SATHYABAMA
INSTITUTE OF SCIENCE AND TECHNOLOGY
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SCHOOL OF SCIENCE & HUMANITIES

DEPARTMENT OF CHEMISTRY

UNIT – I - ORGANIC SYNTHESIS – SCYA5101

UNIT 1

ORGANIC SYNTHESIS

1.1 Synthetic analysis and planning:

Synthetic planning is a construction process that involves converting simple and commercially available molecules into complex molecules using specific reagents associated with known reactions in the retrosynthetic scheme. The overall yield in a multistep synthesis is the product of the yields for each separate step.

1.2 Guidelines for Retrosynthesis:

1. Recognize the functional group in the TM.
2. Disconnect the TM into fragments with known reliable chemical reactions using FGI.
3. During FGI, changing one Functional group to another may alter its reactivity dramatically.
    i. Alcohols and aldehydes are converted by redox reactions with the carbonyl groups are electron withdrawing and alcohols are electron donating groups.
4. Disconnections in the TM proceeds with
    i. Disconnect at the middle of the TM
    ii. Disconnect at the branch point
    iii. Disconnect rings from the chains.
    b. Bonds next to carbonyl group
    c. Bonds joining the aromatic ring to the rest of the molecule.
    d. Using two group disconnections.
5. Some substituents (OMe) are difficult to add in that case it is best to retain them for the synthesis.
6. Some groups are added to the aromatic ring by electrophilic substitution reaction which requires an electron withdrawing group like nitro (o to leaving group).
7. When a series of reactions has been proposed, start a reaction which gives a single product rather than a mixture.
8. When two groups are of equal reactivity, one group is selectively reacted by suitable reagents.
9. When two groups of unequal reactivity, the more reactive can be made to react first.

1.3 Classification:

Synthesis can be grouped into three broad categories: (i) Linear synthesis (ii) Convergent synthesis (iii) Divergent Synthesis.

1.3.1 Linear Synthesis:

In linear synthesis, the target molecule (TM) is synthesized through a series of linear transformations. The TM is assembled in a stepwise manner. E.g.,

A ⟶ B ⟶ C ⟶ D ⟶ E ⟶ F ⟶ G ⟶ H

For the above seven step synthesis, there are total eight components (A to H). If the yield of the intermediate at each step is 80% then,

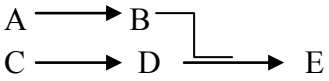
Overall yield of H = 80/100*80/100*80/100*80/100*80/100*80/100 =0.21

Therefore, overall yield % of H = 21%.

1.3.2 Convergent Synthesis

A convergent synthesis is a strategy that aims to improve the efficiency of multistep organic synthesis. In this case, the key fragments of the target molecule are synthesized separately or independently and then joined together at a later stage in the synthesis to make the target molecule. E.g.,

In this sequences of convergent synthesis:



There are five components in two steps (A to E) each with a yield of 50%

The overall yield is given by (50/100)*(50/100) =0.21 =21%

1.3.3 Divergent Synthesis

A divergent synthesis is a strategy with the aim to improve the efficiency of chemical synthesis. It is often an alternative to convergent synthesis or linear synthesis. In this strategy divergent synthesis aims to generate a chemical compound (1) by first reacting a molecule with a set of reactants. The next generation of compounds is generated by further reactions with each compound in generation 1. This methodology quickly diverges to large numbers of new compounds.

1.4 Definitions

Target Molecule: The molecule to be synthesized.

Retrosynthesis: The logical processes of analysing the structure of the target molecule to discern a possible synthesis step by step and is represented by ⟹

Disconnection: A conceptual cleavage of a bond to break the molecule into possible starting materials.

Transformations (tfs): A disconnection of a strategic bond in the target molecule.

Synthons: the charged species formed during the disconnection process.

Retron: The functional group containing portion of the target material.

Synthetic equivalents: A chemical compound available commercially for a synthon.

FGA(Functional group Addition)- addition of Functional group during a strategic bond breaking.

FGI (Functional Group Interchange)-Changing of one functional to another to disconnect a bond.

Functional group Removal(FGR): Deletion of functional group in the target molecule for the successive steps to form synthons.

Ring Disconnection (RGD): cyclic ring structure is disconnected to form aliphatic molecules.

Chain Disconnection(CHD):Acyclic structure or appendage in the ring structure is removed.

Arrow Notations

Reaction Arrow is denoted by " → "

Delocalization arrow by " ⟷ "

Equilibrium arrow by " ⇌ "

Curved arrow (electron movement) " ↷ "

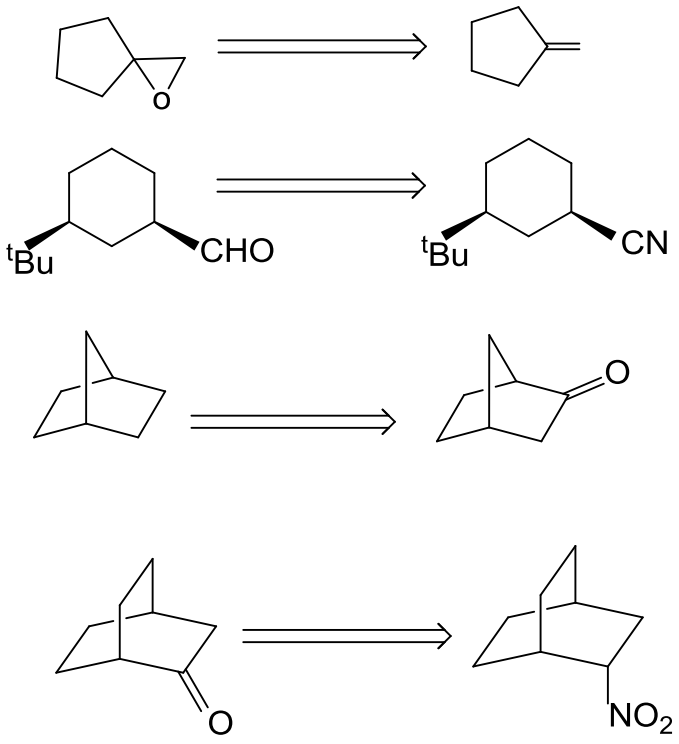
Fish-Hook arrow (one electron) " ↷ "

Retrosynthetic arrow " ⟹ "

TM can be made from the substrate. (Reverse of the synthetic reaction).

Test for Knowledge

Predict the conversions:



1.5 Synthons:

Depending on nucleophilic and electrophilic role, synthons are classified as electron donors (d) and electron acceptors (a) and are numbered with respect to the relative position of the FG and the reactive carbon atom.

Donor synthons: Neagtive polarized synthons denoted by 'd'

Eg: Alkyl anions, R^-; cyanide CN^- ; acetylide $RC\equiv C^-$

Acceptor synthons: Positive polarized synthons denoted by 'a'

Eg; Alkyl R^+; Acyl cation Ar^+; acylinium RCO^+;

According to the position of FG,

Alkyl synthons: Alkyl synthons without functional groups and are used as alkylating agents.

d^0: Electronegative heteroatom of the FG forms a covalent bond with acceptor synthons.

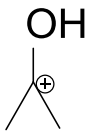
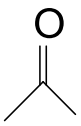
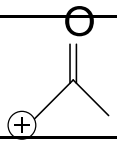
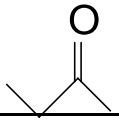
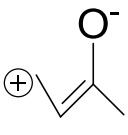
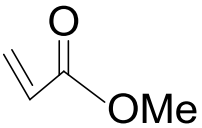
a^1d^1: If the C1 atom of the FG itself is reacting then it is a^1 (for acceptor synthons) and d^1 (for donor synthons)

a^2d^2: If the C-2 carbon atom (mainly relative to carbonyl group) to the FG is reactive.

a^3d^3: If the C-3 carbon atom is reactive relative to FG

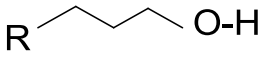
Type	synthons	Synthetic equivalents
d^0	MeS^-	MeSH
d^1	CN^-	KCN
d^2	$^-CH_2CHO$	CH_3CHO
d^3	$^-C{=}CCOOMe$	$CH_2{=}CHCOOMe$

Acceptor synthons

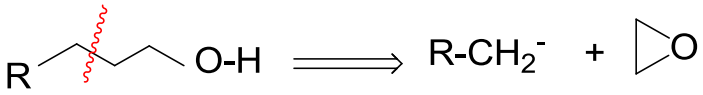
Type	synthons	Synthetic equivalents
a^0	$^+PMe_2$	$ClPMe_2$
a^1		
a^2		
a^3		

1.6 Retrosynthesis of MonoFunctional Disconnections

Example 1

Consider the formation of primary alcohol, 

,it can be formed by disconnecting the alcoholic bond to form



Leads to the formation of synthon and ethylene oxide.

Synthon can be formed by,

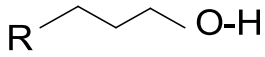
$$R\text{-}CH_2^- \Longrightarrow RCH_2MgBr \Longrightarrow RCH_2Br \Longrightarrow RCH_2OH$$

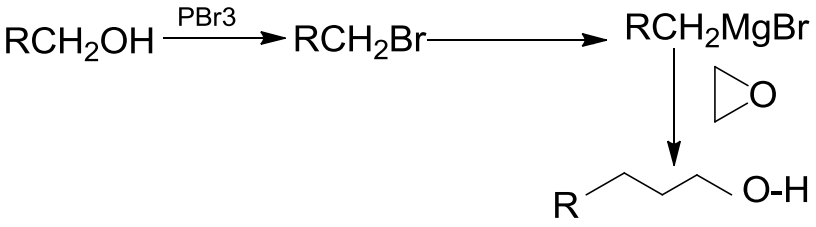
$$R\text{-}CH_2\text{-}O\text{-}H \Longrightarrow R^- + HCHO$$

The R^- synthon is formed by,

$$R^- \Longrightarrow RMgBr \Longrightarrow RBr \Longrightarrow ROH$$

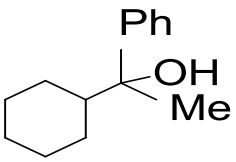
The synthetic equivalents are HCHO, ethylene oxide and ROH

Synthesis of 

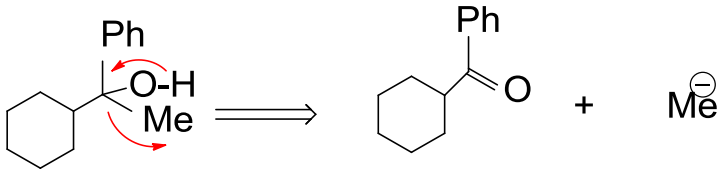


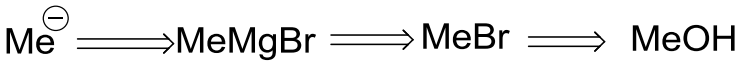
Example 2-Tertiary alcohol disconnection:

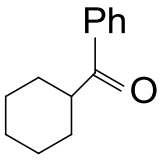
The target molecule is



The disconnection can be of

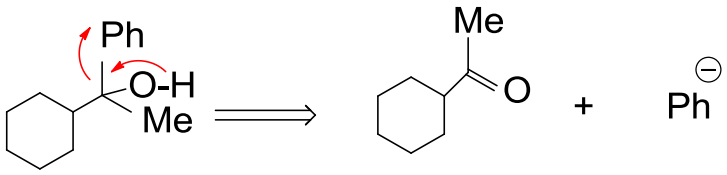




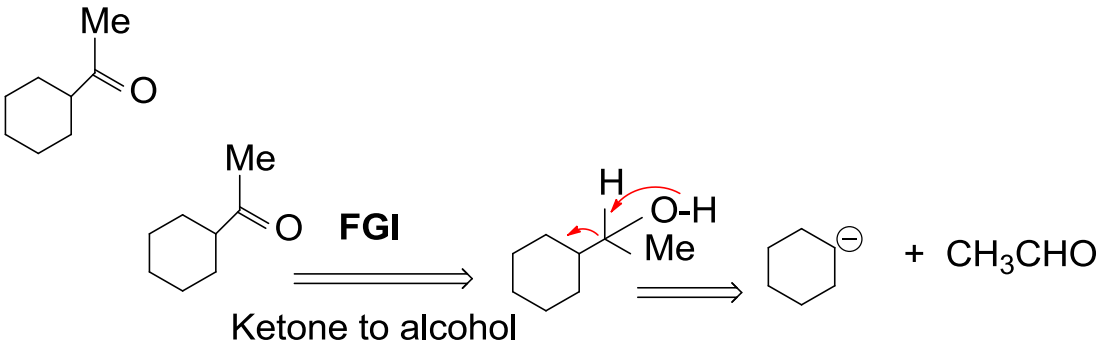
The formation of the synthon  is difficult.

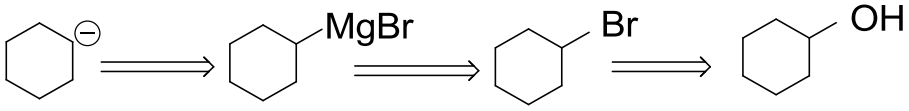
Hence, the disconnection can be

Retrosynthesis



Synthon, Ph^- can be obtained

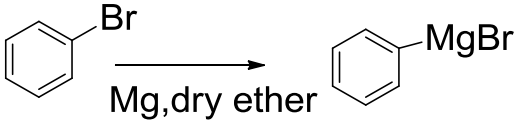




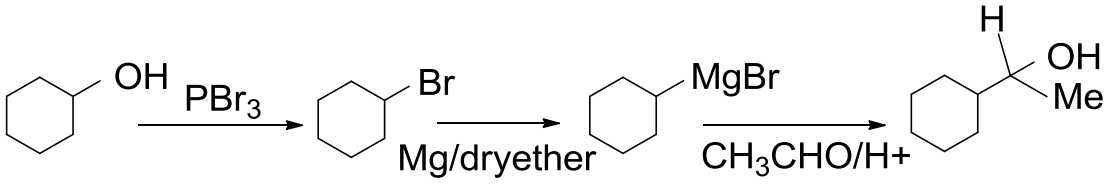
Starting materials are cyclohexanol, acetaldehyde and bromobenzene.

Synthesis:

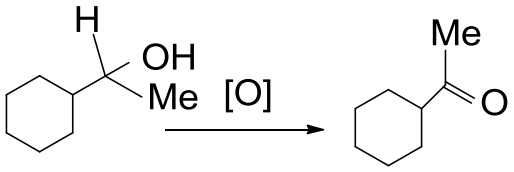
1)Phenyl magnesium bromide from Bromobenzene.



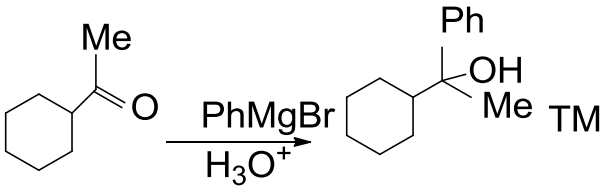
2) Cyclohexanol to methyl Ketone



Alcohol to ketone



3)Reaction of ketone with PhMgBr to form TM

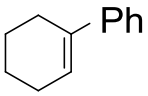


Example 3- Alkene disconnection

By FGI of an alkene to alcohol and then followed by alcohol disconnection.

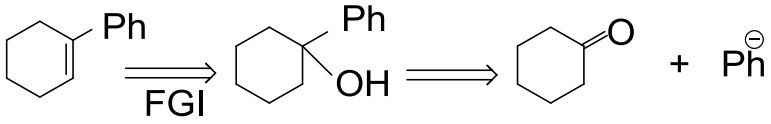
By Wittig reaction. (the reaction is not applicable if the double bond is a part of the ring)

a) By alcohol disconnection:

The target molecule is, 

The disconnection proceeds by conversion to 3^0 alcohol and then disconnected.

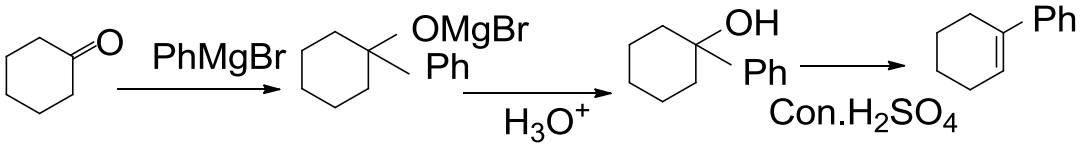
Retrosynthesis:



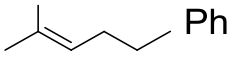
Synthon, Ph^- is obtained by

The synthetic equivalents or starting materials for the reaction is cyclohexanone and bromobenzene.

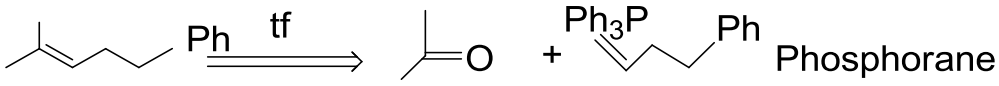
Synthesis of the TM,
Reaction of cyclohexanone with phenyl magnesium bromide followed by dehydration.



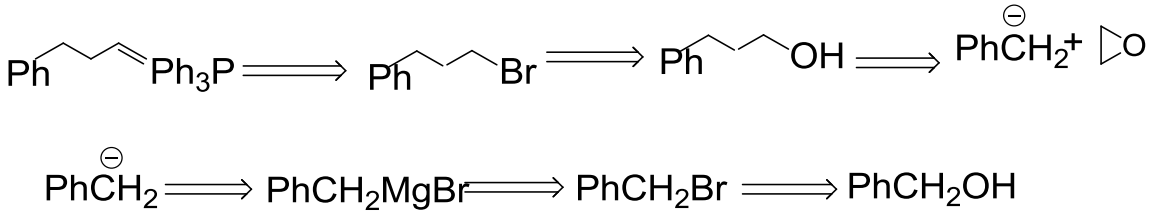
b) Alkene disconnection by Wittig reaction.
The Target Molecule,



Retrosynthesis:

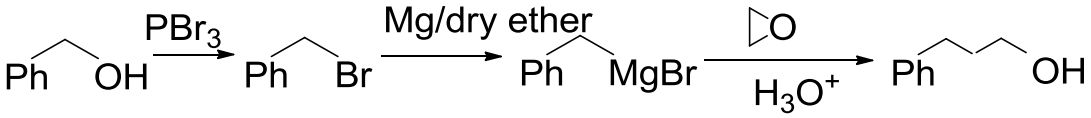


Phosphorane is obtained by

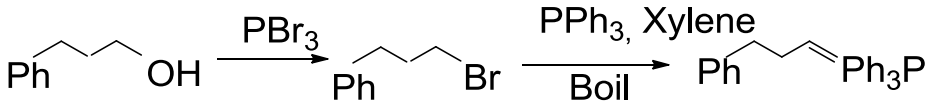


The starting materials for the reaction are benzyl alcohol,acetone, ethylene oxide.

Synthesis:
1) Phosphorane is prepared from benzyl alcohol.

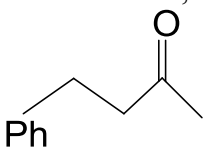


2) Reaction of phosphorane with acetone to form TM



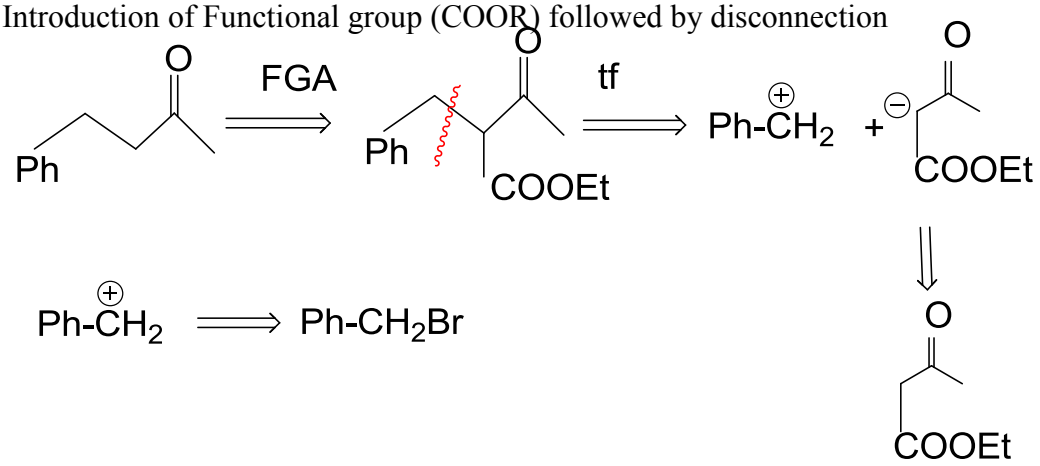
Example 4- Ketones disconnection
Methyl ketones are disconnected by acetonylation reaction (introduction of CH_3COCH group).
Symmetrical ketones are disconnected through ethylformate.
Unsymmetrical ketones are disconnected via alcohol disconnection.

a) Methyl ketones disconnection,

Target molecule is 

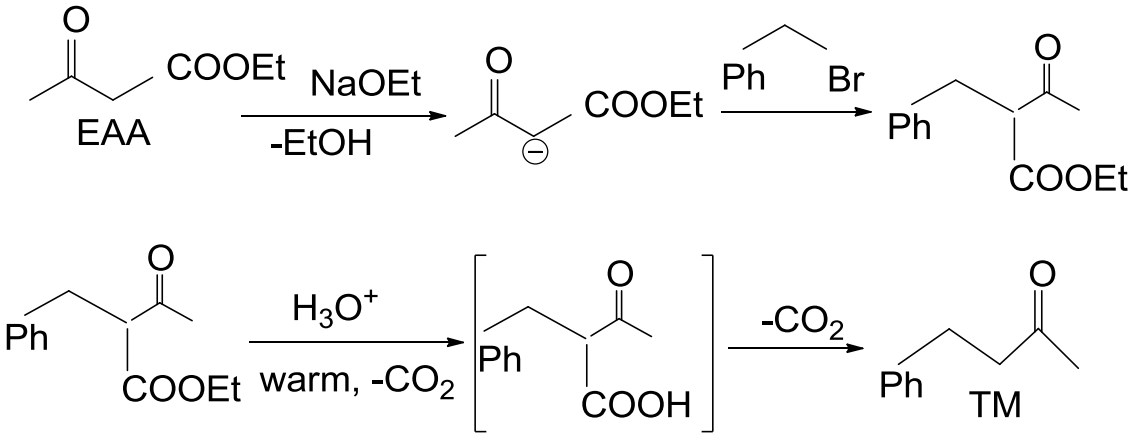
Retrosynthesis approach:

a) Introduction of Functional group (COOR) followed by disconnection

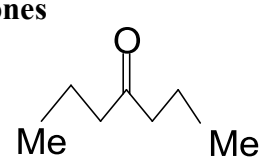


The synthetic equivalents or starting materials for the reaction are ethyl acetoacetate and benzyl bromide.

Synthesis:

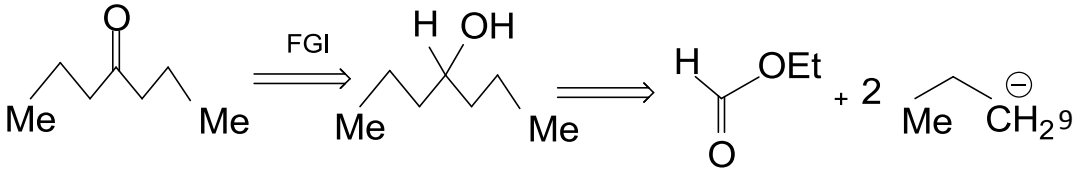


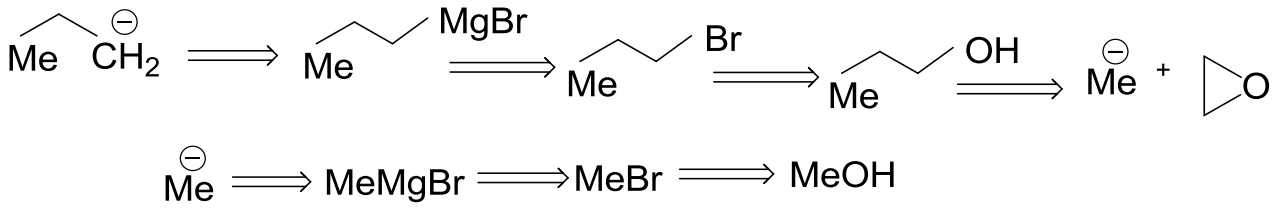
b) Symmetrical Ketones

Target Molecule is 

Retrosynthesis:

By FGI to 2^0 alcohol and then disconnected.

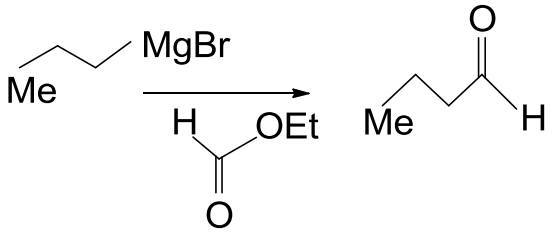




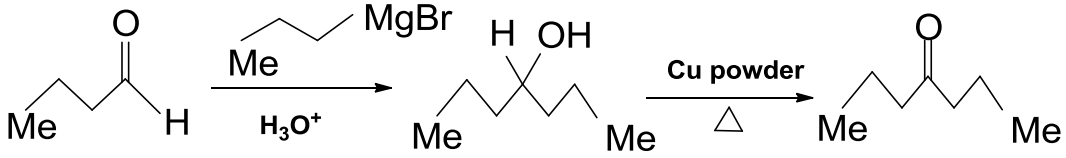
The synthetic equivalents or starting materials for the reaction are ethyl formate, methanol and ethylene oxide

Synthesis:

Preparation of Propyl Magnesium bromide from methanol and ethylene oxide.

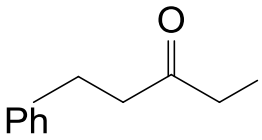


Reaction of Propyl Magnesium bromide with ethyl formate to form aldehyde.



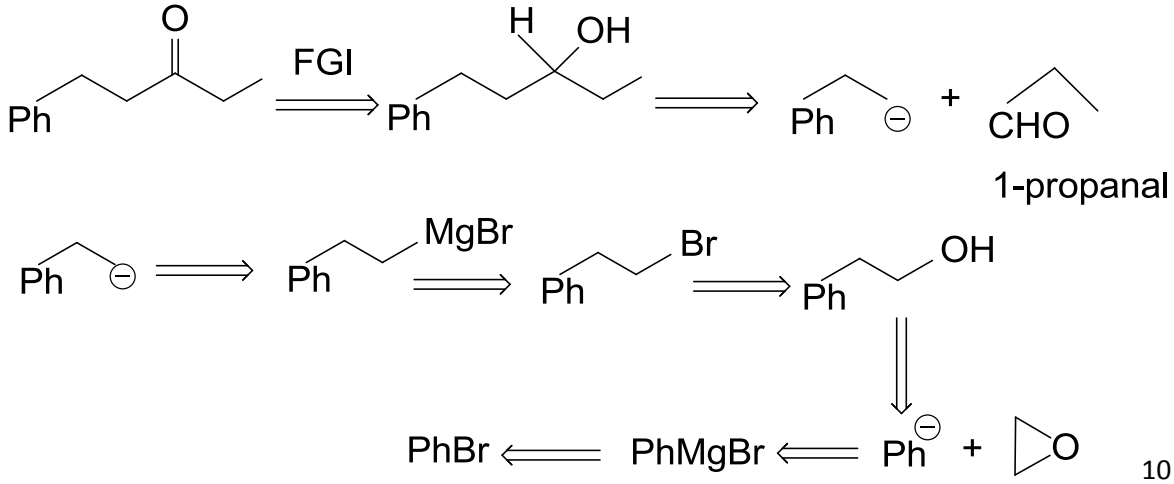
c) Unsymmetrical Ketones

Target Molecule is



Retrosynthesis:

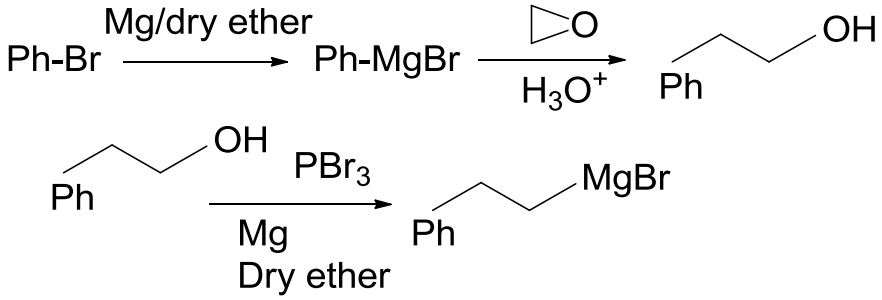
Conversion of 2^0 alcohol and disconnection



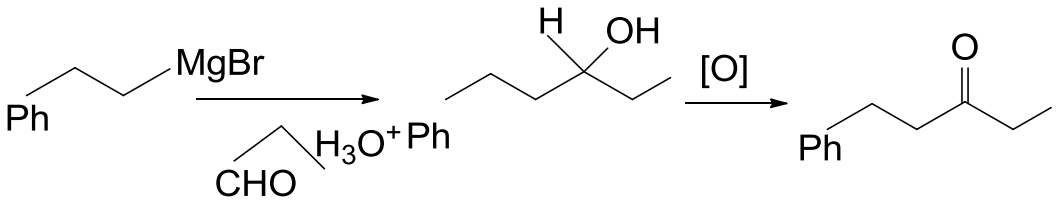
The synthetic equivalents or starting materials for the reaction are propanal, bromobenzene and ethylene oxide.

Synthesis:

Reaction to phenyl ethyl magnesium bromide



Reaction with propanal to 2^0 alcohol and oxidation



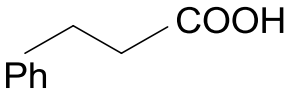
Example 5 Carboxylic acid disconnection

a) Conversion to aldehyde cyanodhydrin

b) Disconnection to CO_2

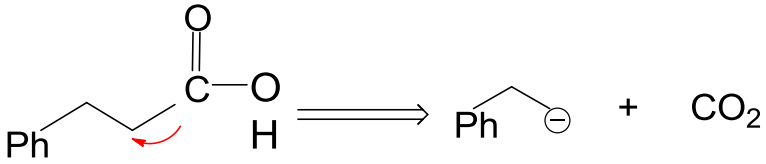
Example1 :

The target acid molecule is

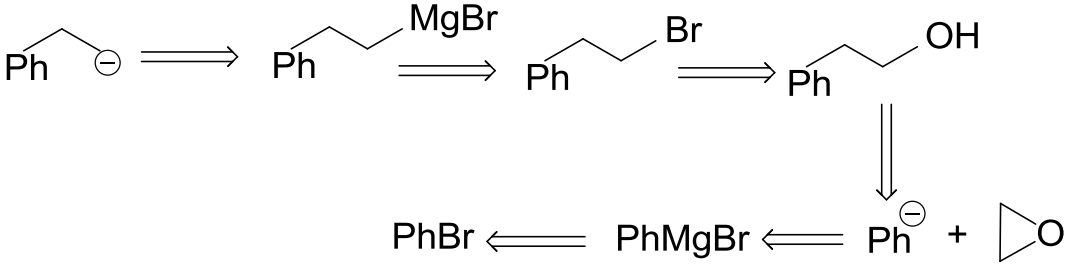


Retrosynthesis

By CO_2 disconnection



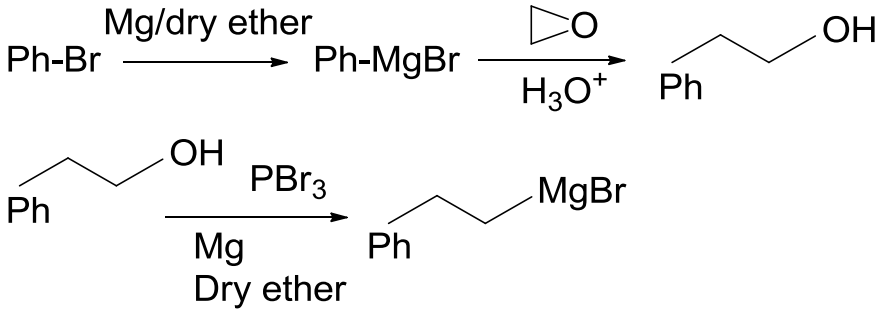
The synthon is further disconnected,



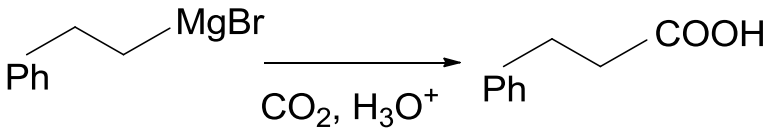
The synthetic equivalents or starting materials for the reaction are CO_2, bromobenzene and ethylene oxide.

Synthesis:

Formation to phenyl ethyl Magnesium Bromide

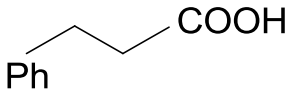


Reaction with CO_2

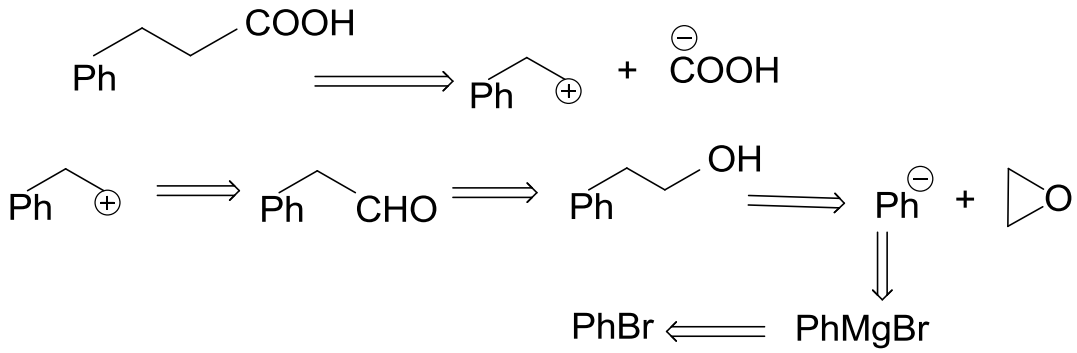


Second approach:

Target molecule:

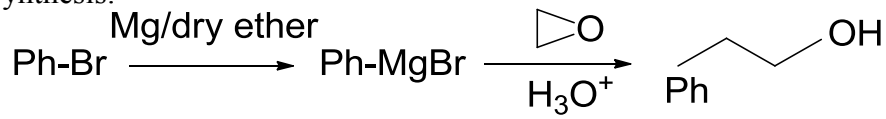


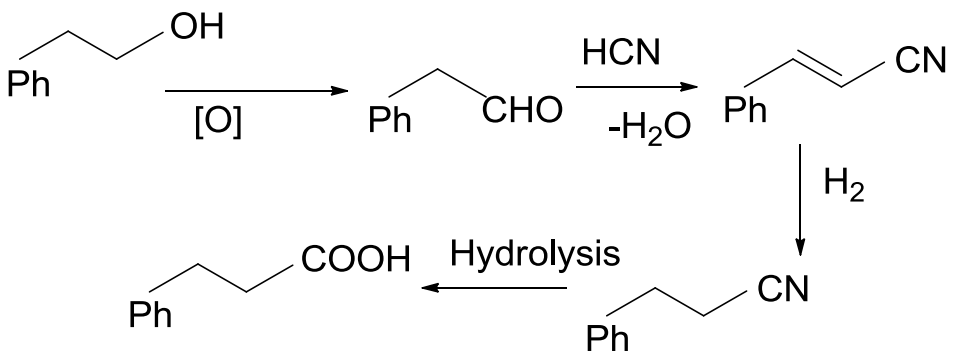
Retrosynthetic approach:



The synthetic equivalents or starting materials for the reaction are HCN, bromobenzene and ethylene oxide.

Synthesis:



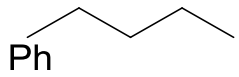


Example 6- Alkane Disconnection

FGA to form alcohol disconnection.

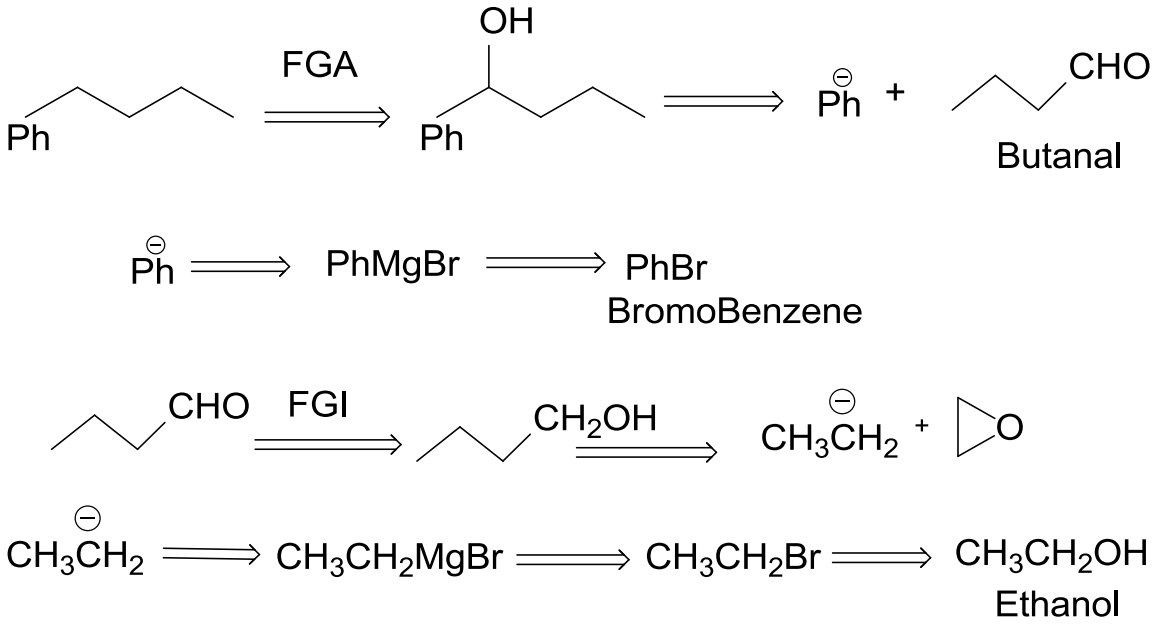
Eg 1:

Target Molecule:



Retrosynthesis approach:

FGA to form alcohol followed by disconnection

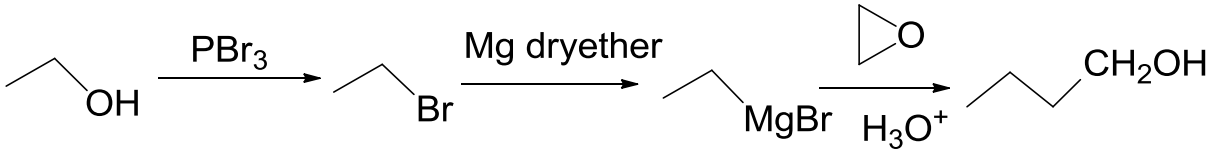


The starting materials or synthetic equivalents for the reaction are Ethanol, Ethylene oxide and bromo benzene.

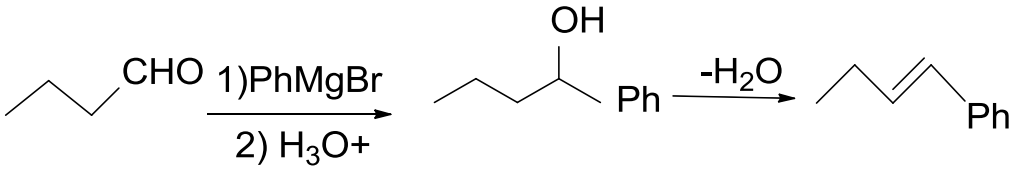
Synthesis:

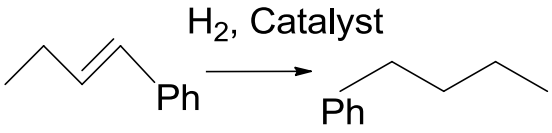
Formation of butanal, Phenyl Magnesium bromide followed by their reaction to form TM

Formation of Butanal

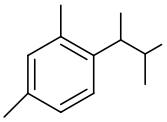


Reaction of Butanal with Phenyl Magnesium bromide

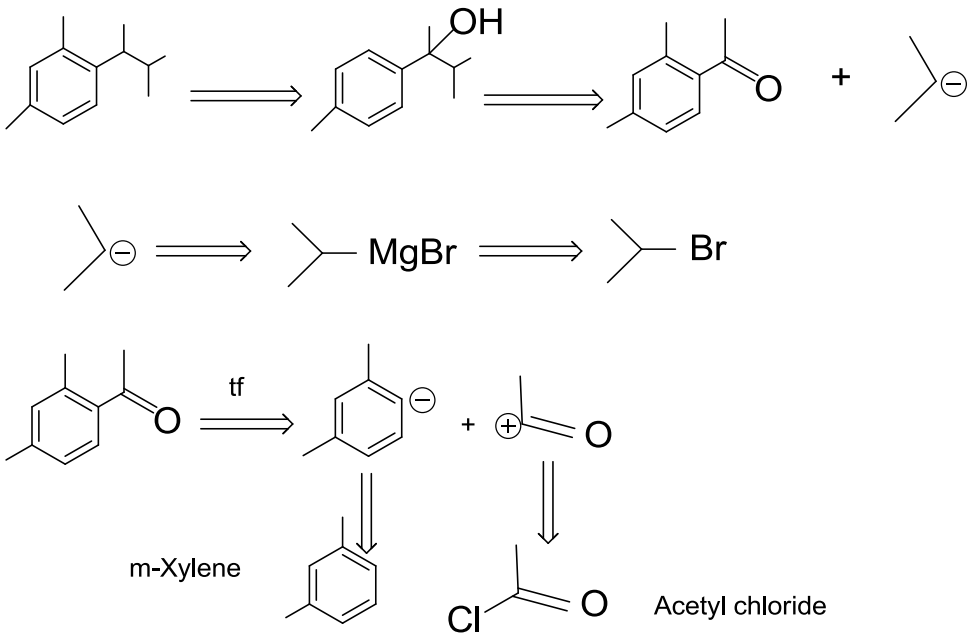




Eg: 2

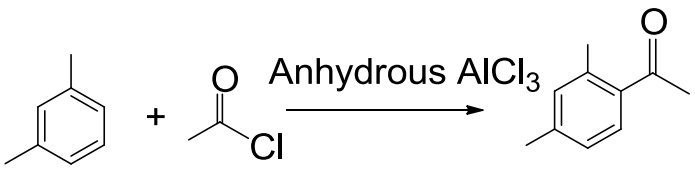
Target Molecule: 

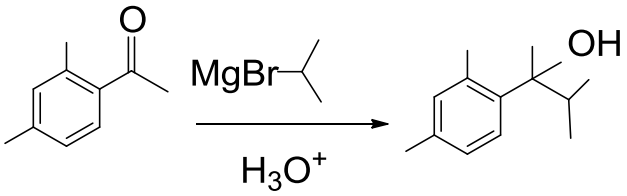
Retrosynthesis:



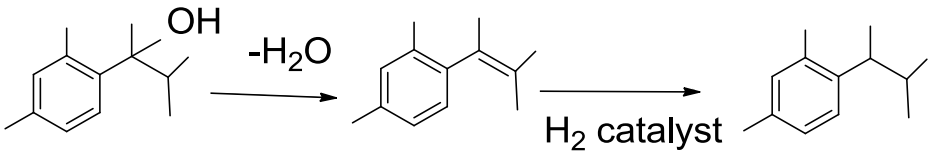
The starting materials or synthetic equivalents for the reaction are m-xylene, acetyl chloride and Isopropyl bromide.

Synthesis:
Acetylation of m-xylene by Friedel-craft's reaction





Alcohol undergoes dehydration followed by hydrogenation



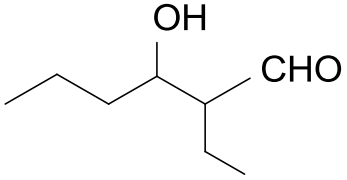
1.7 Retrosynthesis of Bi functional disconnections

The alcoholic –OH group can be easily disconnected hence bifunctional disconnections are described for oxygen containing functional groups only. The bifunctional disconnections are further classified based on the relative distance between two functional groups like 1,2; 1,3; 1,4; 1,5; 1,6-bifunctional disconnections. Since they are oxygen containing functional groups they are abbreviated as 1,3-di O, 1,5-di O, 1,6-di O

Example 1 1,3-di O functional group disconnections

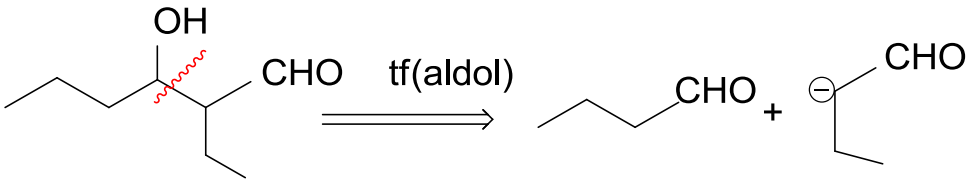
Represents aldol and can be applied to α,β unsaturated carbonyl compound.

