

**Principles of Organic Synthesis**  
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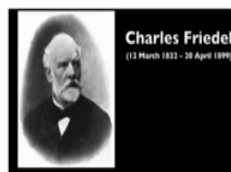
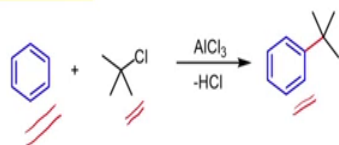
**Lecture-6: Formation of Aliphatic Carbon-Carbon Bonds: Acid Catalysed Reactions**

Welcome you all to the formation of aliphatic carbon-carbon bonds using acid as the catalyst. In this module so far we had two lectures. In the first lecture, we saw the principles of the acid catalyzed carbon-carbon bond formation and the reactions of alkenes, aldehydes, ketones and 2 methyl pyridine, while the second lecture was focused on the Mannich reaction. In this lecture, we will see the Friedel-Crafts and Prins reactions.

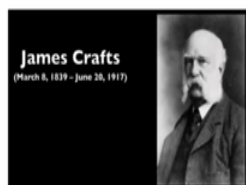
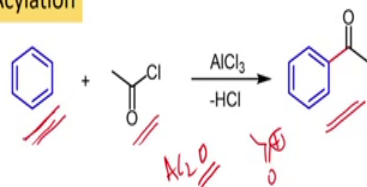
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Friedel-Crafts Reactions

Alkylation



Acylation

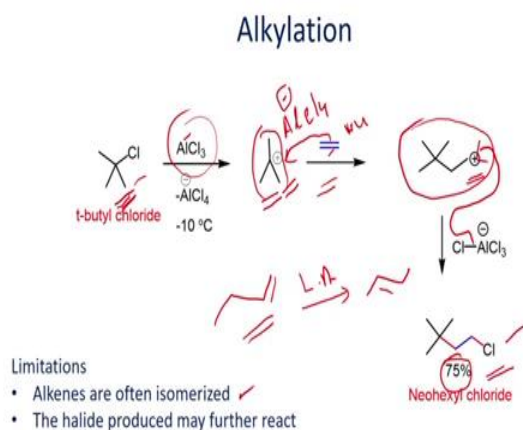


All of you know very well about the Friedel and Crafts reactions. The reaction of alkyl halide in the presence of Lewis acid with aromatic system gives the substituted compound. In this reaction, aluminum chloride reacts with tertiary butyl chloride to give a carbocation intermediate, which acts as an electrophile and undergoes reaction with benzene to give the alkyl benzene as a product where you form a carbon-carbon bond.

In place of alkyl halide, you can use acid chloride or acid anhydride as the acyl source. When you react with Lewis acid, you will be able to generate an acylium cation, which can act as an electrophile and undergo reaction with the aromatic system to give the ketone as the product. We

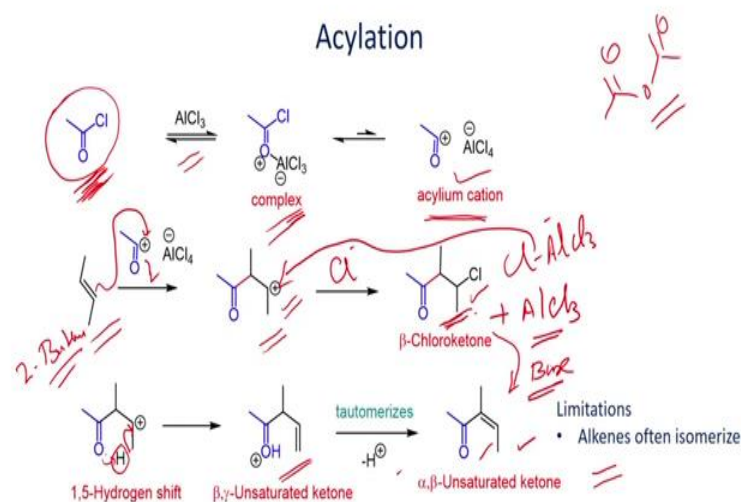
will study in detail these reactions when we study the aromatic electrophilic substitution reaction. In this class, we will focus on the reaction of alkenes in place of arene.

