Principles of Organic Synthesis
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Lecture 26
Sulfur and Silicon Containing Reagents

Welcome you all to principles of organic synthesis. At present, we study phosphorus, sulfur, silicon, boron and tin containing reagents. In the last lecture, we studied the phosphorus containing reagents. In this lecture, we will study the preparation and application of sulfur and silicon containing reagents for the fundamental and important organic transformations.

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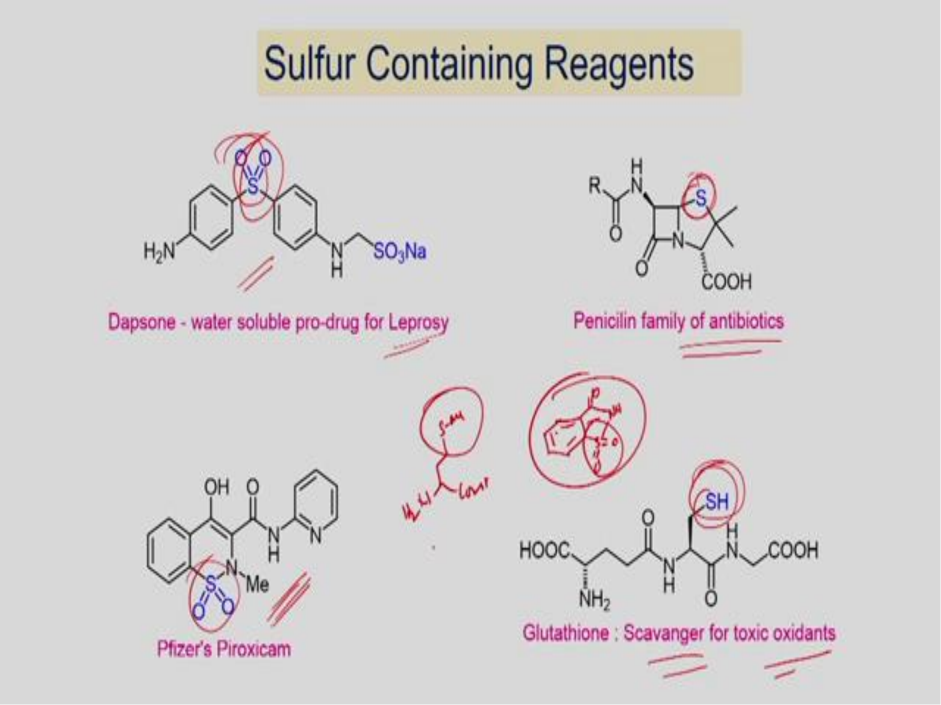

Sulfur Containing Reagents

Dapsone - water soluble pro-drug for Leprosy

Penicilin family of antibiotics

Pfizer's Piroxicam

Glutathione : Scavanger for toxic oxidants

Sulfur containing compounds find wide applications in agricultural, biological, material and synthetic sciences. For examples, dapsone bearing sulfone unit is water soluble pro-drug for leprosy, penicillin having thioether motif is antibiotic, piroxicam having sulfone functional group is utilized to relieve the pain as well as swelling in arthritis and glutathione is used as scavenger for toxic oxidant. In this lecture, we will cover the preparation and application of sulfur based reagents in organic synthesis.

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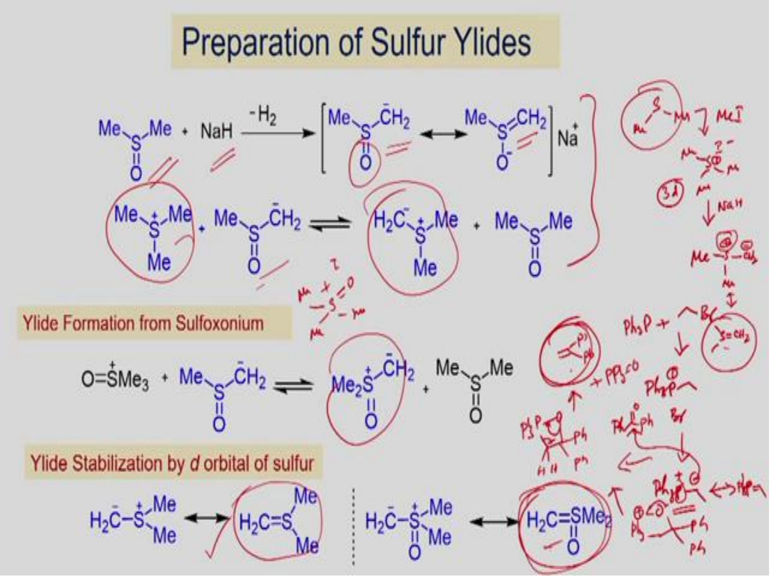

Preparation of Sulfur Ylides

Ylide Formation from Sulfoxonium

Ylide Stabilization by *d* orbital of sulfur

If you remember the last class, where we studied the reaction of phosphine with alkyl halide to form phosphonium salt that was converted to phosphonium ylide. Reaction of the ylide with aldehyde as well as ketone produced the betaine that converted to the four membered cyclic oxaphosphetane, which eliminated phosphine oxide to produce alkene. The strong phosphorous-oxygen double bond facilitates the alkene formation.

Similarly, sulfur ylide can be prepared form sulfonium salt using base, which can react with aldehyde, ketone, imine as well as enone to give the respective three membered compounds. The reaction is diastereoselective with *trans* substitution in the product regardless of the initial stereochemistry. The reaction is most often employed for the preparation of epoxides with methylene transfer.

Let us see the preparation of the ylide. Deprotonation of dimethyl sulfoxide using sodium hydride gives the stabilized carbanion that as base deprotonates trimethylsulfonium salt to produce (dimethylsulfaniumyl)methanide ylide, which is stabilized by *d* orbital of sulfur. Similarly, the deprotonation of sufoxonium salt yields (dimethyloxosulfaniumyl)methanide ylide, which is stabilized by the oxygen.

These are efficient methylene transfer reagents to aldehyde, ketone, imine and enone.

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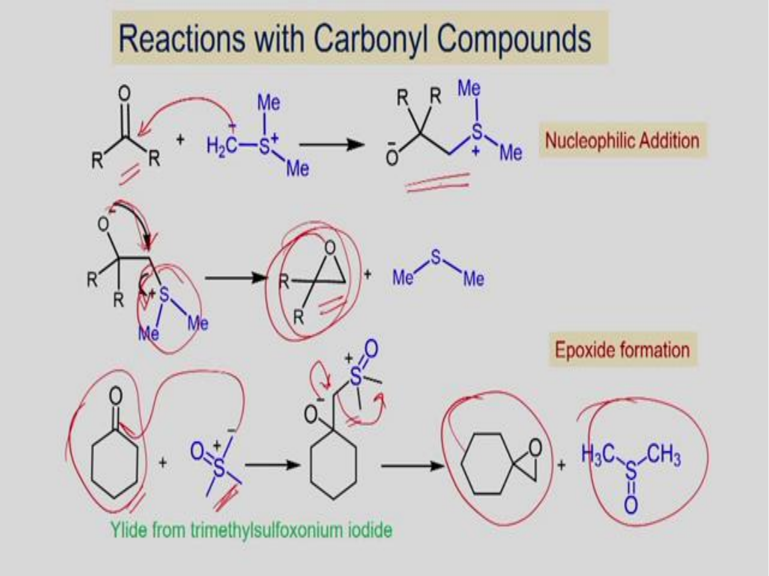

Reactions with Carbonyl Compounds

Nucleophilic Addition

Epoxide formation

Ylide from trimethylsulfoxonium iodide

The ylide undergoes nucleophilic addition to the carbonyl group. The negative charge is transferred to the heteroatom. Because sulfonium cation is a good leaving group and gets expelled to form the epoxide via S_N2 pathway. For an example, cyclohexanone with sulfoxonium ylide gives the epoxide via nucleophilic addition followed by substitution.