Target Molecule:

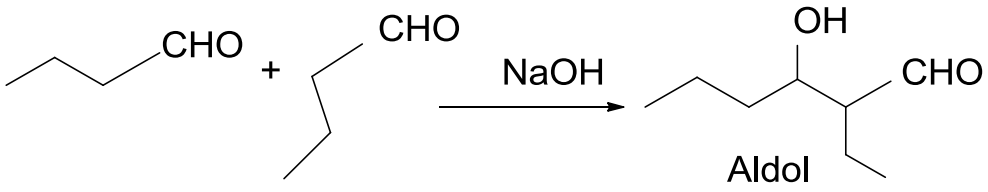


The above aldol can be synthesized by aldolization of butanal. Starting materials are Butanal

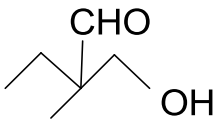
Retrosynthetic approach:



Synthesis:

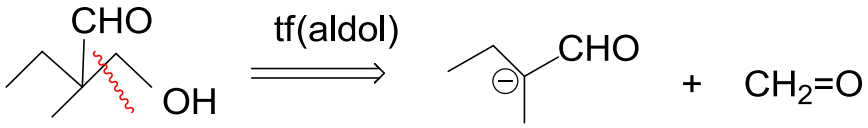


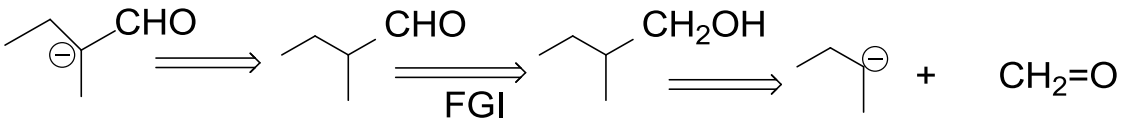
Target Molecule:



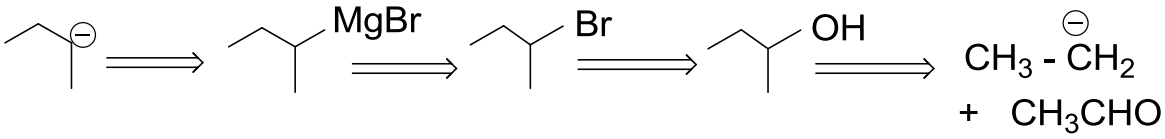
Retrosynthetic approach:

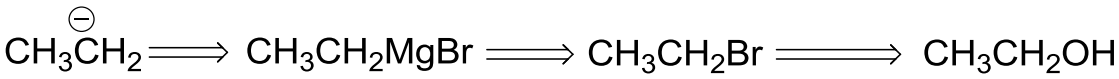
Disconnected to form two aldehydes



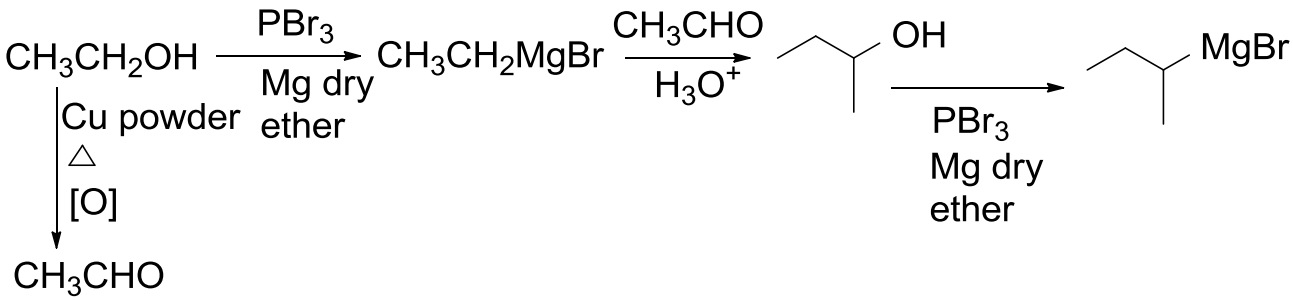


Synthon is further disconnected

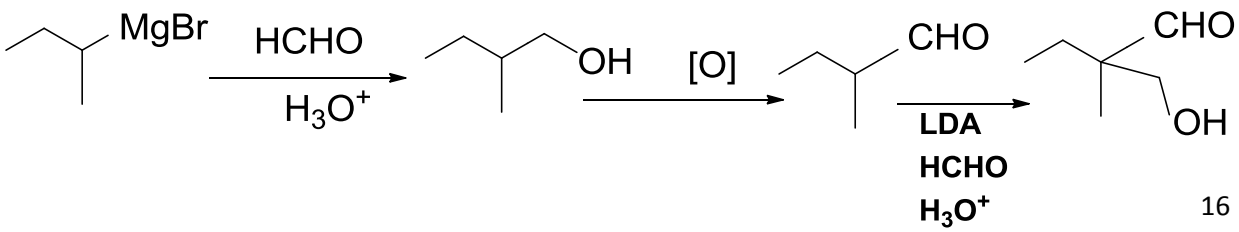




The starting materials are ethanol and formaldehyde.



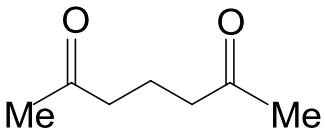
Further reactions of butan-2 magnesium bromide with formaldehyde



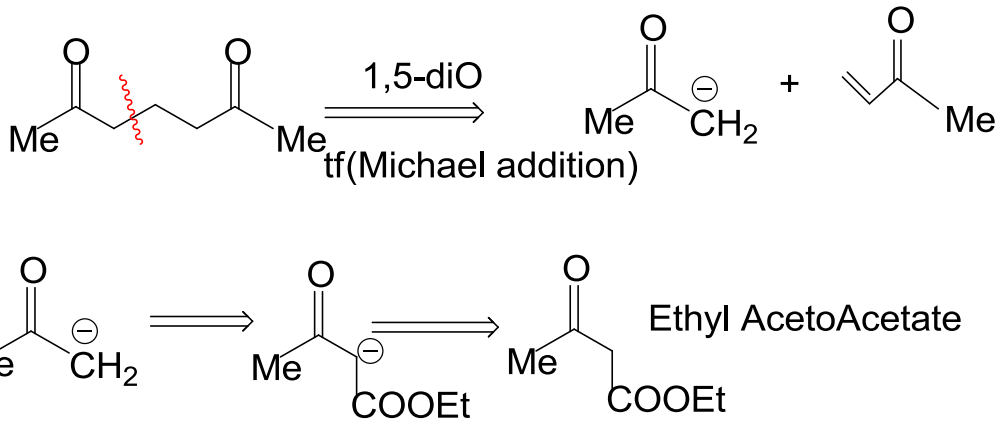
Example 2 1,5 –di functional disconnection

Disconnection takes place by Michael addition reaction. (Addition of carbanion of nucleophile to carbon of an α,β unsaturated carbonyl compound to form conjugate addition compound.)

Target Molecule:



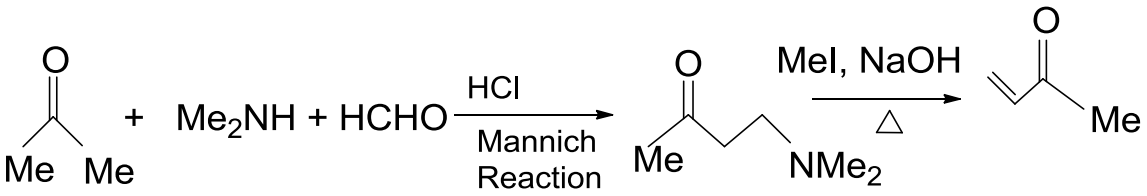
Retrosynthesis:



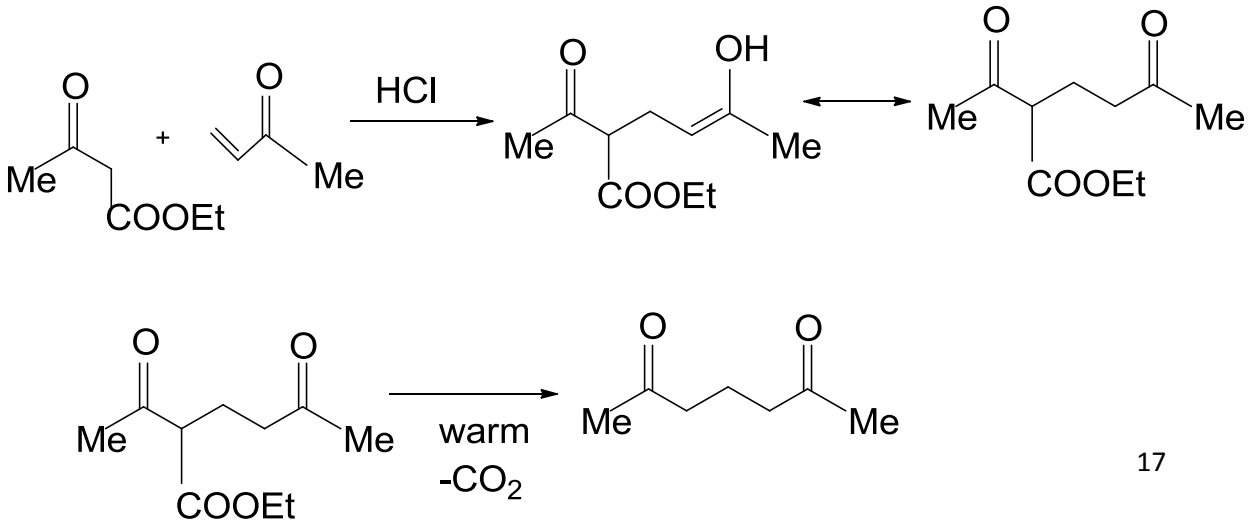
Starting materials are ethyl acetoactetate and methyl vinyl ketone (acetone, dimethylamine, formaldehyde)

Synthesis:

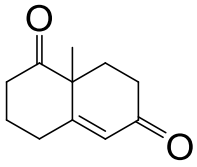
Methylvinyl ketone can be prepared by Mannich reaction



Michael reaction:

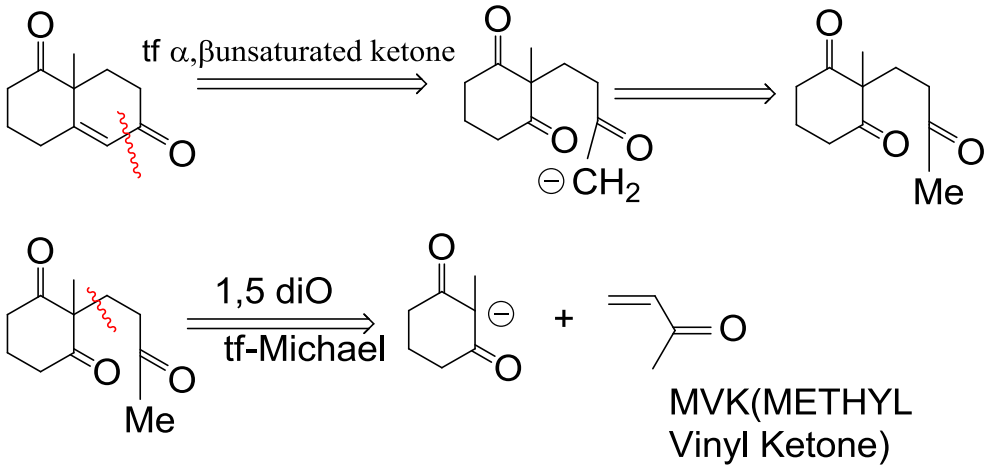


Target Molecule:

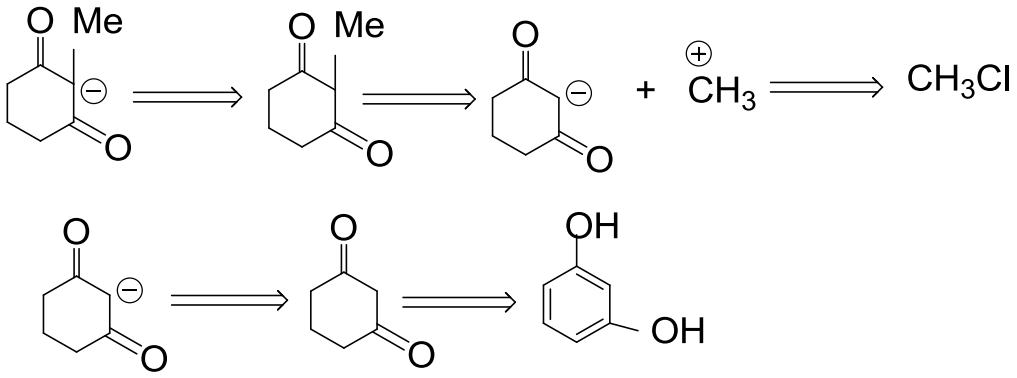


Retrosynthesis:

Formation of carbanion of Michael addition reaction and a MVK(Methyl vinyl ketone)

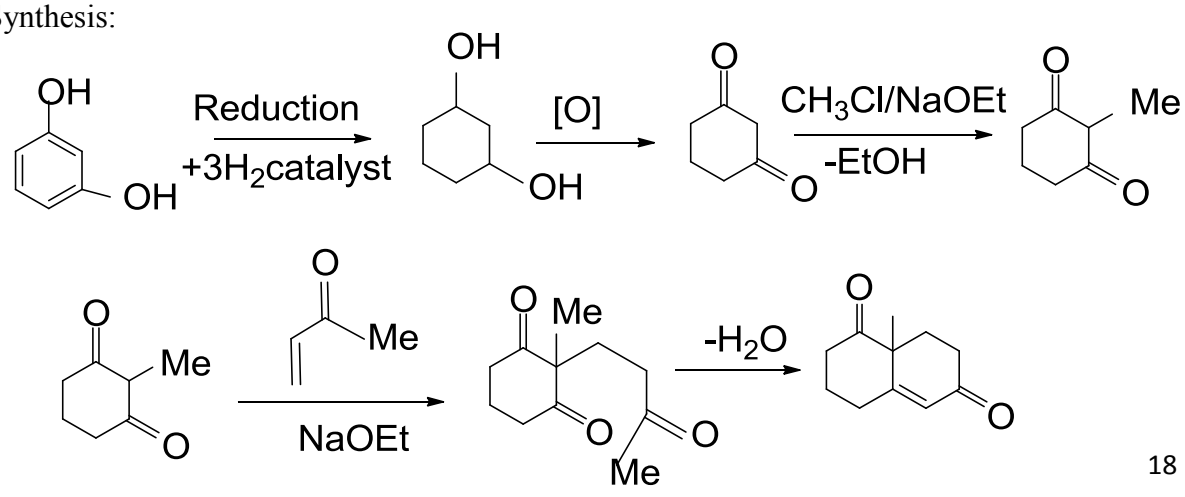


The synthon MVK can be obtained from acetone by Mannich reaction.



Starting materials are Resorcinol, methylchoride and methyl vinyl ketone (acetone, dimethylamine, formaldehyde)

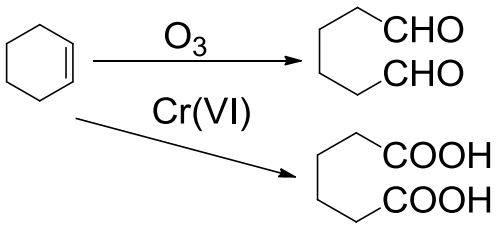
Synthesis:

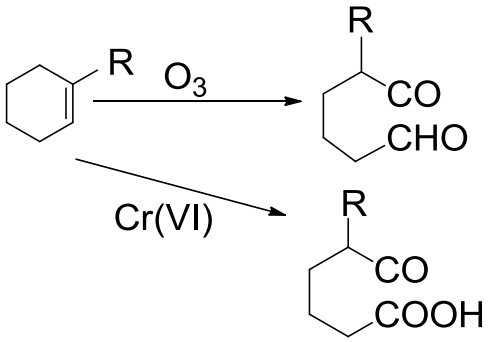


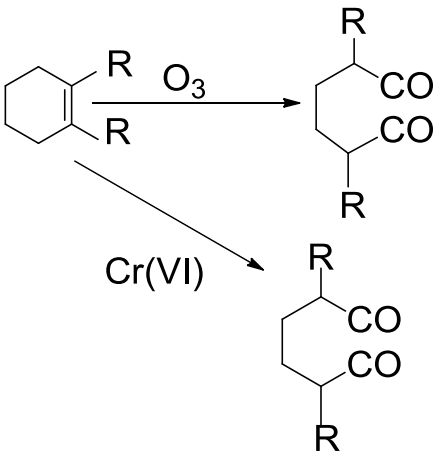
Example 3 1,6-Di O disconnection

Oxidative ring opening of cyclohexene

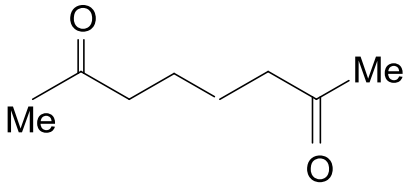
Chemical reactions:





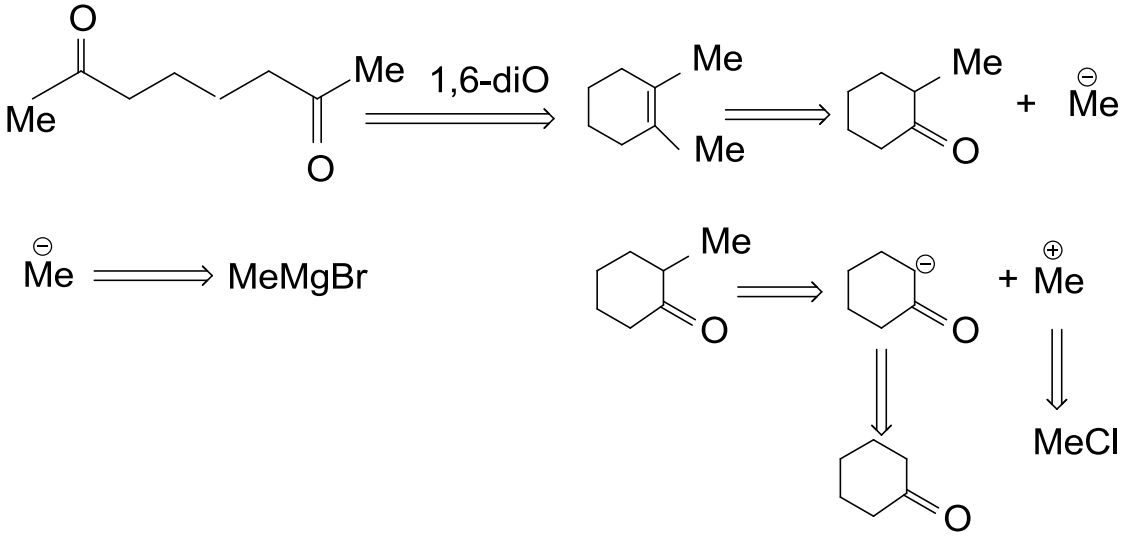


Target Molecule:



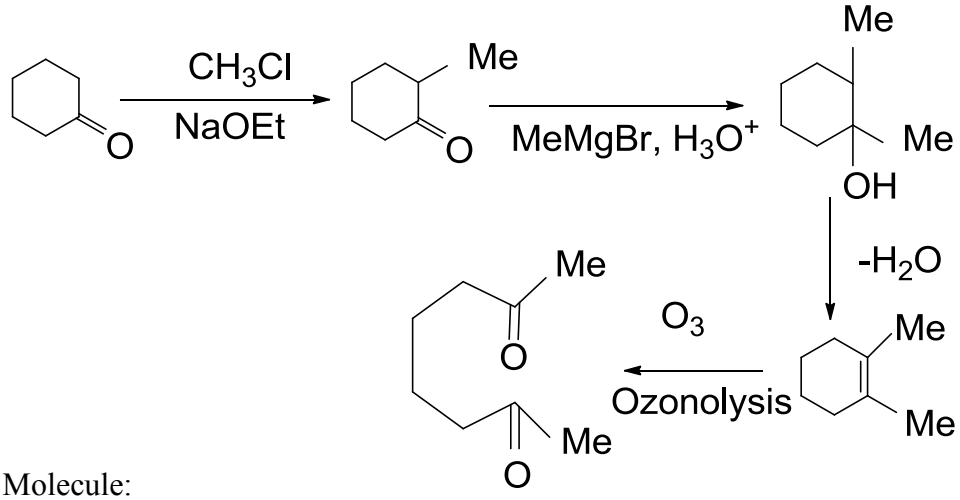
Retrosynthesis:

Ozonolysis of di substituted cyclohexene

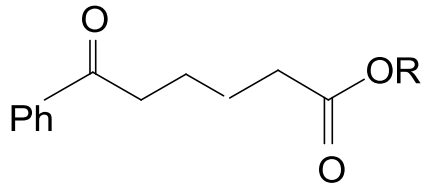


Starting materials for the reaction are cyclohexanone, methyl chloride and methyl magnesium bromide.

Synthesis:

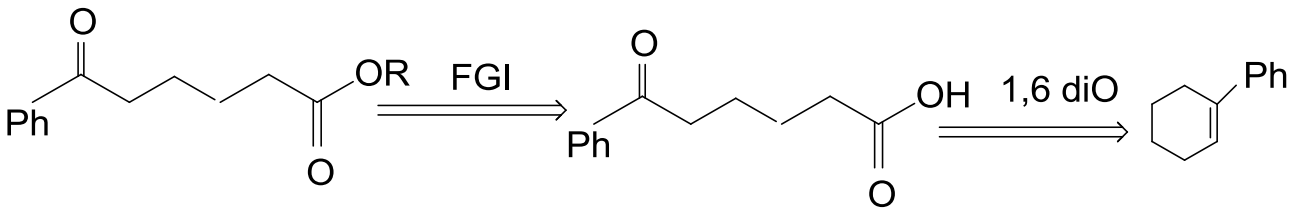


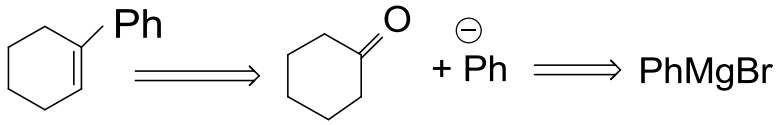
Target Molecule:



Retrosynthesis:

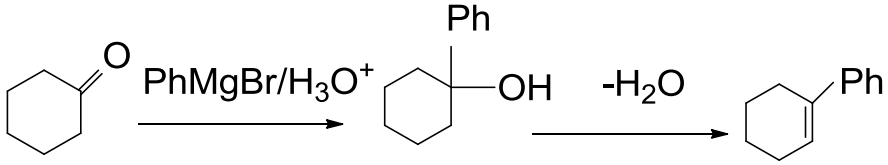
Oxidative ring opening of monosubstituted cyclohexene ring.

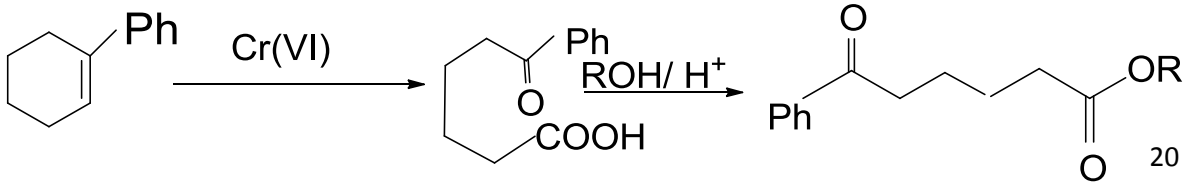




Starting materials for the reaction are cyclohexanone, phenyl magnesium bromide.

Synthesis:

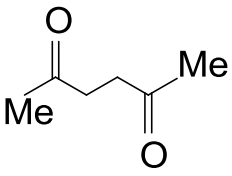




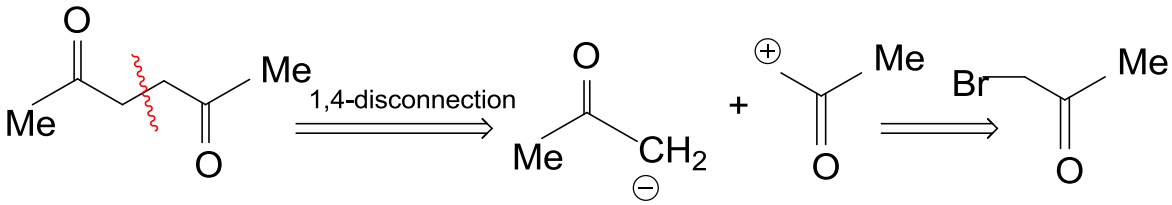
Example 4-1,4-di O disconnection

Heterolysis of carbon-carbon bond.

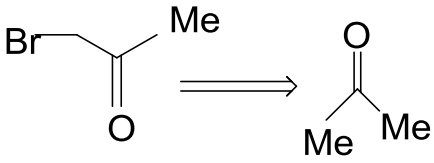
Target Molecule:

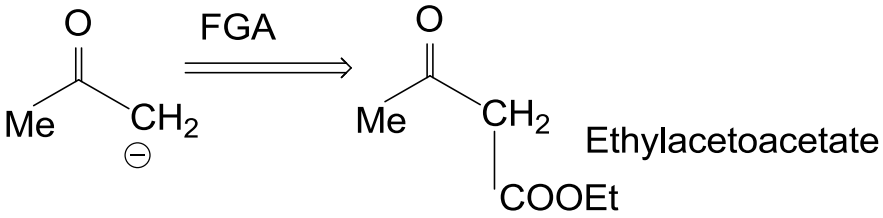


Retrosynthesis:



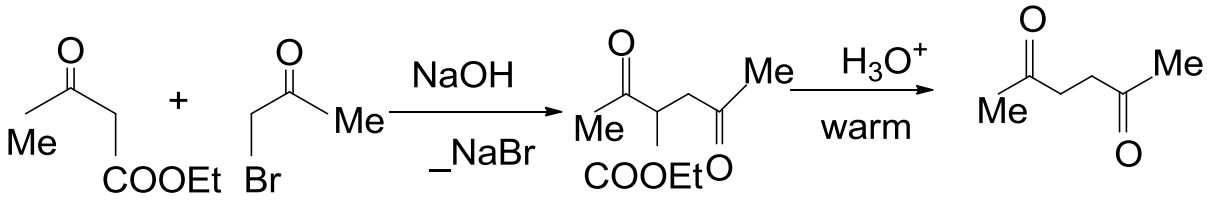
The synthon, can be prepared as



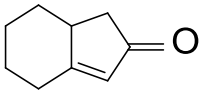


Starting materials for the reaction are Ethylacetoacetate, Bromoacetone.

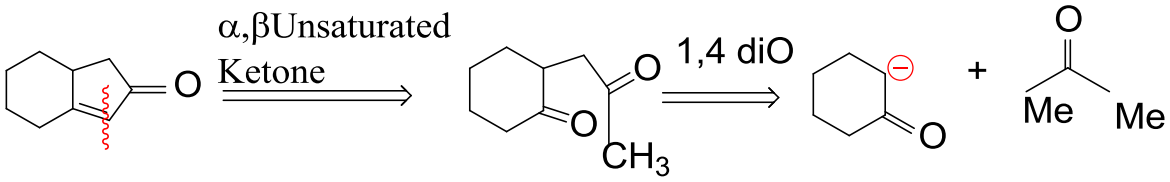
Synthesis:



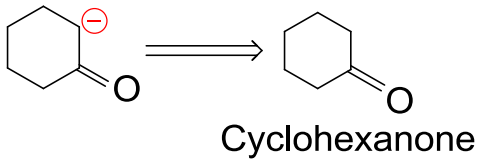
Target molecule:

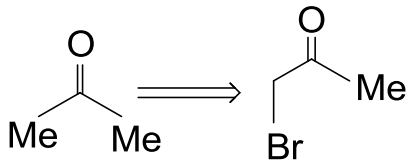


Retrosynthesis:



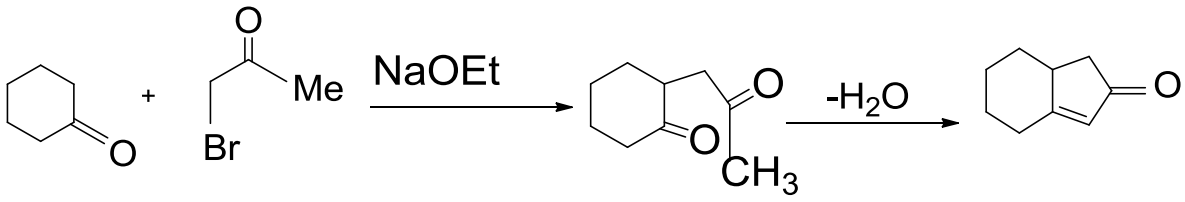
The synthon, can be prepared as





Starting materials for the reaction are cyclohexanone, Bromoacetone

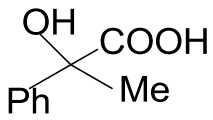
Synthesis:



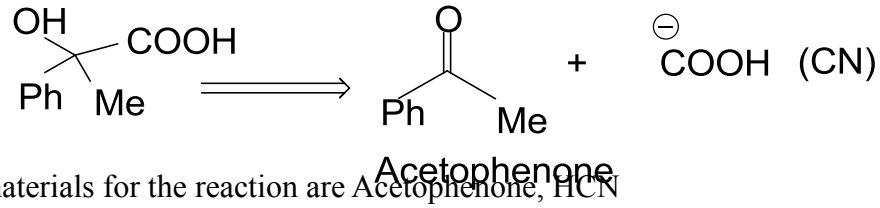
Example 5- 1.2-di O disconnection

Often involve illogical synthon

Target Molecule:

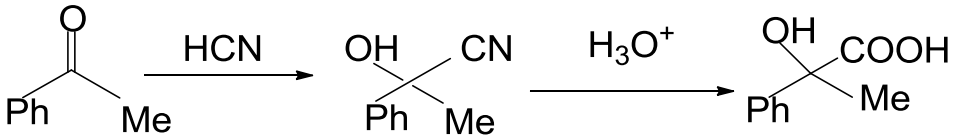


Retrosynthesis:

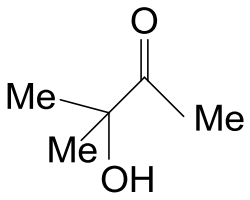


Starting materials for the reaction are Acetophenone, HCN

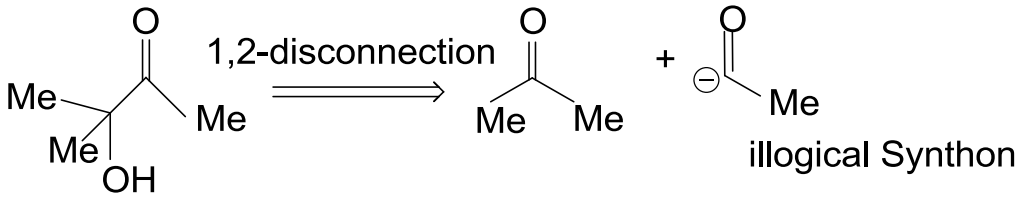
Synthesis:



Target Molecule:

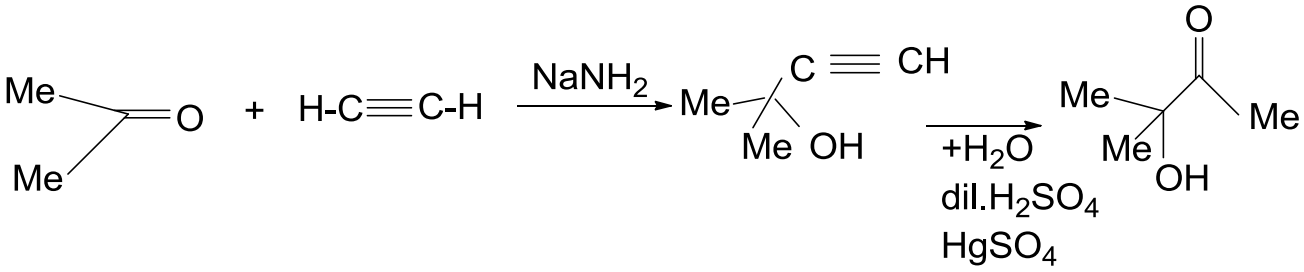


Retrosynthesis:



Starting materials for the reaction are Acetone, acetylene

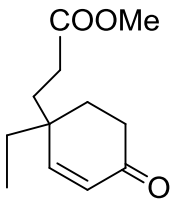
Synthesis:



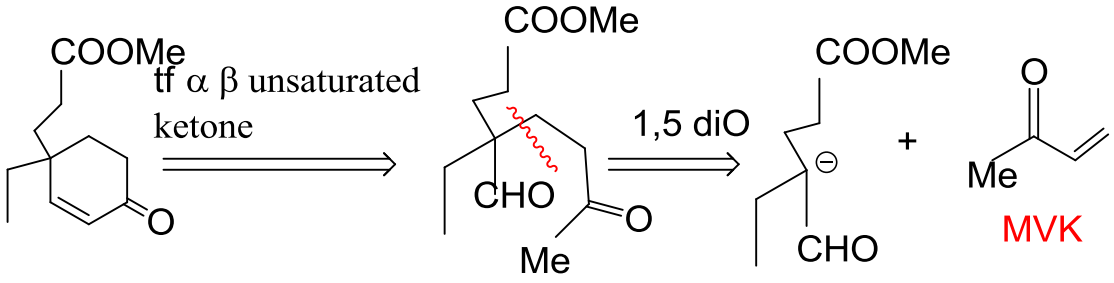
Test for Knowledge 2

Propose a retrosynthetic pathway

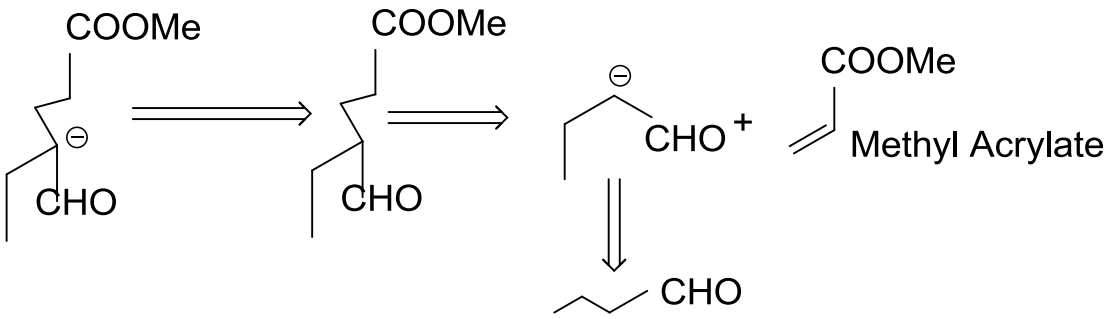
Compound



Retrosynthesis:

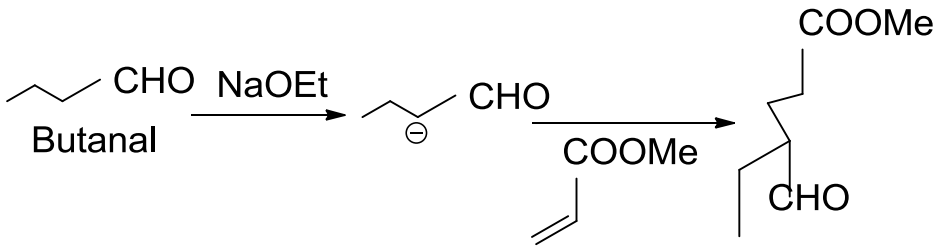


The synthon,

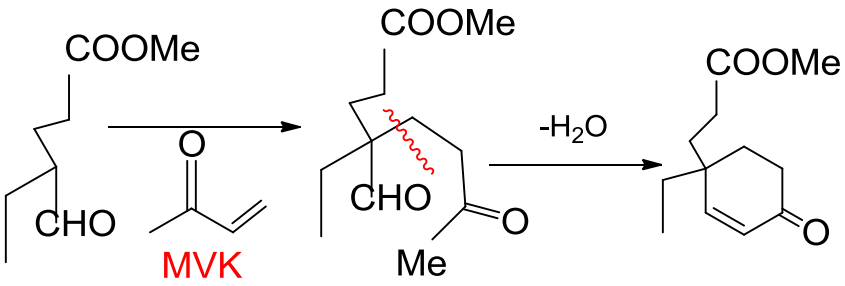


Synthetic equivalents: Butanal , MVK and methyl acrylate.

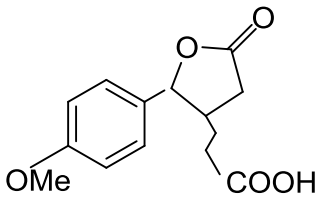
Synthesis:



Michael addition with MVK



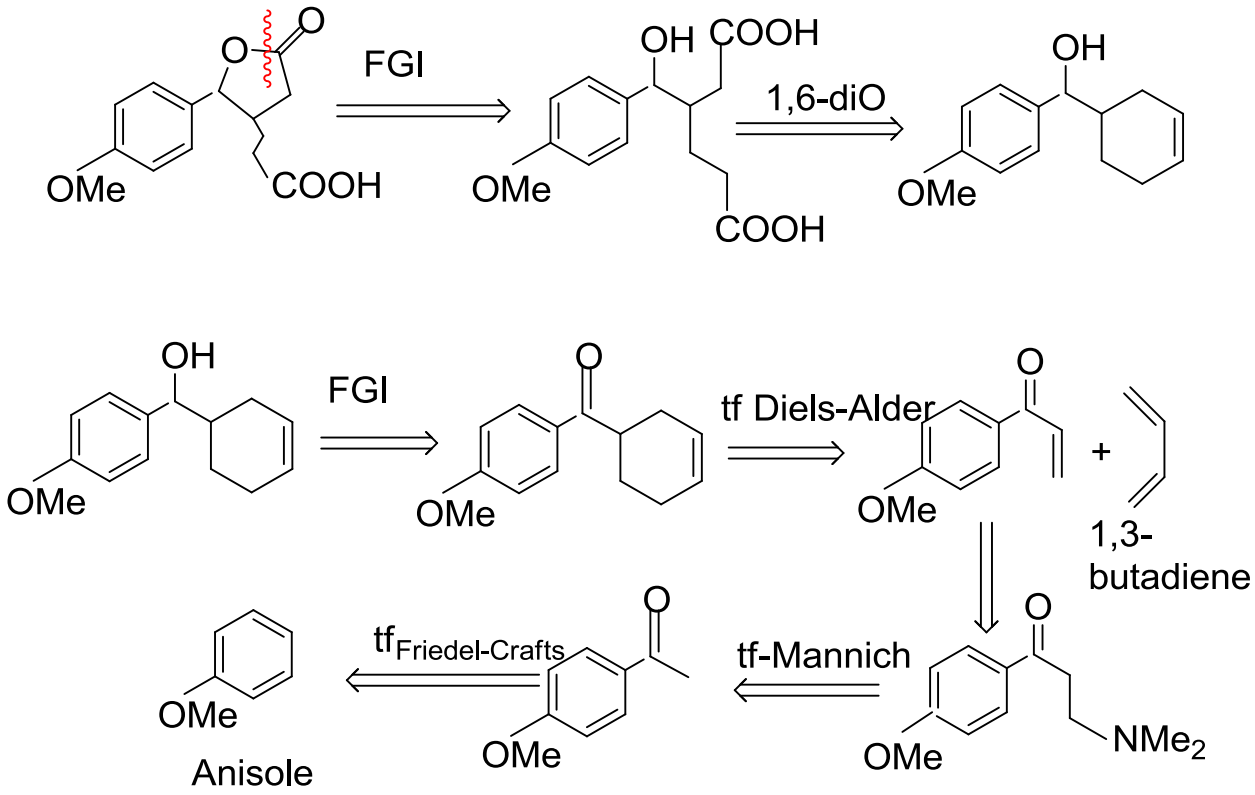
Compound



Compound is a bifunctional group – with carboxylic acid groups at 1 an6 position. Hence the retrosynthetic pathway proceeds by cleavage of cyclohexene ring with oxidizing agents like Cr(VI) along with transformations.

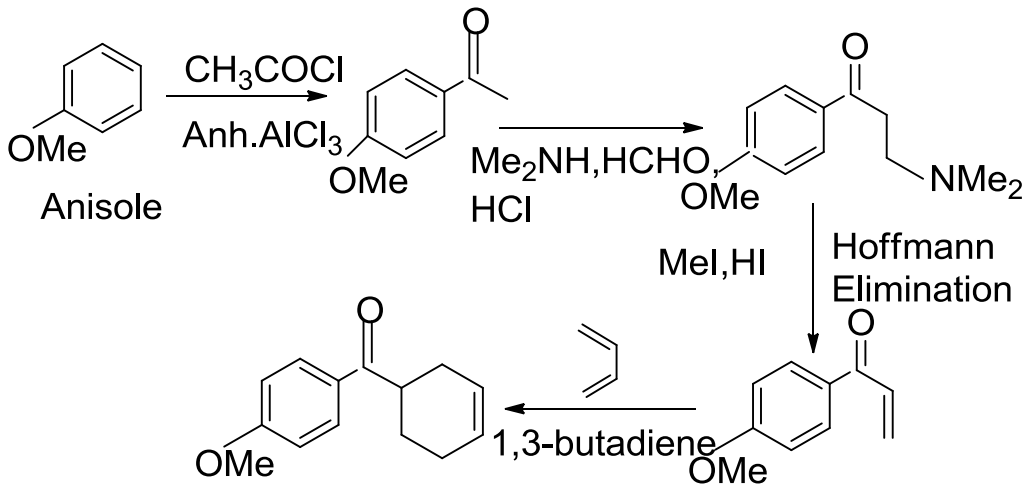
Disconnection takes place next to the carbonyl functional group.

Retrosynthesis:

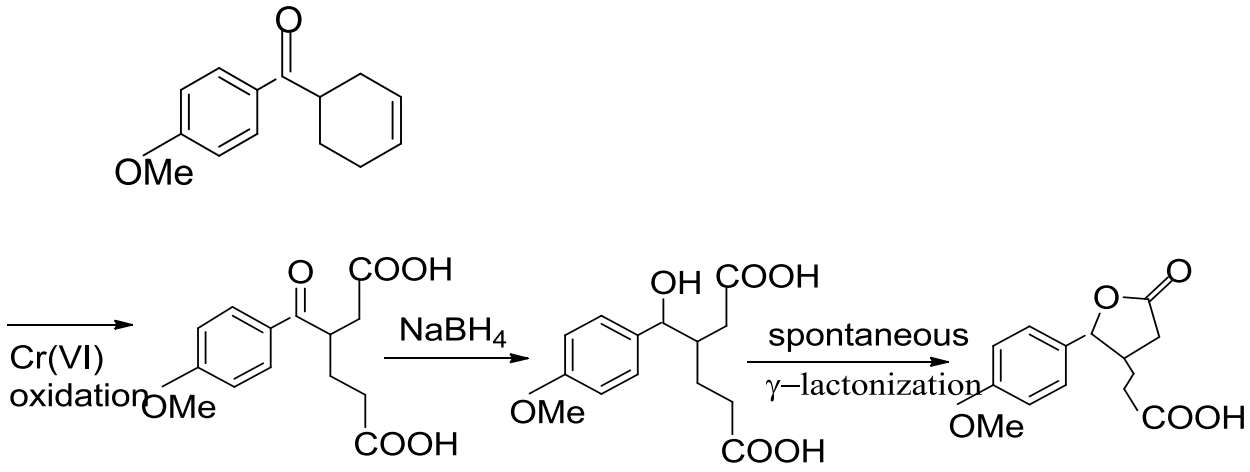


The synthetic equivalents or the raw materials for the reaction are anisole and 1,3 butadiene.

Synthesis:



1,6-diO cleavage



1.8 Protecting Agents

Organic synthesis involves polyfunctional substrates. It is therefore necessary to protect a functional group in order to carry out a reaction at some other functional group without any interference. After the reaction is completed, the protected group can be deprotected.

1.8.1 Protection Reagent: A molecular framework used to block the reactivity of a particular functional group in a substrate with polyfunctional groups under specified conditions.

Eg: alcohols are protective agent for acids.

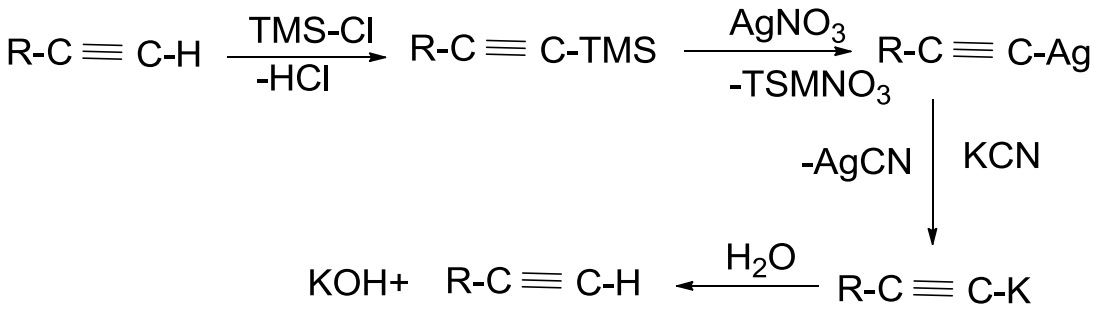
1.8.2 Characteristics of Protective agent:

It should be chemoselective in its reaction with the functional group to be protected.
The protected group should be stable/resistant enough to survive the reaction conditions maintained for performing the desired reactions.
After the reaction, the protected group should be easily and chemoselectively removed under mild conditions without affecting the rest of the molecule.

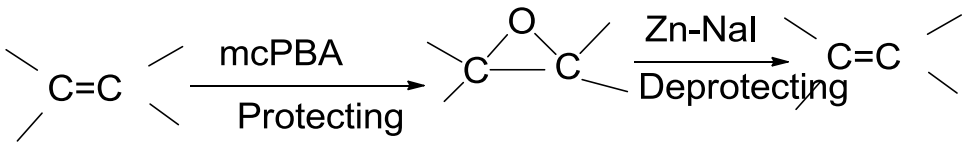
Example 1 :

Protection of active C-H bond.

Terminal alkynes are protected with chloro trimethyl silane and deprotected by $AgNO_3$/KCN –Corey' s method.



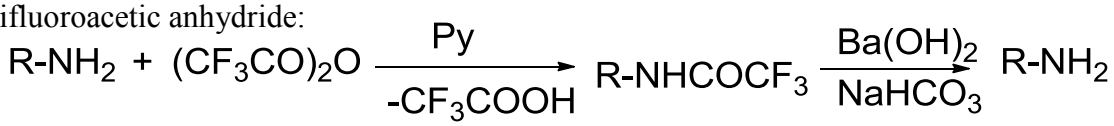
Alkenes can be protected by epoxidation reaction and deprotected by treatment with ZnI-NaI acetic acid.