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Here tertiary butyl chloride reacts with aluminum chloride and generates the tertiary carbocation, which acts as the electrophile and undergoes reaction with alkene that acts as a nucleophile to give a primary carbocation. The latter reacts with chloride ion to give the alkyl chloride as the product. In this reaction, we use tertiary butyl chloride and ethylene as the substrates, which readily undergo the addition reaction to give neohexyl chloride. The reaction depends on the nature of the substrates. For example, if we use alkene, like butene, which can undergo isomerization in the presence of Lewis acid and can give a mixture of compounds. In addition, the resultant alkyl chloride can also undergo reaction with Lewis acid to generate a carbocation that can react further with alkene to give addition product. However, in the present reaction, we use ethylene, which does not undergo isomerization. Similarly, the product neohexyl chloride is also less reactive compared to *tert*-butyl chloride. Therefore, the reaction is selective.

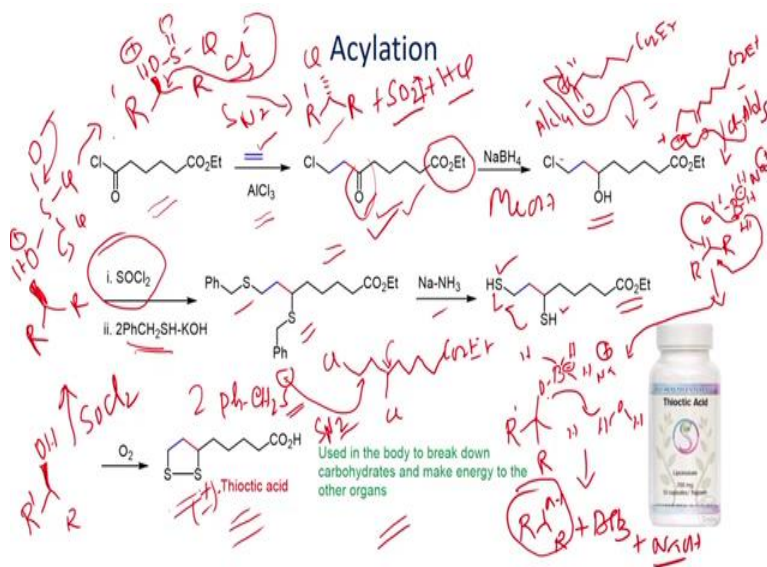
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Here an example is given for the acylation. When you react acetyl chloride with aluminum chloride, you will be able to form acylium cation that can undergo reaction with 2-butene to give a secondary carbocation. This can react with chloride ion to give  $\beta$ -chloroketone as the product. Alternatively, the secondary carbocation can convert into  $\beta,\gamma$ -unsaturated ketone through 1,5-hydrogen shift. Tautomerization can give  $\alpha,\beta$ -unsaturated ketone. On the other hand, base mediated dehydrochlorination of  $\beta$ -chloroketone can also produce  $\alpha,\beta$ -unsaturated ketone.

In place of acid chloride, you can also use acid anhydride. However, the alkenes have limitation. You cannot use all the alkenes as we have seen just now, they can undergo rearrangement in the presence of Lewis acid and can lead a mixture of products.

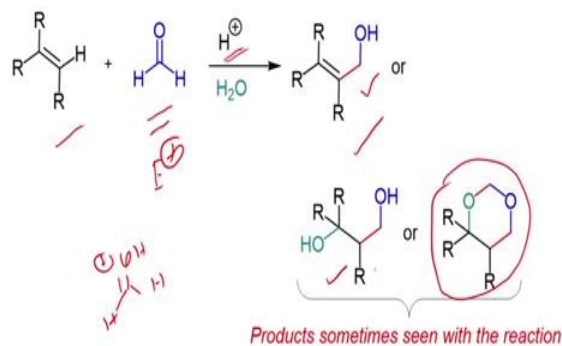
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Application of the acylation reaction is shown here. Acid chloride with ethylene in the presence of aluminum chloride gives the primary alkyl chloride. The reduction of the keto group using  $\text{NaBH}_4$  gives secondary alcohol, which reacts with  $\text{SOCl}_2$  to give the dichloro derivative. Nucleophilic substitution ( $\text{S}_{\text{N}}2$ ) with thiol in the presence of  $\text{KOH}$  gives the thioether. Treatment with  $\text{Na}/\text{NH}_3$  gives the dithiol, which converts to disulfide in the presence of oxygen. Hydrolysis of the ester group gives thioctic acid, which we use to break down carbohydrates and to make energy to the other organs.