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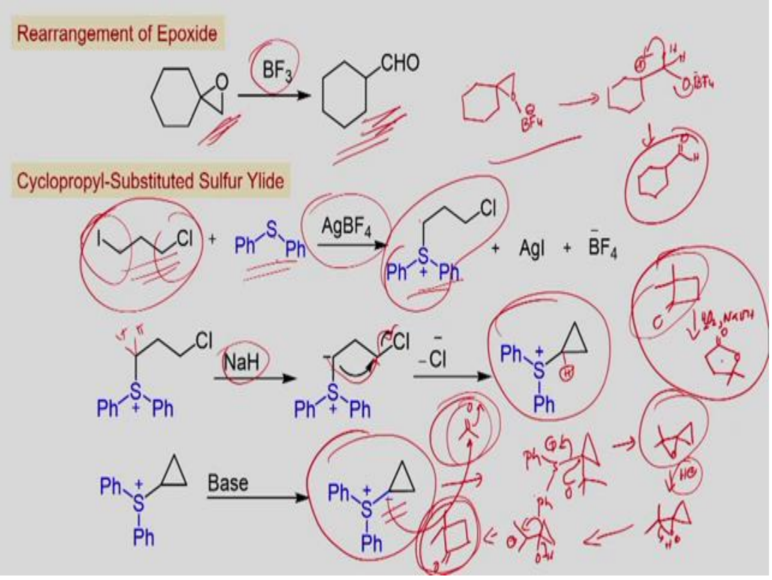

Rearrangement of Epoxide

Cyclopropyl-Substituted Sulfur Ylide

The epoxide can be rearranged to cyclohexanecarboxaldehyde using BF_3. Lewis acid opens up the epoxide to give the tertiary carbocation, which converts to the aldehyde by 1,2-hydride shift.

Now let us see the preparation of cyclopropyl substituted sulfur ylide. Diphenyl sulfide with 1-chloro-3-iodopropane using $AgBF_4$ gives sulfonium salt. Deprotonation using NaH gives carbanion, which undergoes S_N2 reaction to give cyclopropyl derivative. Deprotonation using base gives sulfonium ylide that can react with carbonyl compounds to give the corresponding epoxide.

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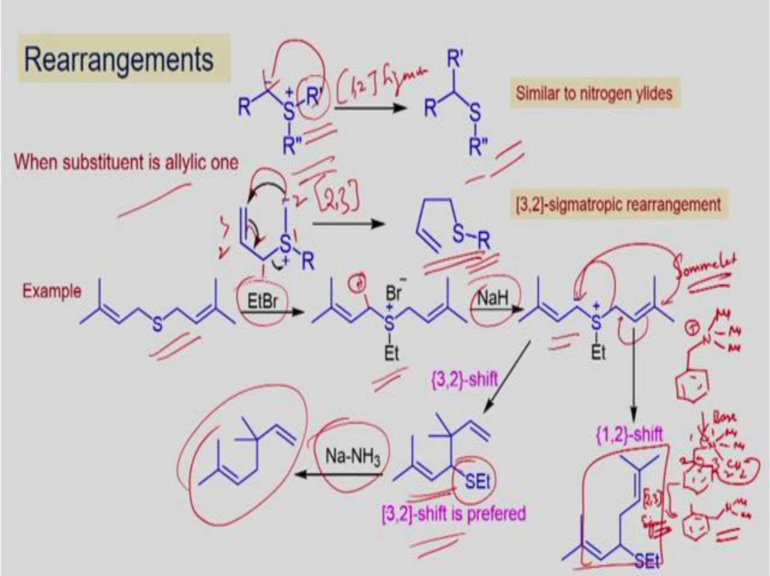

Rearrangements

Similar to nitrogen ylides

When substituent is allylic one

[3,2]-sigmatropic rearrangement

Example

[3,2]-shift is prefered

If you remember the rearrangements of quaternary ammonium salts, where the nitrogen ylide leads [1,2]- and [2,3]-sigmatropic rearrangements. Similarly, sulfur ylide exhibits sigmatropic rearrangements. The first example shows [1,2]-sigmatropic rearrangement, where R’ migrates to the α-carbon. Similarly, the allyl sulfonium ylide leads [2,3]-sigmatropic rearrangement to homoallyl derivative. For example, the diallyl sulfide with ethyl bromide forms the salt, which can be converted to the ylide that can lead [1,2]- and [2,3]-sigmatropic rearrangements. Desulfurization using sodium in liquid ammonia can produce the alkene derivatives.

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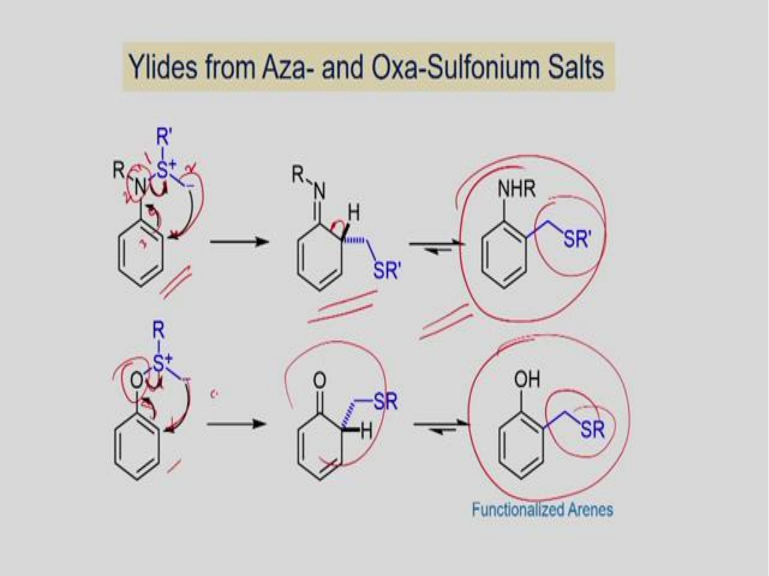
Ylides from Aza- and Oxa-Sulfonium Salts

Functionalized Arenes

Now look at the rearrangement of aza- and oxa-sulfonium ylides. The first example shows the [2,3]-sigmatropic rearrangement of the aza-sulfonium ylide to the *ortho*-position of the aromatic ring. Similarly, oxasulfonium ylide leads to the [2,3]-sigmatropic rearrangement to yield the *ortho*-substituted phenol.