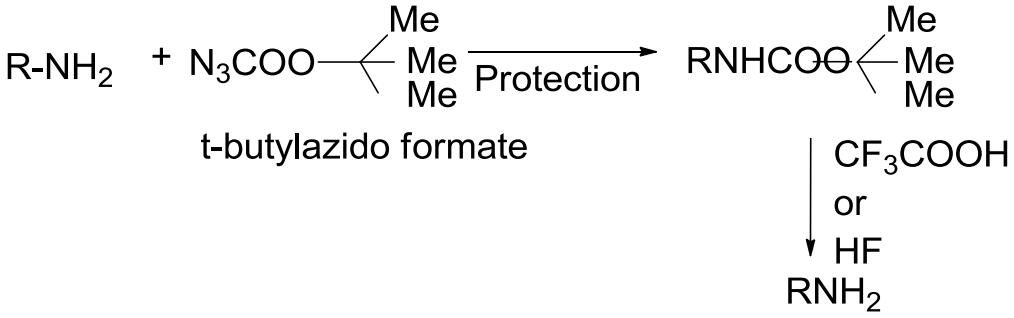
Example 2

Protection of Amino groups:

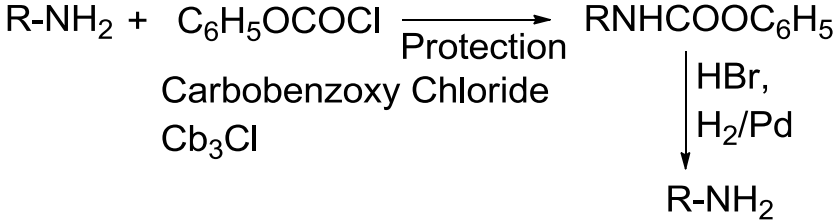
1) Trifluoroacetic anhydride:



2) tert-butylazido formate:



3)Carbobenzoxy chloride:

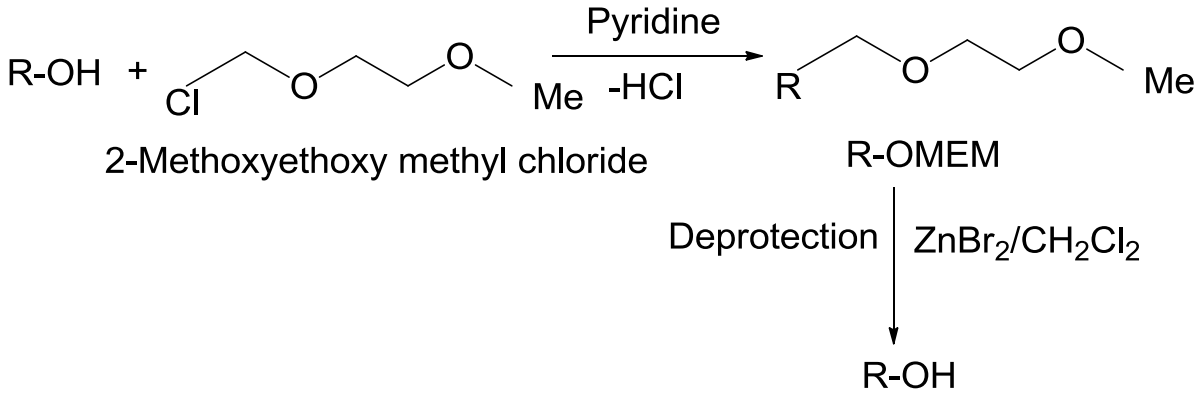


Example 3

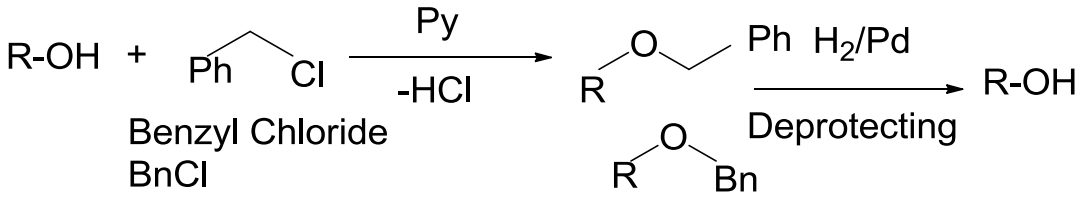
Protection of alcohol group:

1)Acetic anhydride:

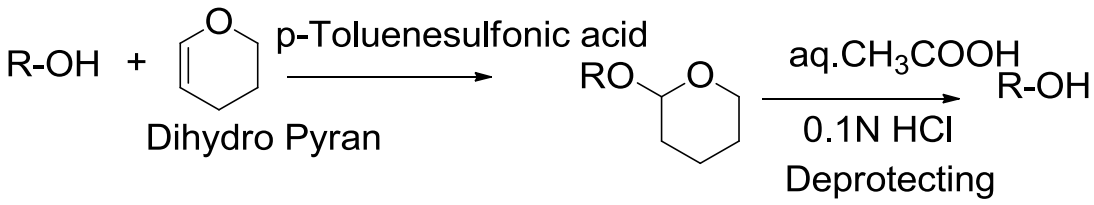
2)MEMCl



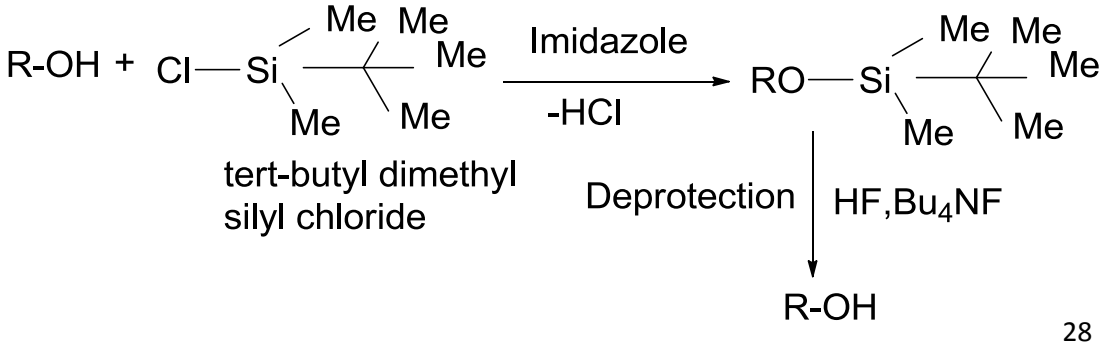
3) Benzyl chloride



4) Dihydropyran (DHP)



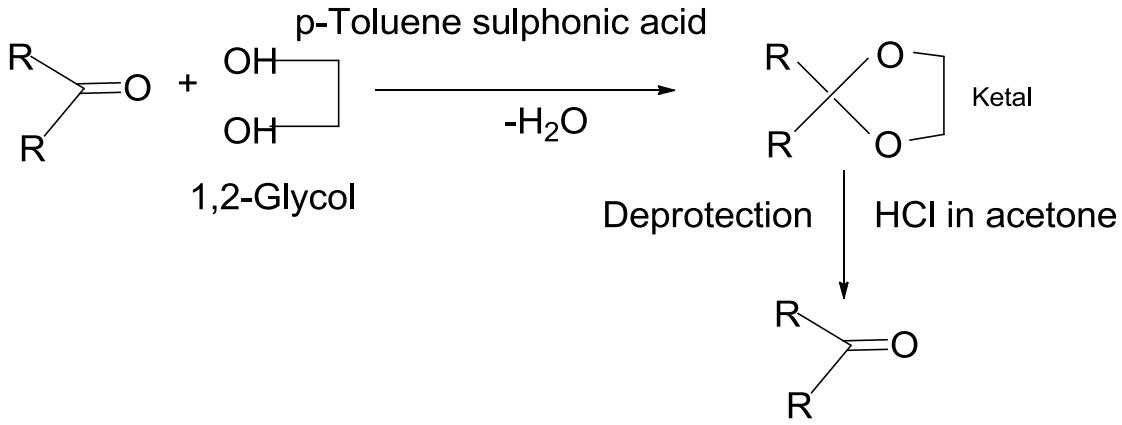
5) Butyl dimethylsilyl chloride



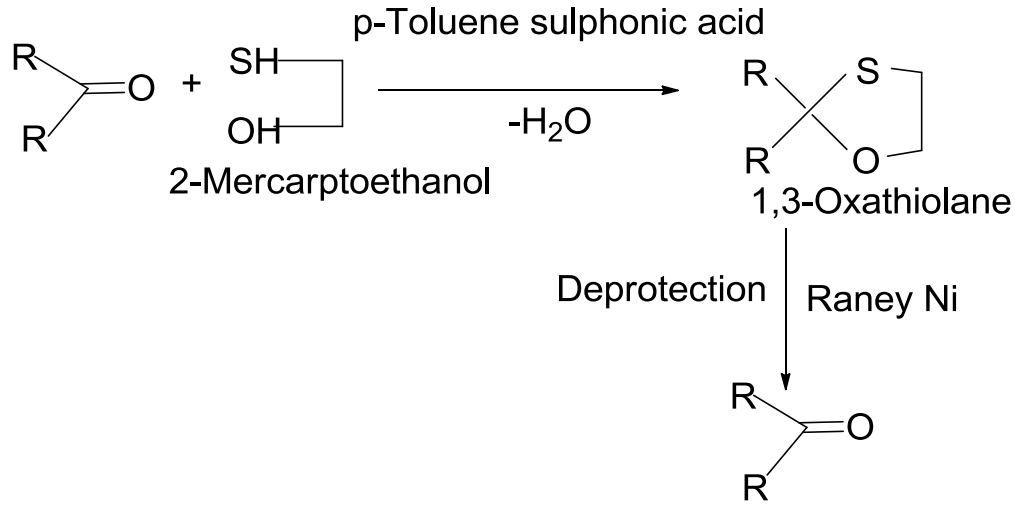
Example 4:

Protection of aldehydes and ketones

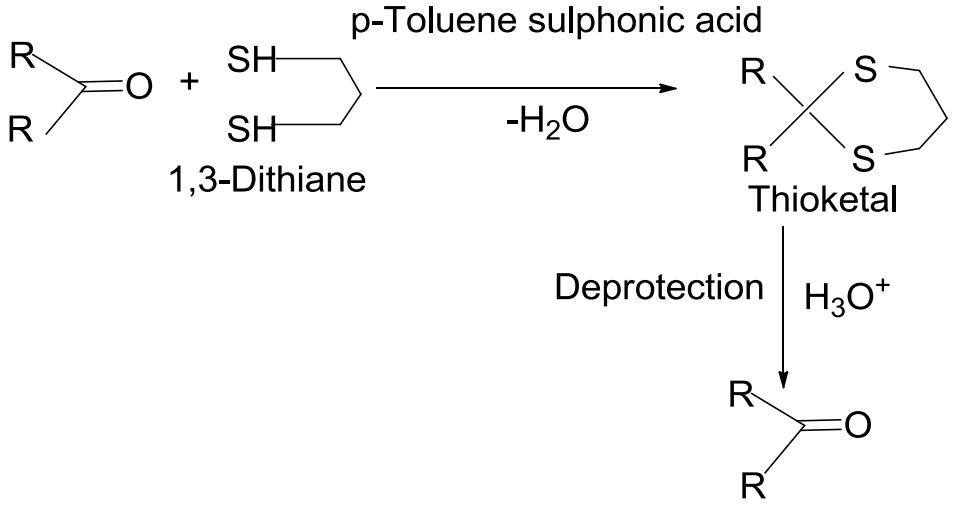
1) 1,2 glycol



2) Mercaptoethanol



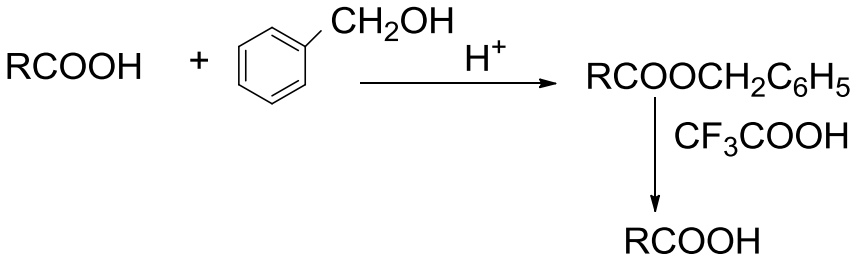
3)1,3-Dithiane



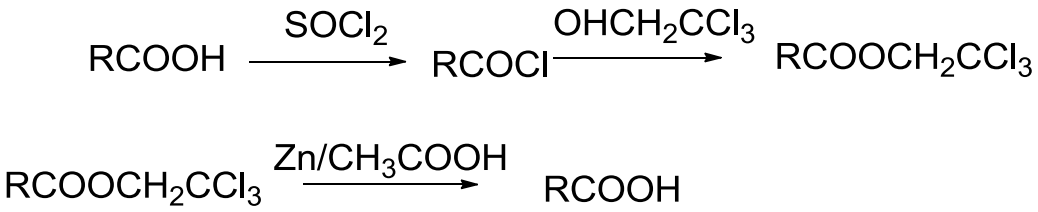
Example 5

Protection of acid group

1) Benzylalcohol



2)Trichloro ethylalcohol



TEXT / REFERENCE BOOKS

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2. Gould E. S., Mechanism and Structure in Organic Chemistry Holt, Rinehart and Winston Inc., 1959.

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SCHOOL OF SCIENCE & HUMANITIES

DEPARTMENT OF CHEMISTRY

UNIT – II -REAGENTS IN ORGANIC CHEMISTRY– SCYA5101

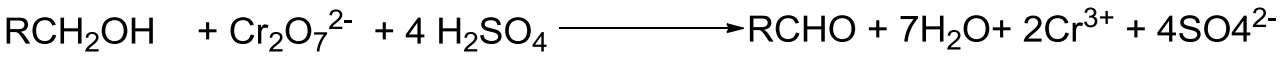
UNIT 2

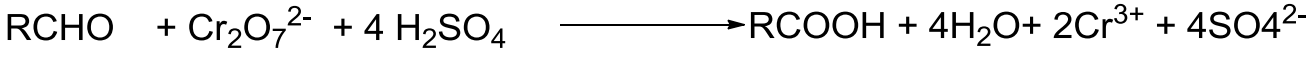
REAGENTS IN ORGANIC CHEMISTRY

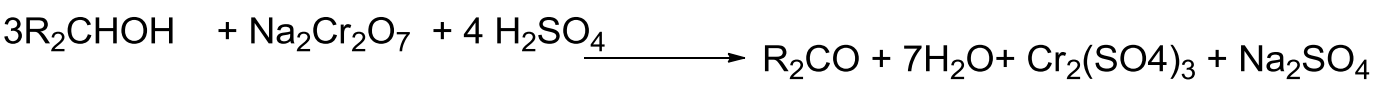
2..1 Oxidising agents

2.1.1 Potassium dichromate in acidic medium- $K_2Cr_2O_7$

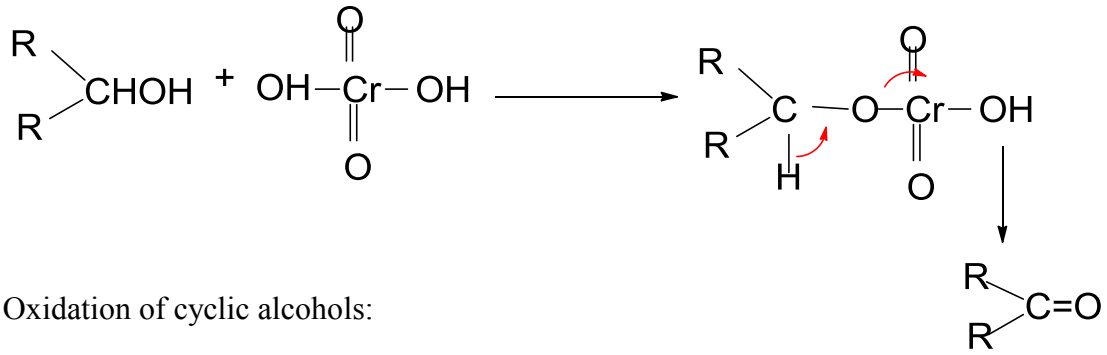
1) Oxidation of alcohols:



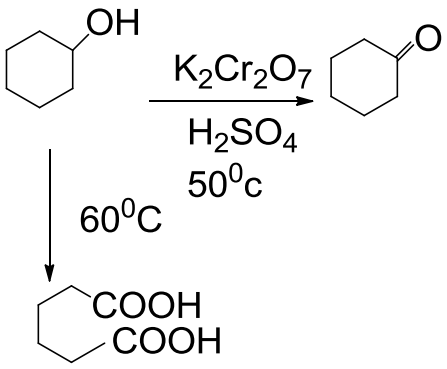




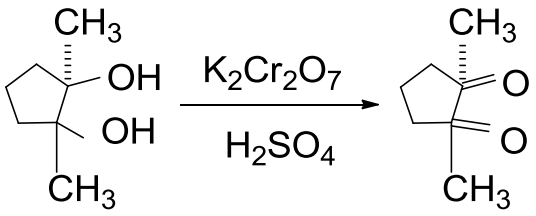
Mechanism:



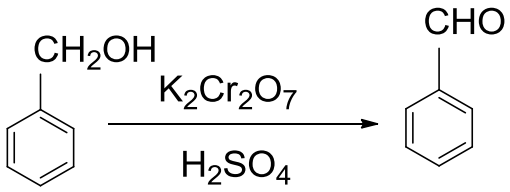
2) Oxidation of cyclic alcohols:



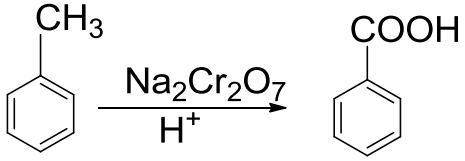
3) Oxidation of cyclic diols:



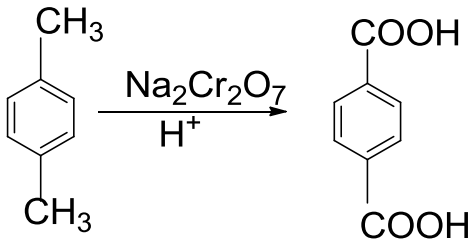
4) Oxidation of aromatic alcohols

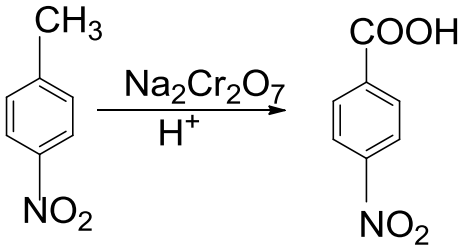


5) Oxidation of aromatic side chains:



6) Oxidation of aromatic side chains:

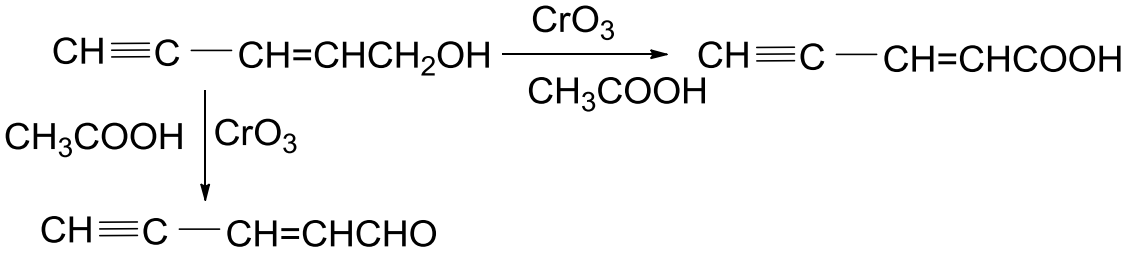


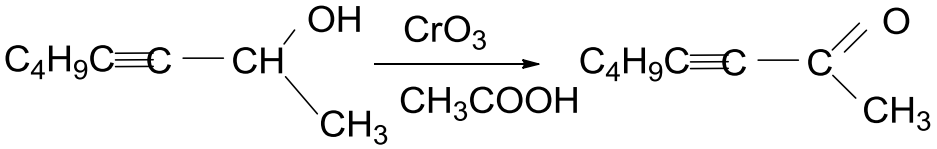


2.1.2 Jones Reagent:

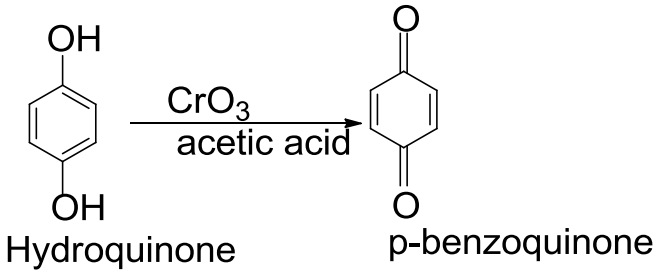
It is a CrO_3 –acetate in acid medium. It is used for oxidation of alcohol with double and triple bond, allylic or benzylic CH bonds. The reaction is carried out at 0-20^oC.

1) Oxidation of alcohol

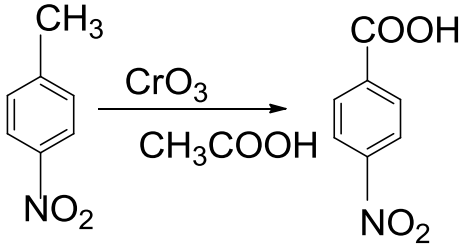




2) Oxidation of aromatic alcohols

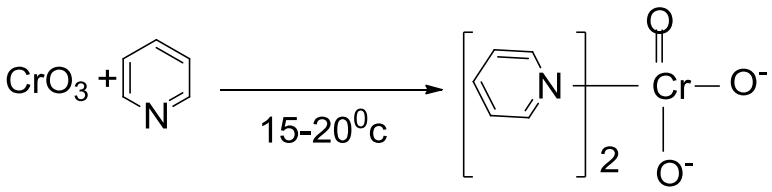


3) Oxidation of aromatic side chains:



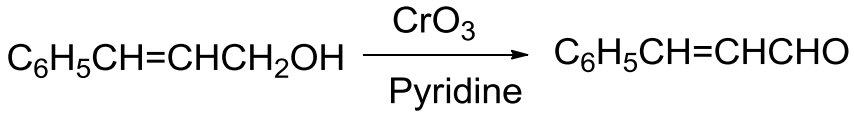
2.1.3 Chromium trioxide-Pyridine complex

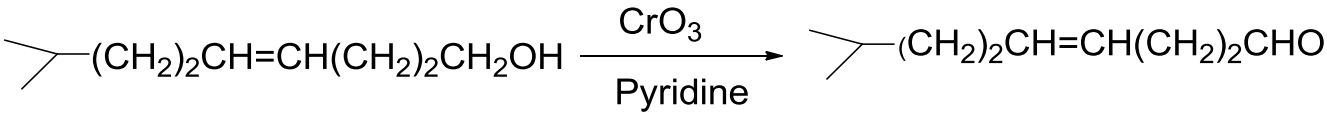
a) Sarett Reagent:



b) Collins reagent: Chromium trioxide-Pyridine complex in dicholromethane solvent.

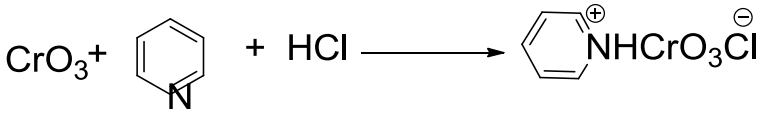
1) Oxidation of alcohols:



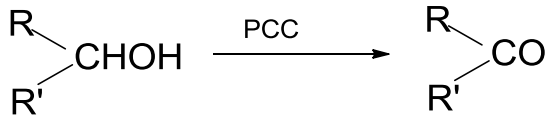


c) Pyridinium chlorochromate [PCC]

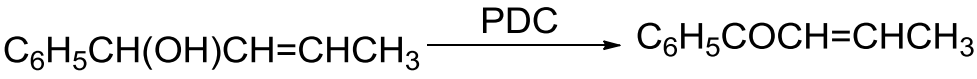
It is prepared by dissolving CrO_3 in pyridine solution and HCl.



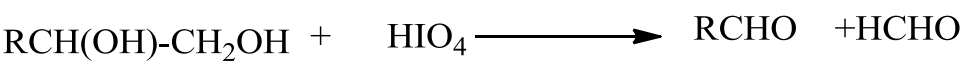
1) Oxidation of alcohols:



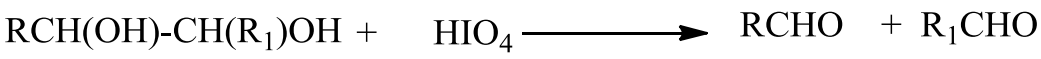
d) Pyridium dichromate:PDC- $[C_5H_5\overset{\oplus}{N}H]_2Cr_2O_7$
Oxidation of alcohol:

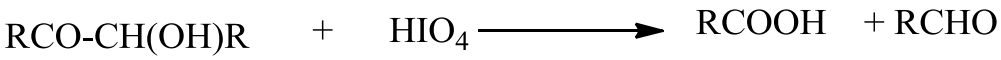


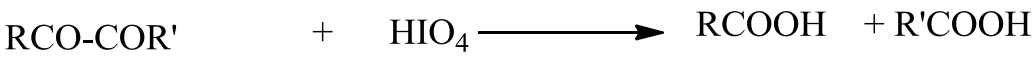
2.1. 4 Periodic acid : HIO_4
Used for the cleavage of adjacent 1,2 diols.

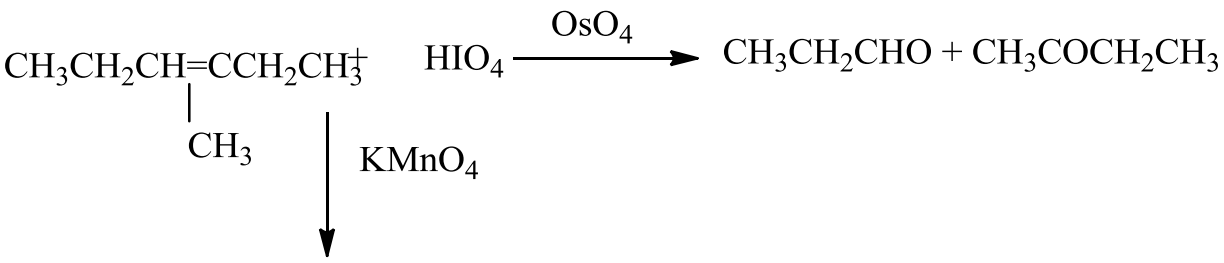


Periodic acids:

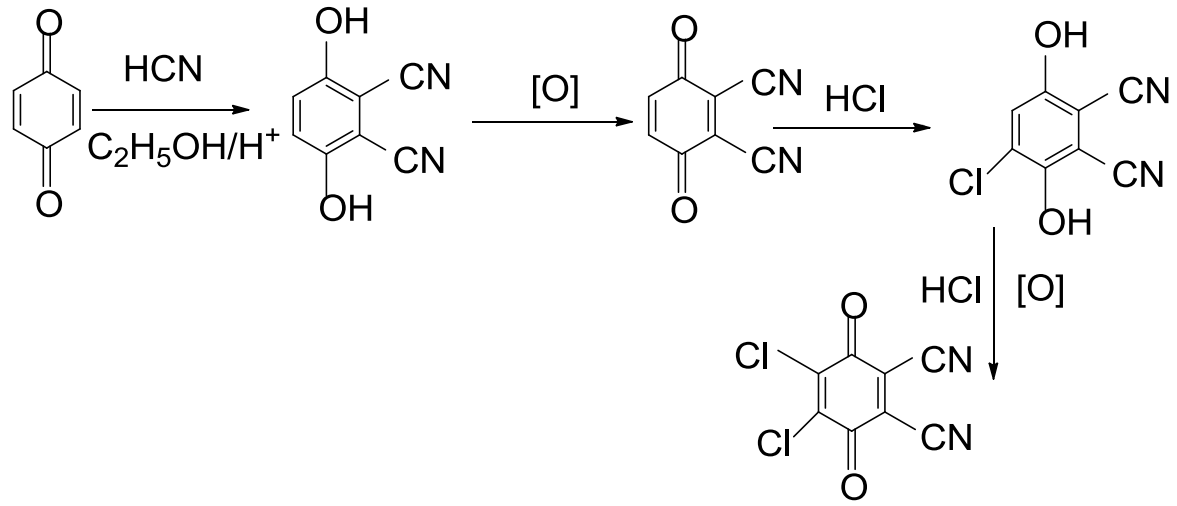








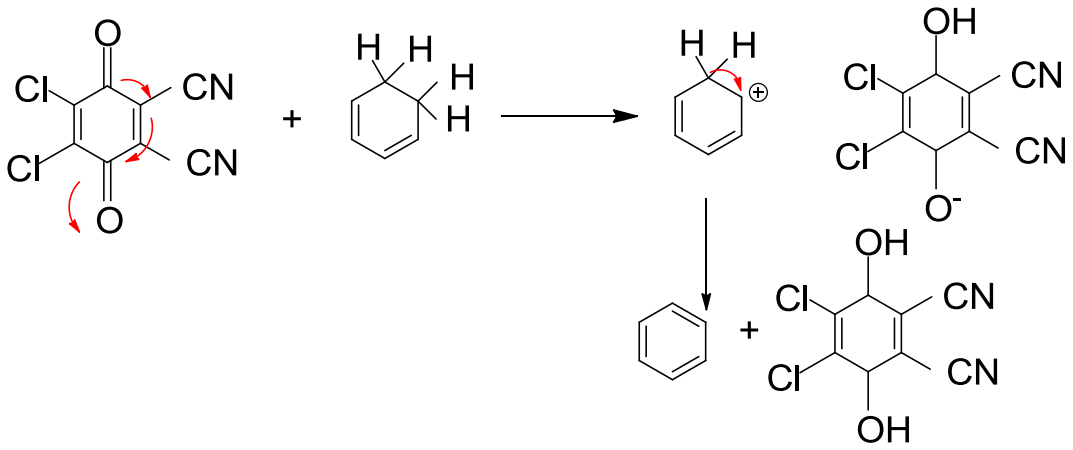
2..1.5 DDQ- 2,3 dichloro 5,6 dicyano 1,4 benzoquinone
Preparation:
By treating with 1,4 hydroquinone with HCN followed by oxidation and acid treatment.



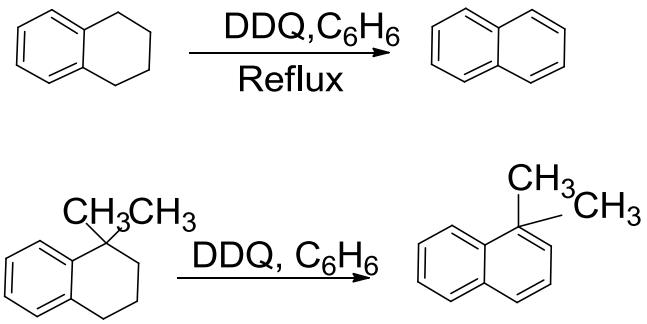
It decomposes in water and inert towards THF and dioxane.

Chemical Reactions:

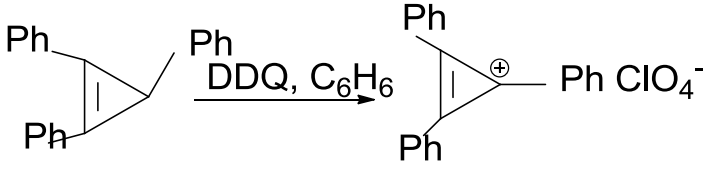
1) Aromatisation or Dehydrogenation: Solutions of DDQ in benzene are red in colour.



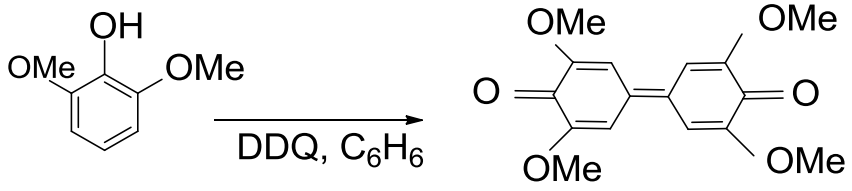
2) Bicyclic systems:

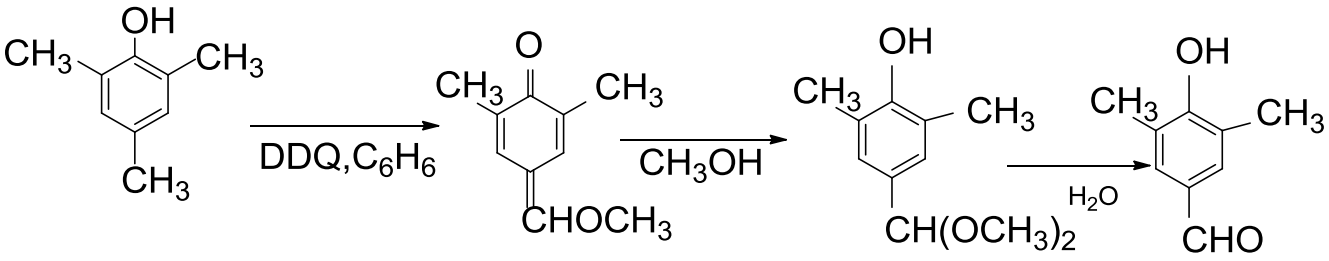


3) Forms salts of aromatic cations.

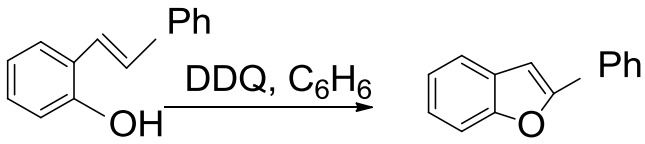


4) Oxidation of Phenols

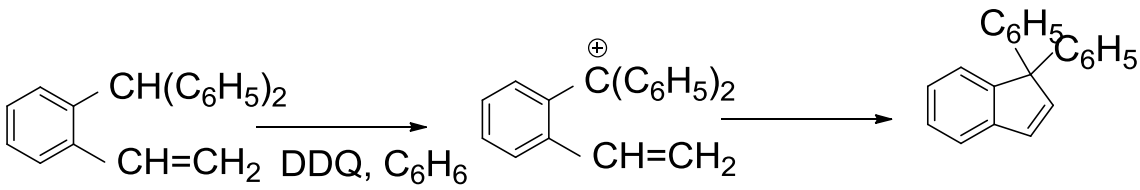




5) Oxidation cyclization:



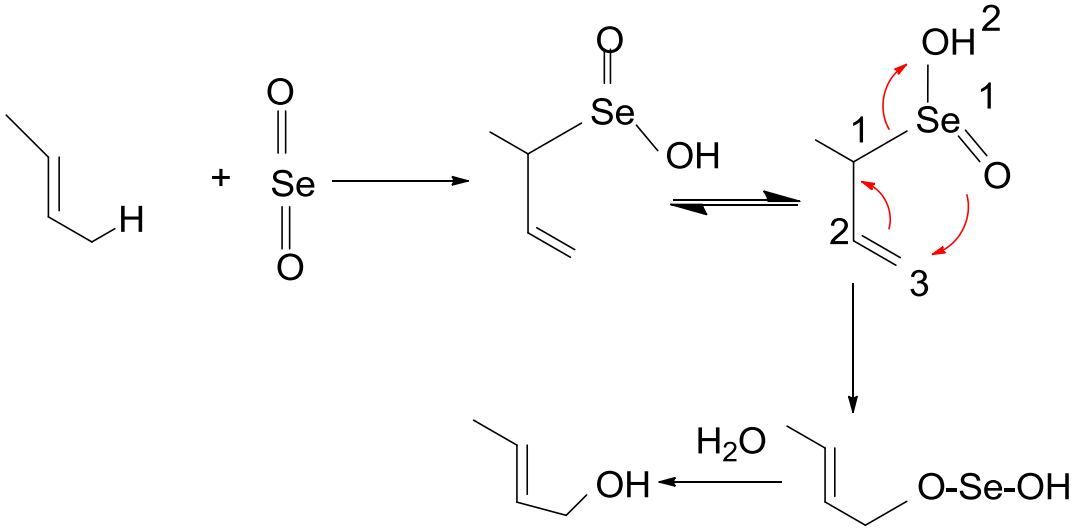
6) Intramolecular cyclization:



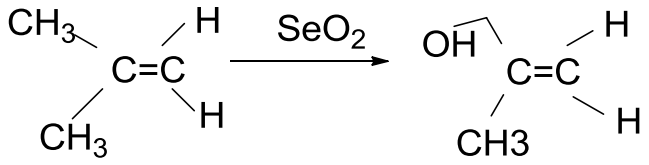
2.1.6 SeO_2

Oxidation of allylic benzylic C-H fragments to allylic and benzylic alcohols (α,β unsaturated carbonyl compounds)

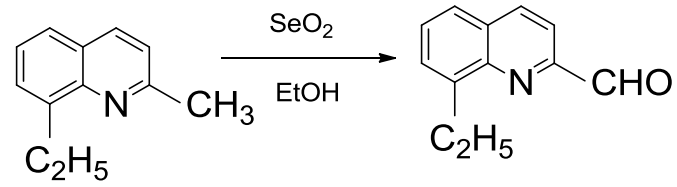
Mechanism: Initial ene reaction of allylic compound to SeO_2 to give allylic selenic acid, undergoes a 2,3 sigmatropic rearrangement followed by hydrolysis –allylic alcohols.

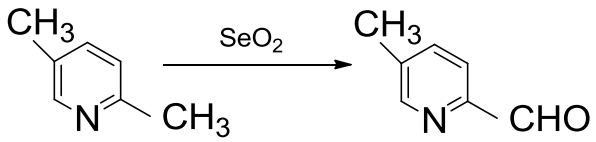


1) Reactions with allylic compound:

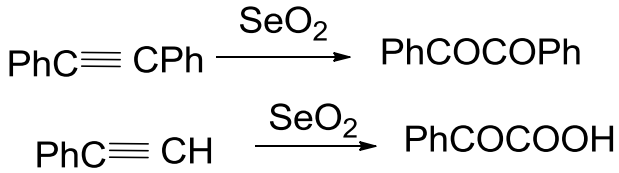


2) In aromatic heterocycles, the methyl group in α position with respect to nitrogen is oxidised to aldehyde.

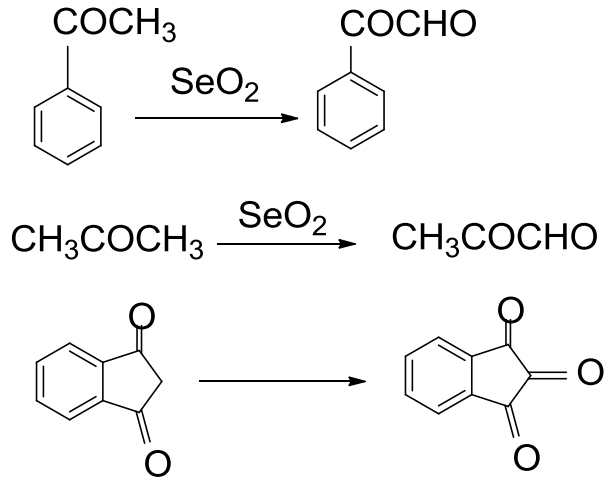




3) Oxidation of acetylenes:

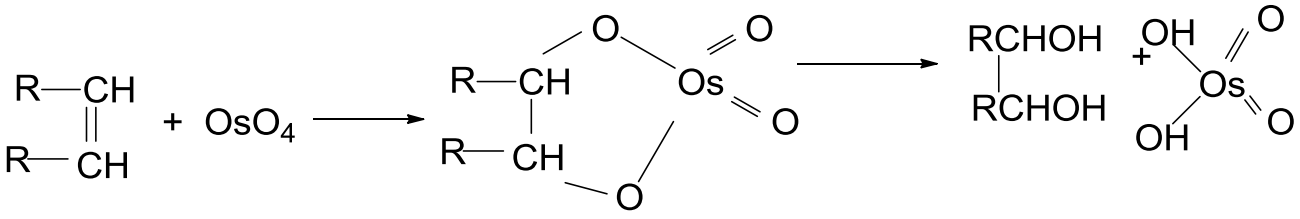


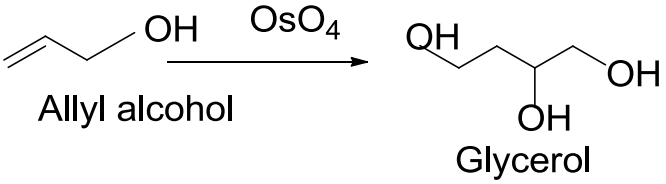
4) Oxidation of carbonyl compound:

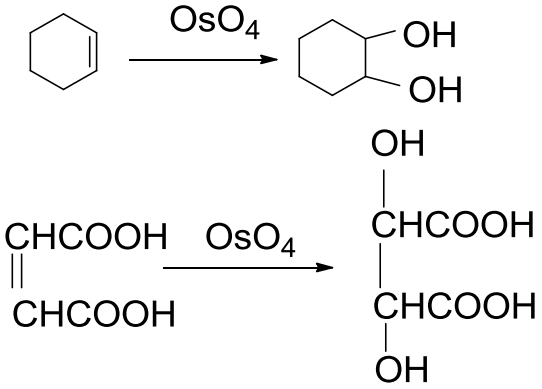


2.1.7 Osmium tetroxide OsO_4

Toxic, volatile and its vapours are dangerous to eyes. It is a reagent used mostly for cis-hydroxylation of C-C double bonds.

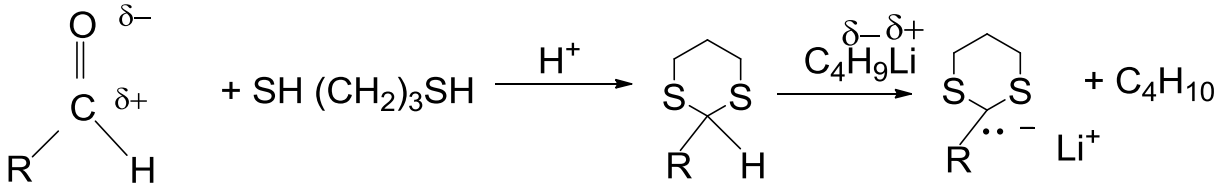






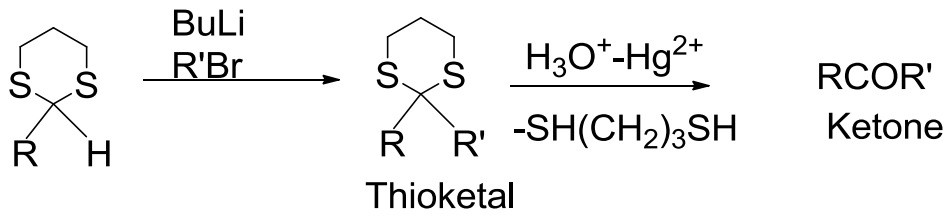
2.1.8 1,3-dithiane

The carbonyl carbon of aldehyde is partially positive i.e.,electrophilic therefore attacked by the nucleophile. Reaction of an aldehyde with 1,3 propane dithiol and further reaction with butyl lithium the carbon becomes negatively charged –Umpolung (polarity reversal).

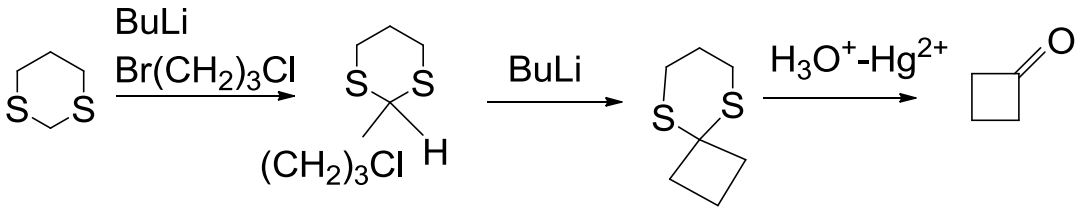


Reactions:

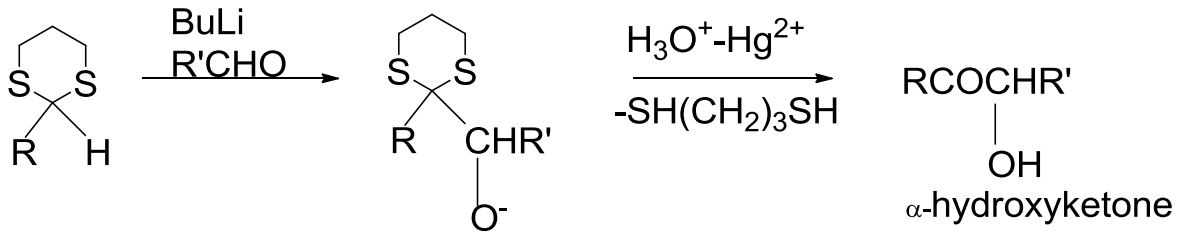
1) Conversion of aldehyde to ketone



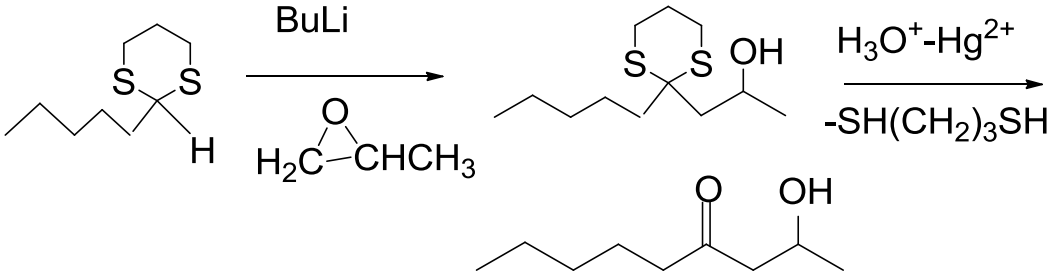
2) Conversion of dihalides to 3-7 membered cyclic ketones



3) Reaction with aldehyde it gives α-hydroxy ketones.