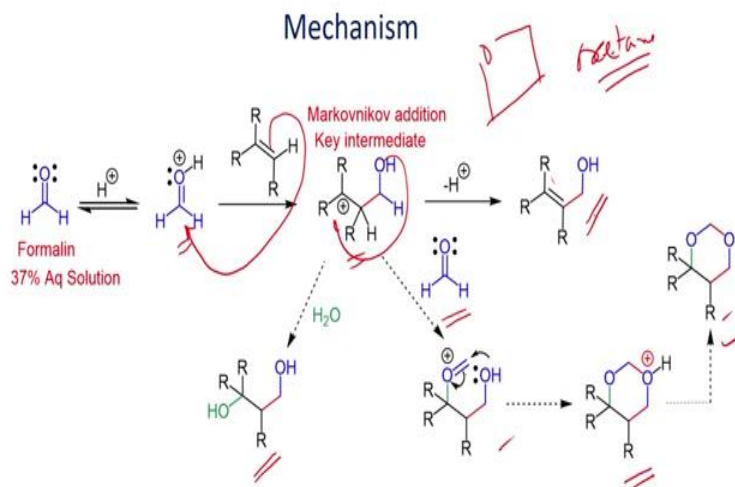
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### The Prins Reaction



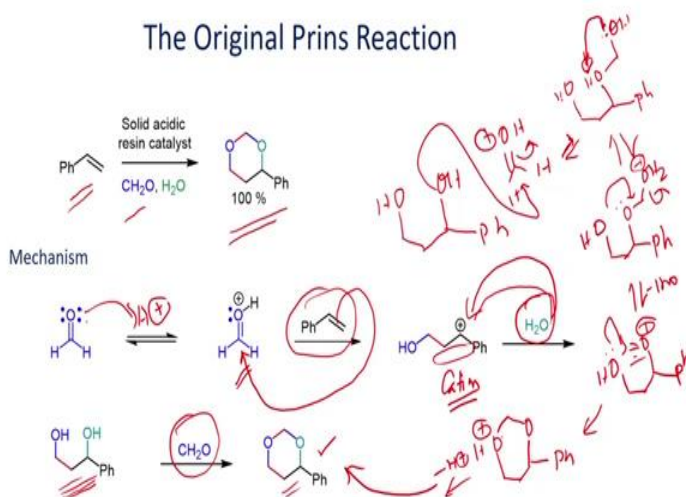
Now let us look at the Prins reaction. In the original Prins reaction, formaldehyde undergoes protonation with acid to give the more electrophilic protonated species, which leads to addition reaction with alkene to give a cation. The latter reacts with water to give alcohol or diol or cyclic acetal. The product formation depends on the nature of the alkene and acid.

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Let us see the mechanism. Formaldehyde with acid forms the protonated species, which undergoes addition with alkene to give a carbocation that is the key intermediate in the Prins reaction. If you look at, it is a simple Markovnikov addition. The carbocation depends on the reaction condition gives either 1,2-diol, allylic alcohol or acetal. Removal of a proton can produce allylic alcohol, while reaction with water can give the diol. The diol can further react with formaldehyde to give an oxonium ion, which can undergo intramolecular addition with hydroxy group to give the acetal.

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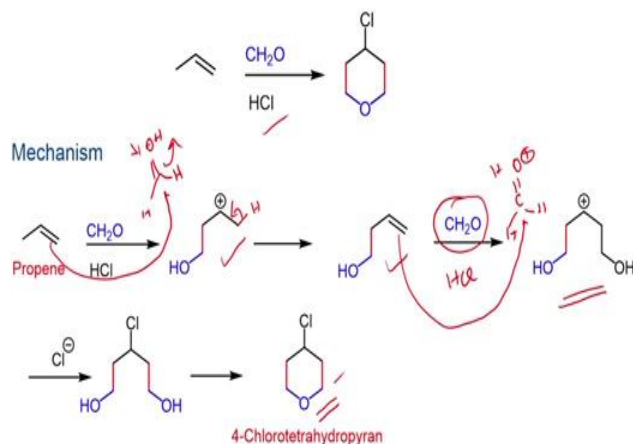


Now, let us look at an example for the cyclic acetal formation. When you react styrene with formaldehyde in the presence of the solid resin as a catalyst you will be able to generate cyclic acetal as the product in quantitative yield. The mechanism involves the protonation of the formaldehyde to form a more reactive electrophile, which can undergo addition with styrene to give benzylic carbocation as the key intermediate that with water produces 1,3-diol. Reaction of benzylic OH group with protonated formaldehyde via addition followed by dehydration, gives oxonium ion, which undergoes intramolecular cyclization to give the cyclic acetal.