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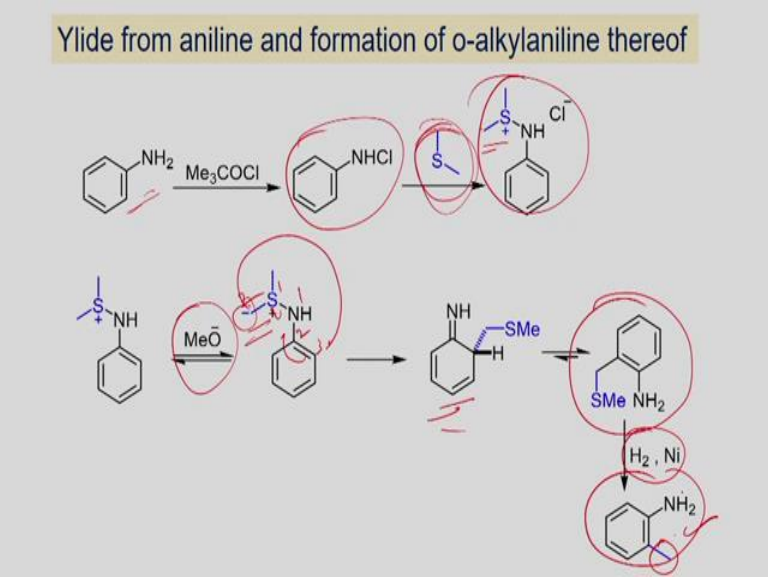
Ylide from aniline and formation of o-alkylaniline thereof

As we have seen above, here is an another example for the [2,3]-sigmatropic rearrangement of azasulfonium ylide. Aniline with t-butyl hypochlorite produces N-chloroaniline, which reacts with dimethyl sulfide to produce sulfonium chloride. Deprotonation using methoxide gives the sulfonium ylide, which leads [2,3]-sigmatropic rearrangement to give *ortho*-substituted aniline. Desulfurization by nickel catalyzed hydrogenation yield 2-methylaniline.

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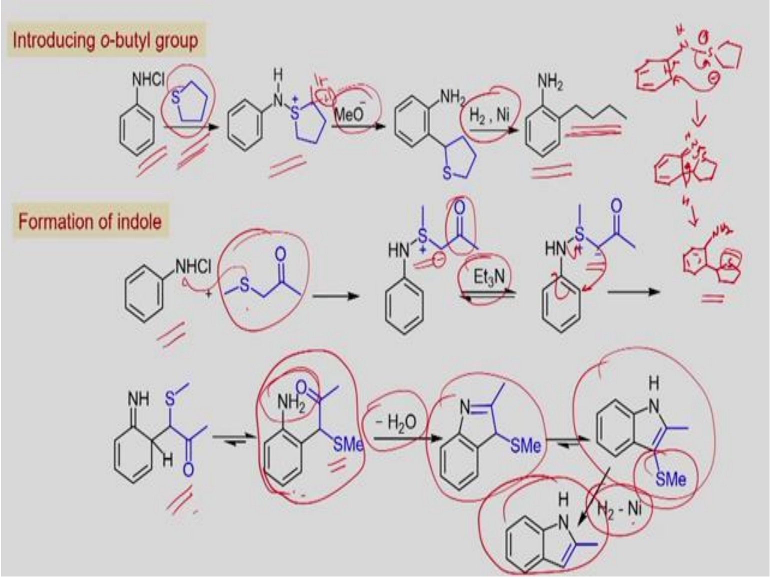

Introducing *o*-butyl group

Formation of indole

The above strategy has been extended for the synthesis of 2-butylaniline and 2-methyl indole. N-Chloroaniline with tetrahydrothiophene produces the aza-sulfonium chloride, which can be converted to the ylide by deprotonation using methoxide. [2,3]-Sigmatropic rearrangement gives the *ortho*-substituted aniline, which has been desulfurized by hydrogenation to yield 2-butylaniline. Similarly, N-chloroaniline with 1-methyl thio-2-propanone gives the sulfonium chloride, which deprotonates to yield the ylide. [2,3]-Sigmatropic rearrangement followed by condensation produces the indole derivative. Desulfurization using catalytic hydrogenation provides 2-methyl indole

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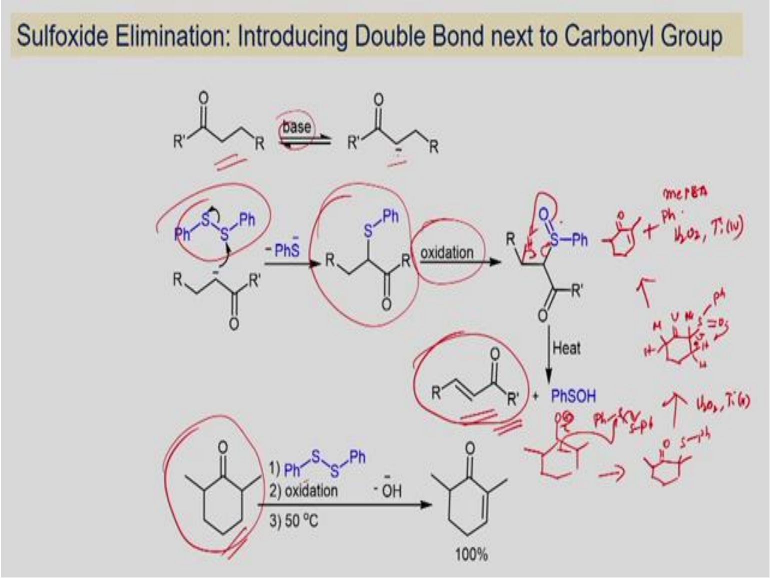

Sulfoxide Elimination: Introducing Double Bond next to Carbonyl Group

So far we have seen the sulfur ylide chemistry. Now let see the use of sulfoxide for the construction of α,β-unsaturated double bond. Deprotonation followed by substitution of carbonyl compound with disulfide produces the thioether derivative. Oxidation using peracid yields the sulfoxide, which undergoes elimination to produce conjugated double bond . The sulfoxide is converted to thiol if hydrogen present at the β-carbon atom via a five membered cyclic transition state.

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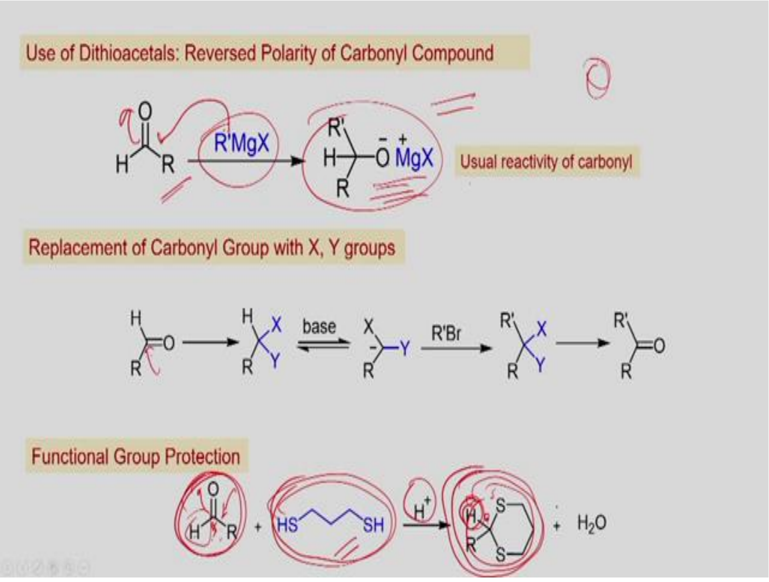

Use of Dithioacetals: Reversed Polarity of Carbonyl Compound

Usual reactivity of carbonyl

Replacement of Carbonyl Group with X, Y groups

Functional Group Protection

Sulfur chemistry also plays important role in the reverse polarity of carbonyl compound. For example, aldehyde reacts with Grignards reagent to give addition product where the carbonyl group acts as the electrophile. On the other hand, when you react the aldehyde with 1,3-dithiol, you will be able to form dithioacetal. Deprotonation using base can give the stabilized carbanion, which can now act as a nucleophile. Thus, the polarity of the carbonyl can be reversed via forming the dithioacetal of the aldehyde, which find wide applications in organic chemistry.