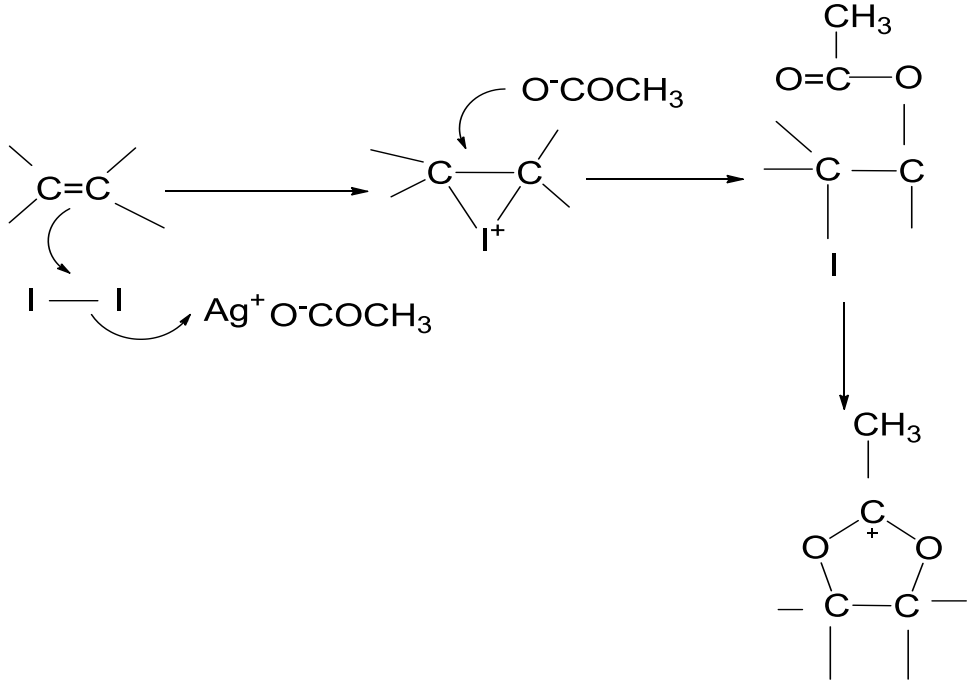


4) Act as nucleophile

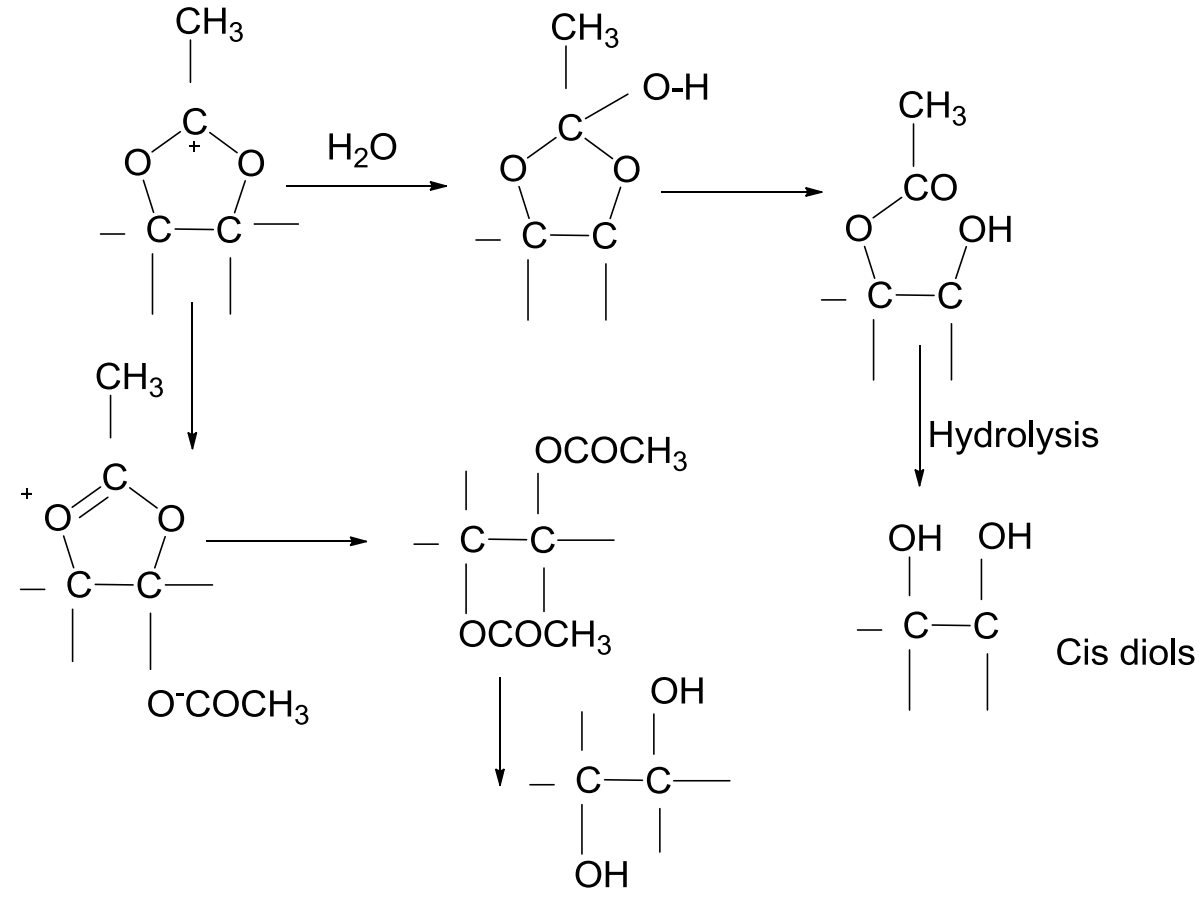


2.1.9 Woodward and Prevost Hydroxylation

Alkene is reacted with iodine and silver salt in wet conditions (Woodward Method)-Cis diols; dry conditions (Prevost method)- trans diols.



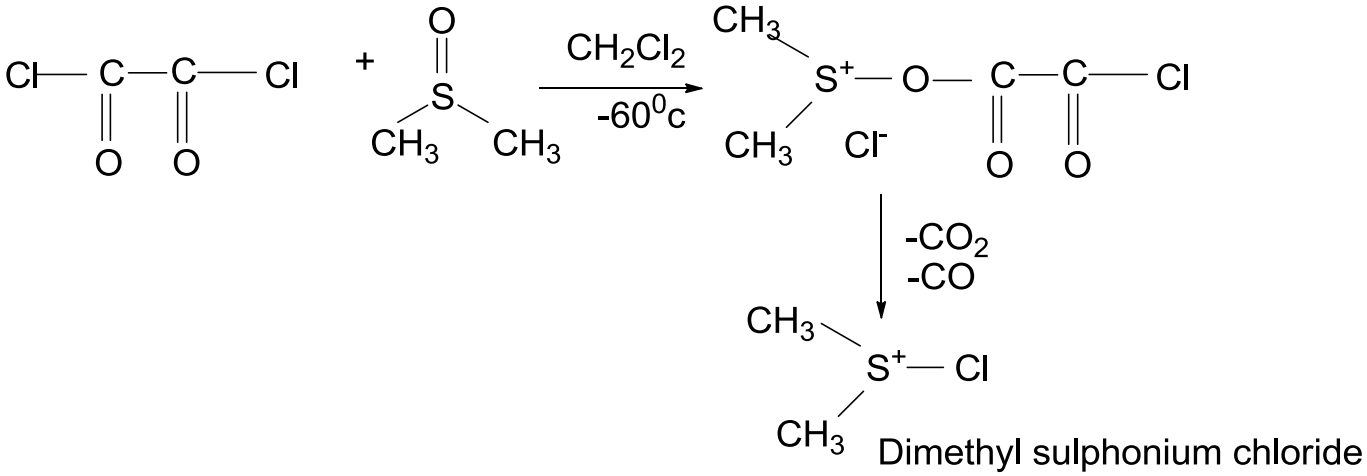
Woodward prevost

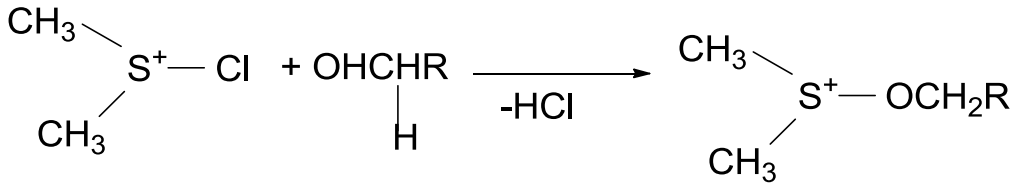


2.1.10 Swern oxidation

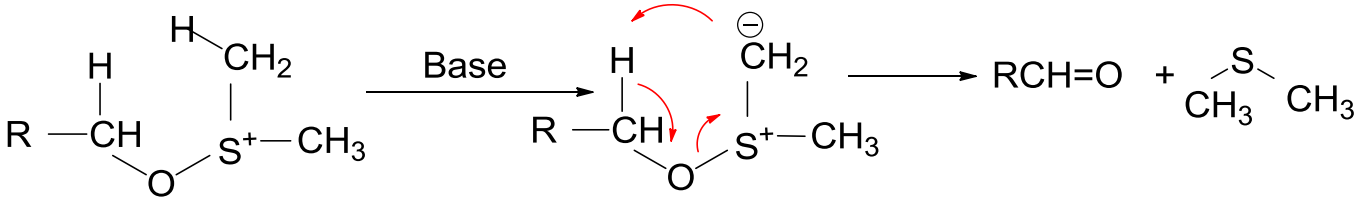
Mild reagent used for the oxidation of alcohol to aldehyde/ ketones in the presence of oxalyl chloride, dimethylsulphoxide and a base (trimethyl amine) at low temperatures.

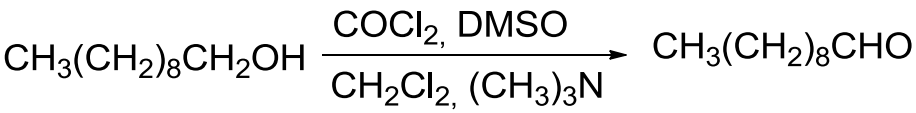
The first step is the replacement of one chlorine atom by the oxygen atom of DMSO followed by attack of alcohol at the electrophilic sulphur atom to give alkoxy sulfonium salt.





The salt undergoes proton abstraction by the base to form an ylide which fragments to aldehyde and ketone by an intramolecular concerted process.

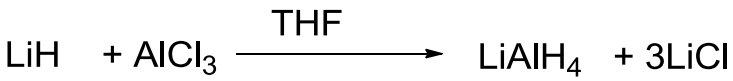




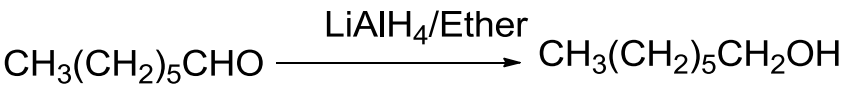
2.2 Reducing Agents

2.2.1 Lithium Aluminum hydride-$LiAlH_4$

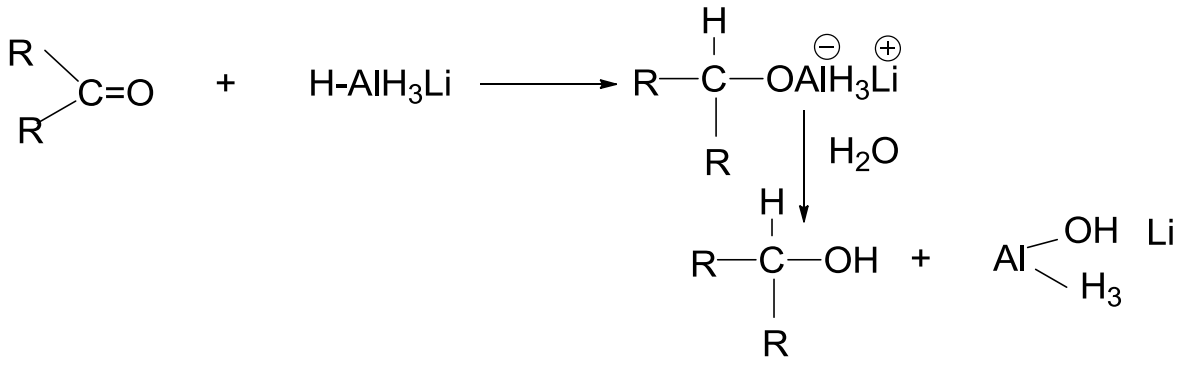
Preparation: Treating LiH to $AlCl_3$ in THF medium.

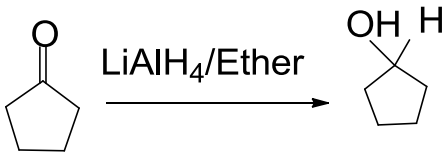


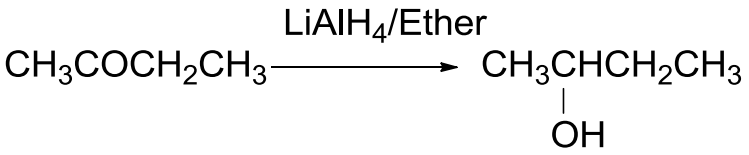
Act as Reducing agent: Reduces aldehydes, ketones, acids, esters ,acid chlorides and epoxides to alcohols. Reduces amides, nitriles, azides, nitro groups to amines.
Reduces polar functional groups except alkenes and alkynes.
1) Reduction of carbonyl group:

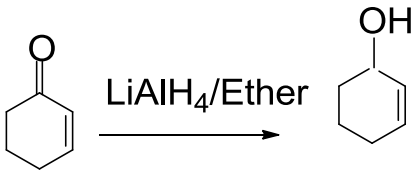


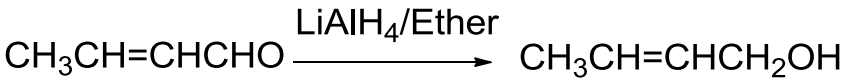
Mechanism:



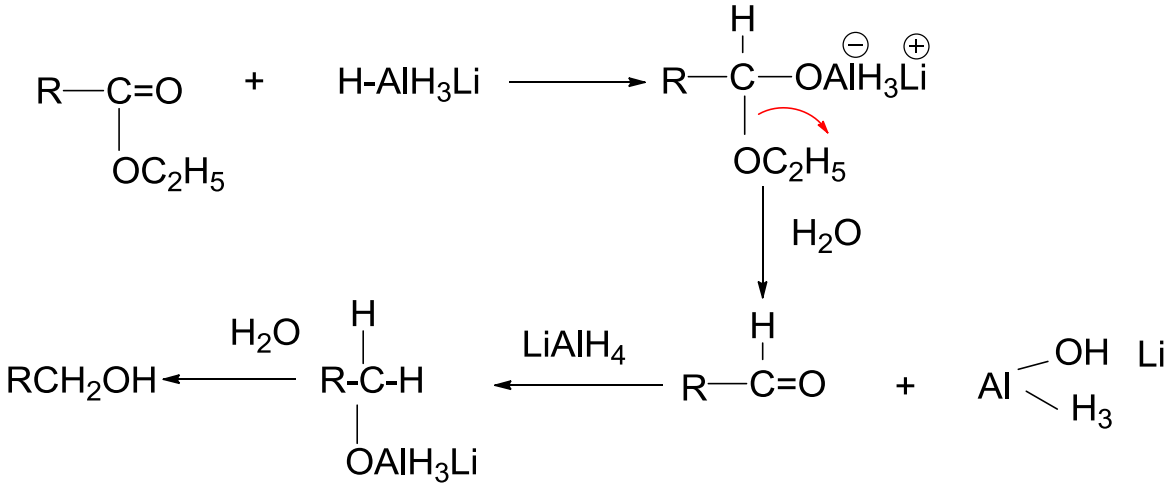




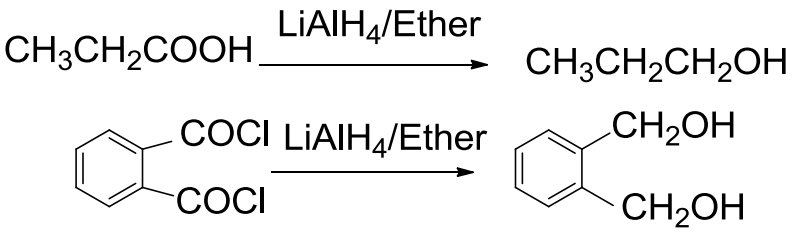


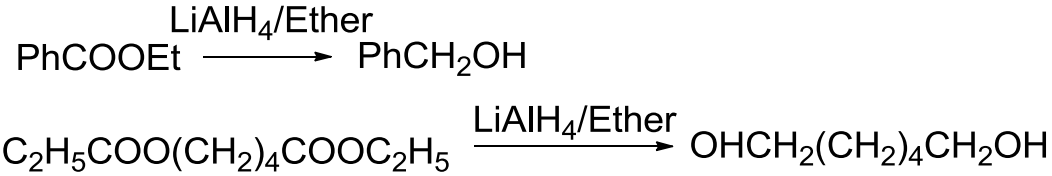


2) Reduction of acids and its derivatives:
The reactivity is RCOCl> RCOOR>$RCONR_2$> RCN> RCOOH
Mechanism:



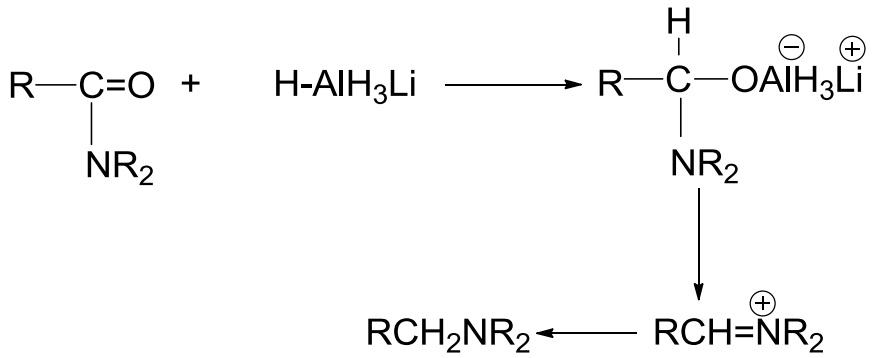
3) Reduction of acids and its derivatives:

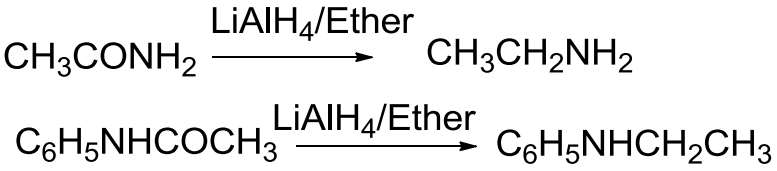




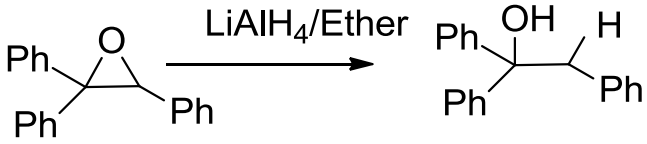
4) Reduction of amide to amine

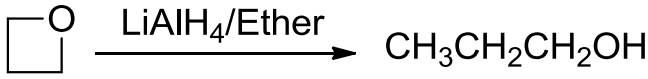
Mechanism:

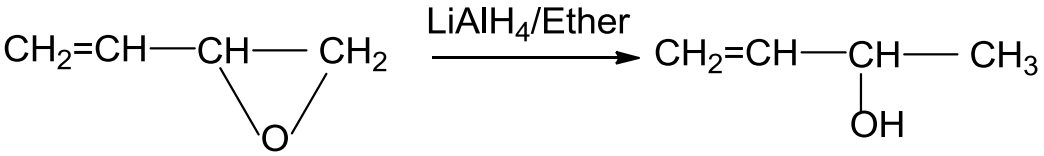




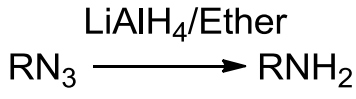
5) Reduction of epoxide: The Nucleophile attacks the less hindered carbon atom to form corresponding alcohol.

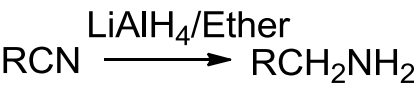


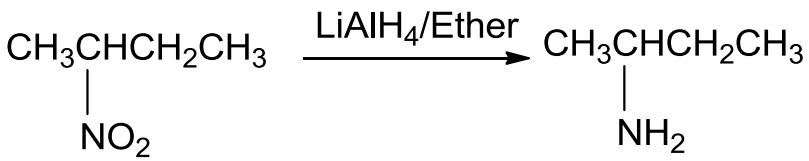


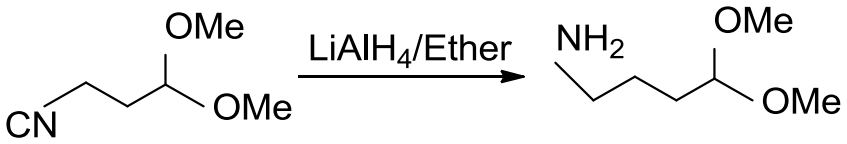


6) Reduction of azides, nitriles

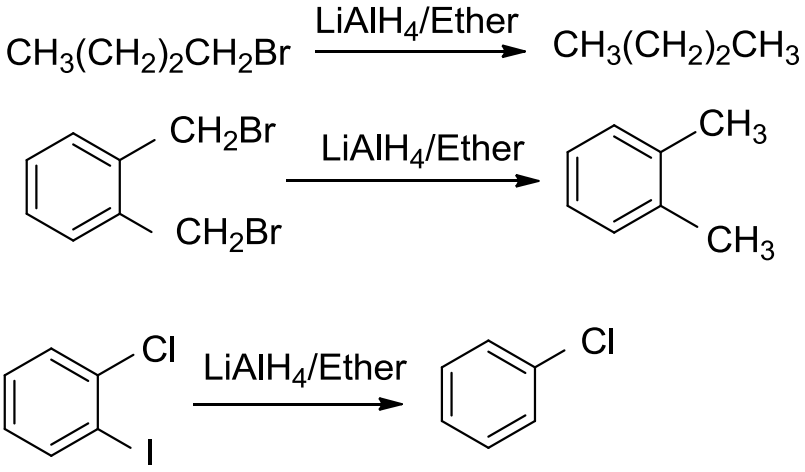






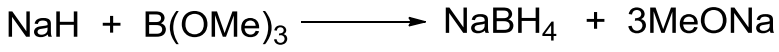


7) Reduction of alkyl halides:



2.2.2 Sodium borohydride-$NaBH_4$

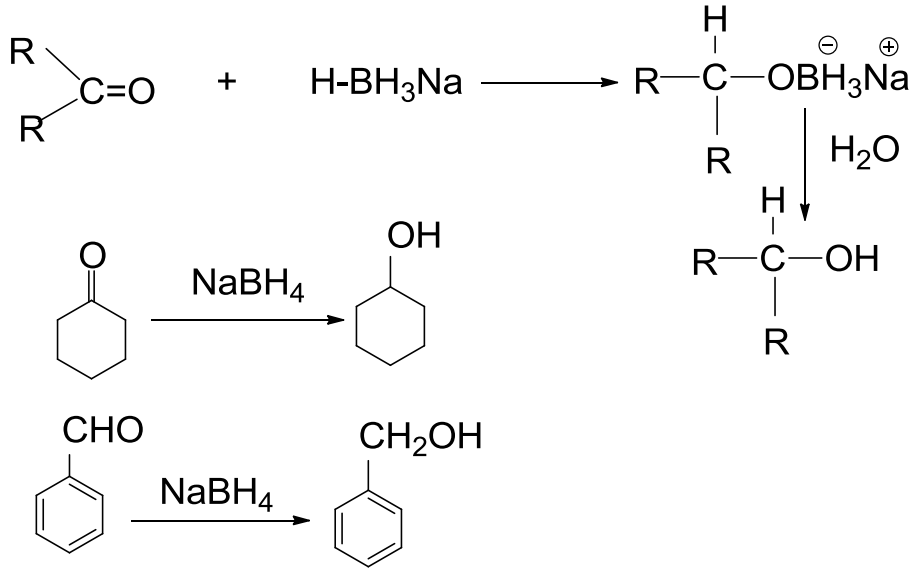
Preparation: reacts with sodium hydride with methyl borate.



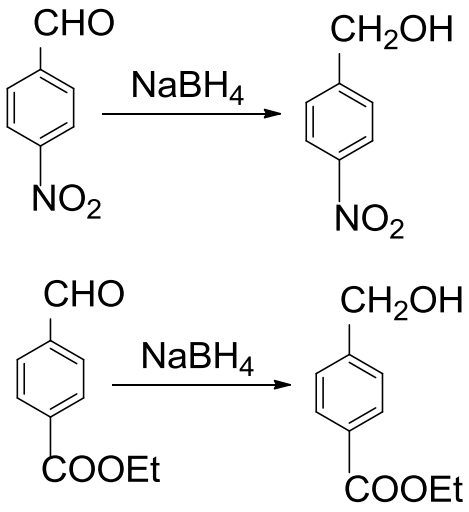
Reacts in aqueous medium and reacts slowly.Reduces aldehydes and ketones. Inert towards cyano, nitro, amido, ester, acids, lactones. Epoxides.

1) Reduction of aldehyde and ketone

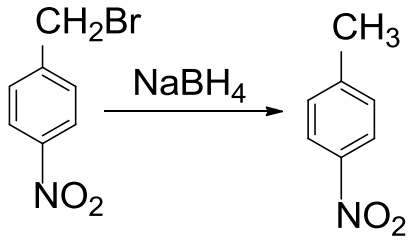
Mechanism:



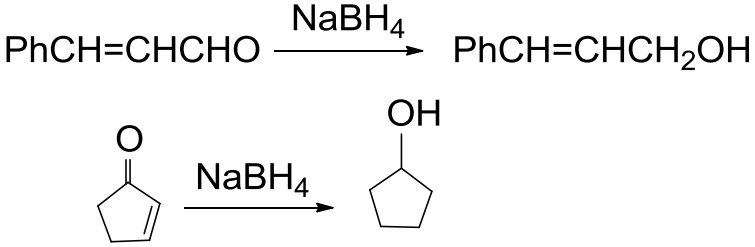
Reduction of aldehyde and ketone



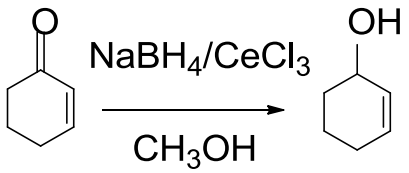
2) Reduction of alkylhalide:



3) Reduction of α ,β unsaturated carbomnyl compound



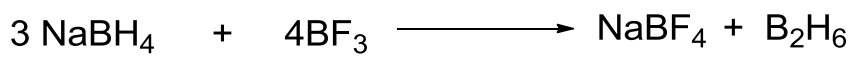
2.2.3 Luche's reagent –Mixture of sodium borohydride and cerium chloride. In a cyclic unsaturated ketones, the unsaturation remains unaffected with this reagent.



2.2.4 Borane-BH_3

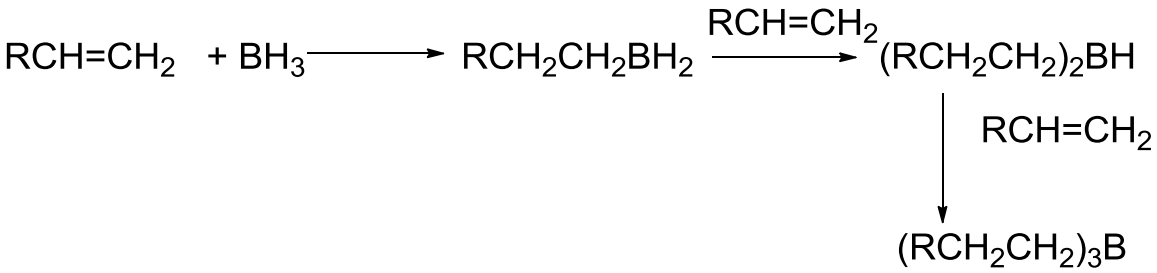
Preparation:

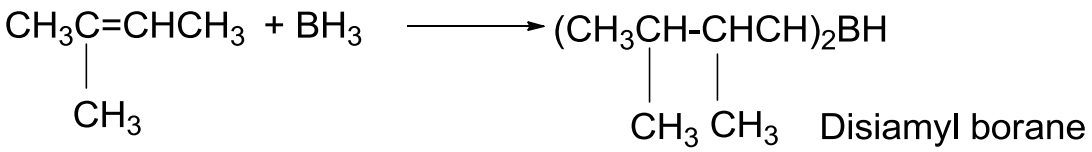
Borane exists as its gaseous dimer, Diborane B_2H_6. It is commercially available in the form of complexes with THF and is prepared from borohydride and boron trifluoride.

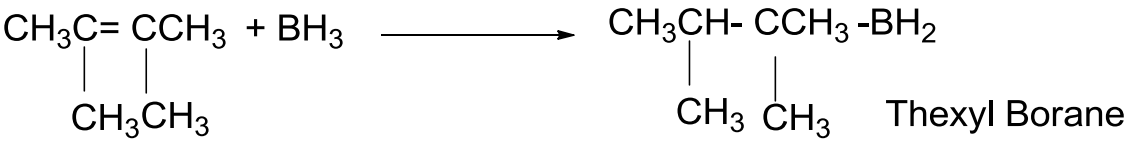


Properties:
Reacts with C=C, CΞC bond and adds hydrogen by hydroboration reaction.

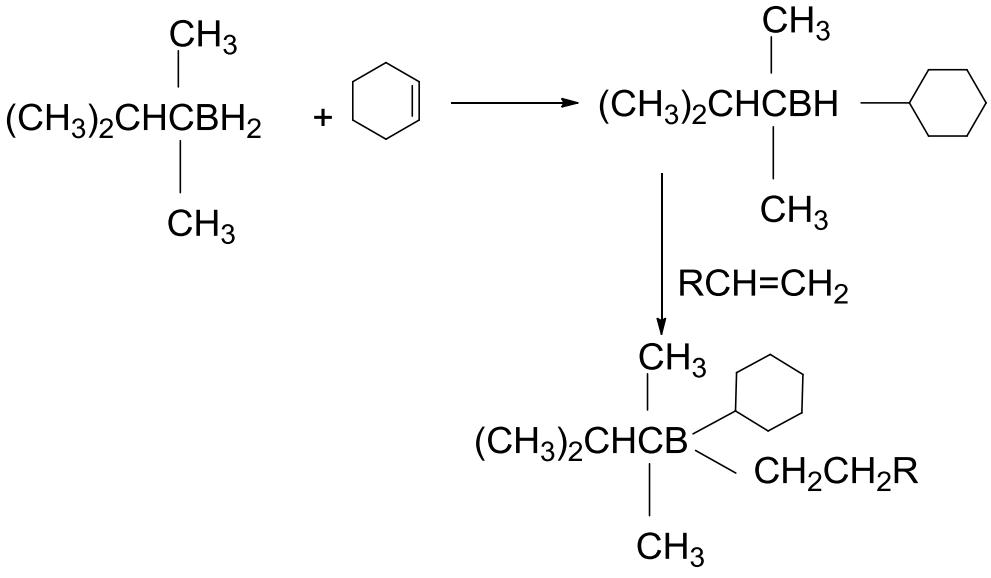
1) Hydroboration of olefins:
Borane reacts with olefins to form alkyl boranes.



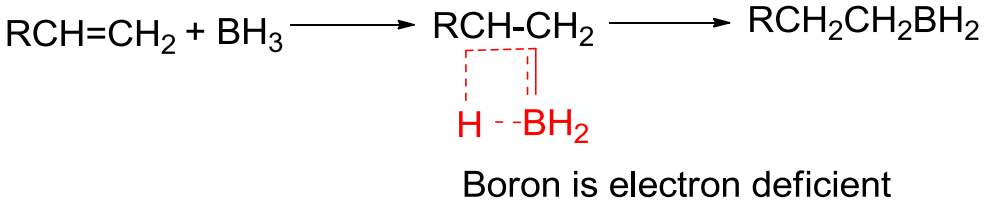




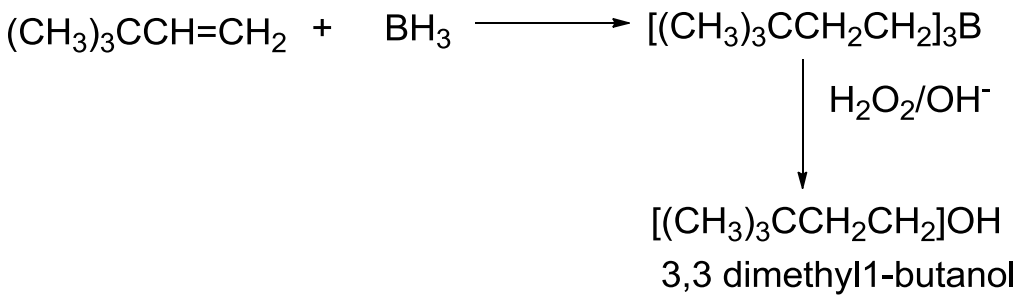
Mixed alkyl boranes can be obtained.

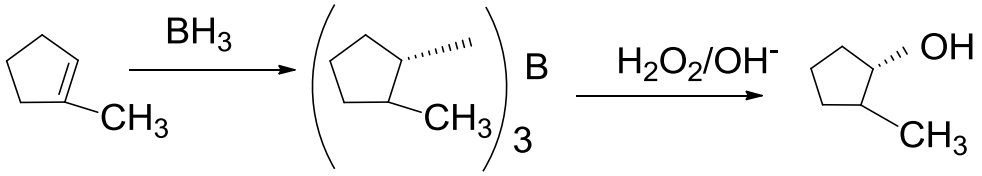


Mechanism:

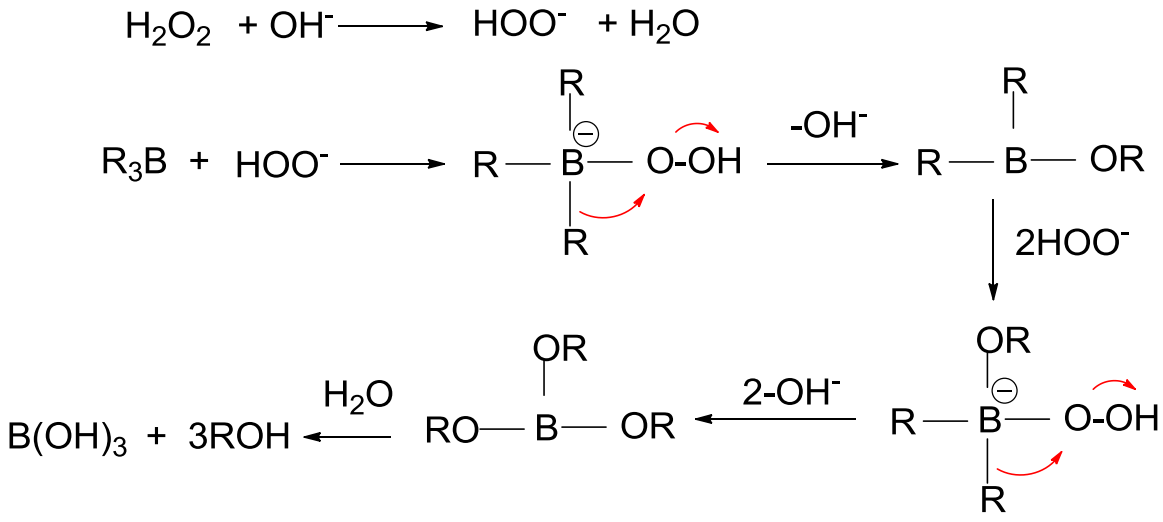


2) Hydroboration and oxidation- Regioselective reaction.
Olefin is converted to alcohol-AntiMarkownikoff's rule.

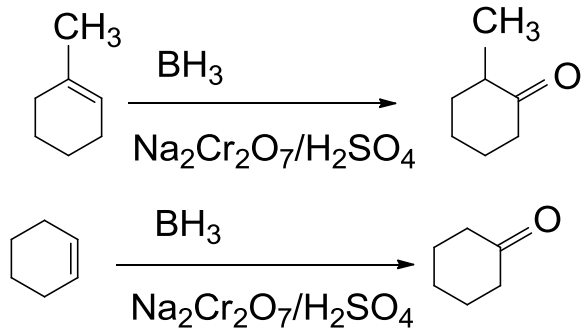




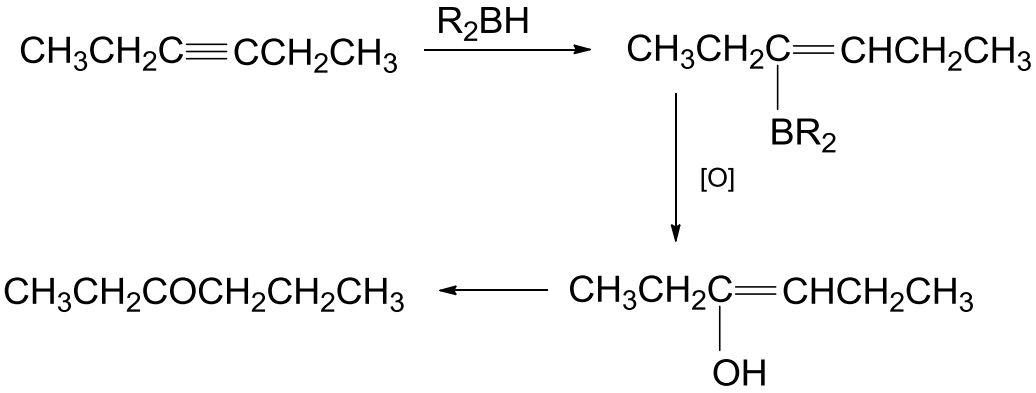
Hydroboration and oxidation:
Mechanism:



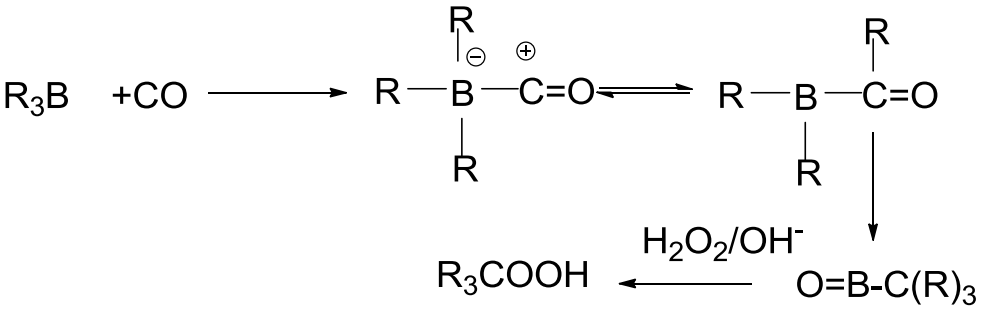
3) Hydroboration with dichromate as oxidising reagent.
Olefins to ketones

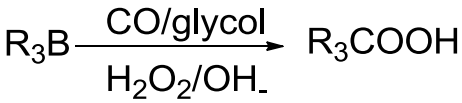


4) Hydroboration of acetylenes: Acetylene bond is converted to ketone.



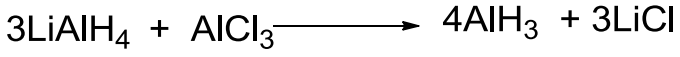
5) Carbonylation: Organoboranes can be converted to acids by treating with CO followed by oxidation





2.2.5 Aluminum hydride-AlH_3

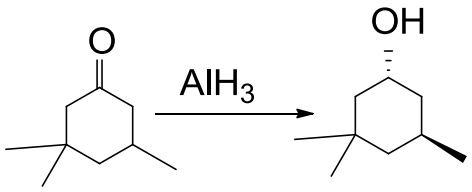
Preparation: Reaction of lithium aluminum hydride with aluminum chloride.



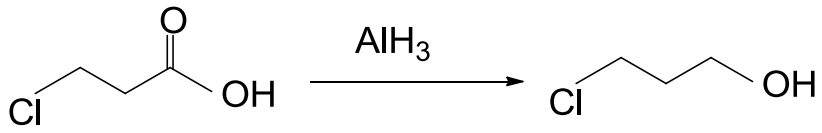
Reaction:

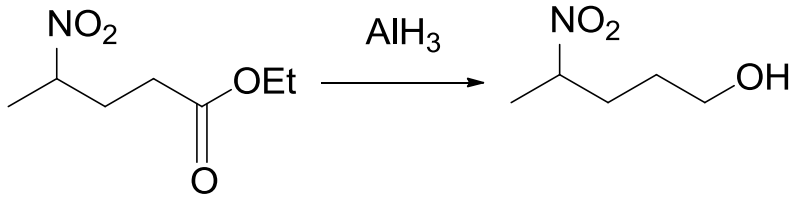
Reduces ketone, acid derivatives to alcohol. Unaffected by halogens and nitro group.

1) Ketone:

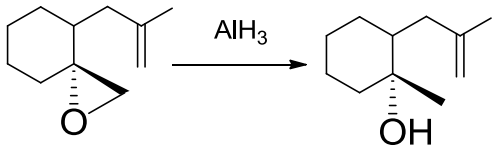


2) Halides and nitro group containing acid derivatives:





3) Epoxides:



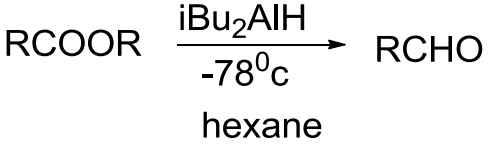
2.2.6 DIBAL-Diisobutylaluminumhydride

DIBAL can be **prepared** by heating triisobutylaluminium (itself a dimer) to induce beta-hydride elimination:

$(i\text{-}Bu_3Al)_2 \rightarrow (i\text{-}Bu_2AlH)_2 + 2\ (CH_3)_2C{=}CH.$

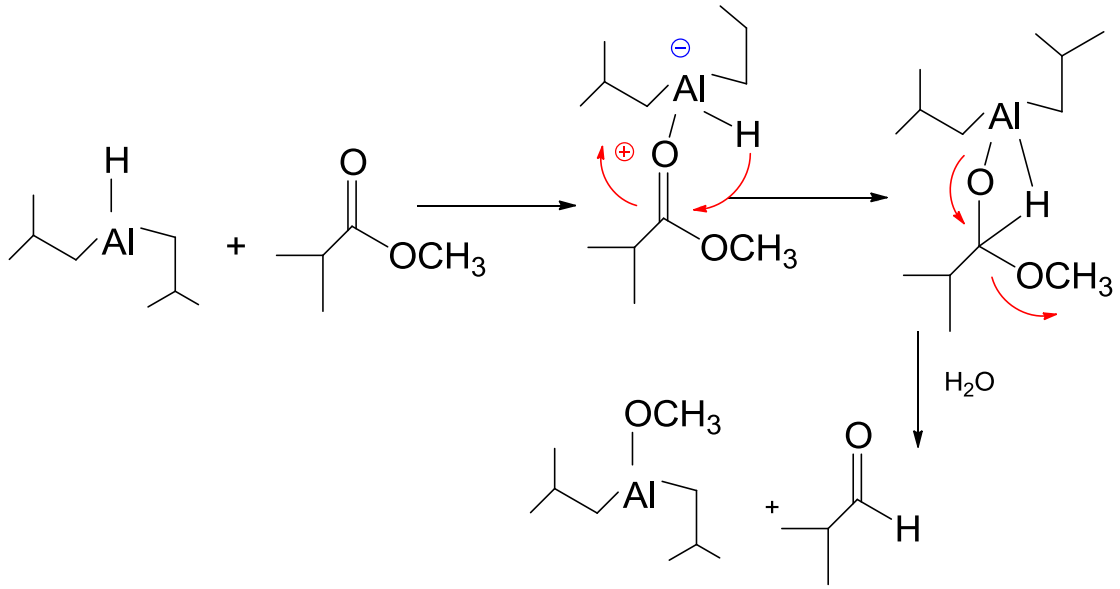
Chemical properties:

1) Esters:

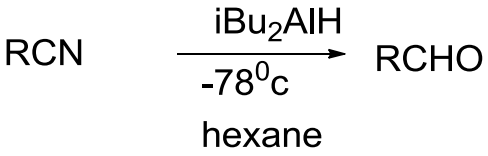


DIBAL is an hydride donor at low temperature -78^{0}C and act as an electrophilic reducing agent.

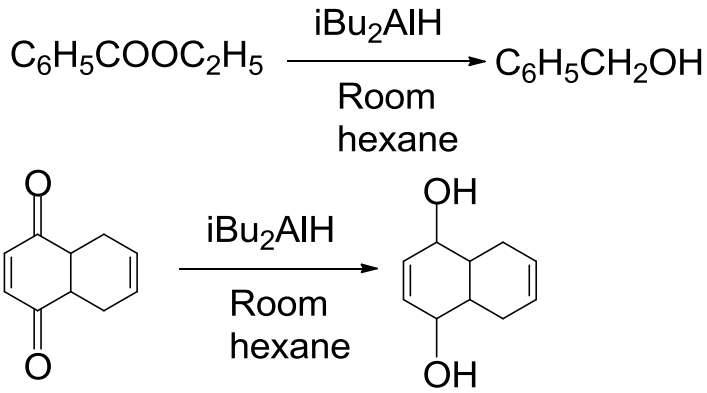
Mechanism:



2) Nitriles to aldehydes



3) Esters to alcohol

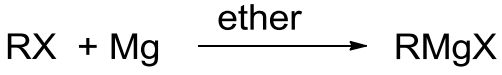


2.3 Grignard's Reagent-Organometallic Reagent

Organic compounds with a carbon-metal bond. CH_3Li, C_2H_5MgBr.Excludes compound where the metal atom is bonded through heteroatom.CH_3ONa. Electro negativity of carbon is 2.5 which is much higher than most of the metals which lie between 0.9-1.8

Preparation:

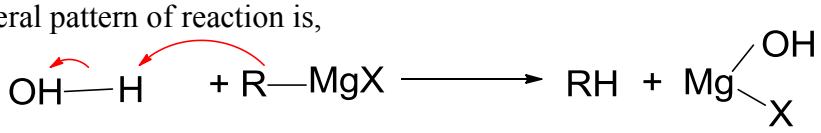
By direct reduction of alkyl halide with the metal.

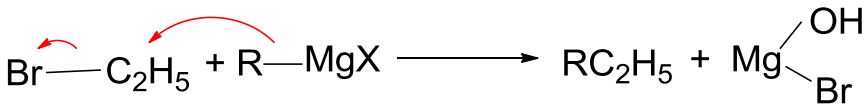


Properties: Colourless, hygroscopic solids. Fairly stable in air. The carbon-metal bond is highly polar. The carbanion with an unshared pair of electrons act as nucleophile thereby Grignard reagent undergoes both Nucleophilic substitution and addition reactions.

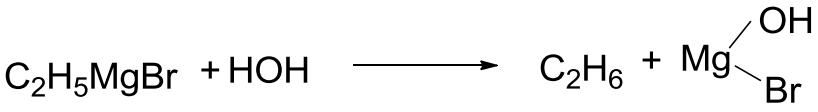
Nucleophilic Substitution Reactions:

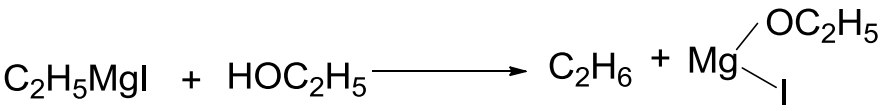
The general pattern of reaction is,



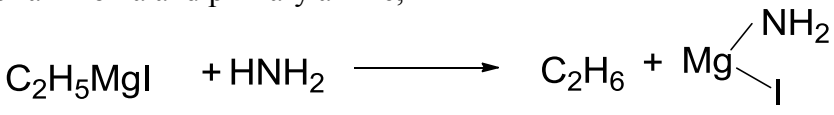


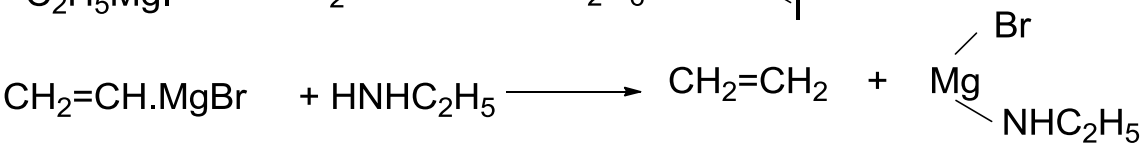
1) Reactions with active hydrogen compounds: Compounds in which hydrogen is attached to highly electronegative atom can be easily dissociated as proton are known as active hydrogen.