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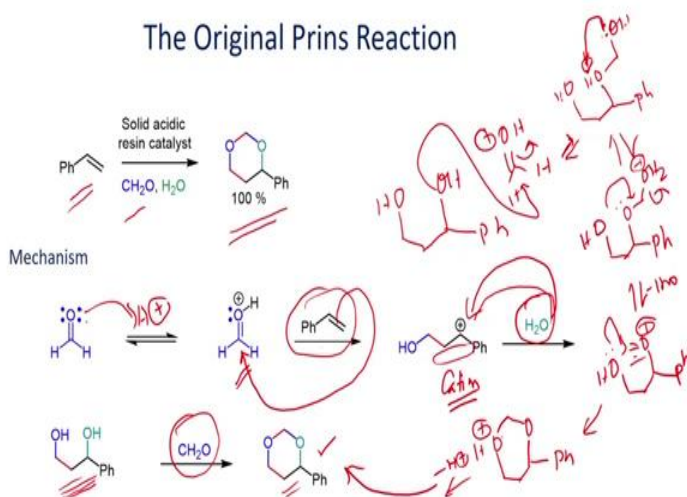
### Synthesis of Tetrahydropyran



Now let us look at an example of the alkyl alkene. When you react propene with formaldehyde in the presence of HCl, you will be able to form the cyclic ether as the product. If you look at the mechanism, propene undergoes reaction with formaldehyde to give a secondary carbocation, which loses a proton to give homoallylic alcohol. The double bond of the product undergoes reaction with protonated formaldehyde to give addition product with a secondary carbocation. Reaction with chloride ion can give chlorinated diol, which in the presence of acid can convert into the six membered cyclic ether.