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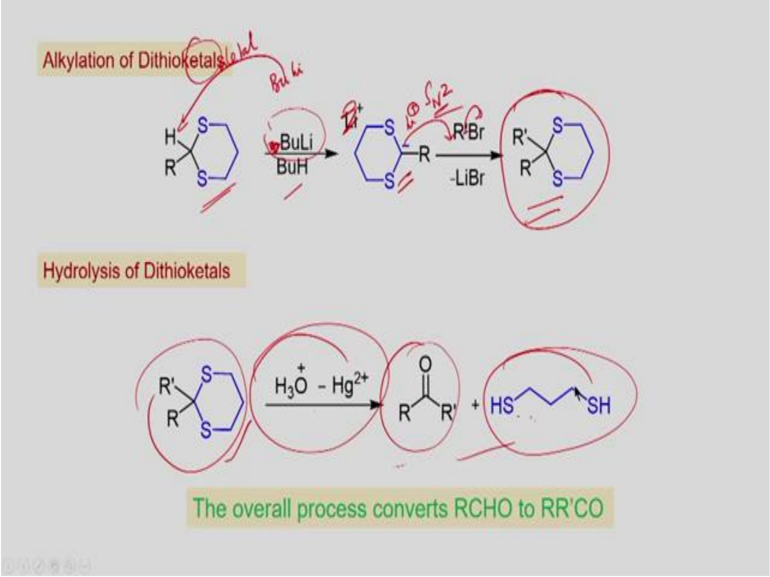
Alkylation of Dithioketals

Hydrolysis of Dithioketals

The overall process converts RCHO to RR'CO

For example, deprotonation of the dithioacetal produces the carbanion, which undergoes S_N2 reaction with alkyl bromide. Hydrolysis of the dithioacetal using acid produces the ketone. Thus, this chemistry can be used for the transformation of aldehyde to ketone. The carbanion is stabilized by the sulfur *d* orbital.

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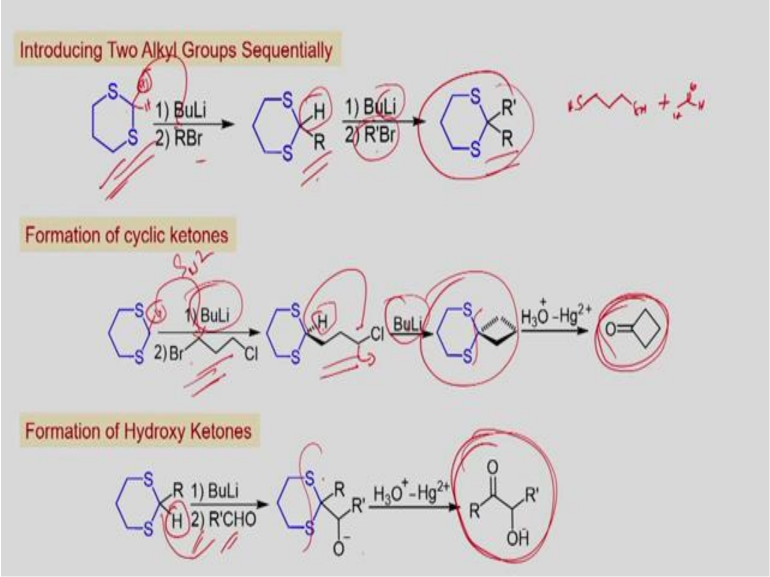
Introducing Two Alkyl Groups Sequentially

Formation of cyclic ketones

Formation of Hydroxy Ketones

Here the first example involves the use of dithioacetal of formaldehyde, which can be sequentially reacted with two equiv of alkyl halides that on hydrolysis can give the ketone. Similarly, the dithioacetal can be reacted with 1,3-dihalide sequentially, which on hydrolysis gives cyclobutanone. The dithioacetal can also be reacted with one equiv of alkyl halide followed by one equiv of aldehyde, which on hydrolysis can produce α-hydroxy ketone.

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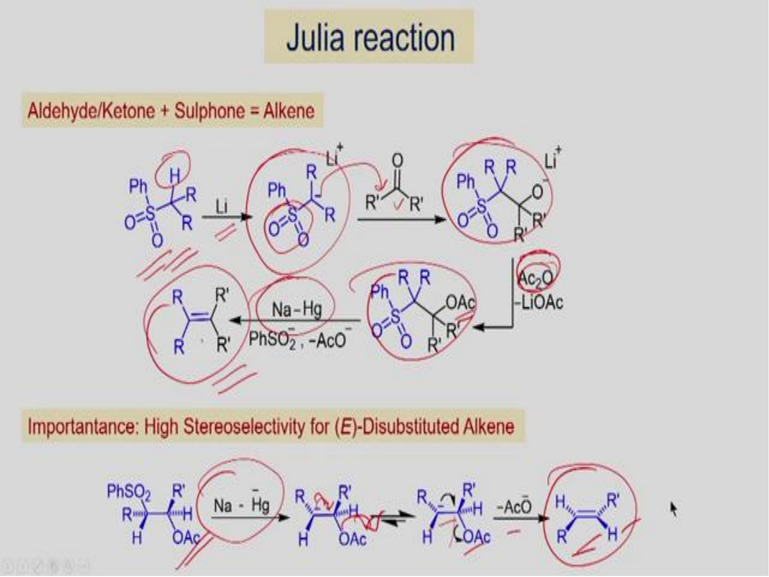

Julia reaction

Aldehyde/Ketone + Sulphone = Alkene

Importantance: High Stereoselectivity for (*E*)-Disubstituted Alkene

So far we studied the sulfur ylide, sulfoxide in elimination and dithiacetal based reactions. Now let us focus on the use of sulfone anion in alkene formation. Deprotonation of phenyl sulfone produces the carbanion, which undergoes addition to aldehyde to produce alkoxide. Functionalization of the alkoxide with acetic anhydride followed by reduction using Na(Hg) in ethanol gives the alkene via the vinyl radical intermediate. The reaction is stereoselective and produces *E*-alkene, which is known Julia olefination.

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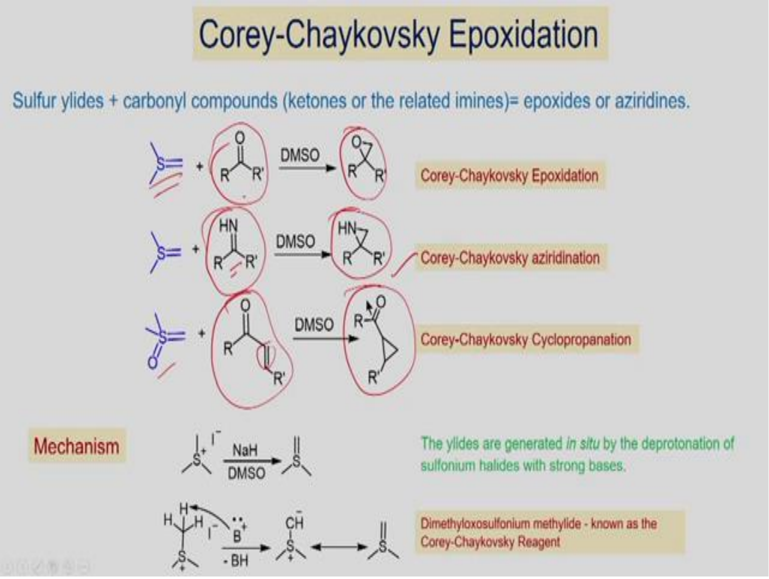

Corey-Chaykovsky Epoxidation

Sulfur ylides + carbonyl compounds (ketones or the related imines)= epoxides or aziridines.