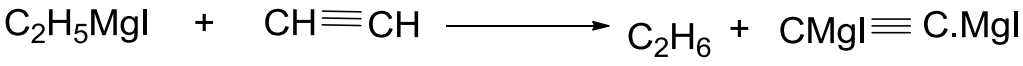


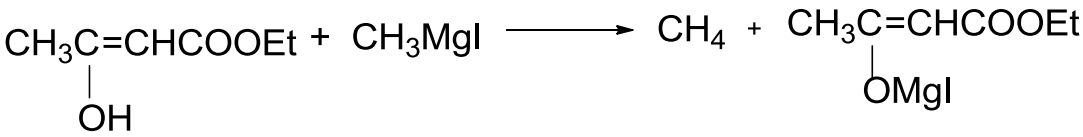
In case of ammonia and primary amine,



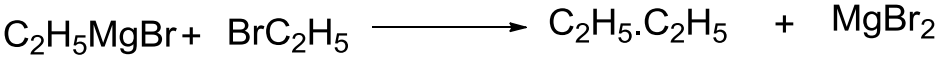


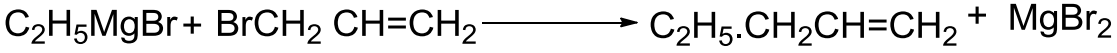
2) Reaction with acetylene and enolic form of acetoacetic ester

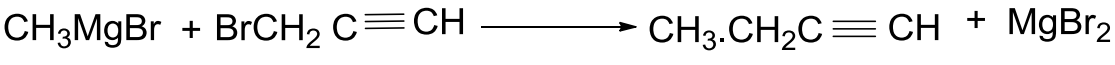




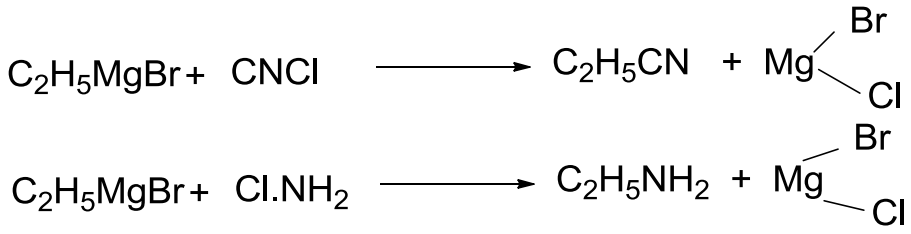
3) Reaction with organic halides







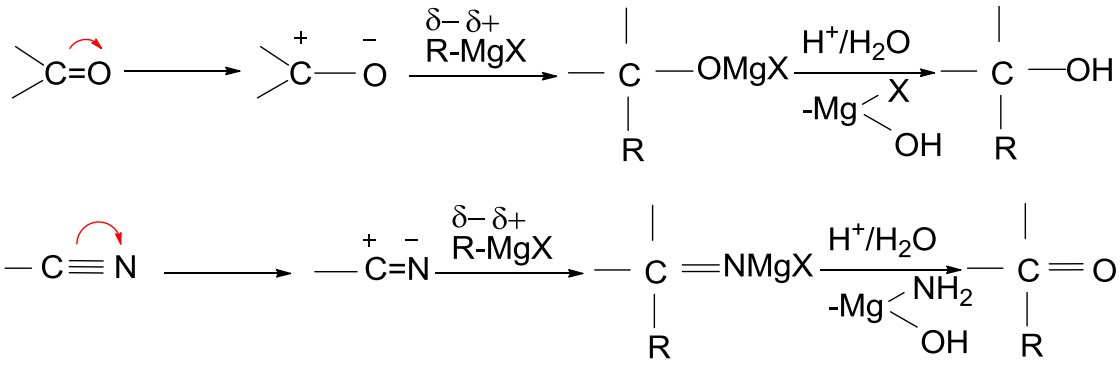
4) Reaction with cyanogen chloride and chloramines:



b) Nucleophilic Addition:

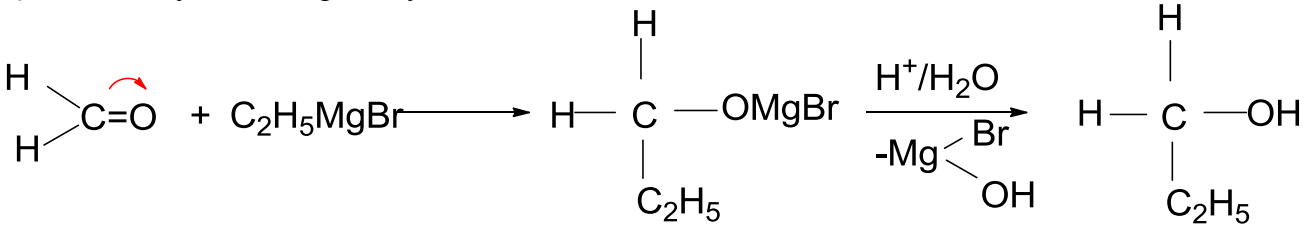
Grignard Reagents reacts with compounds having carbon-oxygen, carbon-sulphur, carbon-nitrogen multiple bonds to form addition products which on hydrolysis forms variety of compounds

General Mechanism of Nucleophilic addition



1) Addition to aldehydes

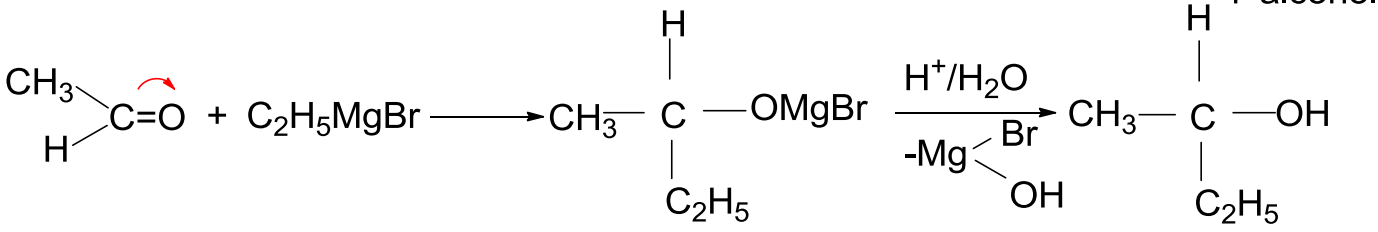
a) Formaldehyde: forms primary alcohols



Propanol

1°alcohol

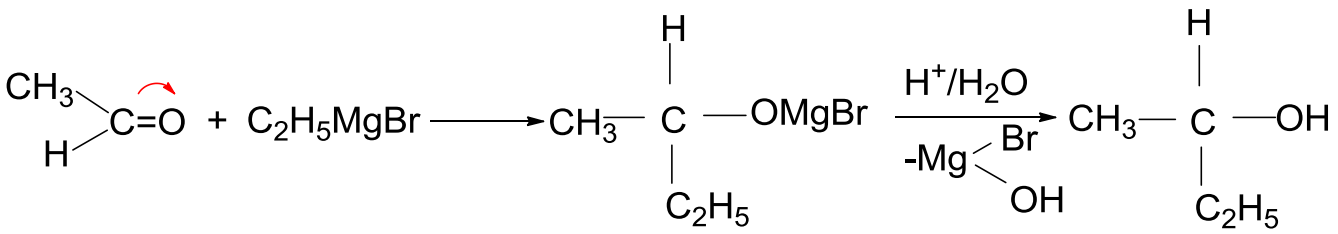
b) acetaldehyde – forms secondary alcohols



2-Butanol

2° alcohol

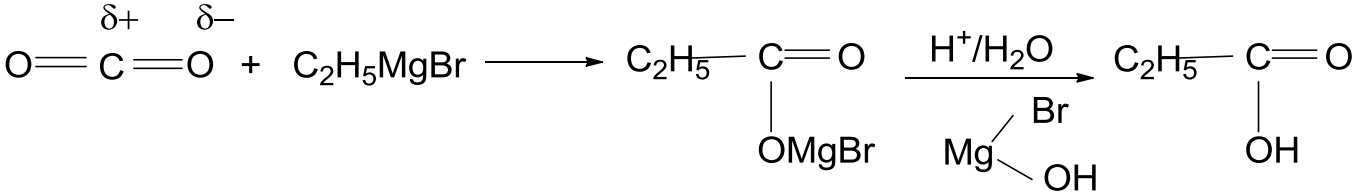
c) ketones-forms tertiary alcohols



2-Butanol

2° alcohol

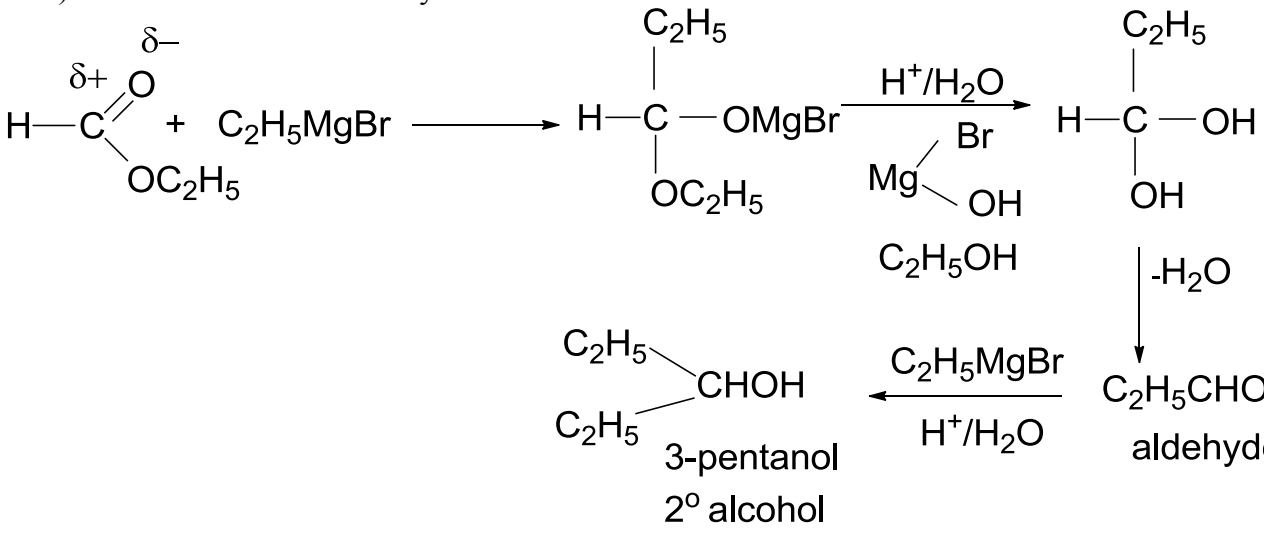
2) Addition to CO_2: Forms acids



Acids

3) Addition to Esters:

a) Formic esters: forms aldehyde

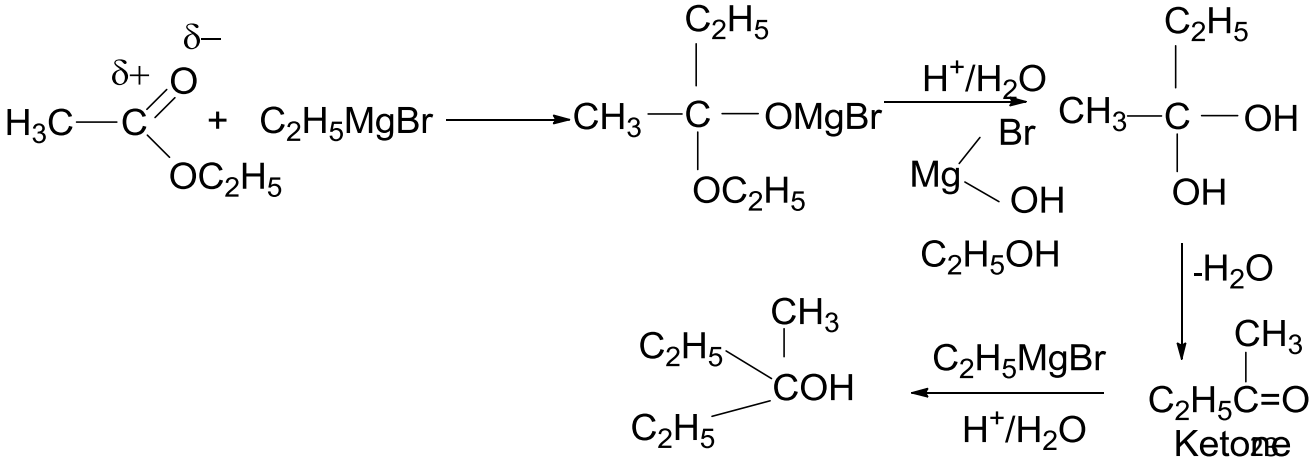


3-pentanol

2° alcohol

aldehyde

b) esters- forms ketones

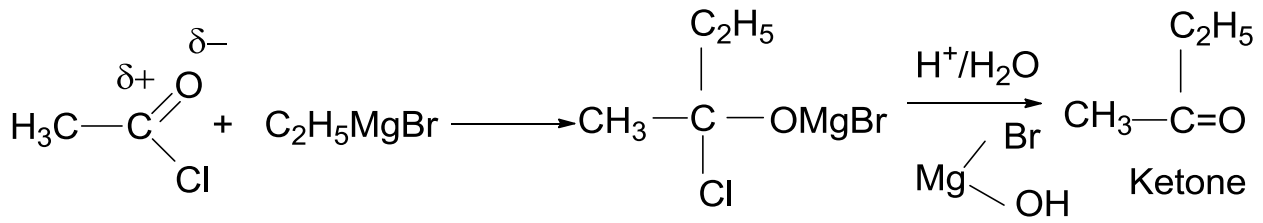


3-Methyl 3-pentanol

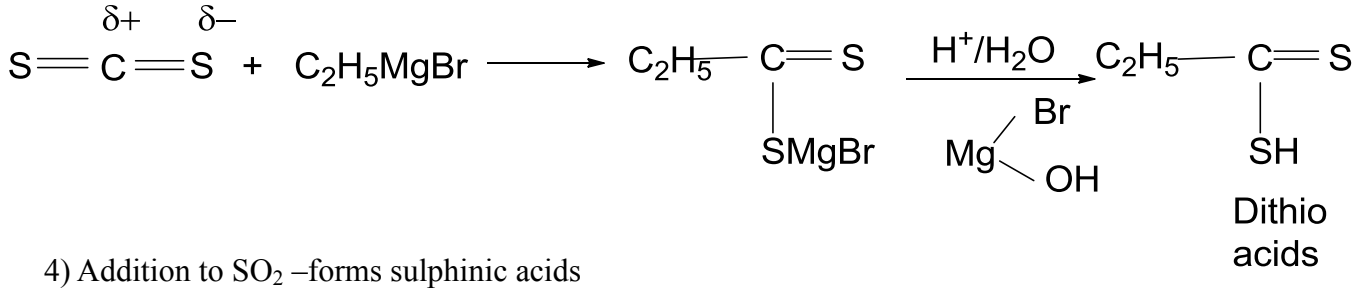
3° alcohol

Ketone

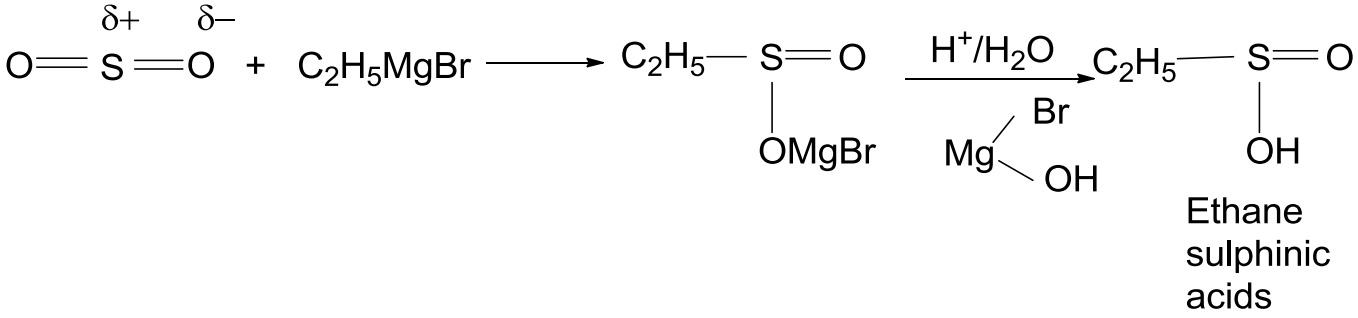
c) Acid chlorides- Forms ketones



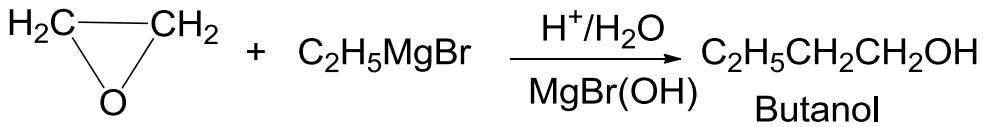
3) Addition to CS_2- forms dithioic acids



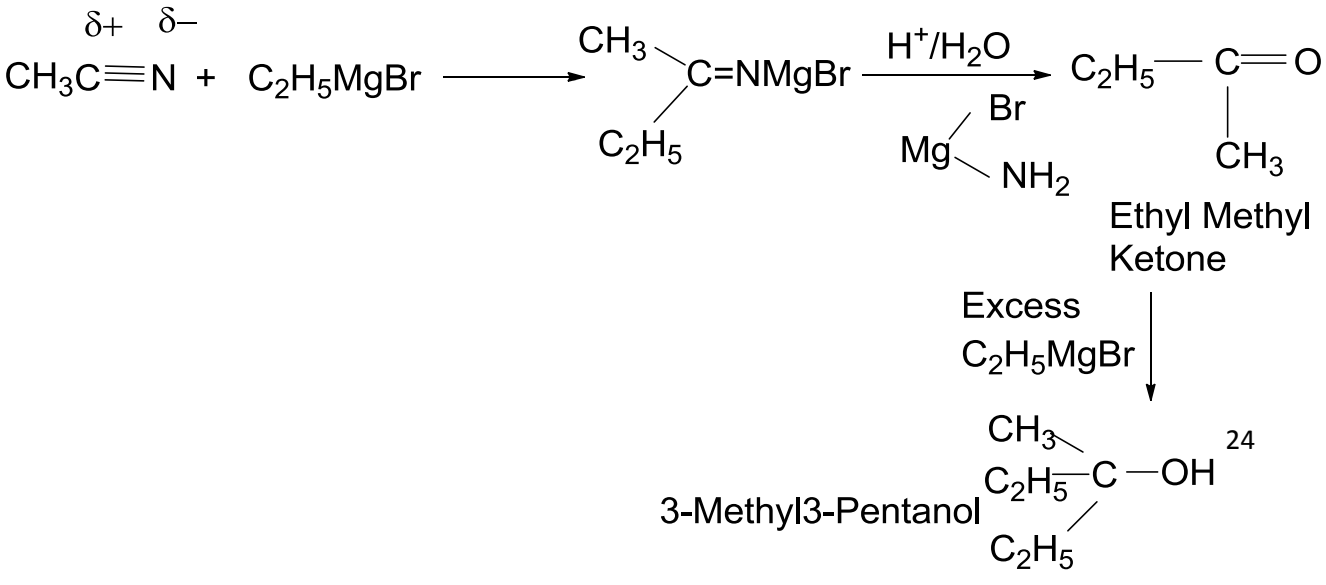
4) Addition to SO_2 –forms sulphinic acids



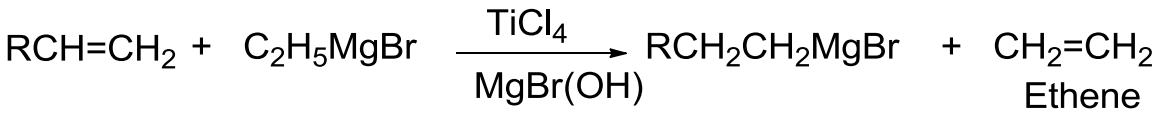
5) Addition to ethylene oxide- forms alcohols



6) Addition to alkyl cyanides-forms ketones.

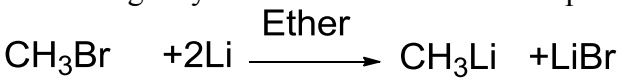


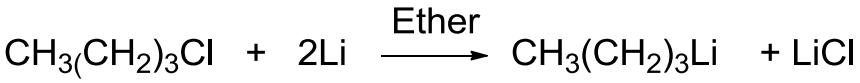
7) Addition to carbon-carbon double bonds:



2.3.1 Organolithium Compounds

Alkyl lithium: Heating alkyl halide with Lithium in the presence of benzene or ether.

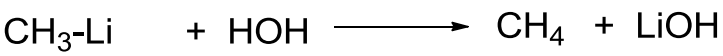




Properties- Colourless liquids; mainly covalent in nature, Reacts with Lewis base. More reactive than Grignard Reagent.

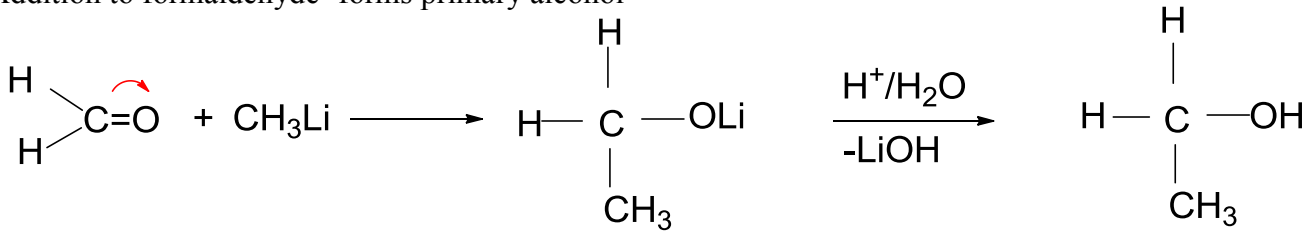
Nucleophilic Substitution Reaction:

1) Reaction with active hydrogen : Forms alkanes



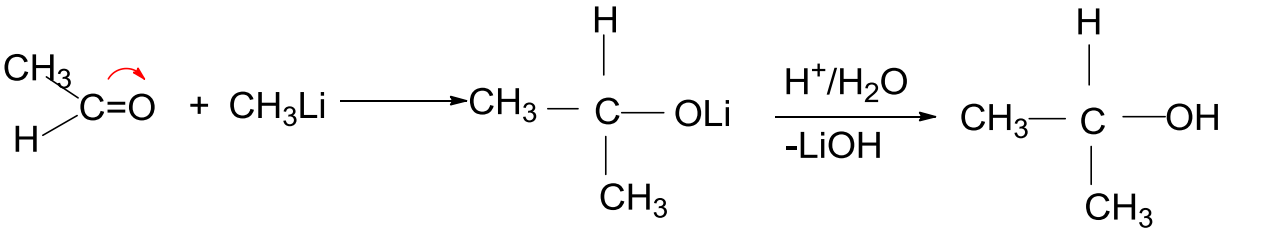
2) Nucleophilic Addition Reaction: Reacts with aldehydes, ketones similar to Grignard's reagent

Addition to formaldehyde- forms primary alcohol



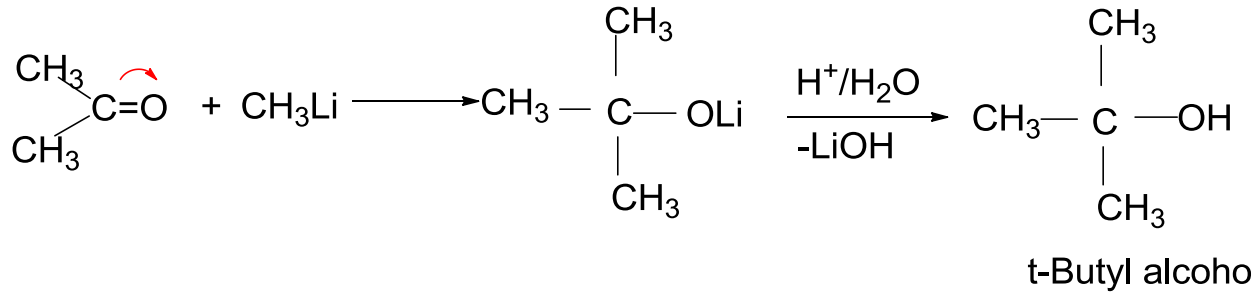
Ethanol
1°alcohol

2) Addition to aldehyde-forms secondary alcohol



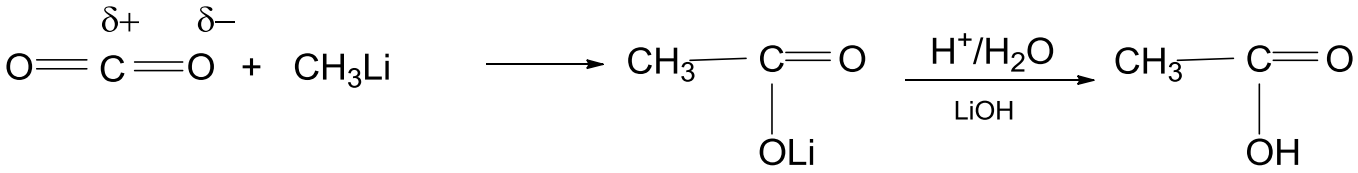
Isopropyl alcohol
2° alcohol

3) Addition to ketone- forms tertiary alcohol



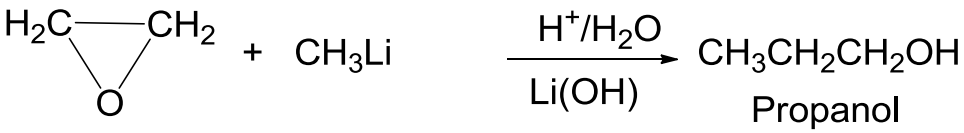
t-Butyl alcohol

4) Addition to CO_2- forms acids



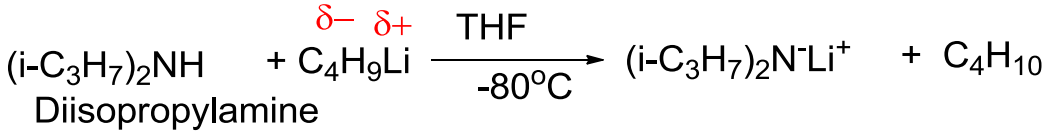
Acids

5) Addition to epoxide- forms alcohols.



2.4 Lithium diisopropyl amide-LDA

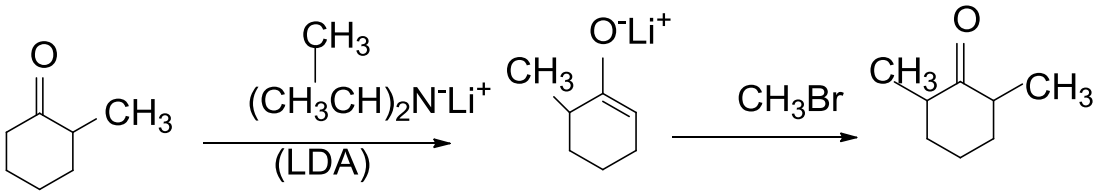
Prepared by treating a solution of diisopropylamine in THF with n-butyllithium.

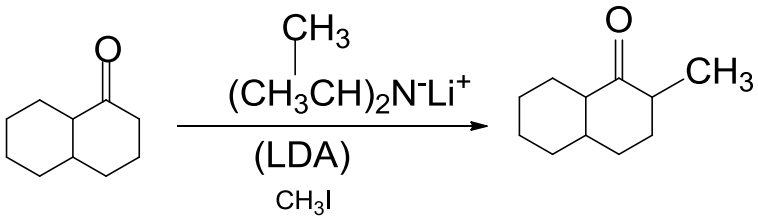


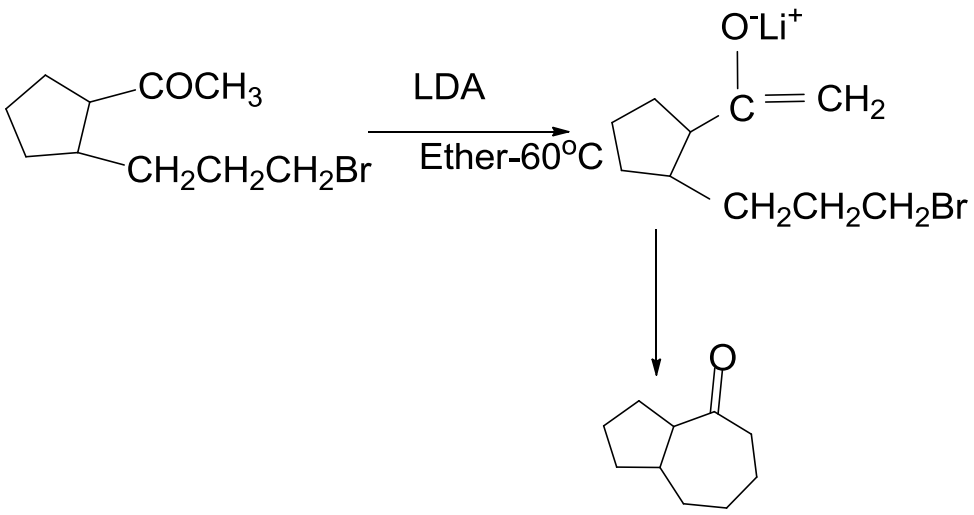
Properties:

Basic in nature, relatively soluble in ether. Converts carbonyl compound to corresponding enolates

Alkylation of carbonyl compound by S_N2 reaction

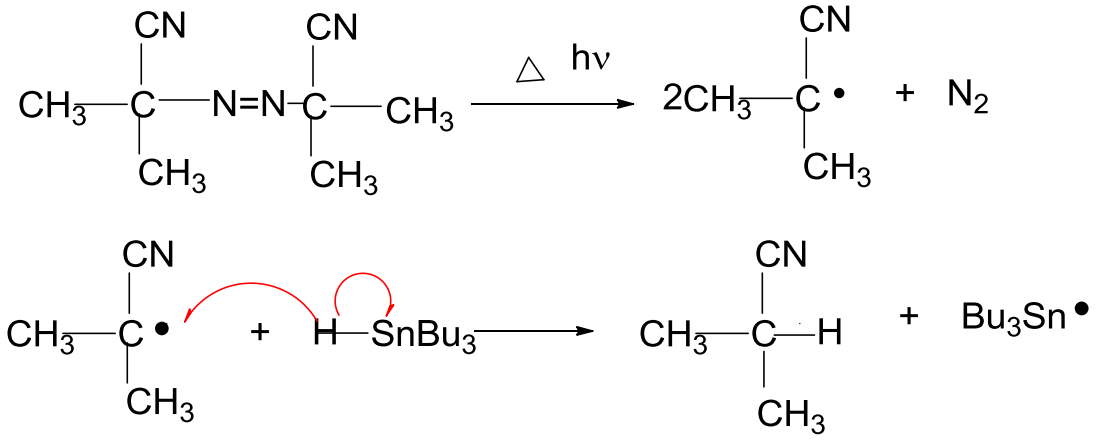




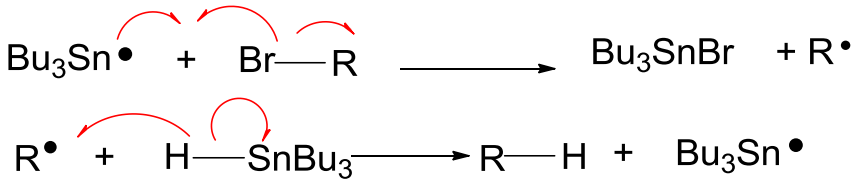


2.5 Tributyl tin hydride (Bu_3SnH)

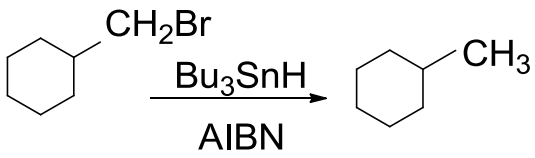
Converts alkyl halide to alkane. Reaction proceeds with an radical initiator AIBN. The tributyl tin radical abstracts a halogen from alkyl halide since Sn-H bond is weak can't abstract C-H bond from the alkyl group. The reaction is energetically favoured as it form Sn-Br and C-H bond which are far stronger than the Sn-H and C-Br bond.

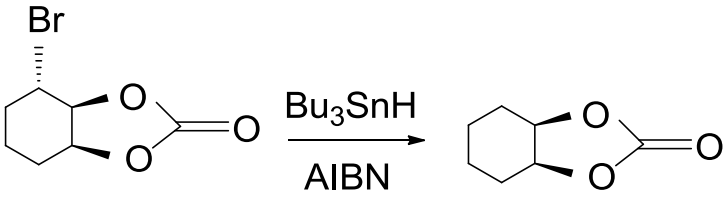


Tributyl tin radical reaction with alkyl halide

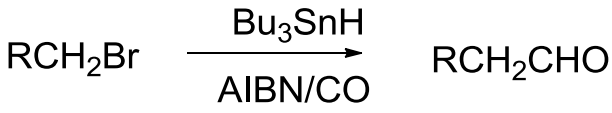


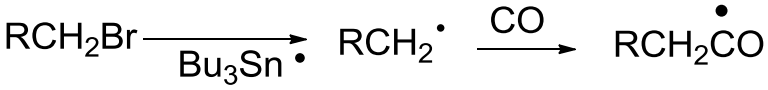
1) Converts alkyl halide to alkane



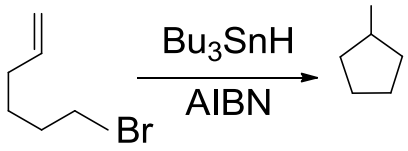


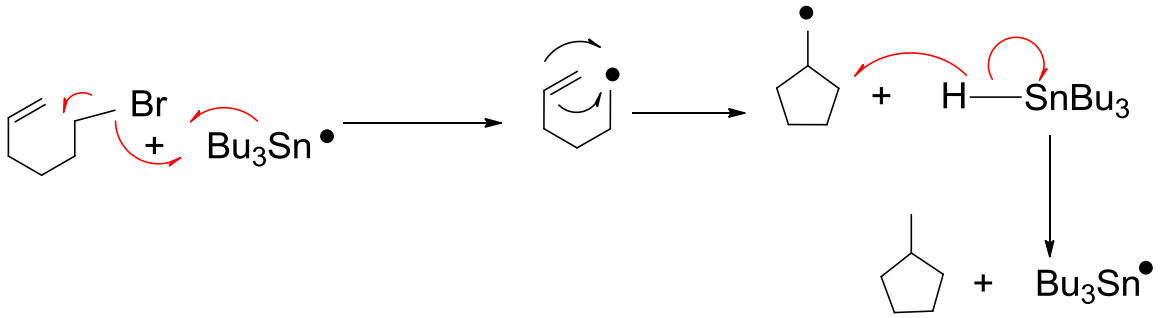
2) Converts alkylhalide to aldehyde



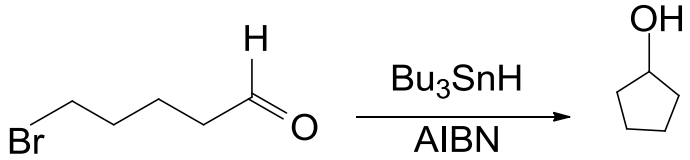


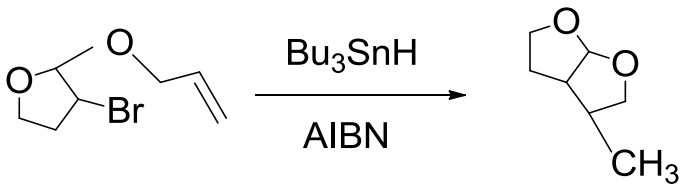
3) Intramolecular addition of a free radical to alkene to from 5membered ring





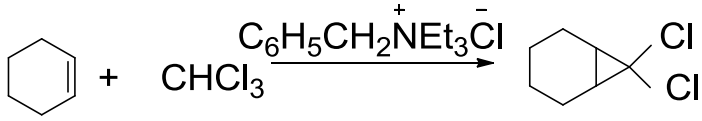
4) Intramolecular addition from aldehyde to alcohol





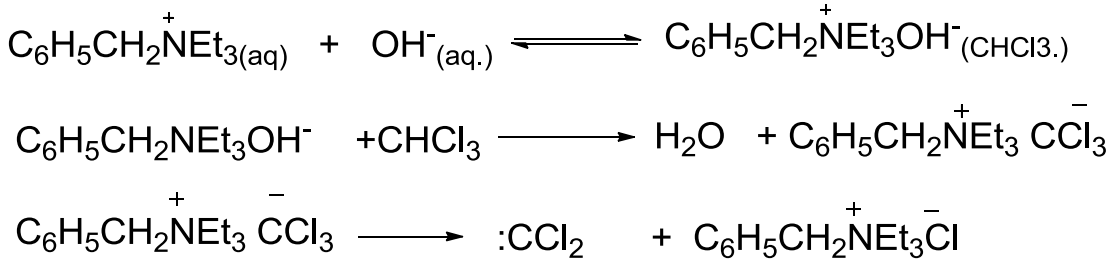
2.6 Phase transfer catalysis

Compounds whose addition to a two-phase organic water system transfers a water soluble reactant to the organic phase where a homogeneous reaction takes place thus enhancing the rate of the reaction.



7,7-dichloro-bicyclo[4.1.0]heptane.

Chloroform reacts with base to yield dichlorocarbenes which adds to a double bond to form dihydrocyclopropane.

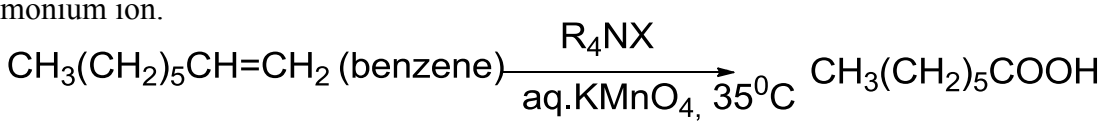


Phase Transfer catalysis

$C_6H_5CH_2\overset{+}{N}Et_3OH^-$ soluble in both water and organic

Small amounts of benzyl triethyl ammonium chloride is added.

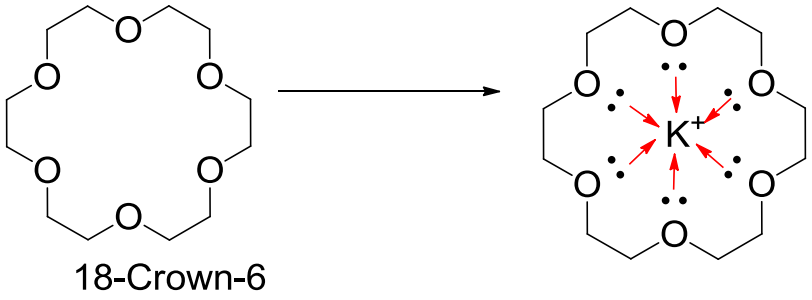
Example 2 oxidation of alkene in benzene with $KMnO_4$ in the presence of quaternary ammonium ion.

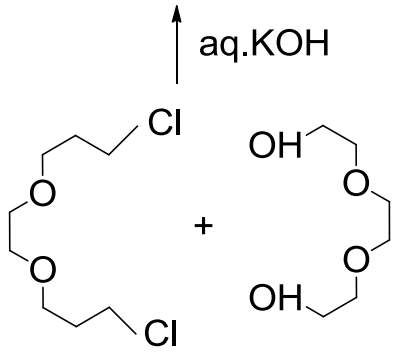


2.7 Crown ethers

Large ring polyethers able to transport ionic compounds into the organic phase. They are polymers of ethylene glycols prepared by reacting a mixture of triethylene glycol and its corresponding dichloride in aqueous KOH.

Relationship between crownether and ion is called host-guest relationship forming a species with hydrocarbon like exterior. The complexed ion is soluble in nonpolar organic solvents.
Reactions:



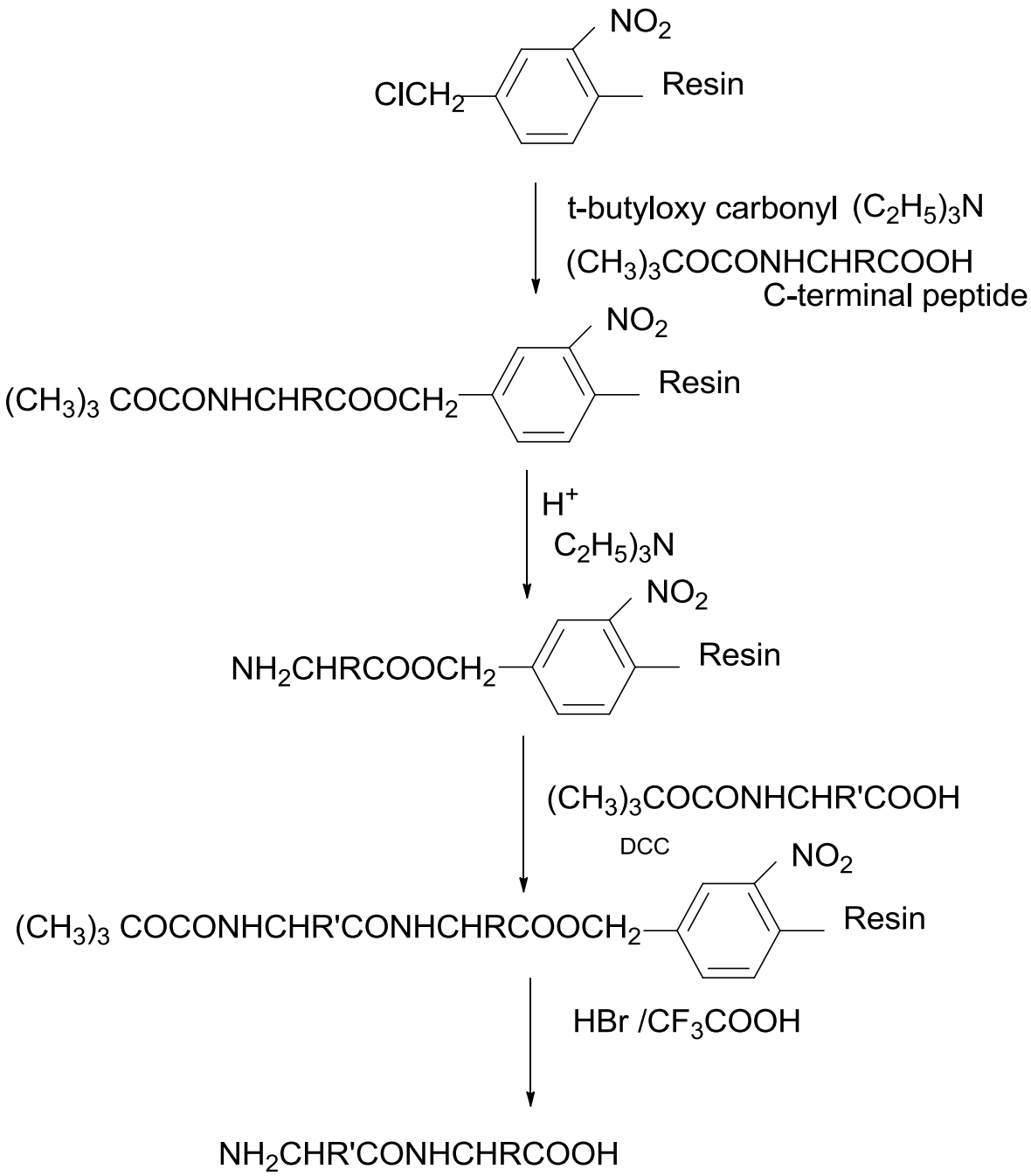


$$KCN + RCH_2X \xrightarrow[\text{benzene}]{\text{18-crown-6}} RCH_2CN + KX$$

$$C_6H_5CH_2Cl + KF \xrightarrow[\text{acetonitrile}]{\text{18-crown-6}} C_6H_5CH_2F + KCl$$

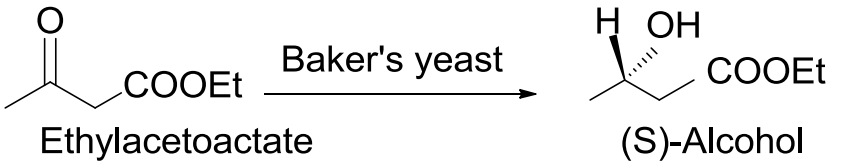
Hence, salts like KF,KCN can be transferred into aprotic solvents by using catalytic amount of 18-crown-6. In the organic phase, the realtively unsolvated anions of these salts can carry nucleophilic substitution reaction on an organic substrate.

2.8 Meerifield solid phase reaction
Solid support is used for the synthesis of polypeptides

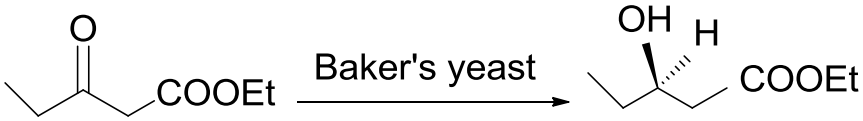


2.9 Baker's yeast

It is an enzyme which bring about the reduction of ketone to optically active secondary alcohol. The enzyme is a chiral catalyst however does not provide the hydrogen atom for reduction. The hydrogen atom is provided by coenzyme NADH. The reduction is carried out using whole cells where both the enzyme and coenzyme are provided by the organism.



