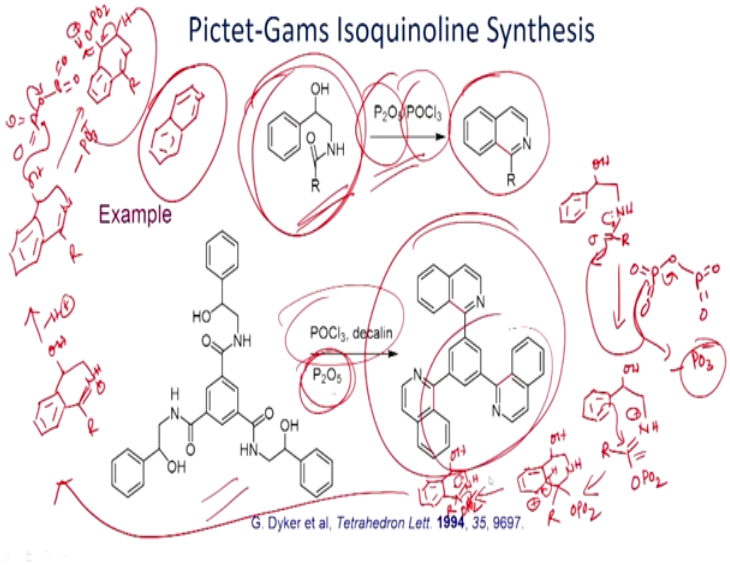

So far we have seen the intermolecular reaction. Now let us look at Pictet-Gams isoquinoline synthesis. Here the amide undergoes intramolecular cyclization in the presence of P_2O_5 or $POCl_3$ to give isoquinoline via the electrophilic aromatic substitution.

Let us look at the reaction pathway. Amide undergoes addition reaction with P_2O_5 to give the iminium ion, which acts as the electrophile. Aryl ring undergoes addition reaction with the iminium ion, which is converted to isoquinoline by removal of PO_3H.

This strategy has been utilized for the transformation of the triamide to the isoquinoline structural framework.

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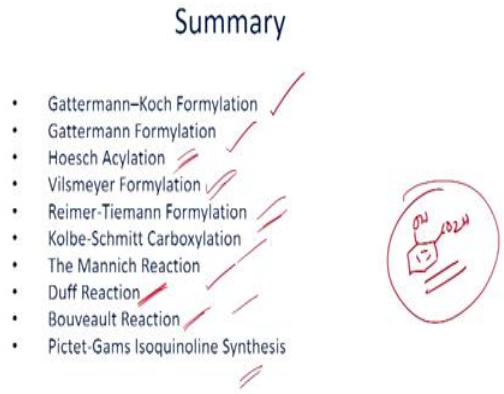

In summary, we have seen the Gattermann-Koch fomlyation, where carbon monoxide with HCl and $AlCl_3$ forms acylium cation, which acts as the electrophile, undergoing the addition followed by elimination reaction. In this way, you can introduce the aldehyde group in aromatic system.

We have seen the Gattermann formylation, where HCN converts to the nitrilium cation, which undergoes addition reaction to give the imine derivative that is hydrolyzed to aldehyde.

Hoesch acylation uses acetonitrile in place of HCN. Depends on the reaction conditions, if acid, ketone forms. On the other hand, if base, nitrile is produced.

Next, we have seen the Vilsmeier formylation where DMF with $POCl_3$ generates an iminium ion, which is known as Vilsmeier reagent, that reacts as the electrophile with aromatic system to give the aldehyde.

Then, we have seen the Reimer-Tiemann formylation, where chloroform reacts with base to produce dichlorocarbene, which acts as the electrophile, and reacts with phenoxide to give salicylaldehyde, while the Kolbe-Schmitt carboxylation, uses carbon dioxide as the electrophile to produce salicylic acid.

We have seen the Mannich reaction, where aldehyde reacts with amine to produce imine that reacts as the electrophile with aromatic system.

Then we have seen the Duff reaction, where phenol reacts with hexamethylenetetramine in the presence of acid to produce aldehyde.

We have seen the Bouveault reaction, where aryllithium reacts with DMF to give the aldehyde.

Then, we have seen the Pictet-Gams isoquinoline synthesis, where aryl amides are converted to isoquinolines in the presence of P_2O_3. With this we conclude this lecture. Thank you very much.