Corey-Chaykovsky Epoxidation

Corey-Chaykovsky aziridination

Corey-Chaykovsky Cyclopropanation

Mechanism

The ylides are generated *in situ* by the deprotonation of sulfonium halides with strong bases.

Dimethyloxosulfonium methylide - known as the Corey-Chaykovsky Reagent

Here is the summary of reaction of the sulfur ylides. Sulfonium ylides react with aldehyde and ketones to produce epoxide, while the reaction imine yields aziridine. In addition, sulfoxonium ylide reacts selectively with enone double bond to produce cyclopropane. Thus, the sulfur ylides can be readily prepared for methylene transfer of aldehyde, ketone, imine and enone to produce versatile building blocks that are important in synthetic chemistry.

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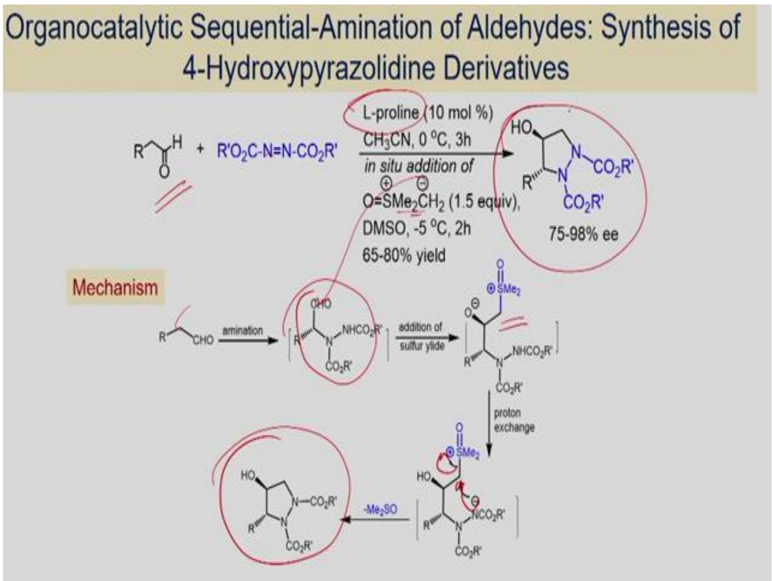

Organocatalytic Sequential-Amination of Aldehydes: Synthesis of 4-Hydroxypyrazolidine Derivatives

Here is the application of the sulfur ylide chemistry for the enantioselective synthesis of 4-hydroxypyrazolidine. Aldehyde with L-proline forms enamine that adds to DEAD to give the chiral α-substituted aldehyde, which reacts with sulfoxonium ylide. Proton transfer followed by nucleophilic substitution yields the product.

So far we have seen the use of sulfur chemistry for the methylene transfer, alkene formation and carbonyl umpolung reactions. Now let us focus on the second part of the lecture where we will study the silicon reagents.

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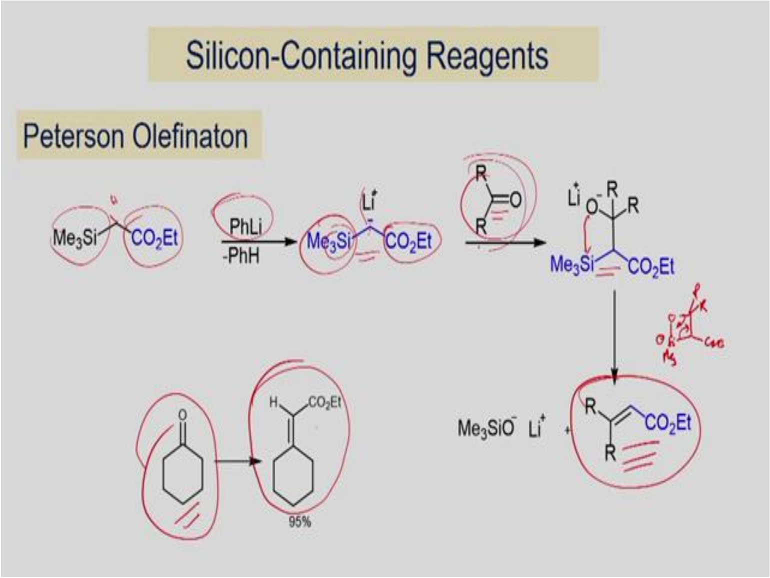
Silicon-Containing Reagents

Peterson Olefinaton

Let us begin with the Peterson olefination where α-silyl carbanion with aldehyde or ketone forms a β-hydroxysilane that undergoes elimination to give the alkene. The β-hydroxysilane can be converted to either *cis* or *trans* alkene using acid or base.

For example, deprotonation of ethyl 2-(trimethylsilyl)acetate using PhLi gives the carbanion, which undergoes addition reaction with aldehyde or ketone to give the alkoxide that can be converted to alkene. Thus, cyclohexanone can be converted to ethyl 2-cyclohexylideneacetate in 95% yield.

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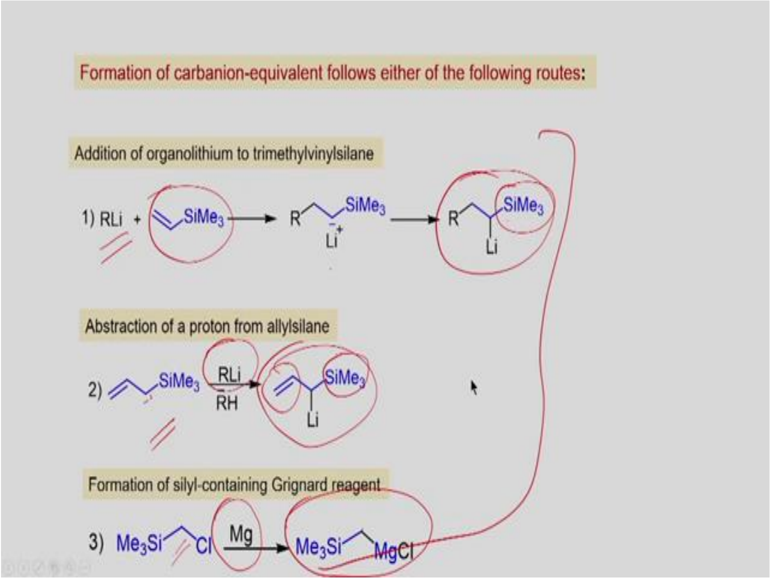
Formation of carbanion-equivalent follows either of the following routes:

Addition of organolithium to trimethylvinylsilane

Abstraction of a proton from allylsilane

Formation of silyl-containing Grignard reagent

Now, let us look at some other methods for the formation of α-silyl carbanion. Addition of organolithium to vinylsilane produces α-silyl carbanion, while allyl silane with organolithium can yield α-silyl carbanion via deprotonation. We can also make α-silyl containing Grignard reagent from (chloromethyl)trimethylsilane.