Ethylacetoactate (S)-Alcohol



EthylβKetovalerate (R)-Alcohol

TEXT / REFERENCE BOOKS

1. March J., and Smith M., Advanced Organic Chemistry, 5th Edition, John-Wiley and Son, 2001.

2. Gould E. S., Mechanism and Structure in Organic Chemistry Holt, Rinehart and Winston Inc., 1959.

3. Carey A. Francis, and Sundberg J Richard., Part A and Part B Advanced Organic chemistry, 5th edition, Springer, 2007.

4. Jonathan Clayden, Nick Greeves and Stuart Warren., Organic Chemstry, 2nd Edition, Oxford Publishers, 2012.

5. Finar I. L., Organic Chemistry, 6th Edition, Pearson Education Asia, 2004.

6. House H.O., Modern Synthetic Reactions, W.A. Benjamin Inc, 1972.

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SCHOOL OF SCIENCE & HUMANITIES

DEPARTMENT OF CHEMISTRY

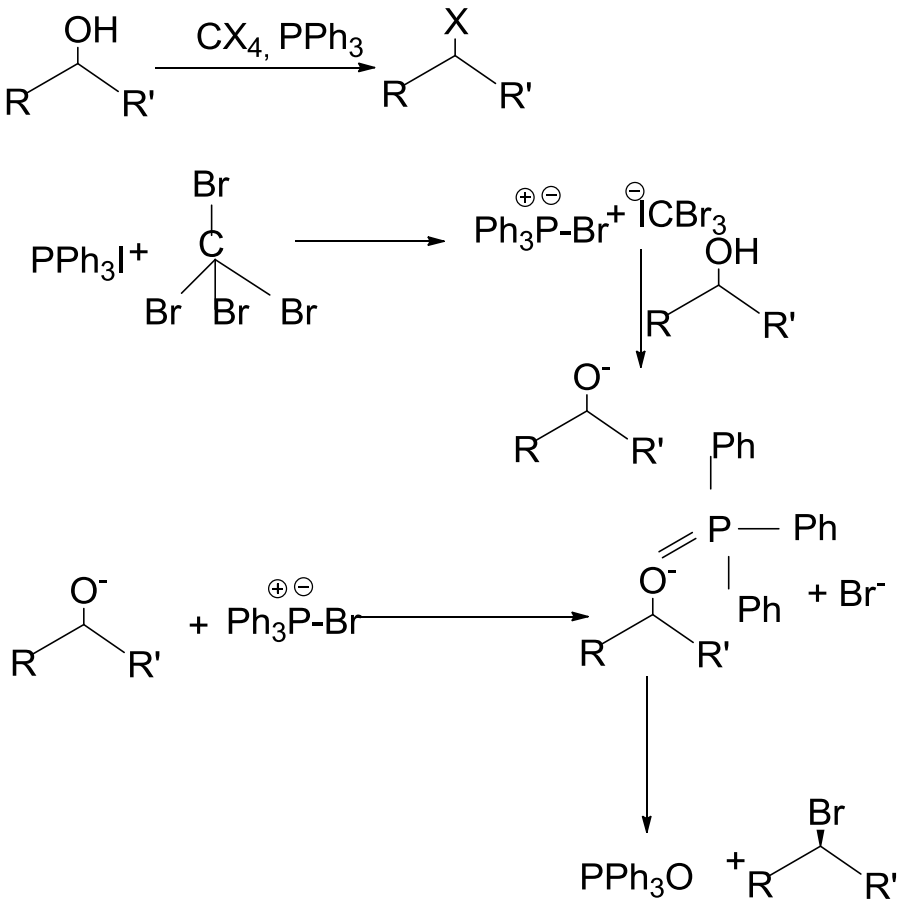
UNIT – I -Named Reactions – SCYA5101

UNIT 3

NAMED REACTIONS

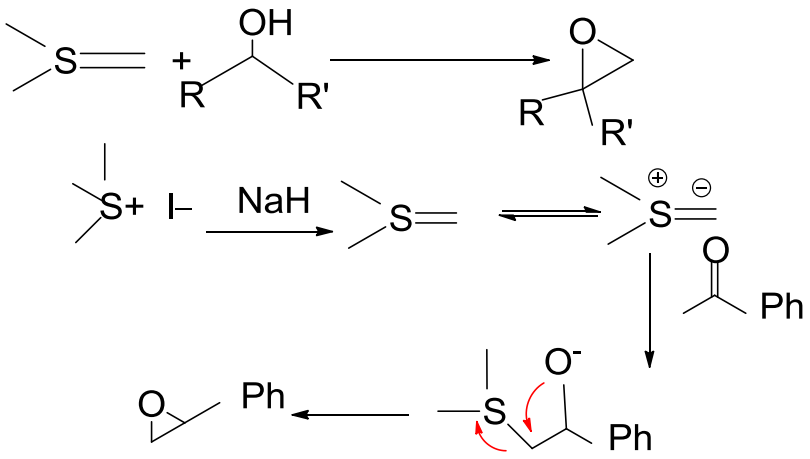
3.1 Appel Reaction:

Conversion of alcohol to alkyl halide in the presence of triphenyl phosphine and CCl_4.

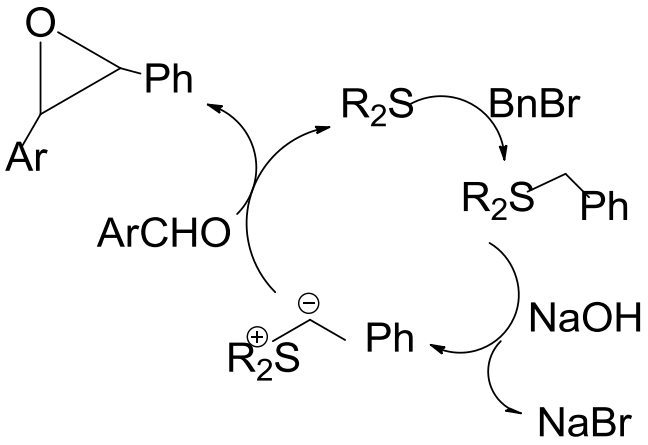


3.2 Corey Chaykovsky reaction

Reaction of sulphur ylides with carbonyl compounds to form epoxides and with imines it form azridines.

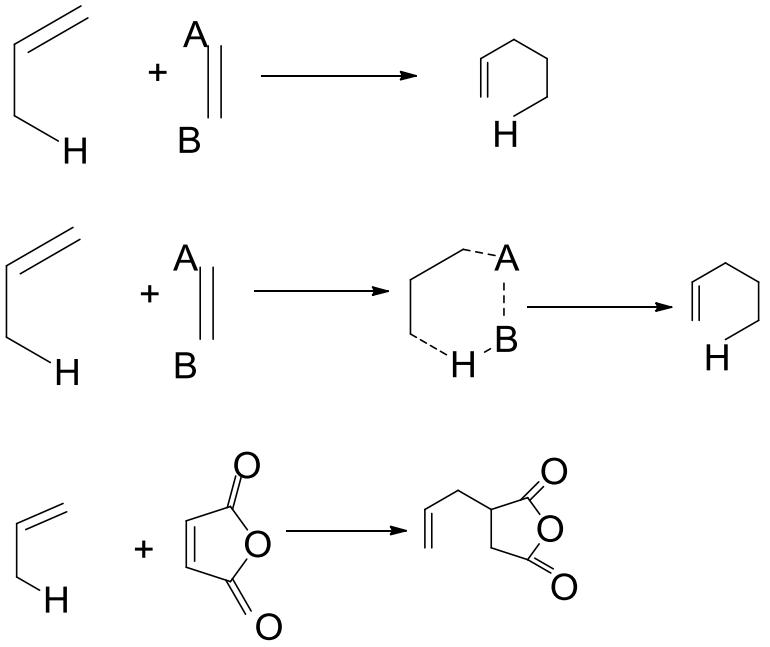


The overall reaction can be summarized as



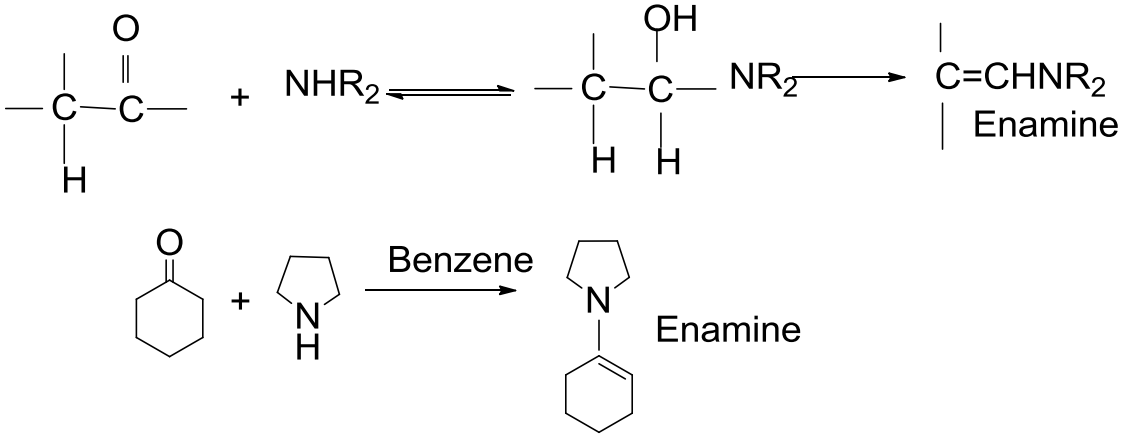
3.3 Ene Reaction:

Addition of an olefin having an allylic hydrogen to a compound containing double bond (C=C, C=O, C=N) with the formation of new sigma bond to the terminal carbon of the allyl group.



3.4 Strok enamine Reaction

Enamines are α,β unsaturated amines and are obtained by the reaction of aldehyde/ketone having α –hydrogen atom with secondary amine in the presence of dehydrating agnet p-TSH. The reaction proceeds in the forward direction by the removal of water.



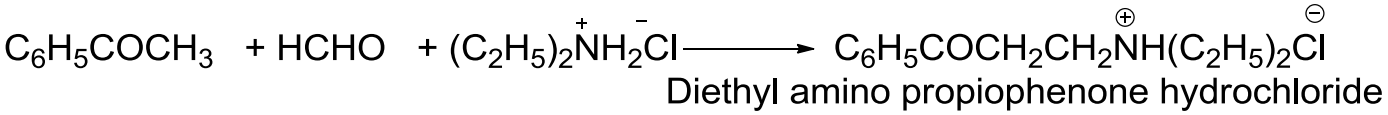
3.5 Mannich Reaction:

It is a condensation reaction between HCHO, ammonia or a primary or secondary amine and a compound containing one or more active hydrogens.

Active hydrogen: ketones, keto-acids, acetoacetic ester, cyano acids and their esters, phenol, nitro, alkynes etc.,

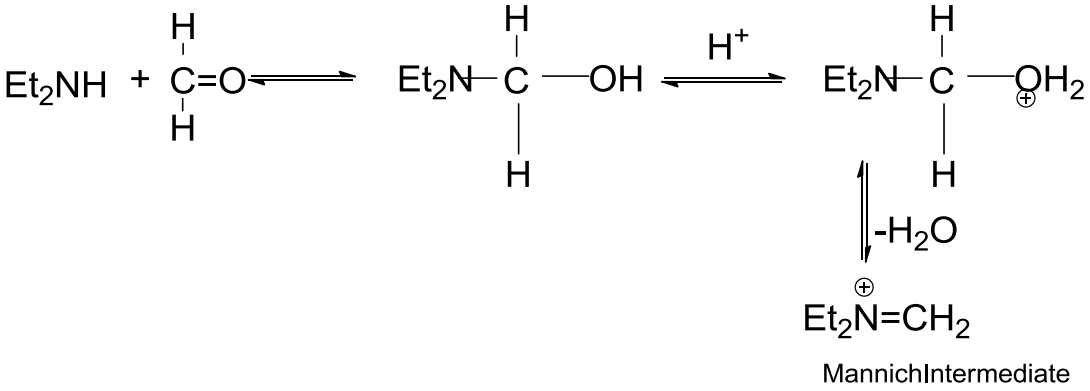
Secondary amines: Dialkyl amines,piperdine or pyrrolidine.

Aldehydes other than HCHO can also be used.

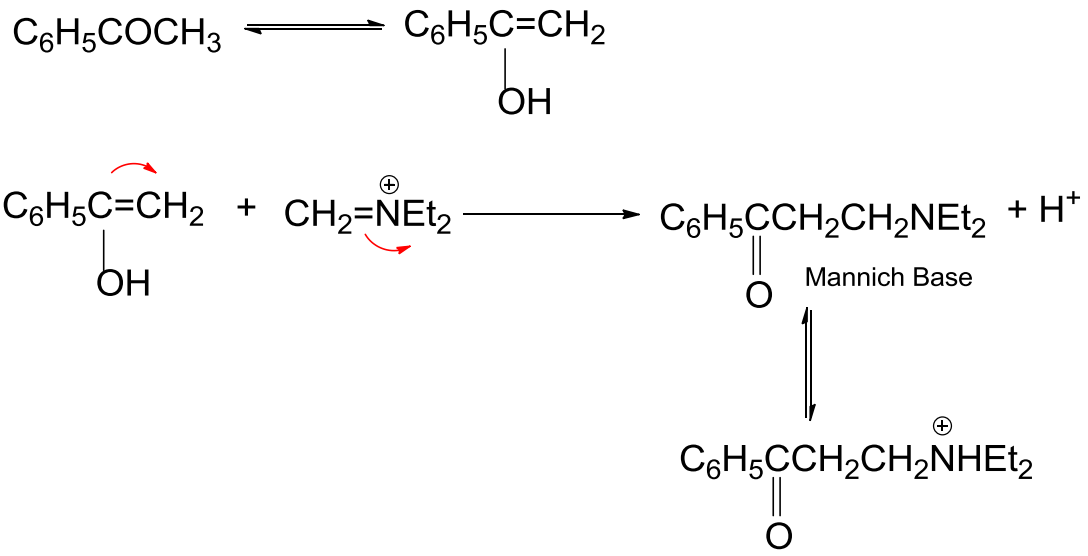


Diethyl amino propiophenone hydrochloride

Mechanism:

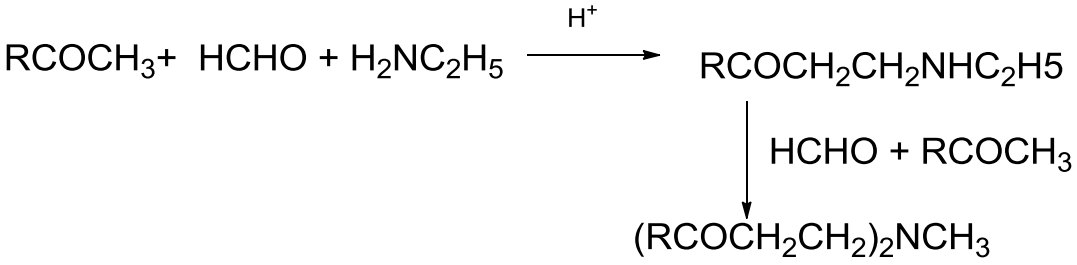


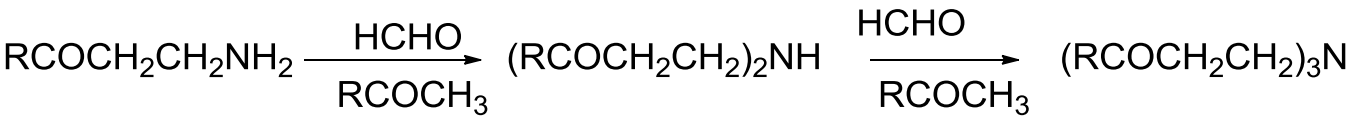
MannichIntermediate

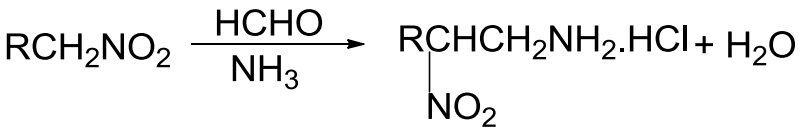


Mannich Base

With primary amine:

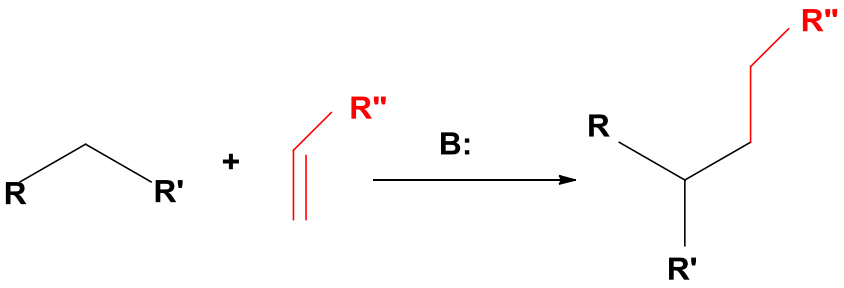




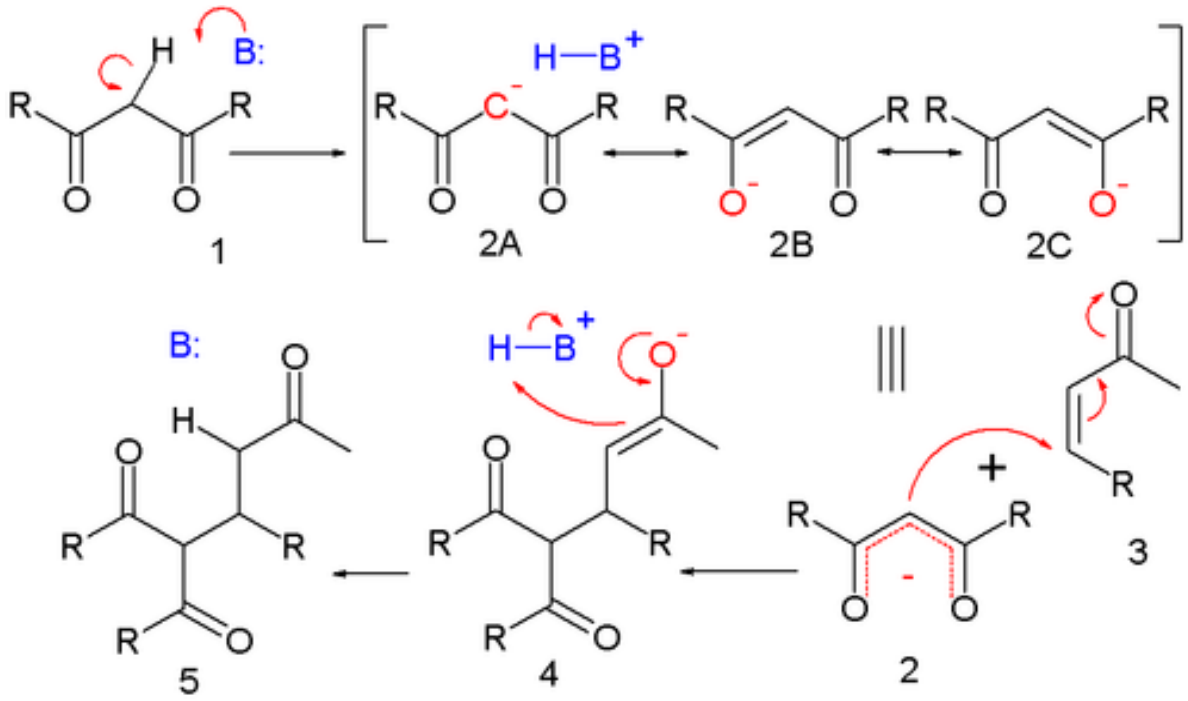


3.6 Michael Reaction:

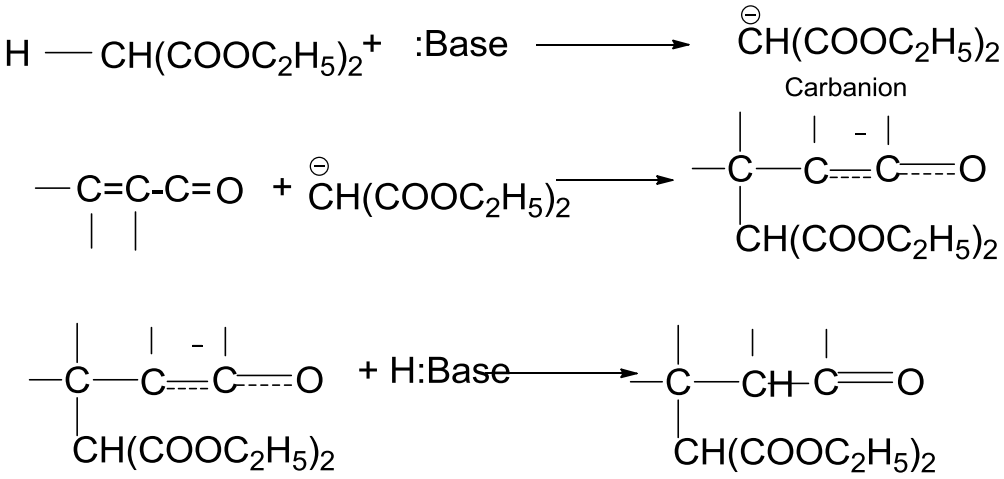
Addition of carbanion of nucleophile to carbon of an α,β unsaturated carbonyl compound to form conjugate addition compound(C-C bond).



Mechanism:

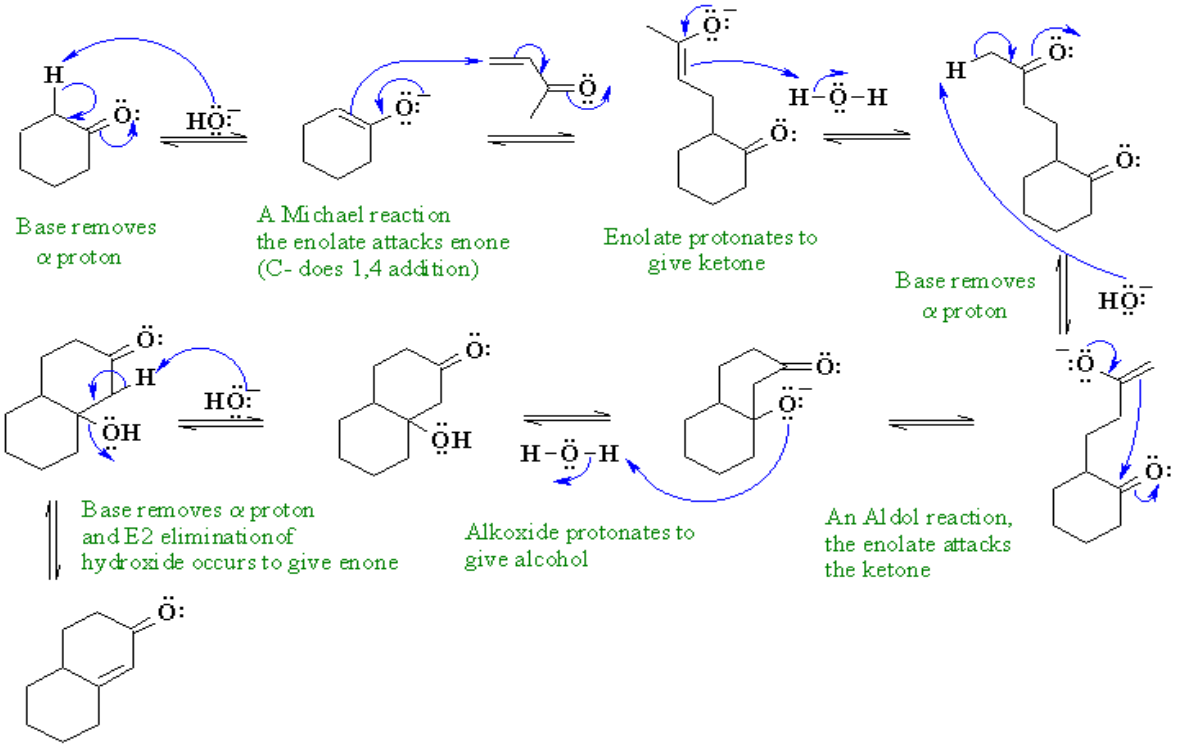


Michael addition Malonic ester

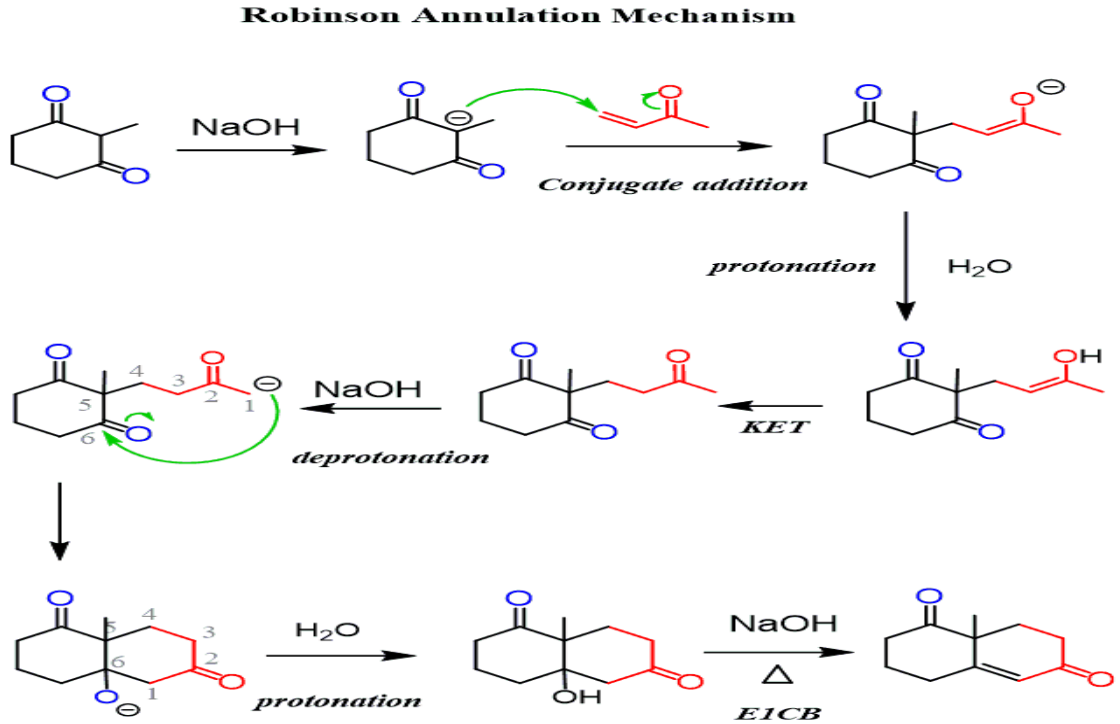


3.7 Robinson Annulation:

Michael addition and intramolecular aldol reaction



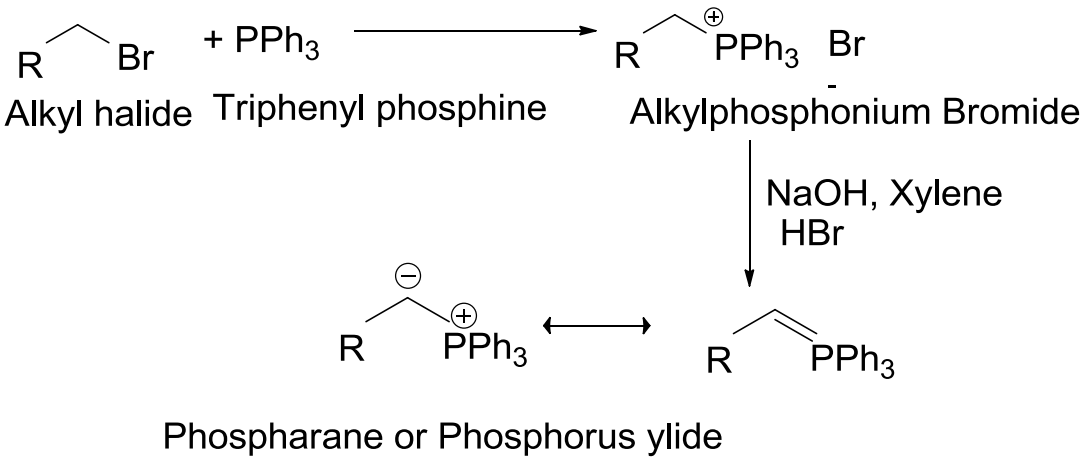
Robinson annulation:



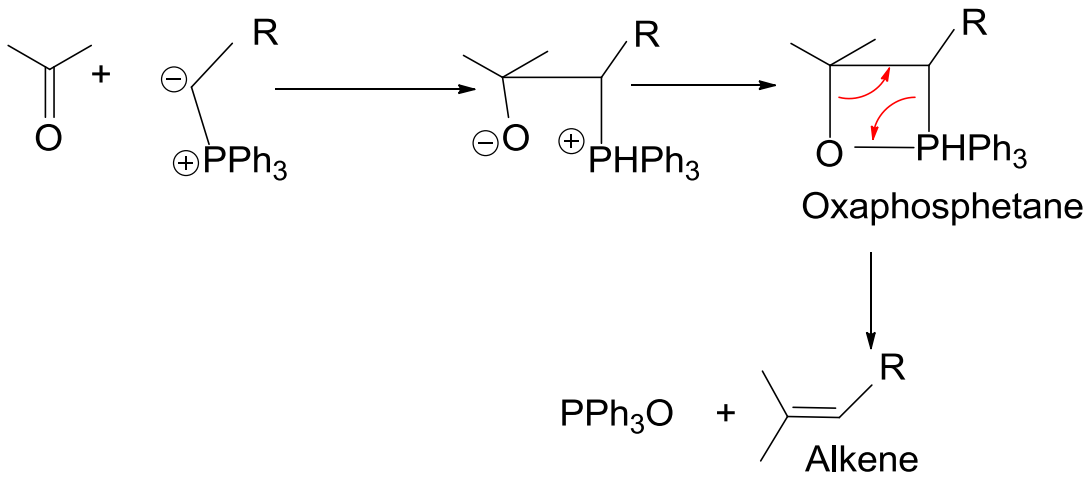
3.8 Wittig Reaction:

Direct conversion of carbonyl group of aldehyde and ketone to alkene using phosphorane or ylide.

The ylide is prepared by treating the alkyl halide with triphenylphosphine having α-hydrogen atom. The resulting phosphonium halide on treatment with alkali in the inert solvent forms the ylide.



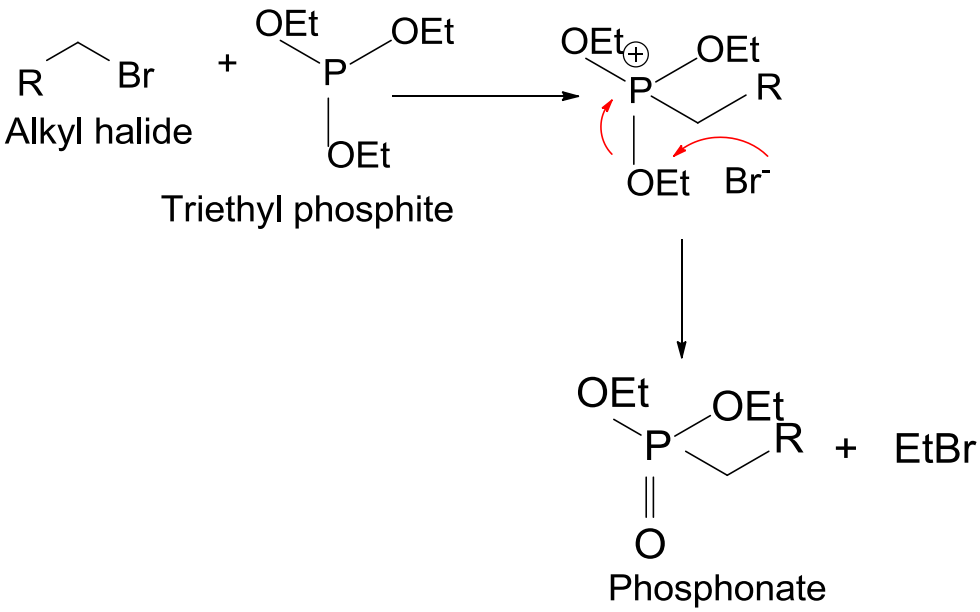
The ylide reacts with a carbonyl group to form oxaphosphetane which undergoes cyclo elimination to give alkene. Elimination.



High affinity of P to oxygen favours cyclo elimination. Stabilised ylides reacts with aldehydes to form E-isomer while the unstabilised ylides forms z-isomer.

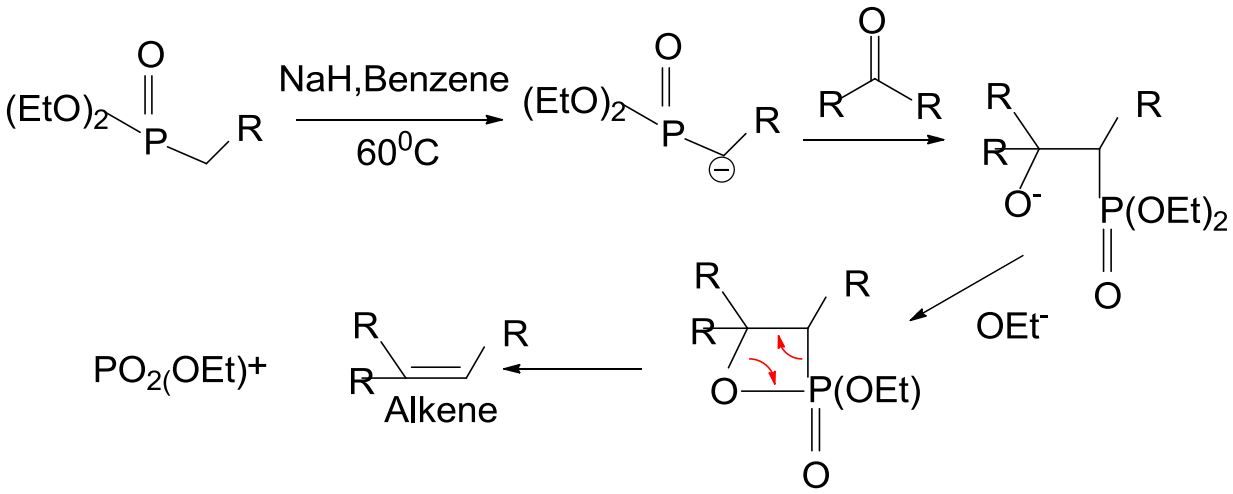
3.9 Arbuzov Reaction:

The Phosphonates required for the formation of alkene is prepared by this reaction.



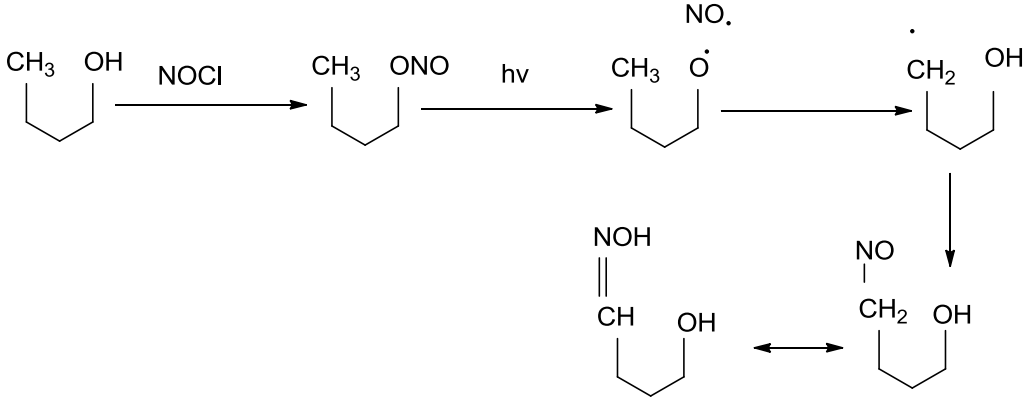
3.10 Horner-Wordsworth-Emmons Reaction

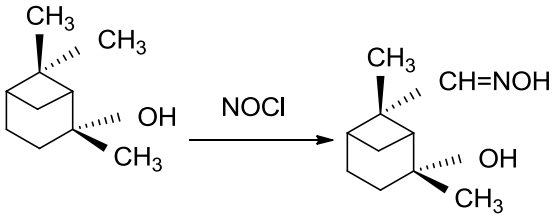
Phosphonates on warming with a base and treating in an inert solvent it forms a stabilised carbanion. The carbanion reacts with carbonyl compound to form alkene (E-isomer).



3.11 Barton Reaction

The methyl group δ to OH group is converted to oxime.

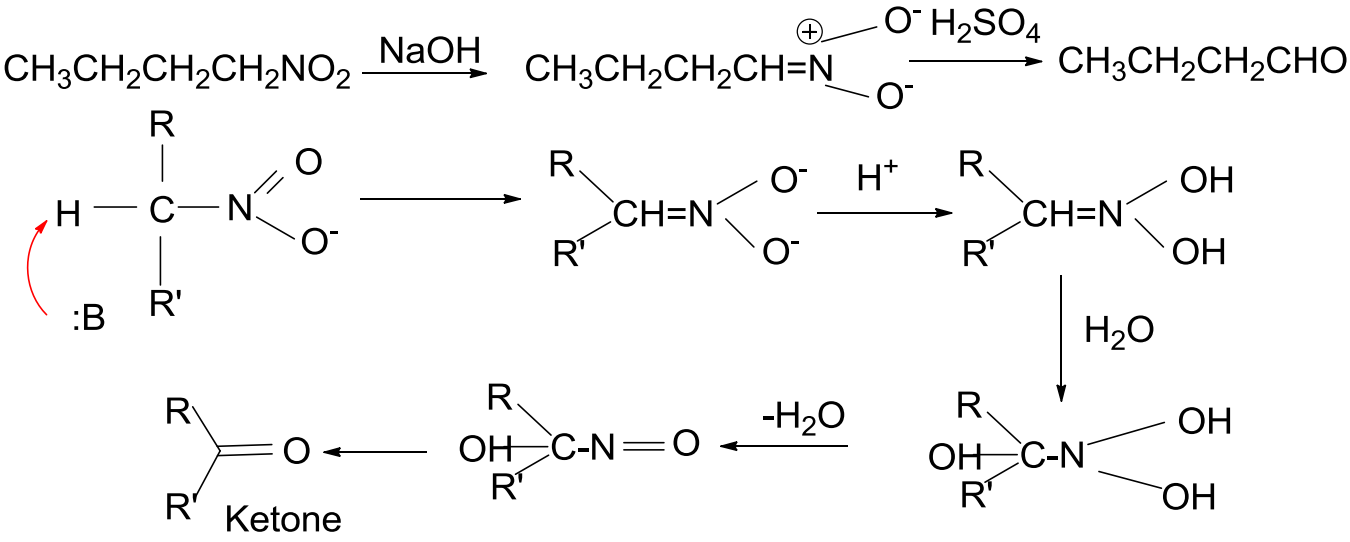




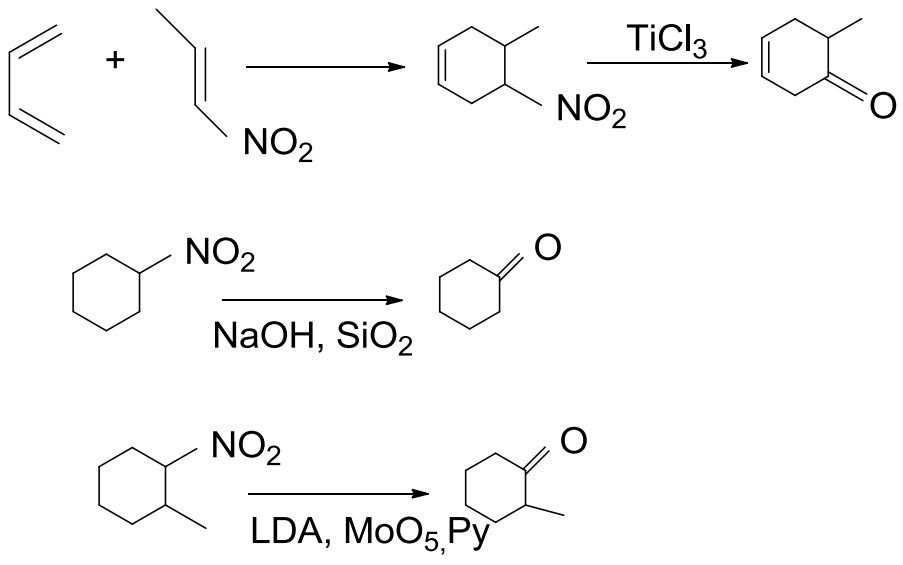
3.12 Nef Reaction

Formation of aldehydes and ketones from nitro group.

Reactions:

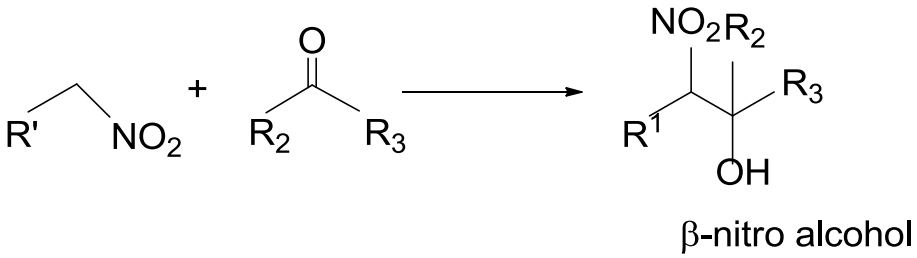


Reactions:



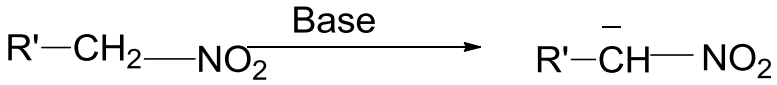
3.13 Henry Reaction

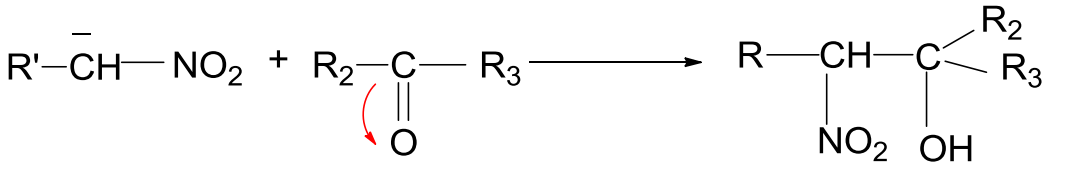
The Henry Reaction is a base-catalyzed C-C bond-forming reaction between nitroalkanes and aldehydes or ketones. It is similar to the aldol reaction, and also referred to as the Nitro Aldol Reaction.If acidic protons are available (i.e. when R = H), the products tend to eliminate water to give nitroalkenes. Therefore, only small amounts of base should be used if the isolation of the β-hydroxy nitro-compounds is desired.



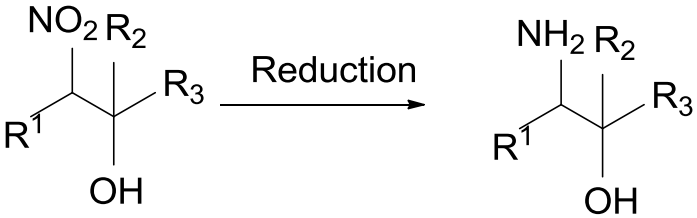
β-nitro alcohol

Mechanism:

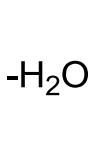


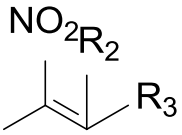


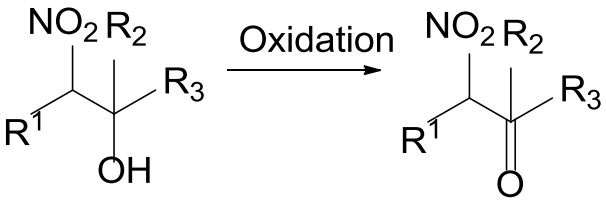
β–nitro alcohol



β-nitro alcohol



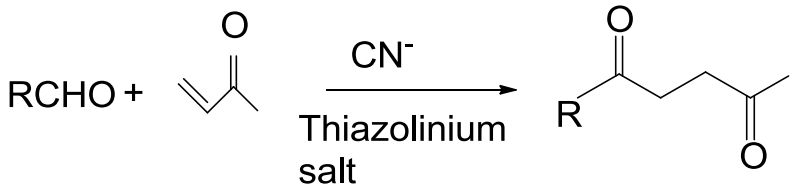


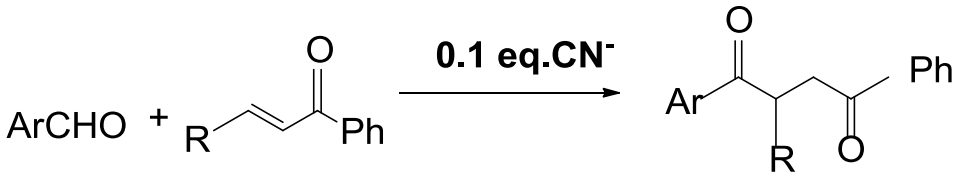


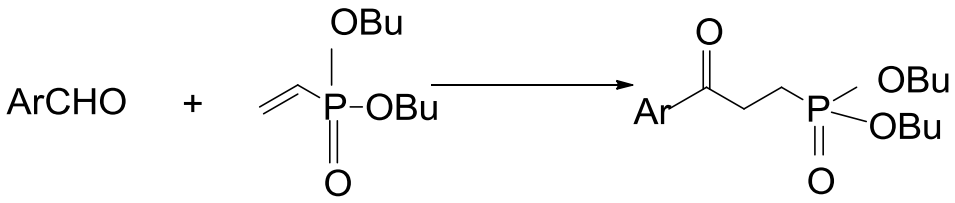
β-nitro alcohol

3.14 Stetter Reaction

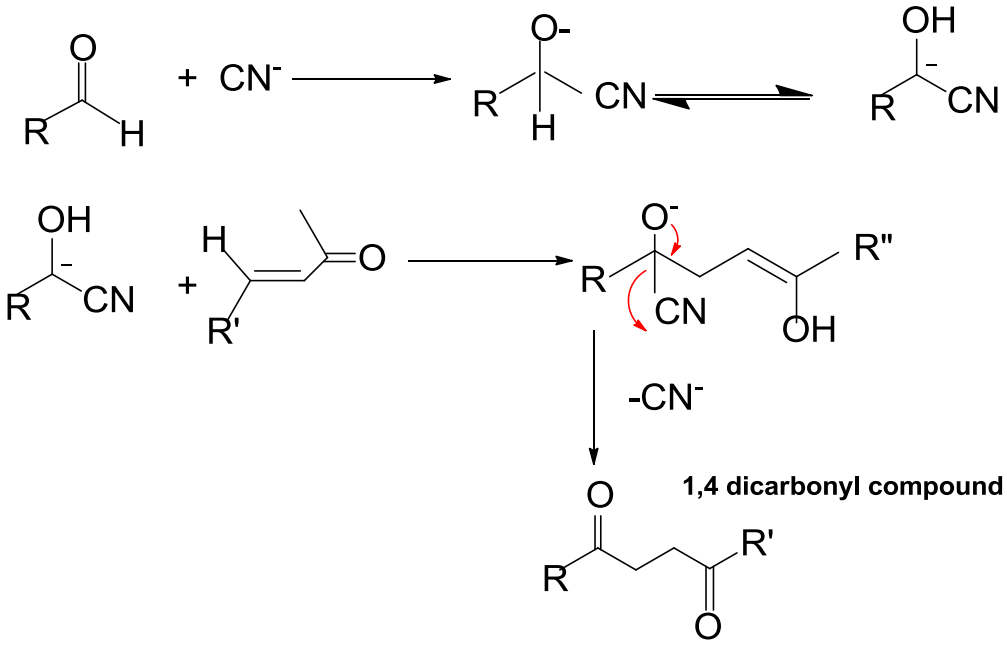
The Stetter Reaction is a 1,4-addition (conjugate addition) of an aldehyde to an a,β-unsaturated compound, catalyzed by cyanide or a thiazolium salt.