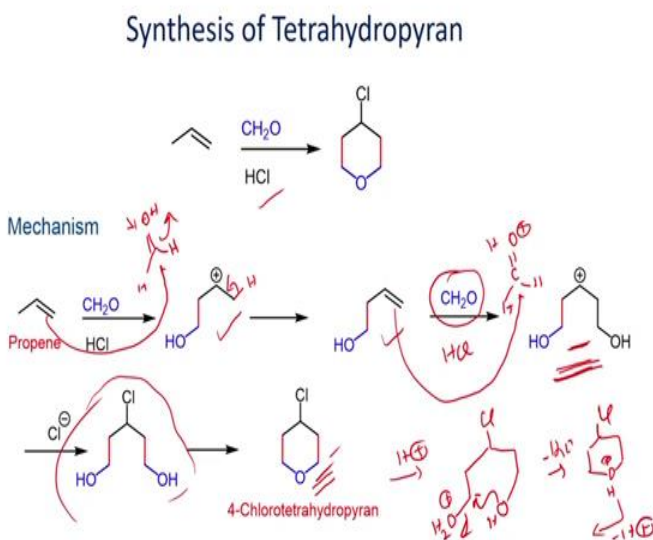


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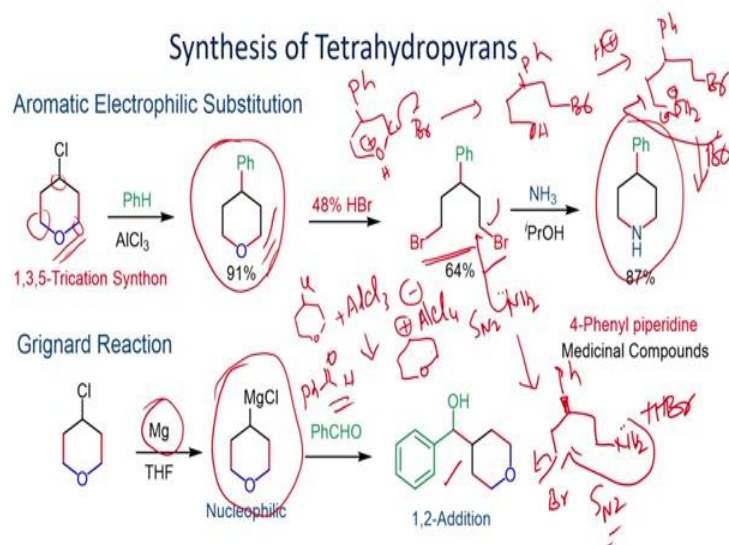
If you look at the previous and this reactions, in the previous one, first the alkene undergoes reaction with formaldehyde to give the benzylic carbocation intermediate, which reacts with water to give the diol that further reacts with formaldehyde to give the oxonium ion, which cyclizes to give the acetal.

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But in later, the alkene undergoes addition reaction with the formaldehyde to give a secondary carbocation, which converts to homoallylic alcohol. The latter further reacts with formaldehyde to give the addition product with a secondary carbocation that reacts with chloride ion to yield the chloro compound. Which then converts to the six membered cyclic ether via the protonation followed by the intramolecular nucleophilic substitution.

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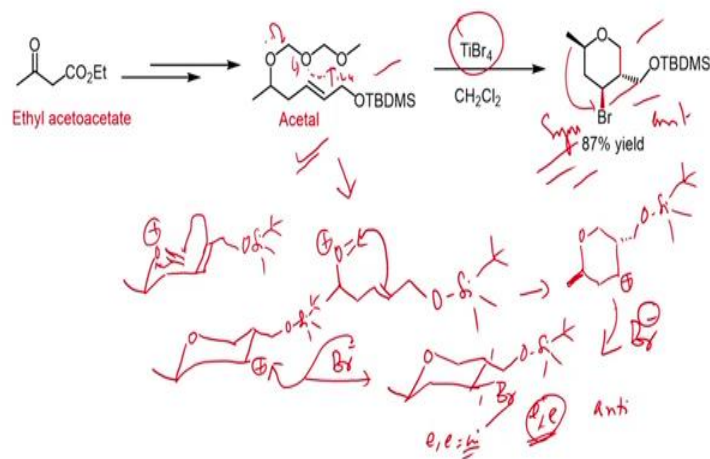


Here the application of the cyclic ether is shown. It can react with benzene in the presence of Lewis acid to give alkylation product. The latter with 40% HBr can give the dibromo compound, which can react with ammonia to yield 4-phenyl piperidine as the product that is important in medicinal chemistry. Thus, 4-chlorotetrahydropyran can be used as a versatile 1,3,5-trication synthon.

The cyclic ether can be further reacted with magnesium to give the Grignard reagent, which can undergo 1,2-addition with benzaldehyde to yield the secondary alcohol as the product.

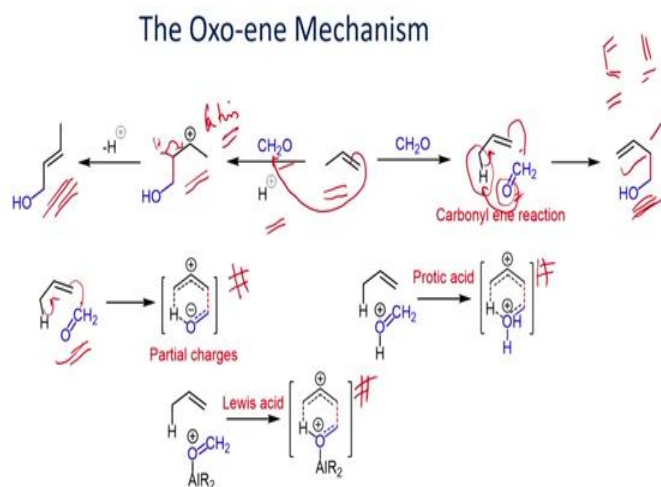
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### Synthesis of Tetrahydropyrans



Here another example is shown. Ethyl acetoacetate can be converted to the acetal derivative, which undergoes cyclization in the presence of titanium(IV) bromide to give the six membered cyclic ether. The mechanism involves the formation of the oxonium ion and intramolecular addition of the double bond to give the secondary carbocation that reacts with bromide ion to yield the bromo derivative. The stereochemistry can be understood through the six membered chair conformation.