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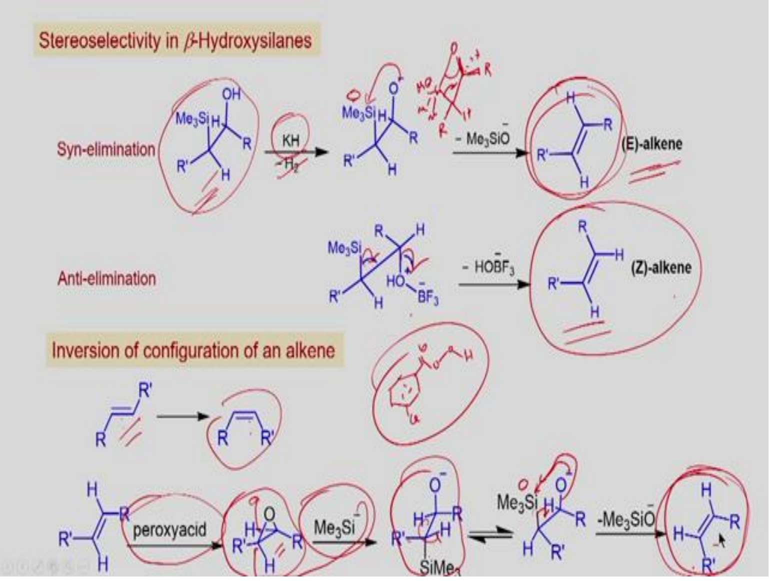

Stereoselectivity in β-Hydroxysilanes

Syn-elimination

Anti-elimination

Inversion of configuration of an alkene

Here is the mechanism of the Peterson olefination. The β-hydroxysilane with base forms the pentacoordinate silicate intermediate that favors *syn*-elimination to afford *E*-alkene. While the reaction with acid, the OH group makes chelation and favors *anti*-elimination to give *Z*-alkene.

Using this strategy, we can invert the configuration of an alkene. For example, epoxidation of *trans*-alkene gives the *trans*-epoxide, which can open up using trimethylsilyl anion to yield the α-silyl alkoxide that can rotate to form the pentacoordinate silicate. The *syn*-elimination produces the *E*-alkene. Thus, using Peterson olefination, we will be able to form both the configurations of alkenes.

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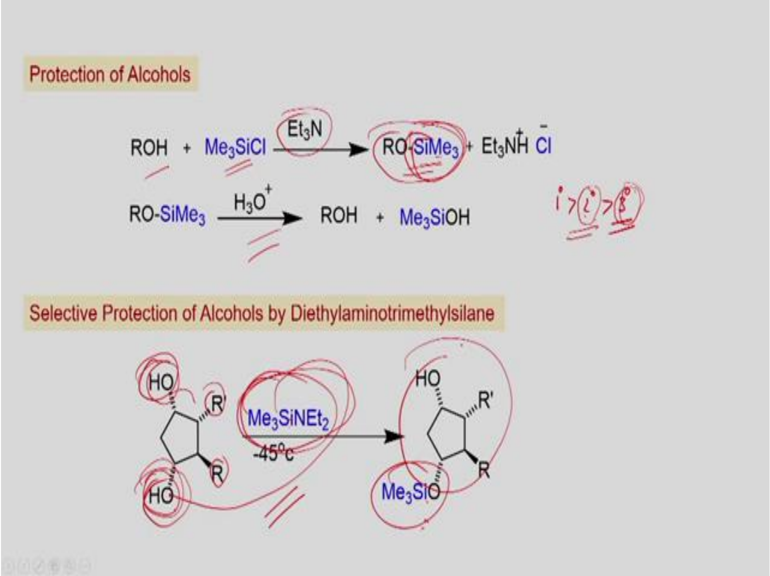
Protection of Alcohols

Selective Protection of Alcohols by Diethylaminotrimethylsilane

Another important application of silyl reagent is the protection of alcohol. We have to often protect alcohol to carry out the organic transformation of other functional group, where silyl reagent plays an important place. Alcohol can be readily protected using silyl chloride in the presence of base to produce silyl ether, which can easily be deprotected using acid. For this purpose, a series of silyl chlorides with bulky substituents have been developed. For example, in the cyclopentane1-1,3-diol, the OH group *anti* to the substituent is protected due to the less steric effect compared to the *syn* OH group.

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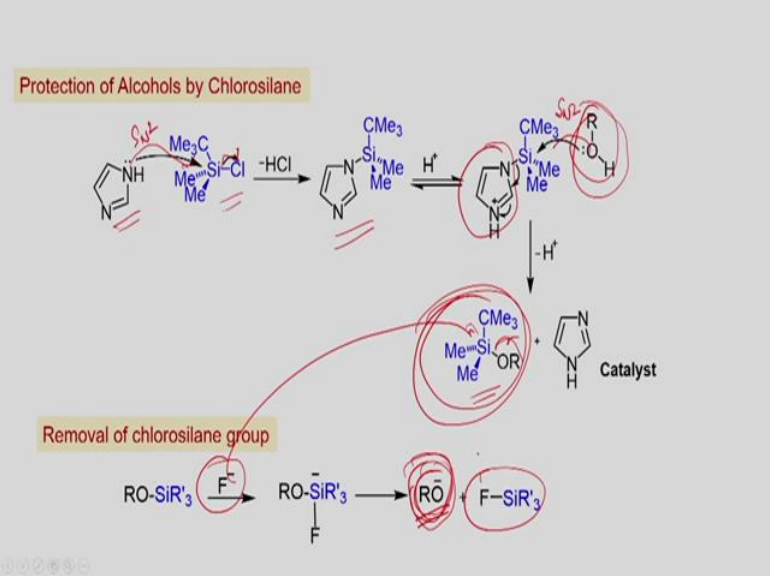
Protection of Alcohols by Chlorosilane

Removal of chlorosilane group

Here is the use of *tert*-butyldimethylsilyl chloride to protect alcohol. The reaction is carried out using imidazole as the catalyst. Imidazole reacts with silyl chloride via S_N2 to produce activated silyl intermediate, which undergoes reaction with the alcohol via S_N2 pathway to give the silyl ether. Fluoride ion is commonly used to cleave the silyl group. The driving force is the formation strong Si-F bond.

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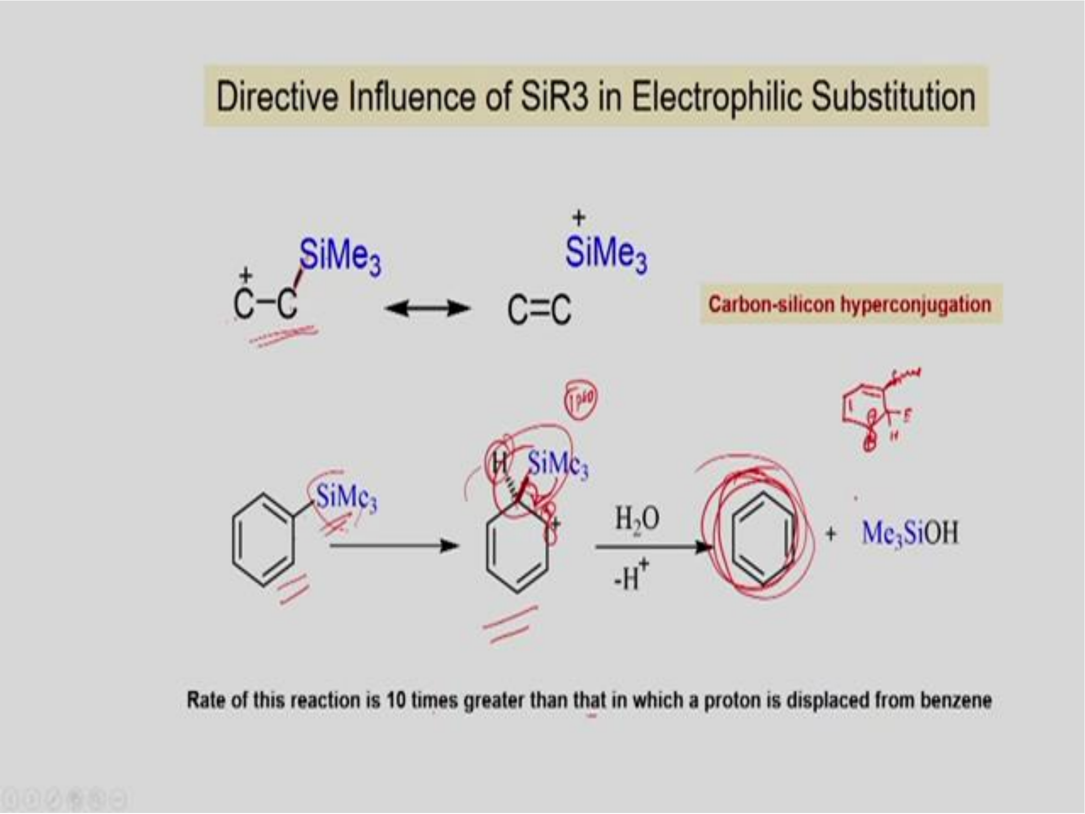