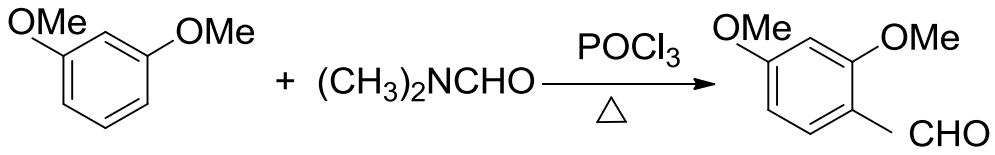


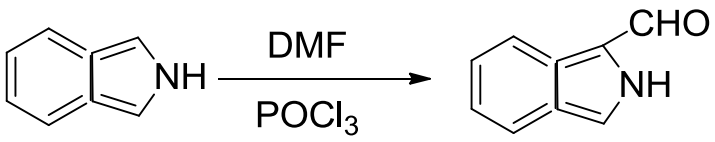
Mechanism:

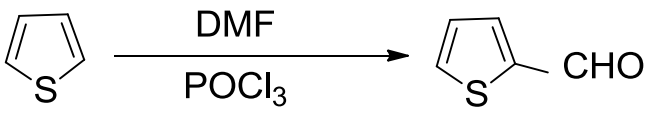


3.15 Vilsmeier-Haack Reaction

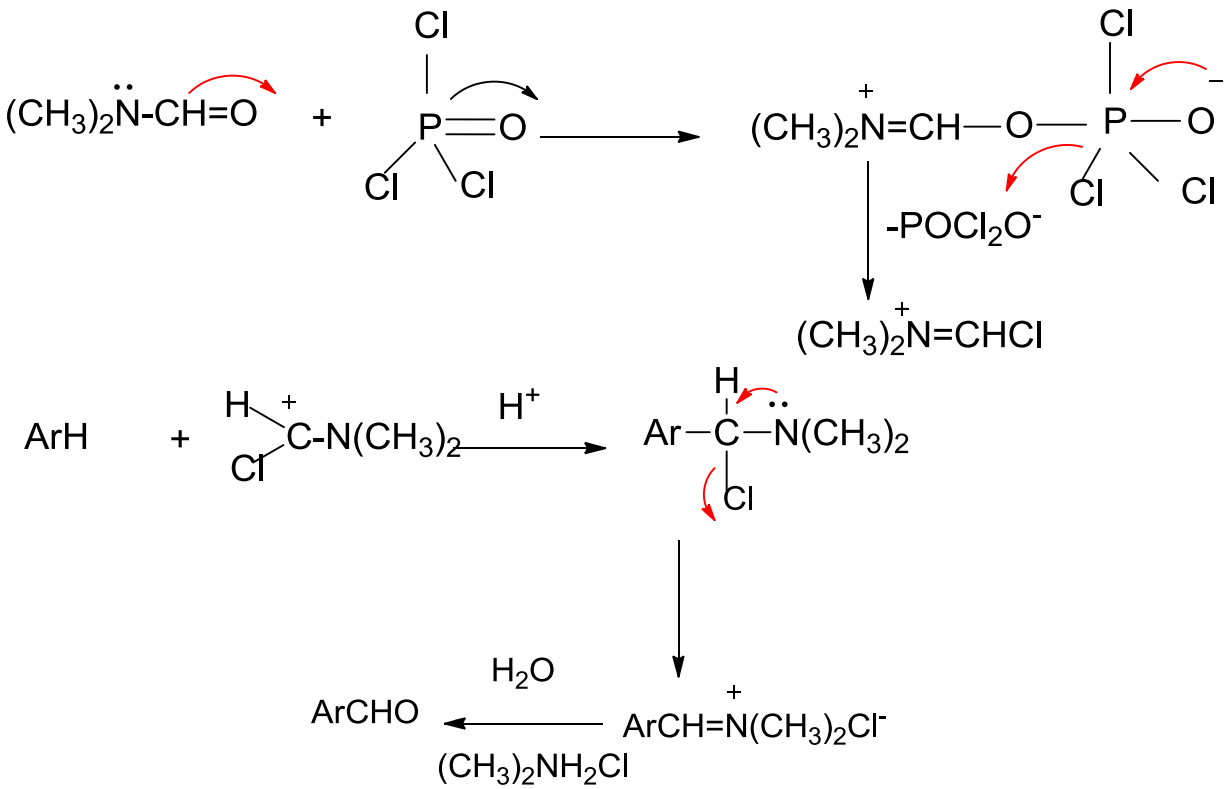
Aromatic /Heterocyclic compounds reacts with disubstituted formamide and $POCl_3$ to give aldehyde.







Mechanism:



3.14 Sharpless asymmetric Epoxidation.

Oxidation of allylic alcohol to epoxides.

Substrate: Allyl alcohol

Oxidant: t-Butylhydroperoxide

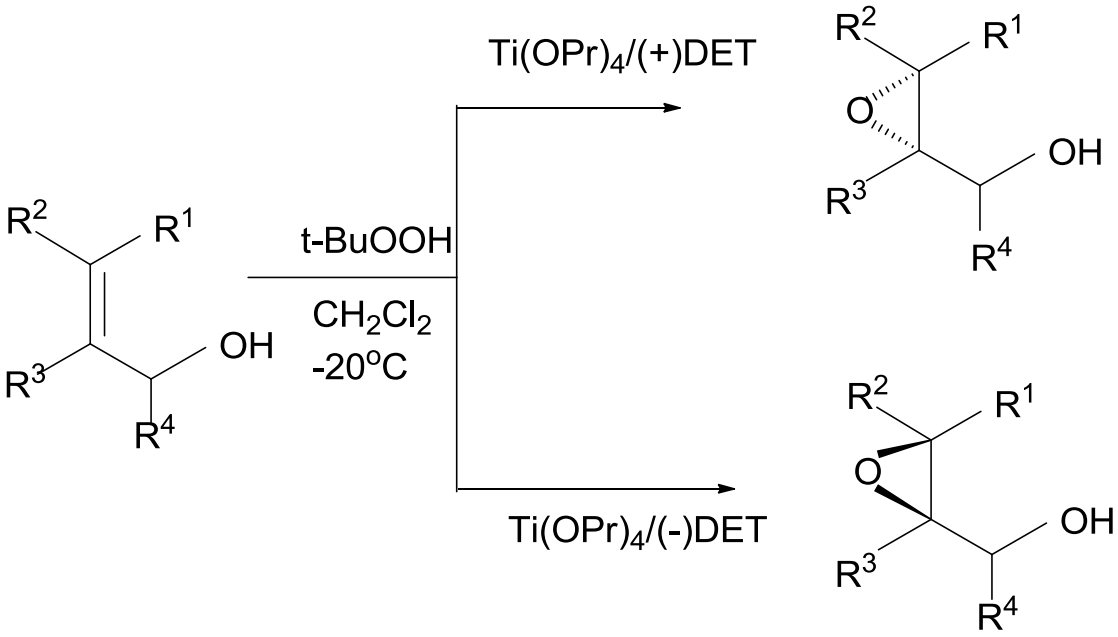
Catalyst: Titanium tetraisopropoxde/Diethyl tartrate

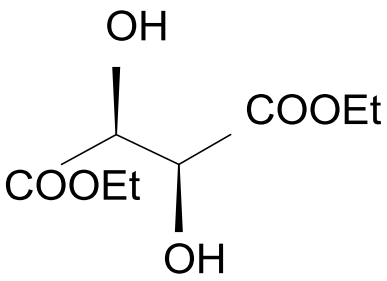
Solvent: Dichloromethane at 20^{o}C.

Stereochemistry: Right [Alcohol] Left

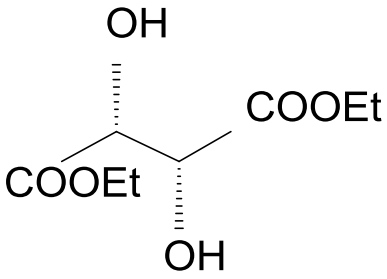
(+)DET	Wedge	Dash
(-)DET)	Dash	Wedge

Reactions:



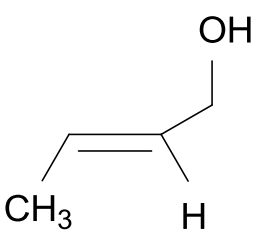


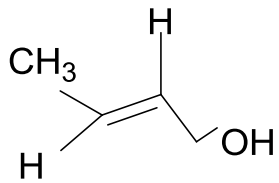
2S,3S (-) Diethyltartrate

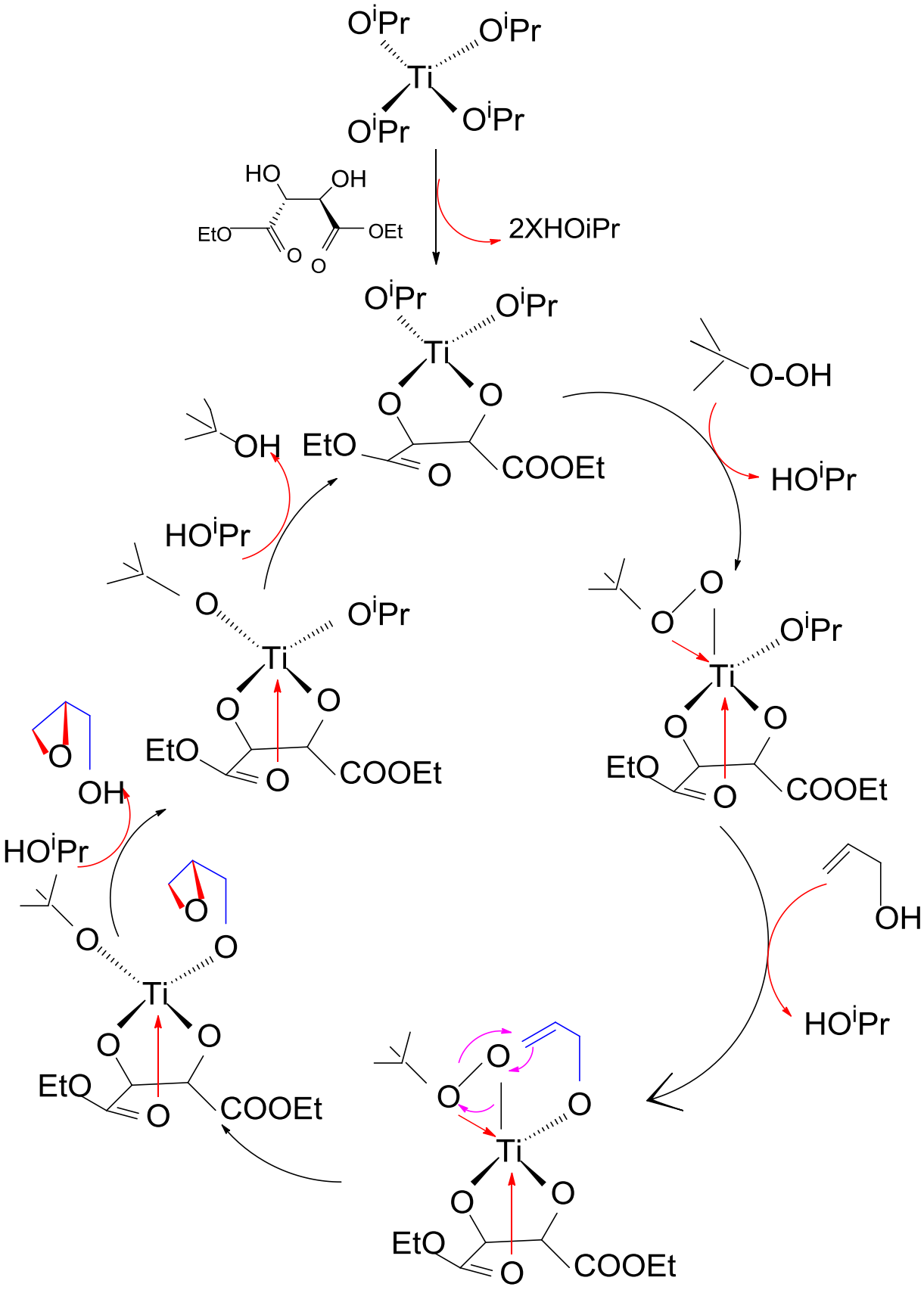


2R,3R (+) Diethyltartrate

Mechanism:

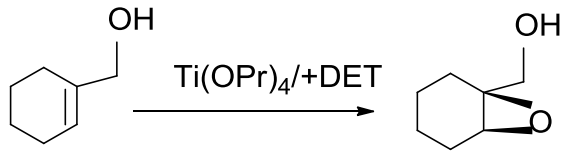


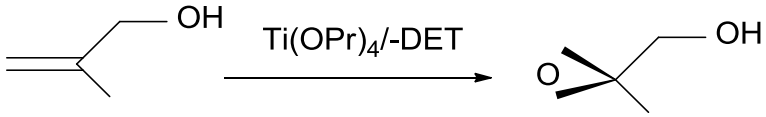



O^iPr
O^iPr
Ti
O^iPr
O^iPr
HO
OH
EtO
OEt
O
O
2XHOiPr
O^iPr
O^iPr
Ti
O
O
EtO
O
COOEt
O-OH
HO^iPr
OH
HO^iPr
O
O^iPr
Ti
O
O
EtO
O
COOEt
O
O
O^iPr
Ti
O
O
EtO
O
COOEt
O
OH
HO^iPr
O
O
Ti
O
O
EtO
O
COOEt
OH
HO^iPr
O
O
O
Ti
O
O
EtO
O
COOEt

Test your Knowledge:

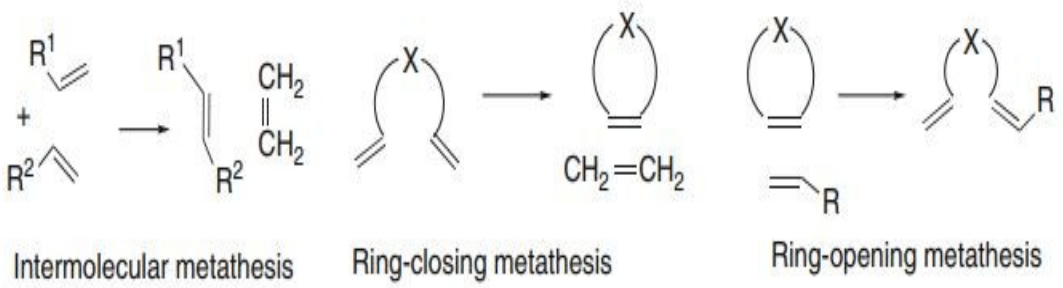
(a) Predict the products:



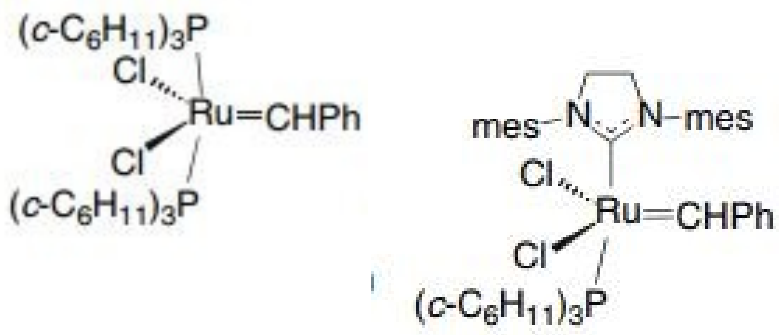


3.15 Grubb's metathesis

The process can be used to close or open or to interchange between double bond components.. The catalyst used is the benzylidene complex of Ru [$RuCl_2$(P c-$(C_6H_{11})_3)_2$ which is a metal carbene- Grubb's catalyst.

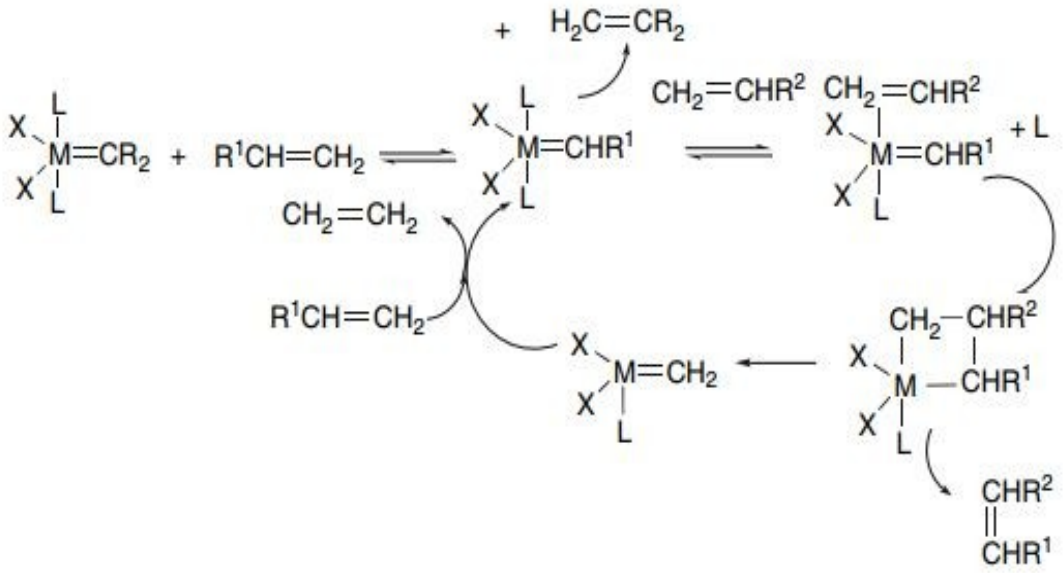


Grubb's catalyst are

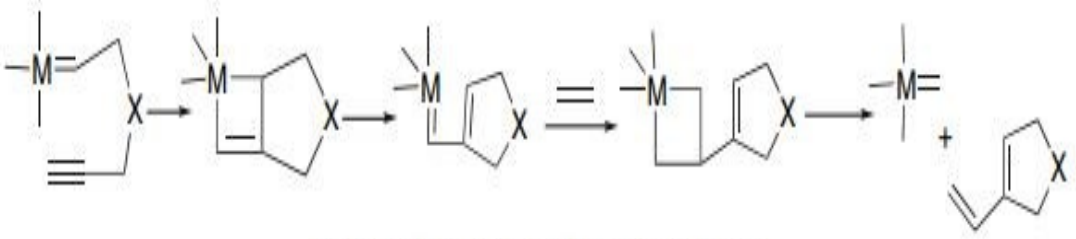


Mechanism:

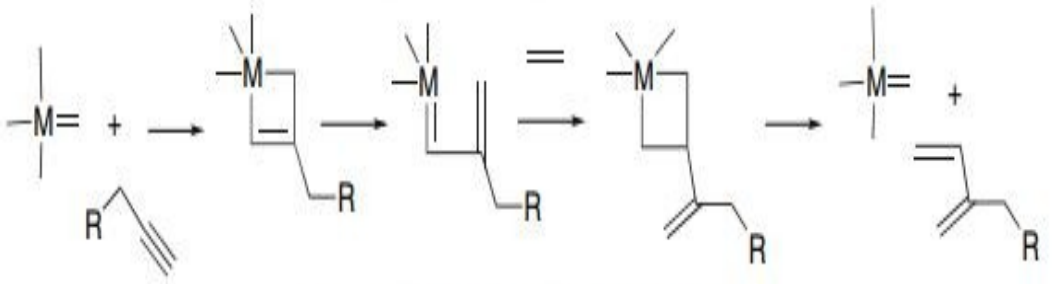
Olefin co-ordination to the metal center. Dissociation of ligand.Formation of metallocyclobutane ring followed by cyclo revision to form olefin.



Intramolecular metathesis:



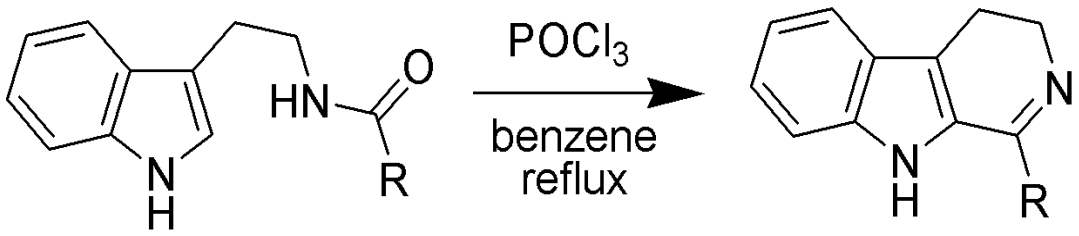
Intramolecular alkene-alkyne metathesis



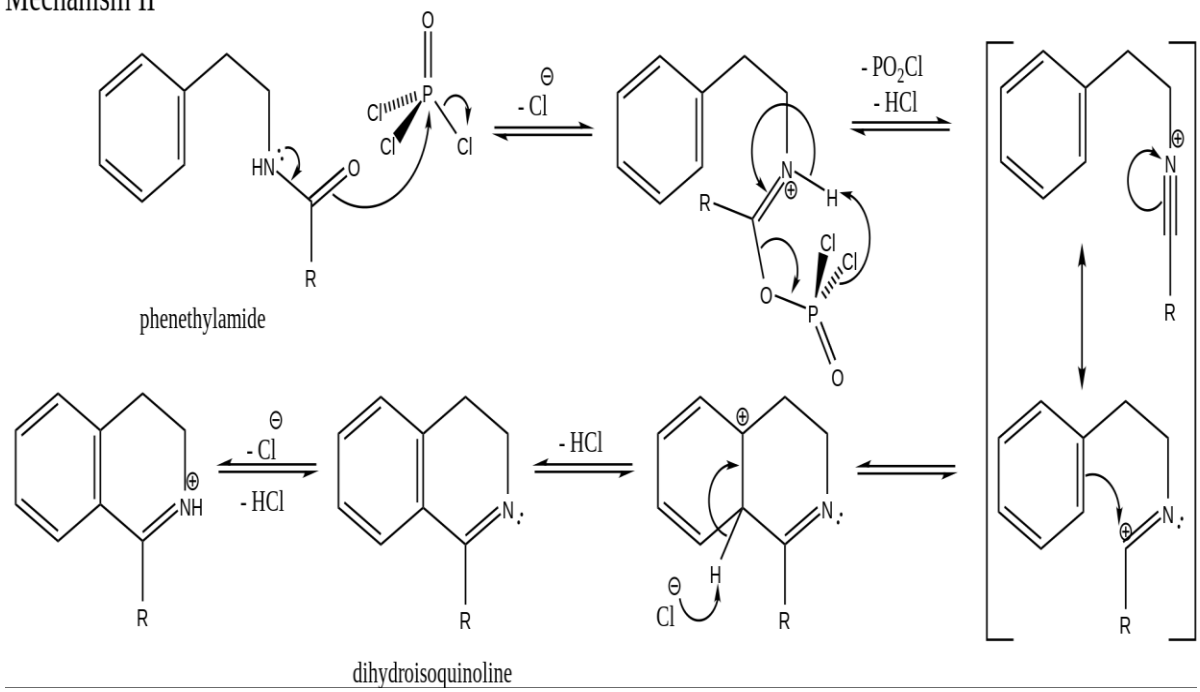
Intermolecular alkene-alkyne metathesis

3.16 Bischler–Napieralski Reaction

The **Bischler–Napieralski reaction** is an intra molecular electrophilic aromatic substitution reaction that allows for the cyclization of β-arylethylamides or β-arylethylcarbamates.. The reaction is most notably used in the synthesis of dihydroisoquinolines, which can be subsequently oxidized to isoquinolines.



Mechanism II



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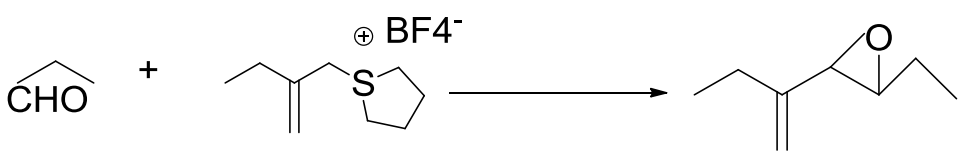
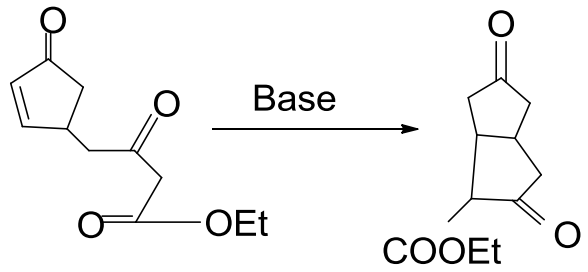
Test your Knowledge:

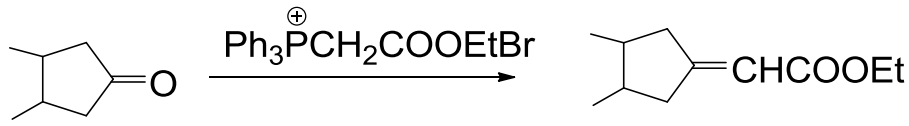
1. Corey-Chaykovsky reaction



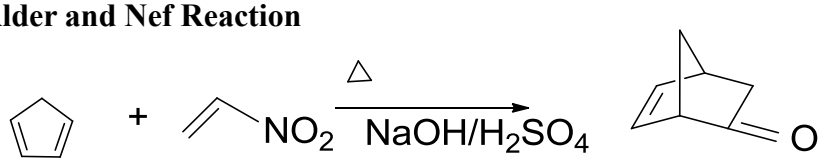
2. Intramolecular Michael reaction



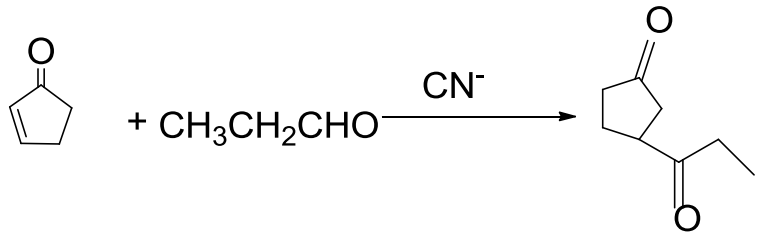
3. Wittig reaction



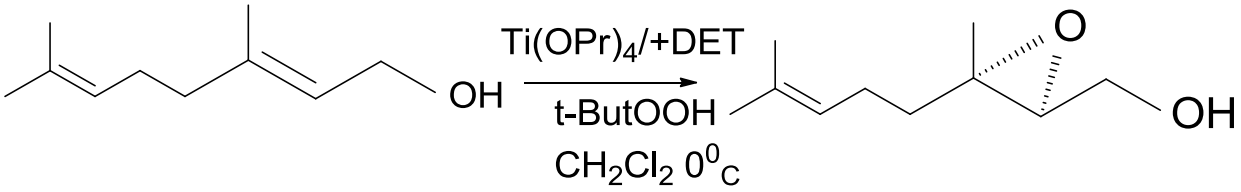
4. Diel Alder and Nef Reaction



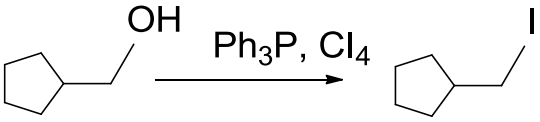
5. Stetter Reaction:



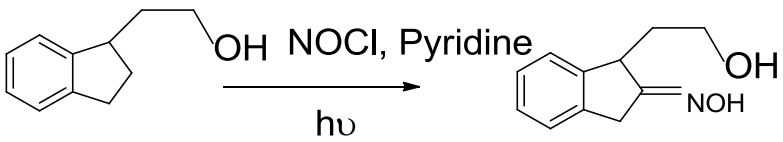
6. Sharpless epoxidation



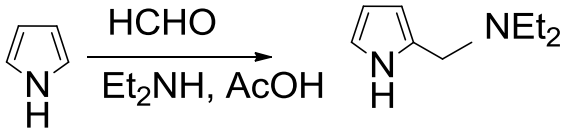
7. Appel Reaction:



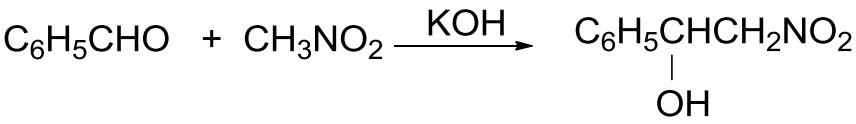
8. Barton Reaction



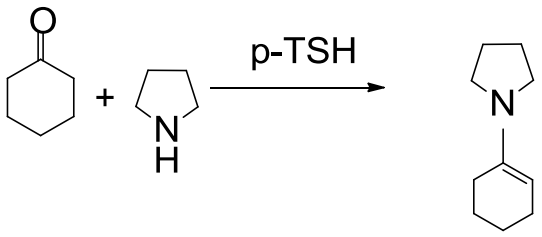
9.Mannich reaction



10.Henry reaction:



11. Strokenamine Reaction:



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SCHOOL OF SCIENCE & HUMANITIES

DEPARTMENT OF CHEMISTRY

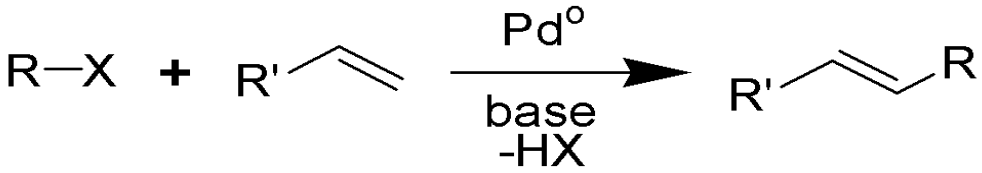
UNIT – IV METAL CATALYSED NAMED REACTIONS – SCYA5101

UNIT 4

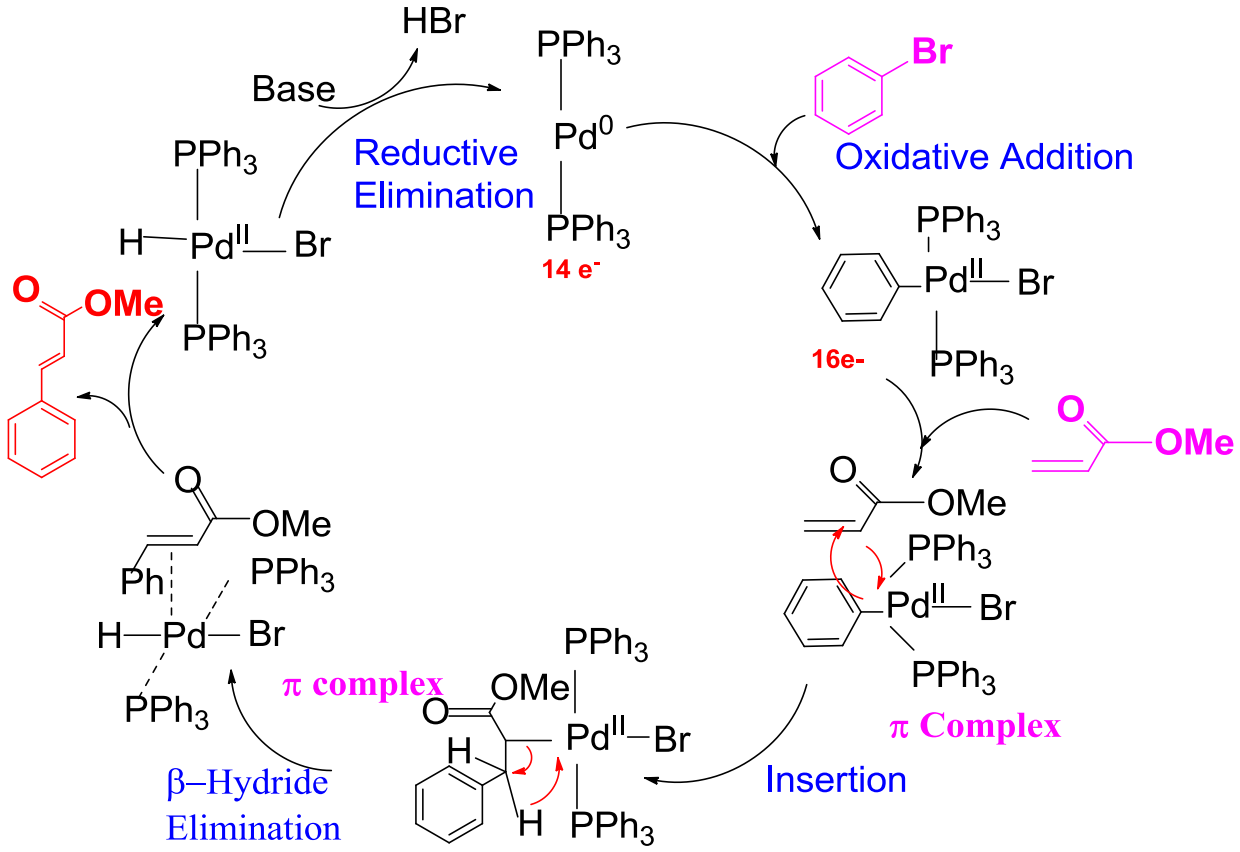
METAL CATALYSED NAMED REACTIONS

4.1 Heck reaction:

It is the chemical reaction of an unsaturated halide with an alkene in the presence of abase and a palladium catalyst or (Pd nanomaterial –based catalyst to form substituted alkene. This reaction was the first example of a carbon-carbon bond-forming reaction that followed a Pd(0)/Pd(II) catalytic cycle, the same catalytic cycle that is seen in other Pd(0)-catalyzed cross-coupling reactions. The Heck reaction is a way to substitute trans- alkenes



Mechanism



The mechanism involves organopalladium intermediates. The palladium(0) compound required in this cycle is generated in situ from a palladium(II) precursor.

Palladium(II) acetate is reduced by triphenylphosphine to bis(triphenylphosphine) palladium(0) and triphenylphosphine is oxidized to triphenylphosphine oxide.

Step 1: Oxidative addition :It increases both the oxidation state and co ordination number of the metal centre.The metal must have a vacant CN site. The reaction in which palladium inserts itself in the aryl to bromide bond.

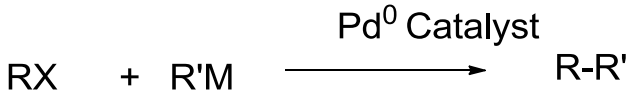
Step 2: Insertion: Palladium then forms a π complex with the alkene and in the alkene inserts itself in the palladium - carbon bond in a syn addition step. Then follows a torsional strain relieving rotation to the trans isomer (not shown) and

Step 3: Beta-hydride elimination: Reaction in which the alkyl group bonded to the metal centre is converted to metal-hydridebond and alkene. The alkyl group must have a hydrogen atom. In this step, with the formation of a new palladium - alkene π complex. This complex is destroyed in the next step.

Step 4: Reductive Elimination: It is an elementary step in organometallic chemistry in which the oxidation state of the metal center decreases while forming a new covalent bond between two ligands. The palladium(0) compound is regenerated by potassium carbonate in the final step.

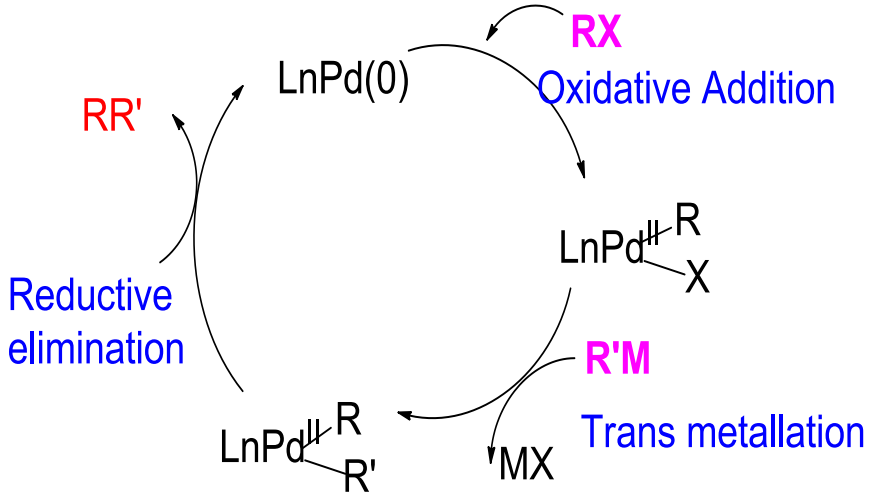
4.2 Metal Coupling Reactions

Palladium catalyst involving cross coupling reactions:



a)Suzuki coupling- Arylboronic acid + aryl halide
b)Stille coupling- Aryl tin+ aryl halide
c) Negishi coupling- Aryl zinc + aryl halide
d)Hiyama coupling- Aryl silyl + aryl halide
e) Kumada coupling-Aryl Li/Mg + aryl halide

Mechanism:



Oxidative addition:

In this oxidation step, the electron count of central metal is increased, the oxidation state is increased and its coordination number is also increased. The conditions for the metal to undergo oxidative addition are:

Metal must be electron rich to donate electrons.

Metal must be co-ordinationally unsaturated. (CN<6)

Metal must be either d^8 or d^{10} system.

Metals with d^0 system doesn't participate in the reaction.

Ligands with EWG (∏-acceptors) decrease the rate of oxidative addition by decreasing the electron density of the metal.

Reductive elimination: In this step, the electron count of central metal is decreased, the oxidation state is decreased and its coordination number is also decreased. The conditions for the metal to undergo reductive elimination are:

Metal must be electron deficient.

Ligands with EWG (∏-acceptors) increase the rate of elimination by decreasing the electron density of the metal.

Ligands undergoing elimination must be cis to each other.

The products formed in elimination must be stable.

Transmetallation:

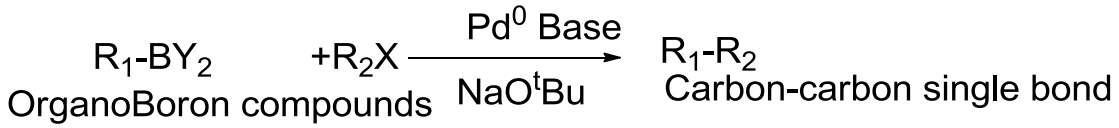
Occurs when an organo metallic reagent reacts with metal halide whose electronegativity is close to the metal.

There is no change in the formal change in the oxidation satte.

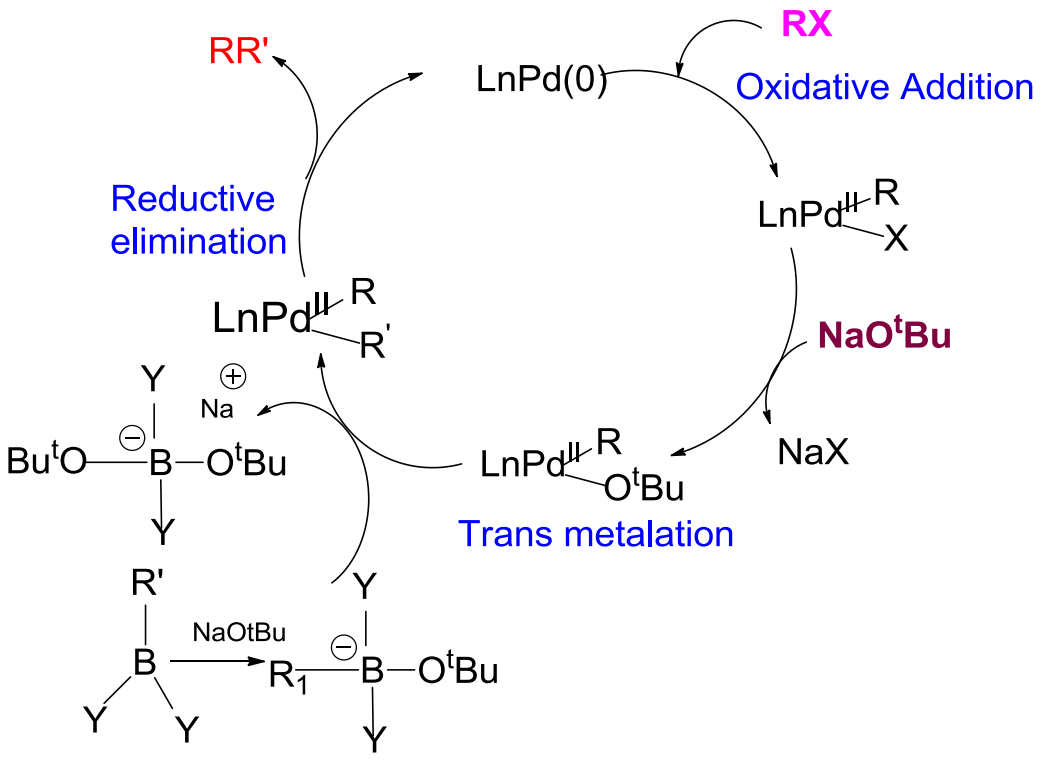
The groups exchanged are cis to each other.

4.3 Suzuki Reaction

It is an organic reaction, classified as a cross-coupling reaction, where the coupling partners are a boronic acid and an organohalide and the catalyst is a palladium(0) complex It is widely used to synthesize polyolefins, styrenes, and biphenyls. The general scheme for the Suzuki reaction is shown below, where a carbon-carbon single bond is formed by coupling an organoboron species (R_1-BY_2) with a halide (R_2-X) using a palladium catalyst and a base.



Mechanism:



The first step is the oxidative addition of palladium to the halide to form the organopalladium species Reaction (metathesis) with base gives intermediate , which via transmetalation with the boron-ate complex (produced by reaction of the boronic acid with base) forms the organopalladium species Reductive elimination of the desired product restores the original palladium catalyst which completes the catalytic cycle.

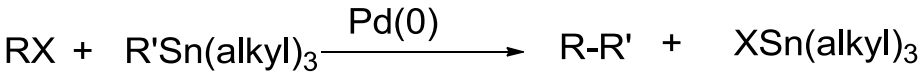
The oxidative addition is the rate determining step of the catalytic cycle. During this step, the palladium catalyst is oxidized from palladium(0) to palladium(II). The palladium catalyst is coupled with the alkyl halide to yield an organopalladium complex. The oxidative addition step breaks the carbon-halogen bond where the palladium is now bound to both the halogen and the R group.

Transmetalation is an organometallic reaction where ligands are transferred from one species to another. In the case of the Suzuki coupling the ligands are transferred from the organoboron species to the palladium(II) complex where the base that was added in the prior step is exchanged with the R_1 substituent on the organoboron species to give the new palladium(II) complex . The organoboron compounds do not undergo transmetalation in the absence of base and it is therefore widely believed that the role of the base is to activate the organoboron compound as well as facilitate the formation of R_2-Pd^{II}-O*t*Bu from R_2-Pd^{II}-X

The final step is the reductive elimination step where the palladium(II) complex eliminates the product and regenerates the palladium(0) catalyst. The order of elimination is Ar-Ar> Ar-R > R-R

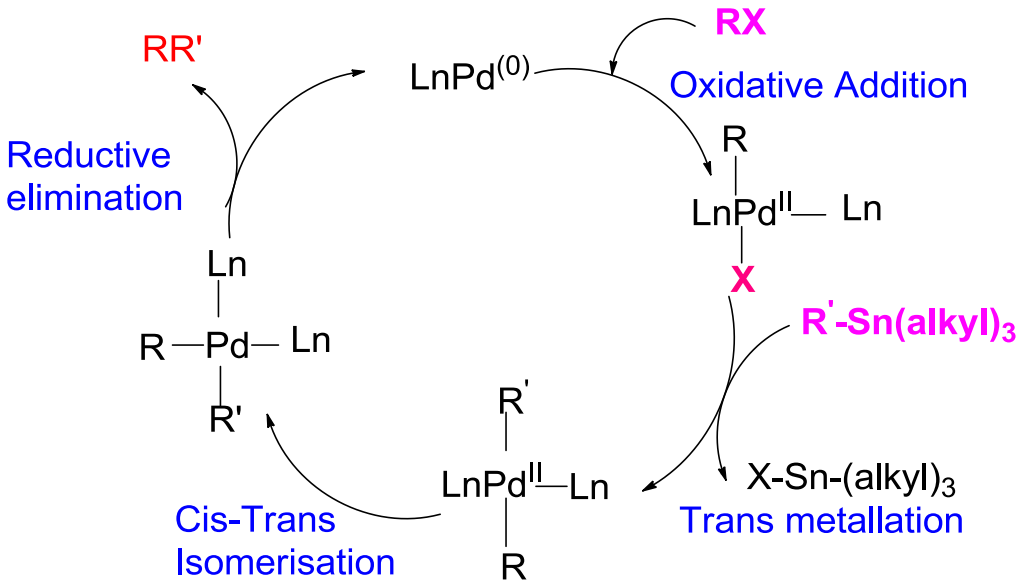
4.4 Stille Coupling

The **Stille reaction** is a chemical reaction widely used in organic synthesis. The reaction involves the coupling of two organic groups, one of which is carried as an organotin compound (also known as **organostannanes**).



Transmetallation is the rate determining step.

Mechanism:



R_1, R_2 - alkyl, alkenyl, aryl
X-Br, I, OTf, OTs
Ln-Phosphine
Alkyl- Me, Bu

Oxidative addition to the 14-electron Pd(0) complex gives a 16-electron Pd(II) species. the anionic ligands, such as OAc, accelerate this step by the formation of $[Pd(OAc)(PR_3)_n]^-$, making the palladium species more nucleophillic. In some cases, especially when an sp^3-hybridized organohalide is used, an S_N2 type mechanism tends to prevail.

Transmetallation: First, when the organostannane initially adds to the trans metal complex, the X group can coordinate to the tin, in addition to the palladium, producing a cyclic transition state. Breakdown of this adduct results in the loss of R_3Sn-X and a trivalent palladium complex with R^1 and R^2 present in a *cis* relationship.