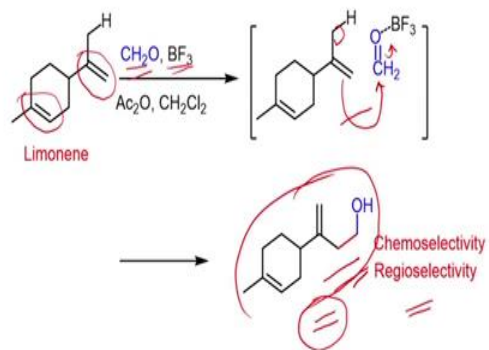
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Now, let us look at the involvement of oxo-ene mechanism in the Prins reaction. The addition of propene with formaldehyde in the presence of acid gives the secondary carbocation intermediate. Deprotonation can give the more substituted double bond or allylic alcohol as the product. Instead, the reaction of propene with formaldehyde affords the homoallylic alcohol as the product, which can be explained through the involvement of the concerted carbonyl or oxo ene reaction. This can be explained through the involvement of the partial charge transition state, which can be stabilized by the protic or Lewis acid. This can lead to the formation of homoallylic alcohol.

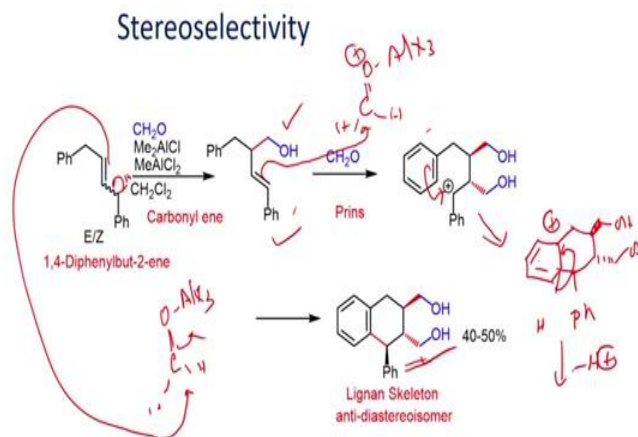
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### The Oxo-ene Mechanism



Look at the reaction of limonene with formaldehyde using  $\text{BF}_3$  to produce the homoallylic alcohol. The reaction is chemo- and regioselective.

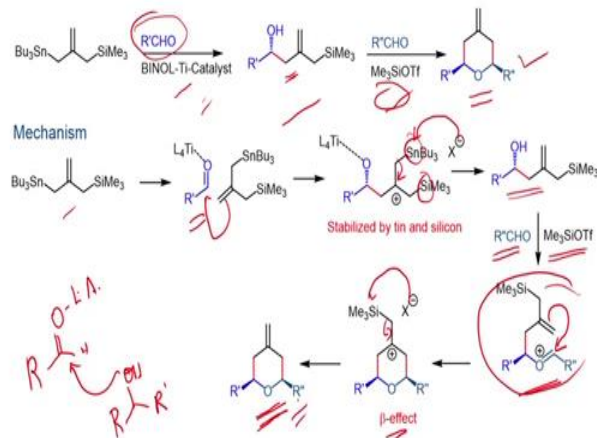
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Now, let us look at another example. The reaction of alkene with formaldehyde via oxa-ene reaction gives the homoallylic alcohol. The latter reacts with another equivalent of formaldehyde via the simple electrophilic addition to give the benzylic carbocation intermediate, which undergoes intramolecular electrophilic aromatic substitution to yield the lignan skeleton. If you look at the stereochemistry, the aldehyde has reacted in the opposite space to give the anti-stereochemistry, which can be explained through the six-membered chair conformation as we have seen earlier.