Directive Influence of SiR3 in Electrophilic Substitution

Carbon-silicon hyperconjugation

Rate of this reaction is 10 times greater than that in which a proton is displaced from benzene

Here is the effect of silyl group in the electrophilic substitution. Phenyltrimethylsilane shows 10 times greater reactivity compared to simple benzene. In this reaction, the electrophile reacts to the carbon that is bonded to the silyl group, because it forms the tetrahedral intermediate, where the C-Si bond stabilizes the vacant *p* orbital at the β-carbon. Therefore, the electrophile undergoes reaction where the carbon is bonded with silyl group.

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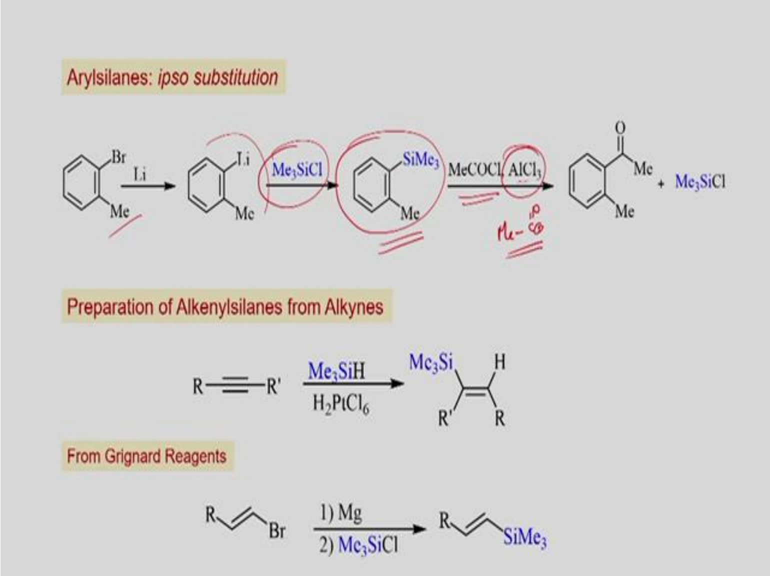
Arylsilanes: *ipso* substitution

Preparation of Alkenylsilanes from Alkynes

From Grignard Reagents

Here is an example for the *ipso* acylation. 2-Bromotoluene with lithium gives aryl lithium, which reacts with TMSCl to give the arylsilane. Lewis acid catalyzed acylation using acetyl chloride takes place at the carbon bonded to the silyl group to give 2-methyl acetophenone.

Now let us look at the preparation and reaction of vinylsilane. Here are two synthetic routes for the preparation of vinylsilane. First method shows the Pt-catalyzed *syn* addition of trimethylsilane to internal alkyne to produce the trimethylsilane, while the second approach focuses on the reaction of vinylmagnesium halide with trimethylsilyl chloride to produce trimethylvinylsilane.

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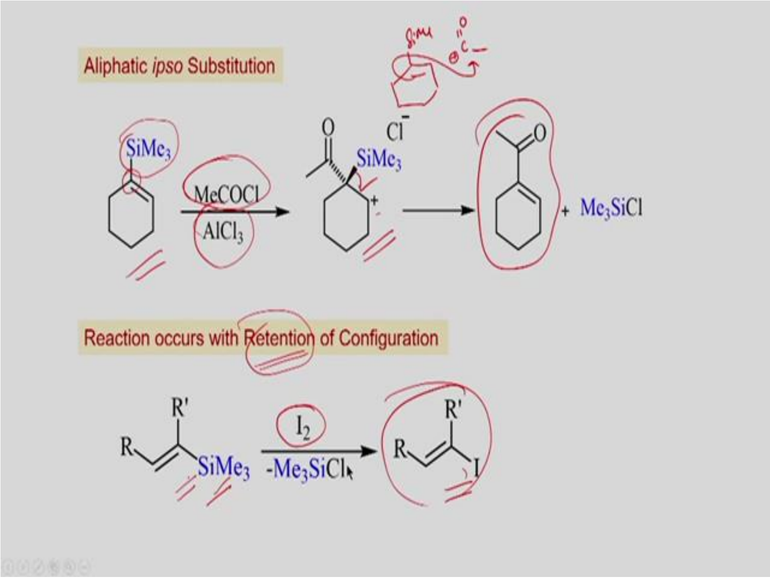
Aliphatic *ipso* Substitution

Reaction occurs with Retention of Configuration

As we have seen in the electrophilic aromatic substitution of arylsilane, vinylsilane can react with electrophile to produce the substitution product. For example, cyclohexenylsilane reacts with acetyl chloride using $AlCl_3$ to produce the ketone. Further, vinylsilane reacts with iodine to give vinyl iodide with the retention configuration.

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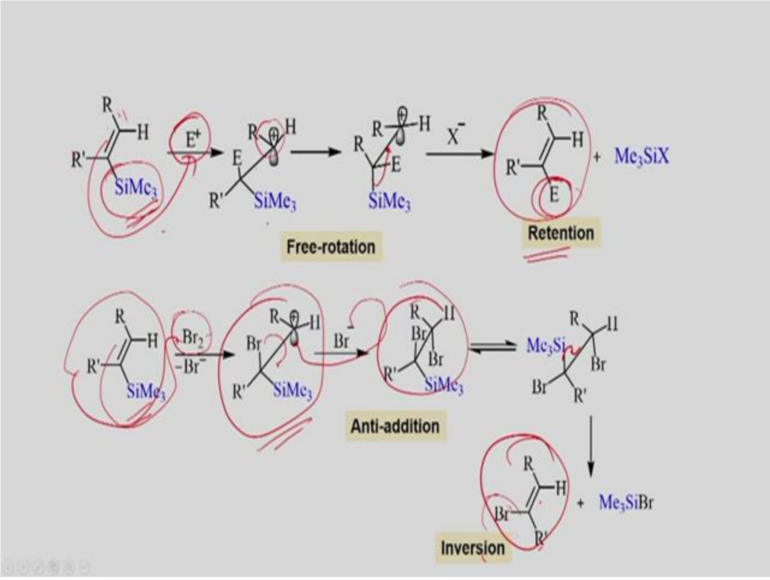

Free-rotation

Retention

Anti-addition

Inversion

Now, let us look at the stereochemistry. Vinylsilane reacts with electrophile at the carbon bonded to silyl group. The carbocation at the β-carbon is stabilized by the C-Si bond through C-C rotation so that C-Si bond is parallel to the vacant *p* orbital, which converts to the alkene with retention configuration.

If you want to invert the configuration of the double bond, vinylsilane is to be reacted with bromine to produce *anti*-addition, which can convert into alkene with inverted configuration via the elimination of trimethylsilyl bromide.

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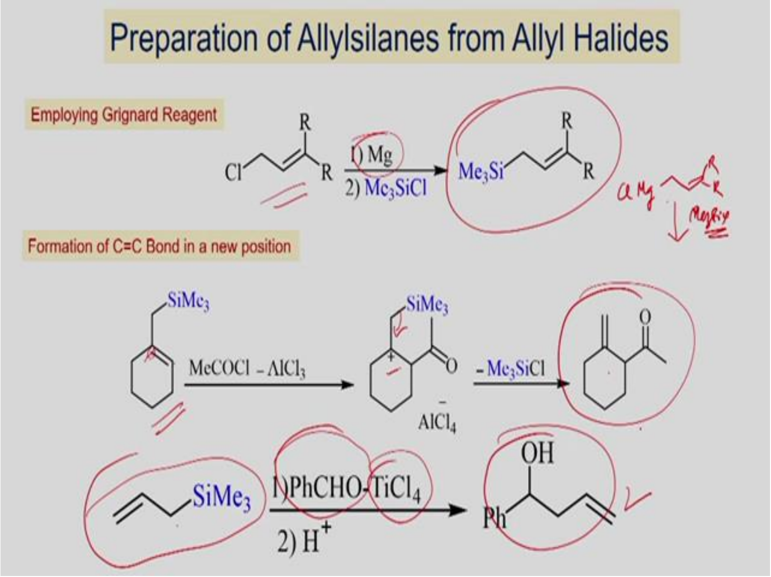

Preparation of Allylsilanes from Allyl Halides

Employing Grignard Reagent

Formation of C=C Bond in a new position

Now, let us look at the preparation of allylsilanes and their reactions. If you have allyl chloride, you can convert to Grignard reagent that can react with trimthylsilyl chloride to produce allylsilane.

Allylsilane is widely used in the synthetic chemistry for carbon-carbon bond formation. For example, (cyclohexenylmethyl)trimethylsilane with acetyl chloride using $AlCl_3$ produces β-silyl carbocation. The driving force is the stabilization of the carbocation by the β-silicon effect. Substitution of the chloride ion on the silyl group leads to the formation of the double bond.

Similarly, allylation of aldehyde can be accomplished using strong Lewis acid to produce allyl alcohol, which is known Sakurai reaction. These are some of representative examples for the allylation that has been well explored.

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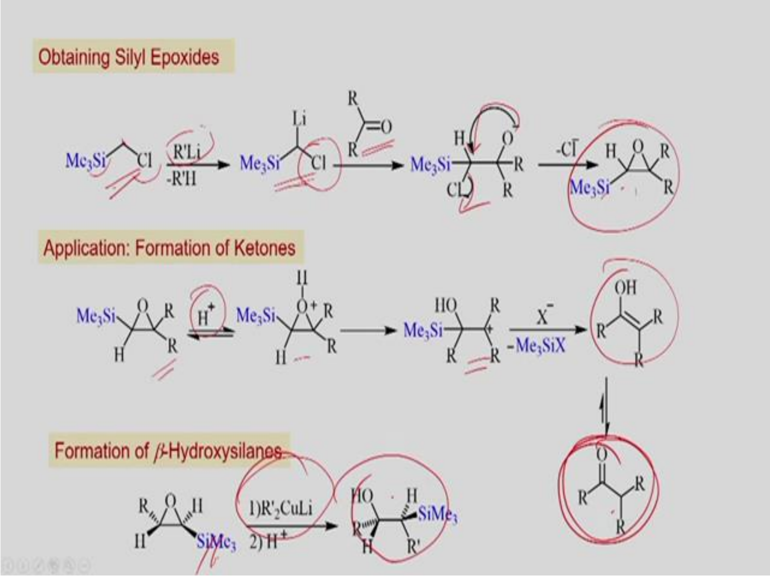

Obtaining Silyl Epoxides

Application: Formation of Ketones

Formation of β-Hydroxysilanes

Here is the preparation and application of silyl epoxide. (Chloromethyl)trimethylsilane with organolithium produces the carbanion, which adds to aldehyde to yield the alkoxide that undergoes S$_N$2 reaction to yield the epoxide. Protonation of the epoxide can lead to the formation β-silyl carbocation. As we have seen above, the halide ion can undergo reaction with silyl group vis S$_N$2 pathway to form double bond. The enol then isomerizes to ketone. Thus, silyl epoxide can be converted to ketone.

The next example shows the nucleophilic opening of the silyl epoxide with organocopper reagent that can lead to β-hydroxysilanes.

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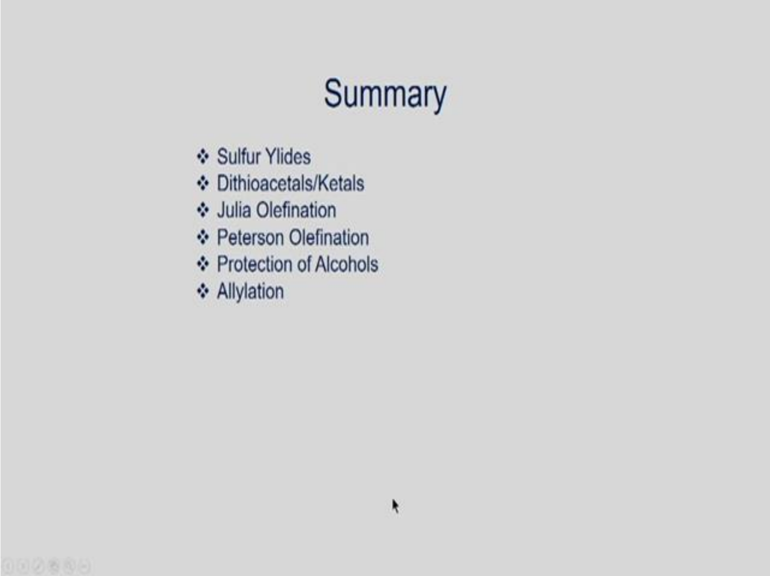

Summary

- Sulfur Ylides
- Dithioacetals/Ketals
- Julia Olefination
- Peterson Olefination
- Protection of Alcohols
- Allylation

In summary, in the first part, we have seen the sulfur ylide chemistry for the preparation of epoxide and sigmatropic rearrangements. Sulfur ylide chemistry is also widely used for the preparation of cyclopropanes and aziridines. We have next seen the use of sulfoxide for the formation of conjugated double bond.

We have then seen the application dithioacetal chemistry, which affords the potential route to reverse the polarity of the carbonyl group. Subsequently, we have looked the reaction of phenyl sulfone with aldehyde to produce *E*-alkene.

In the second part, we have seen the preparation and application of silicon reagents in organic synthesis. We have seen the reaction of α-silyl carbanion for the formation of alkenes, which is known as Peterson olefination. The stereochemistry of olefin can be controlled using acid or base.

Silyl chlorides serve as the excellent reagents for the protection of the alcohol. They are stable under basic conditions, however, they can be easily cleaved using the acid. In case of t-butyldimethylsilyl, we have to use fluoride ion to cleave the silyl group.

We have then seen the preparation and reaction of vinyl and allyl silanes. These reactions require strong nucleophile to activate the electrophile and the driving force for these reaction is the formation of β-silyl carbocation. The carbocation is stabilized by the C-Si bond.

Finally, we have seen the preparation of the silyl epoxide, which readily rearranges to ketone in the presence of acid. Silyl epoxide can be reacted with organocopper to give the β-hydroxy silyl compounds.

As we can see, the sulfur and silicon reagents have wide applications in organic synthesis. With this we conclude this lecture, thank you very much.