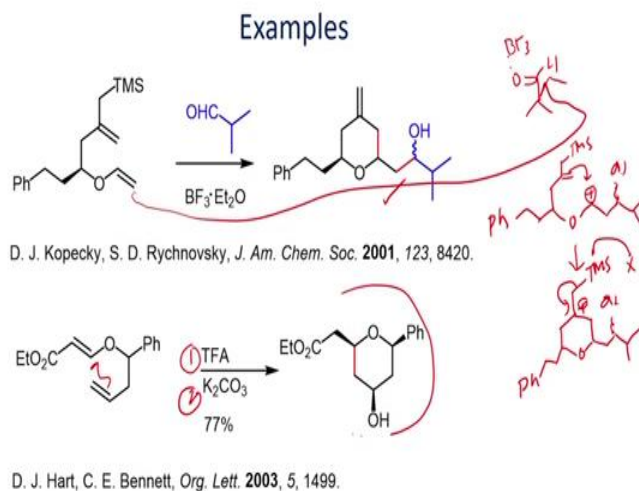
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### Use of Sn and Si to Control Cation Formation



Now let us look at the tin and silicon stabilized carbocation intermediate, which involves the reaction of two different aldehydes to give the cyclic ether as the product. The allyl tin/silicon reagent reacts with aldehyde to give tert-carbocation, which is stabilized by tin as well as silicon. Since tin is more reactive, you will be able to form homoallylic alcohol with silyl substituent. This can further reaction aldehyde to oxonium ion which can react with double to produce a silyl stabilized tert-carbocation, which can convert into the cyclic ether. If you look at here, you can use two different aldehydes and can control the cation formation to produce the cyclic ether as product.

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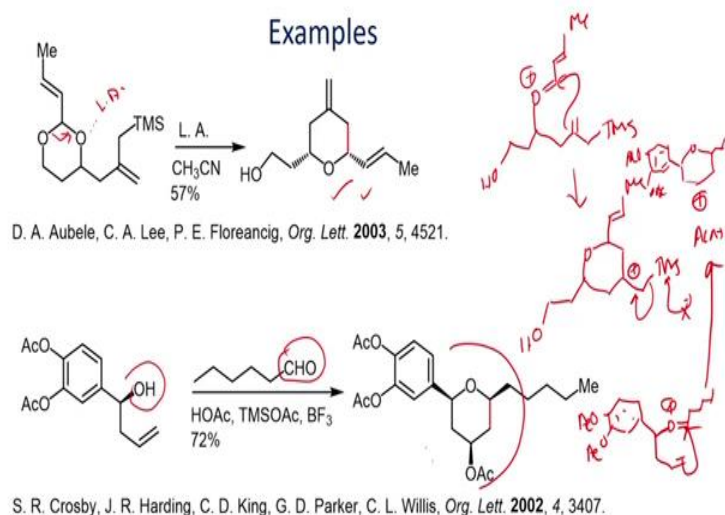


Now let us look at some of literature examples. The reaction of diene with isobutyraldehyde gives the cyclic ether in the presence of  $\text{BF}_3$  as Lewis acid. Chelation of the Lewis acid with aldehyde can activate the carbonyl group, and can undergo addition reaction with the double bond to produce the secondary carbocation intermediate. Which can react with double bond to produce a silyl stabilized *tert*-carbocation that can convert to the cyclic ether.

If you look at other example, where the intramolecular cyclisation followed by hydroxylation takes place in the presence of TFA and  $\text{K}_2\text{CO}_3$ . TFA facilitates the cyclization to produce a secondary carbocation that reacts with base to give cyclic alcohol as the product.



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Here the cyclic acetal with Lewis acid opens up to give a conjugated oxonium ion, which undergoes intramolecular cyclization with a double bond to give a six membered cyclic ether with *tert*-carbocation that is stabilized by silyl group. Desilylation leads to the formation of the product.

The next involves the condensation of the aldehyde with alcohol to generate the oxonium ion intermediate the presence of acid. This can lead to an intramolecular cyclisation to produce a secondary carbocation intermediate, which reacts acetate ion to give the cyclic ether derivative. The stereochemistry of product can be explained through six membered chair conformation as we have seen above.

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## Summary

- ❖ Friedel-Crafts Reaction of Alkenes
- ❖ The Prins Reaction
- ❖ Mechanism and Stereoselectivity

Now let us conclude this lecture. In the beginning, we have seen the reaction of alkenes with acid chloride as well as alkyl halide. The reaction depends on the nature of alkenes as well as alkyl halides. Then, we have seen the Prins reaction, which has wide application in organic synthesis.

Finally, we have the recent developments in the Prins reaction. We have also discussed the mechanism and stereoselectivity of some of the reactions. With these, we conclude the lecture, thank you.