Reductive Elimination:In order for R^1-R^2 to reductively eliminate, these groups must occupy mutually *cis* coordination sites. Any *trans*-adducts must therefore isomerize to the *cis* intermediate

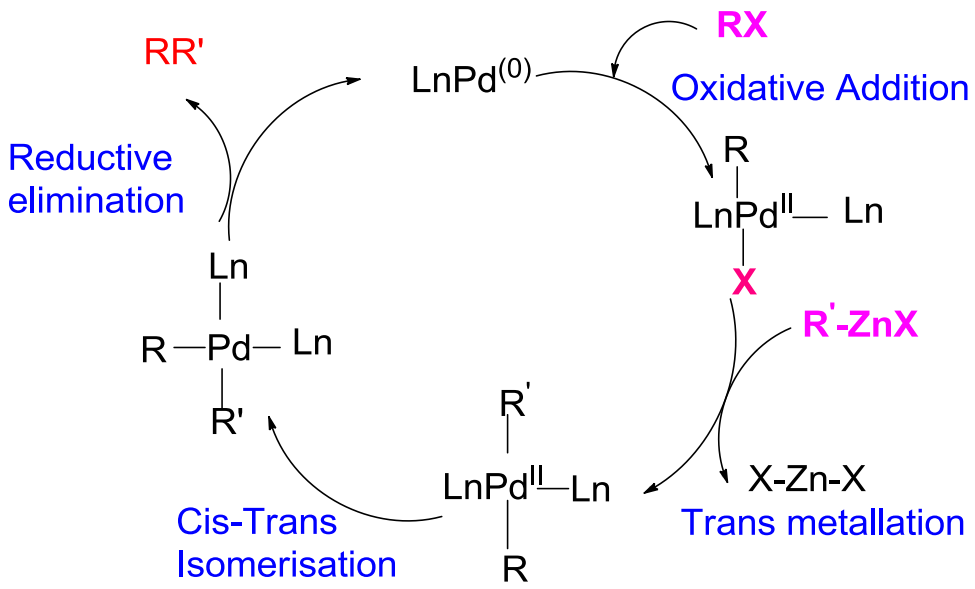
4.5 Negishi coupling

It is a metal catalyzed cross-coupling reaction. The reaction couples organic halides or triflates with organozinc compounds, forming carbon-carbon bonds (c-c) in the process. A palladium (0) species is generally utilized as the metal catalyst.

$$RX + R'ZnX \xrightarrow[Cl_2Pd(PPh_3)_2 \\ (i\text{-}Bu)_2AlH]{Ni(PPh_3)_4} R\text{-}R'$$

Rate determining step is the transmetallation. . Organozincs are moisture and air sensitive, so the Negishi coupling must be performed in an oxygen and water free environment, a fact that has hindered its use relative to other cross-coupling reactions that require less robust conditions (i.e. Suzuki reaction). However, organozincs are more reactive than both organostannanes and organoborates

Mechanism:

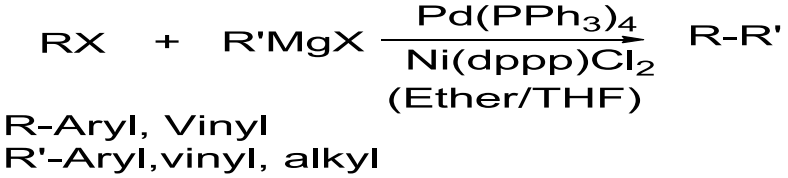


The reaction mechanism is proceeds via a standard Pd catalyzed cross-coupling pathway, starting with a Pd(0) species, which is oxidized to Pd(II) in an oxidative addition step involving the organohalide species. This step proceeds with aryl, vinyl, alkynyl, and acyl halides, acetates, or triflates, with substrates following standard oxidative addition relative rates (I>OTf>Br>>Cl).Next, the transmetalation step occurs where the organozinc reagent exchanges its organic substituent with the halide in the Pd(II) complex, generating the trans- Pd(II) complex and a zinc halide salt. The organozinc substrate can be

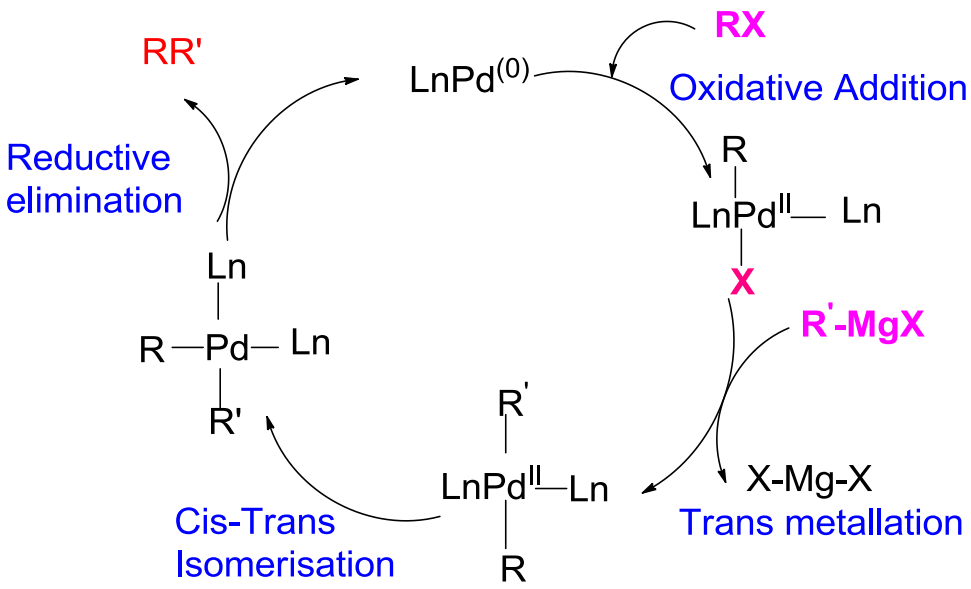
aryl, vinyl, allyl, benzyl, homoallyl, or homopropargyl. Transmetalation is usually rate limiting step. The last step in the catalytic pathway of the Negishi coupling is reductive elimination, which is thought to proceed via a three coordinate transition state, yielding the coupled organic product and regenerating the Pd(0) catalyst.

4.6 Kumada Coupling

It is useful for generating carbon–carbon bonds by the reaction of a Grignard reagent and an organic halide. The procedure uses transition metal catalysts, typically nickel or palladium, to couple a combination of two alkyl, aryl or vinyl groups Kumada Coupling is the method of choice for the low-cost synthesis of unsymmetrical biaryls. The advantage of this reaction is the direct coupling of Grignard reagents, which avoids additional reaction steps such as the conversion of metal complexes.

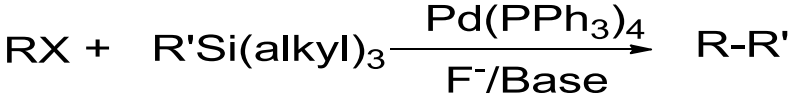


Mechanism:



4.7 Hiyama Coupling

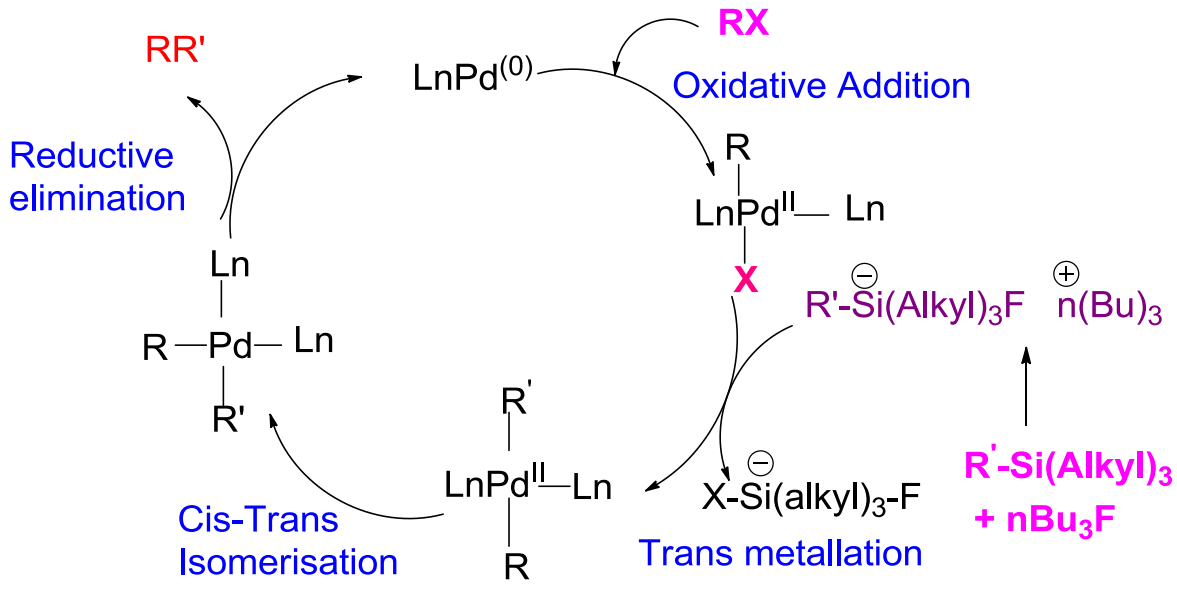
It is a palladium-catalyzed cross-coupling reaction of organosilanes with organic halides used in organic chemistry to form carbon–carbon bonds (C-C bonds).



R-Aryl, Vinyl
R'-Aryl,vinyl, alkyl
B- alkoxy, Methyl

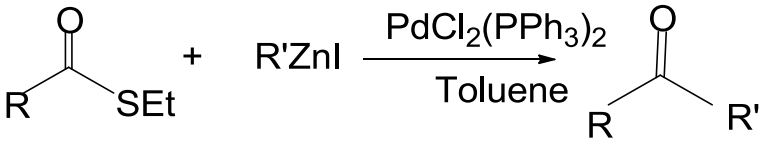
A) Oxidative addition step, in which the organic halide adds to the palladium oxidizing the metal from palladium(0) to palladium(II); a
B) Transmetalation step, in which the C-Si bond is broken and the second carbon fragment is bound to the palladium center; and finally
C) Reductive elimination step, in which the C-C bond is formed and the palladium returns to its zero-valent state to start the cycle. over again

Mechanism:



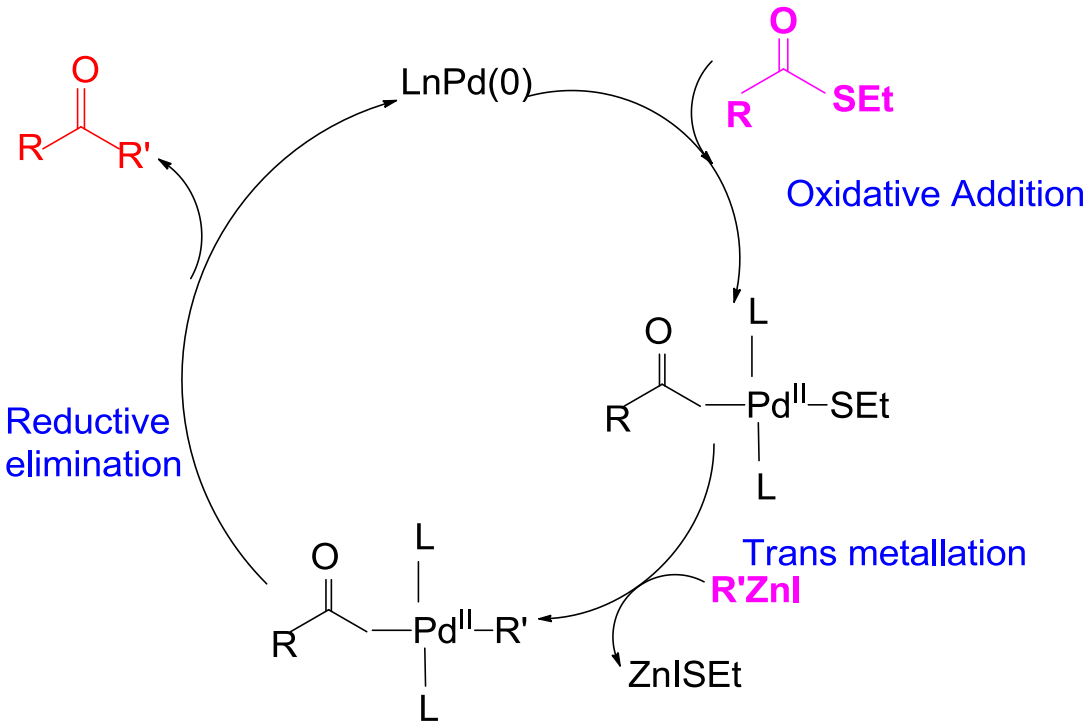
4.8 Fukuyama coupling

It is a coupling reaction taking place between a thioester and an organozinc halide in the presence of a palladium catalyst. The reaction product is a ketone.



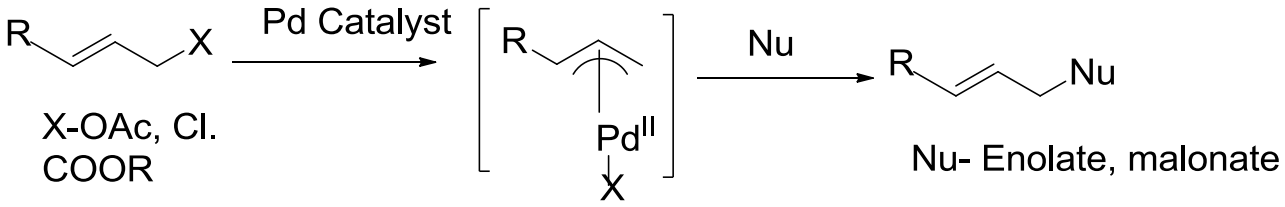
Tolerates wide functional groups to yield the product.

Mechanism: Oxidative addition of the thioester is followed by transmetalation from the zinc compound. Reductive elimination leads to the coupled product.



4.9 Trost-Tsuji coupling

It is a palladium-catalysed substitution reaction involving a substrate that contains a leaving group in an allylic position. The palladium catalyst first coordinates with the allyl group and then undergoes oxidative addition, forming the π-allyl complex. This allyl complex can then be attacked by a nucleophile, resulting in the substituted product..

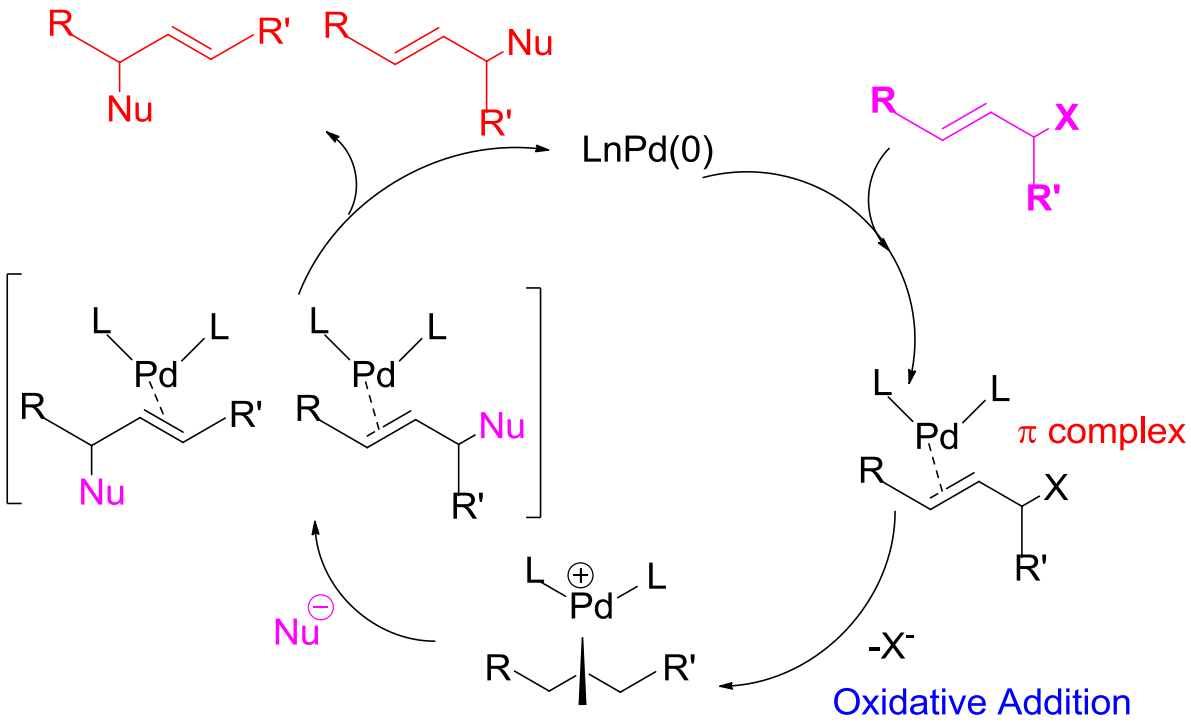


Mechanism:

Trost reaction proceeds with the addition of alkene in which the palladium coordinates to the alkene, forming a π-allyl-Pd0 Π complex. The next step is oxidative addition in which the leaving group is expelled with inversion of configuration and a π-

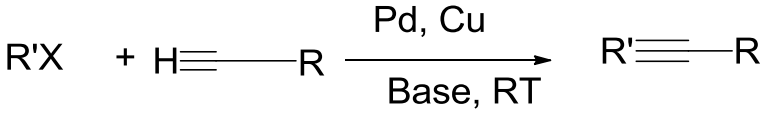
allyl-PdII is created (also called ionization). The nucleophile then adds to the allyl group regenerating the π-allyl-Pd0 complex. At the completion of the reaction, the palladium detaches from the alkene and can start again in the catalytic cycle.

Stabilized or "soft" nucleophiles invert the stereochemistry of the π-allyl complex. This inversion in conjunction with the inversion in stereochemistry associated with the oxidative addition of palladium yields a net retention of stereochemistry. Unstabilized or "hard" nucleophiles, on the other hand, retain the stereochemistry of the π-allyl complex, resulting in a net inversion of stereochemistry.



4.10 Songosharia Reaction

It is a cross-coupling reaction used in organic synthesis to form carbon–carbon bonds. It employs a palladium catalyst as well as copper co-catalyst to form a carbon–carbon bond between a terminal alkyne and an aryl or vinyl halide.



R'-Aryl

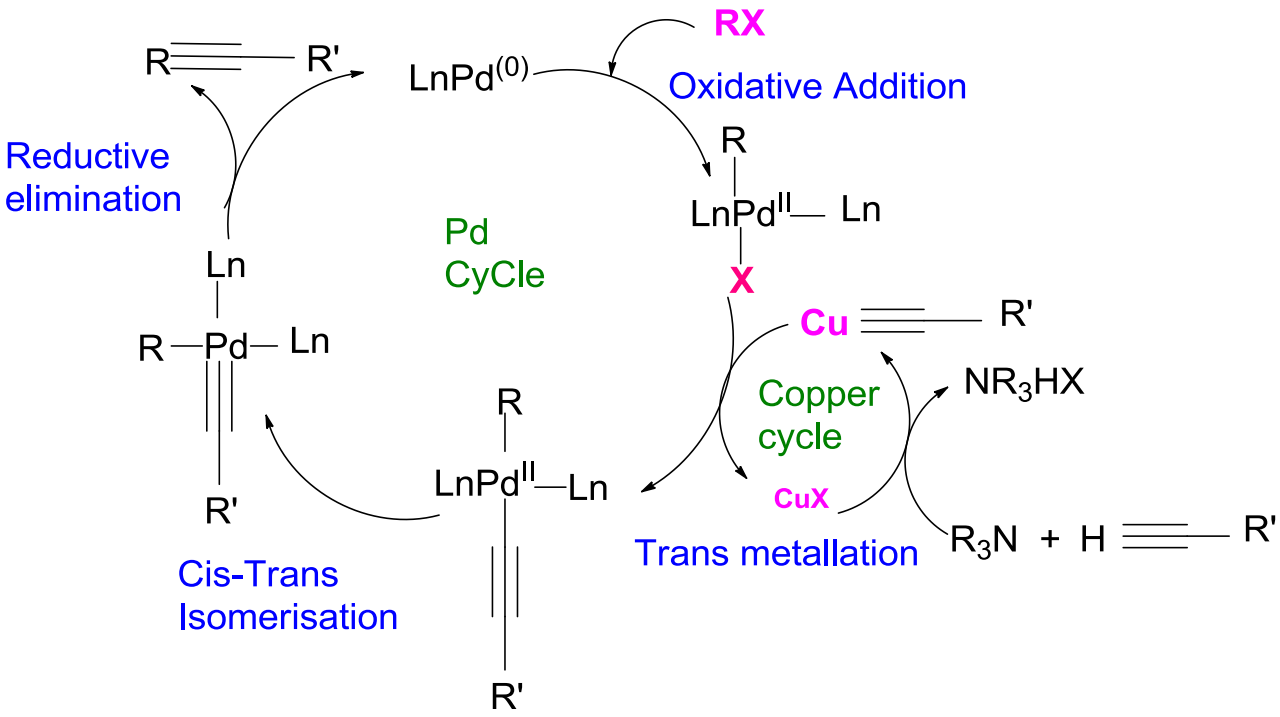
R: Aryl orvinyl

X: I, Br,Cl or OTf

Mechansim:

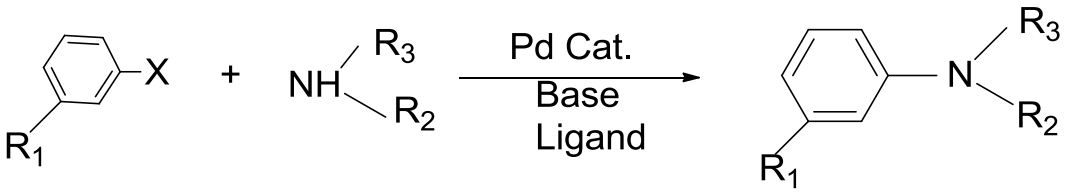
The active Pd^0 catalyst is involved in the oxidative addition step with the aryl or vinyl halide substrate to produce Pd^{II} species .The structure depends on the employed ligands. This step is believed to be the rate-limiting step of the reaction.
The Pd complex reacts with copper acetylide, in a transmetallation step, yielding complex and regenerating the copper catalyst.

For the facile reductive elimination to occur, the substrate motifs need to be in close vicinity, i.e. cis-orientation, so there can be trans-cis isomerisation involved. In reductive elimination the product s expelled from the complex and the active Pd catalytic species is regenerated.



4.11 Buckwald-Hartwig reaction

It is a chemical reaction used in organic chemistry for the synthesis of carbon–nitrogen bonds via the palladium-catalyzed coupling reactions of amines with aryl halides.
The reaction's synthetic utility stems primarily from the shortcomings of typical methods (nucleophilic substitution, reductive amination, etc.) for the synthesis of aromatic C–N bonds, with most methods suffering from limited substrate scope and functional group tolerance.



X-Cl,Br,I,OTf

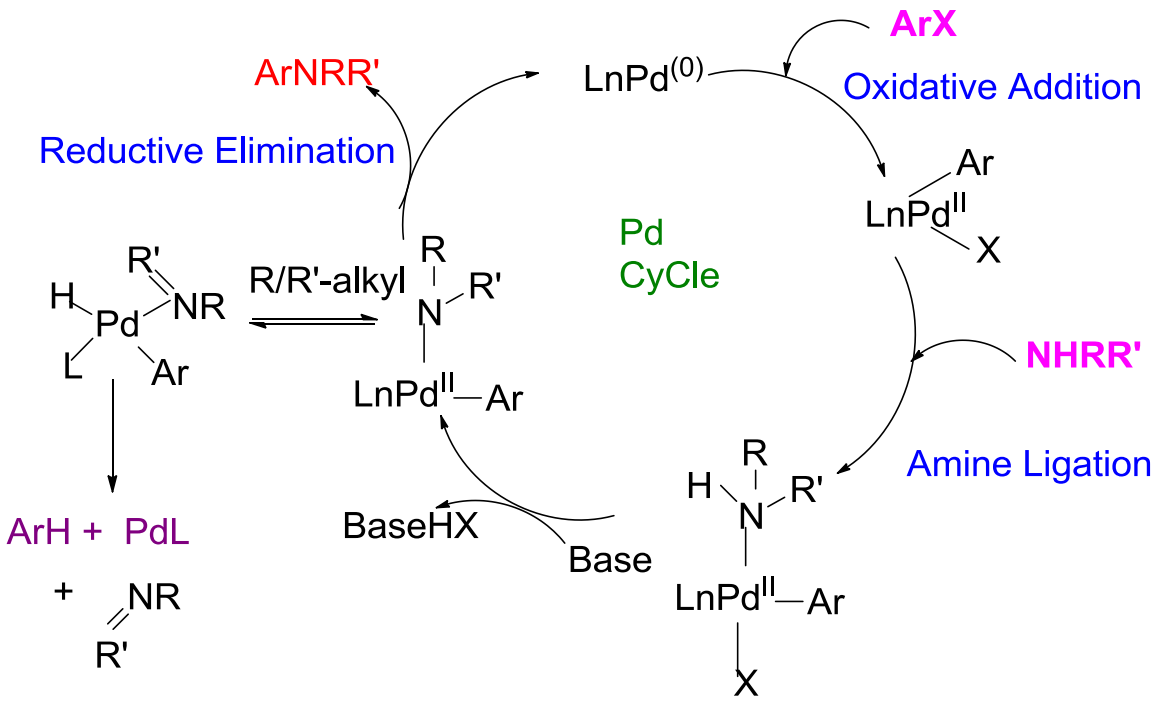
R_2- Alkyl,aryl,H

R_3-alkyl, aryl

Mechanism:

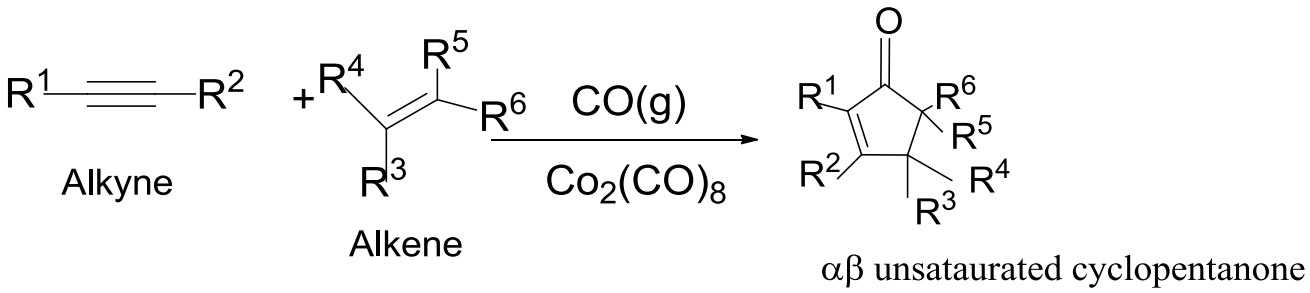
The reaction mechanism include oxidative addition of the aryl halide to a Pd(0) species, addition of the amine to the oxidative addition complex, deprotonation followed by reductive elimination. An unproductive side reaction can compete with reductive elimination wherein the amide undergoes beta hydride elimination to yield the hydrodehalogenated arene and an imine product.

For chelating ligands, the monophosphine palladium species is not formed; oxidative addition, amide formation and reductive elimination occur from L_2Pd complexes. The Hartwig group found that "reductive elimination can occur from either a four-coordinate bisphosphine or three-coordinate monophosphine arylpalladium amido complex. Eliminations from the three-coordinate compounds are faster. Second, β-hydrogen elimination occurs from a three-coordinate intermediate. Therefore, β-hydrogen elimination occurs slowly from arylpalladium complexes containing chelating phosphines while reductive elimination can still occur from these four-coordinate species



4.12 Pauson-khand Reaction

The Pauson-Khand reaction is an organic reaction used to convert an alkyne and alkene to a substituted cyclopentenone under an atmosphere of carbon monoxide and a dicobalt complex catalyst.



αβ unsataurated cyclopentanone

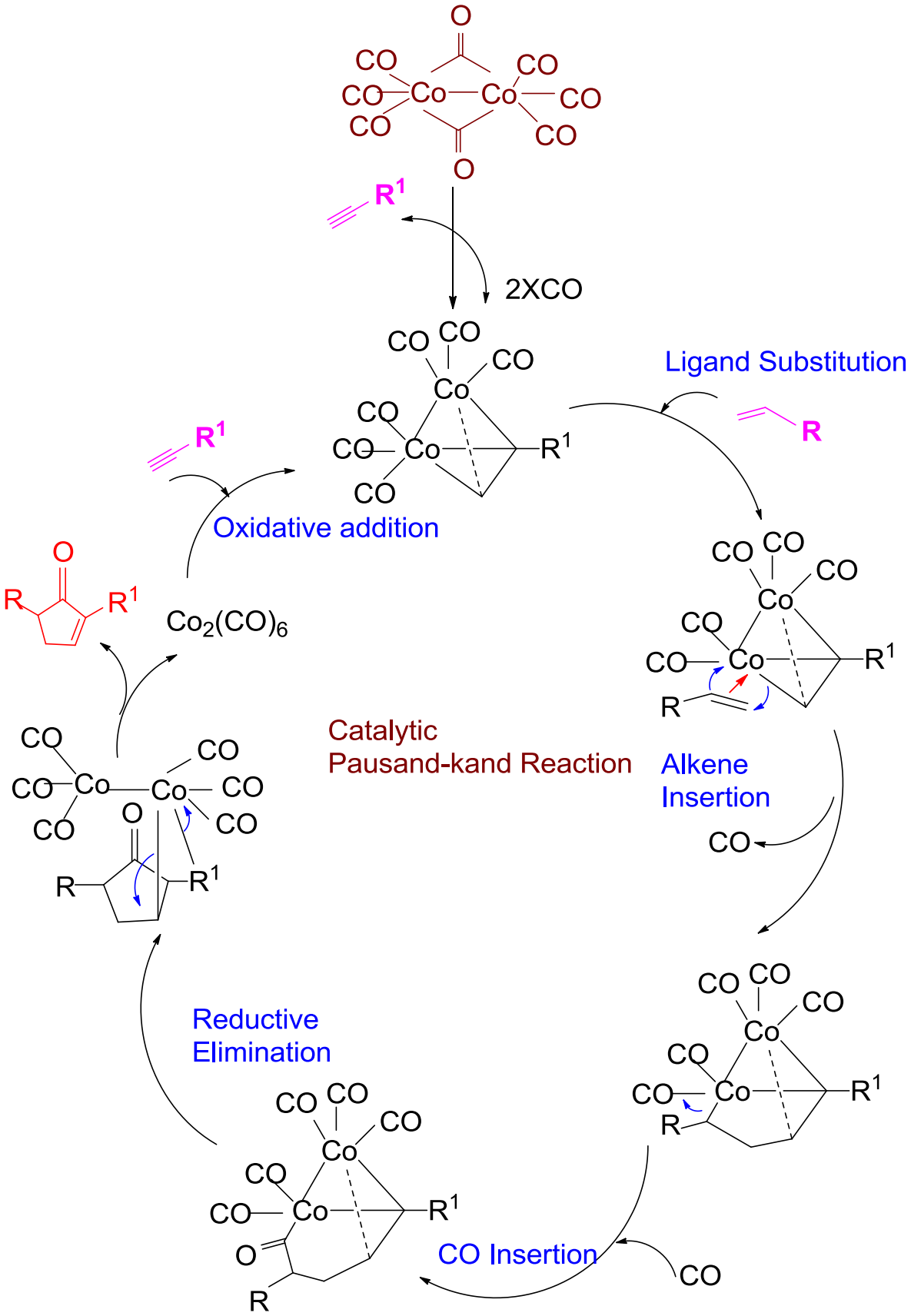
Mechanism

This 2+2+1 cycloaddition reaction begins with the addition of the alkyne to the metal complex followed by ligand substitution of the alkene to expel a CO molecule. Alkene insertion follows and a subsequent CO insertion results in the formation of a carbonyl group. A series of reductive eliminations then yield the final cyclopentenone product and regenerates the cobalt catalyst.

Two steps:

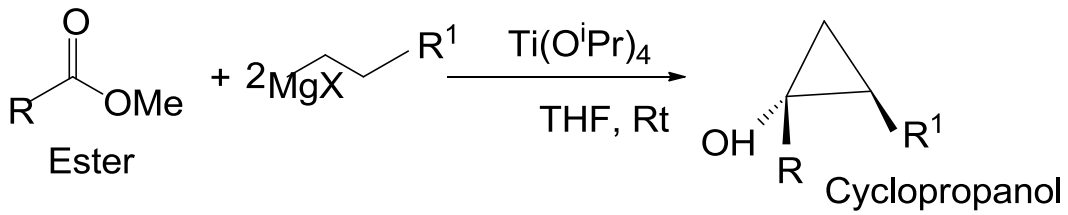
The insertion of the alkene is followed by insertion of carbon monoxide and reductive elimination of one Co unit

Dissociation of the second Co unit gives the resulting cyclopentenone product.


2XCO
Ligand Substitution
Oxidative addition
Catalytic
Pausand-kand Reaction
Alkene
Insertion
Reductive
Elimination
CO Insertion
Co2(CO)6

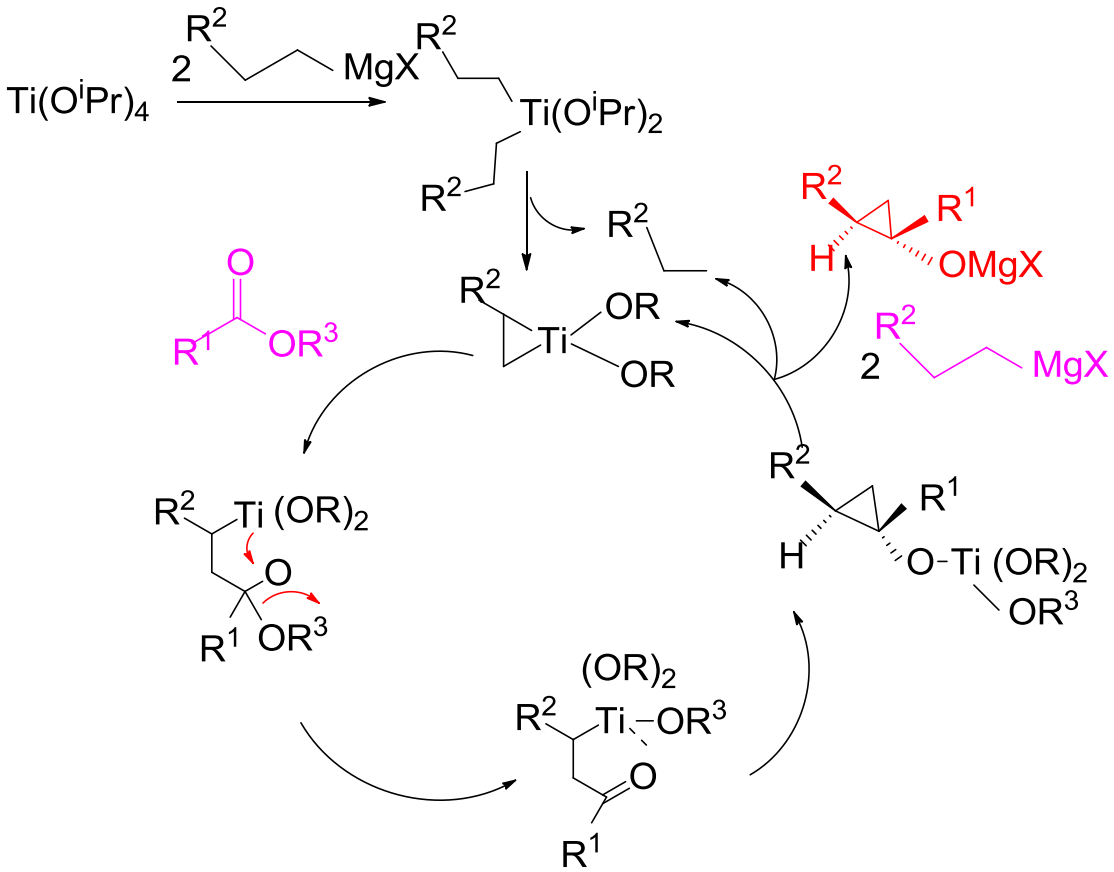
4.13 Kulinkovich Cyclopropanation Reaction

The Kulinkovich Reaction allows the preparation of cyclopropanol derivatives by the reaction of Grignard reagents (ethyl or higher) with esters in the presence of titanium(IV) isopropoxide as catalyst.



Mechanism:

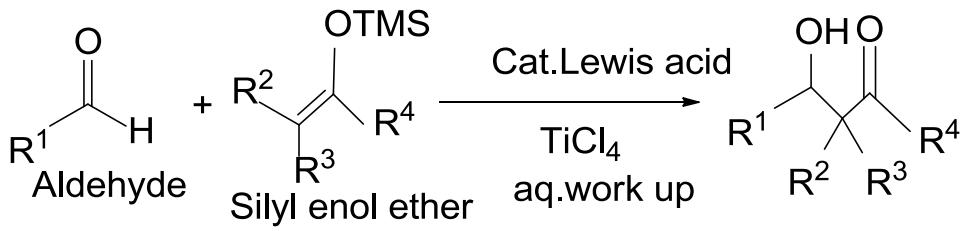
The generally accepted reaction mechanism initially utilizes two successive stages of transmetallation of the committed Grignard reagent, leading to an intermediate dialkyldiisopropyl oxytitanium complex. This complex undergoes a dismutation to give an alkane molecule and a titanacyclopropane bond leads to an oxatitana cyclopentane being rearranged to ketone . Lastly, the insertion of the carbonyl group in the residual carbon-titanium connection forms a cyclopropane ring. tetraalkyloxytitanium compound able to play a part similar to that of the starting tetraisopropyloxytitanate, which closes the catalytic cycle. At the end of the reaction, the product is mainly in the shape of the magnesium alcoholate , giving the cyclopropanol after hydrolysis by the reaction medium.



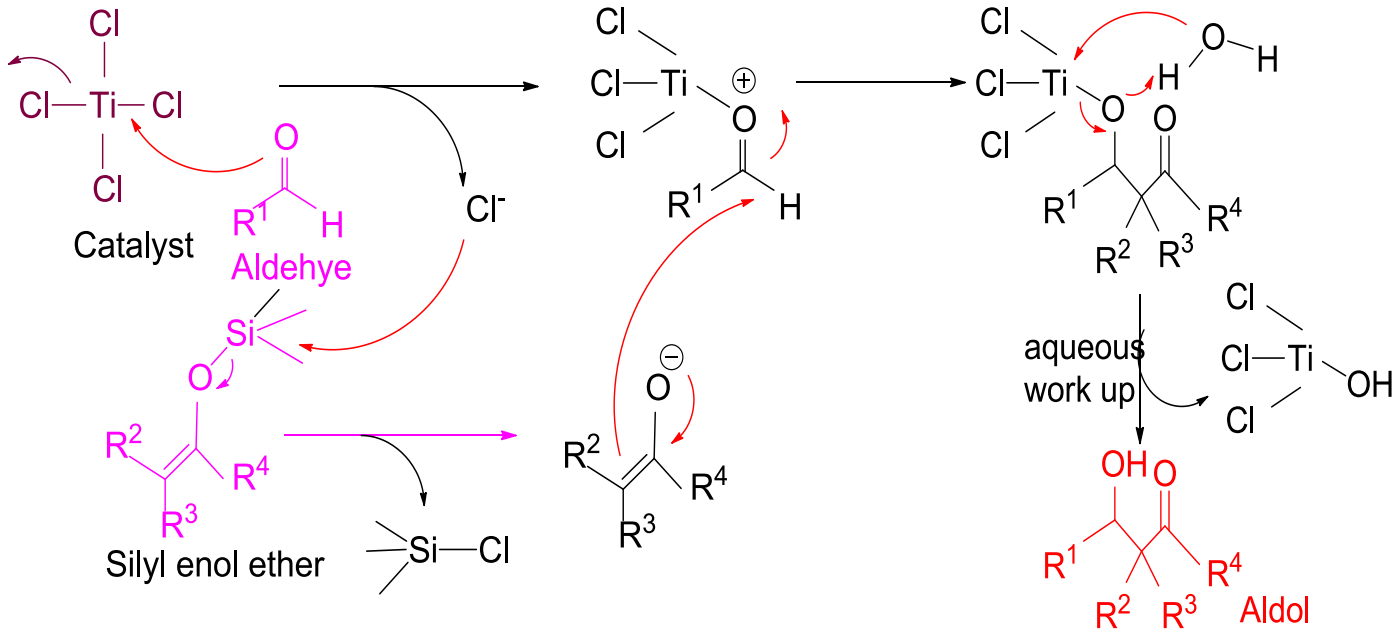
4.14 Mukiyama reaction

It is an organic reaction used to convert an aldehyde and a silyl enol ether to a 1,3 ketol using a Lewis acid catalyst (such as $TiCl_4$), followed by aqueous work-up.

Mechanism begins by coordination of the aldehyde's oxygen to Titanium, which activate the carbonyl for attack while also releasing a chloride ion. The chloride attacks the silicon of the silyl enol ether to form TMSCl and an enolate. The enolate then attacks the activated carbonyl and subsequent aqueous work-up provides the final 1,3 ketol product.

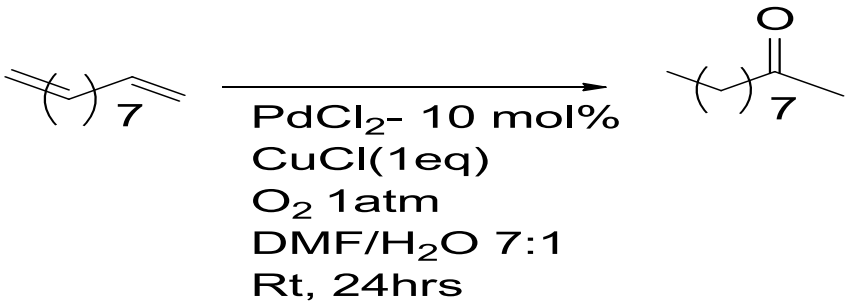


Mechanism

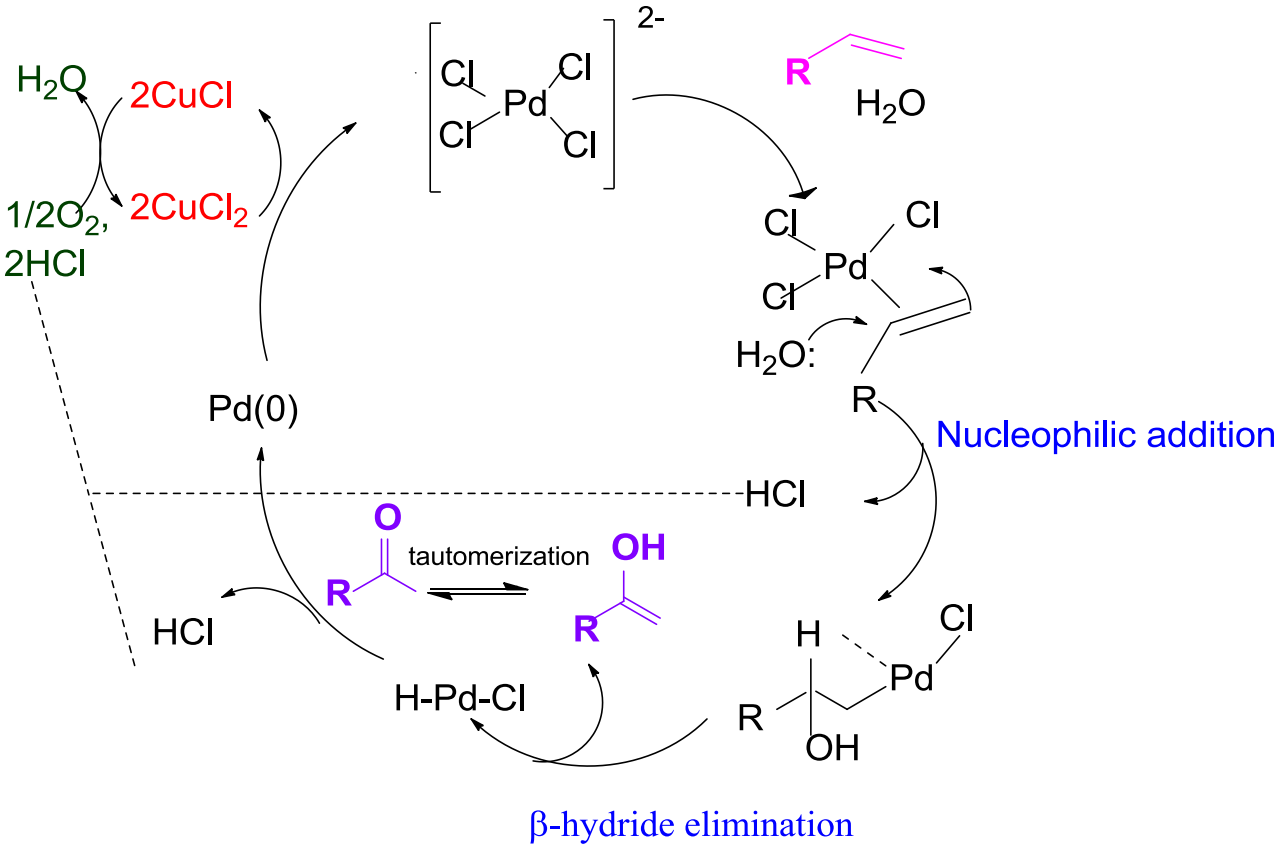


4.15 Wacker oxidation

The **Wacker oxidation** refers generally to the transformation of a terminal or 1,2-disubstituted alkene to a ketone through the action of catalytic palladium(II), water, and a co-oxidant. Variants of the reaction yield aldehydes, allylic/vinylic ethers, and allylic/vinylic amines. Because of the ease with which terminal alkenes may be prepared and the versatility of the methyl ketone group installed by the reaction, the Wacker oxidation has been employed extensively in organic synthesis.

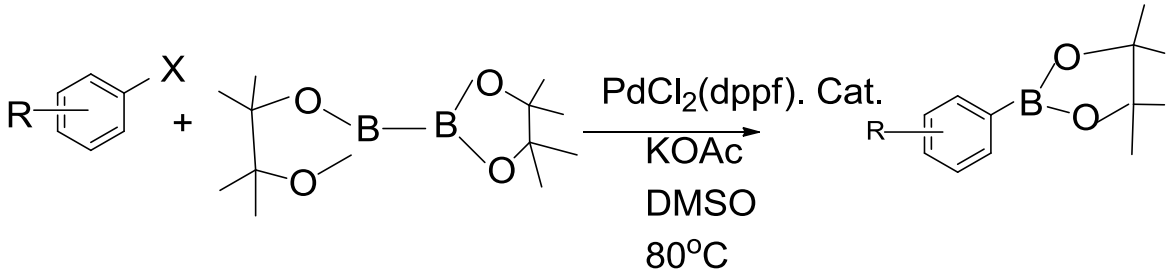


Mechanism

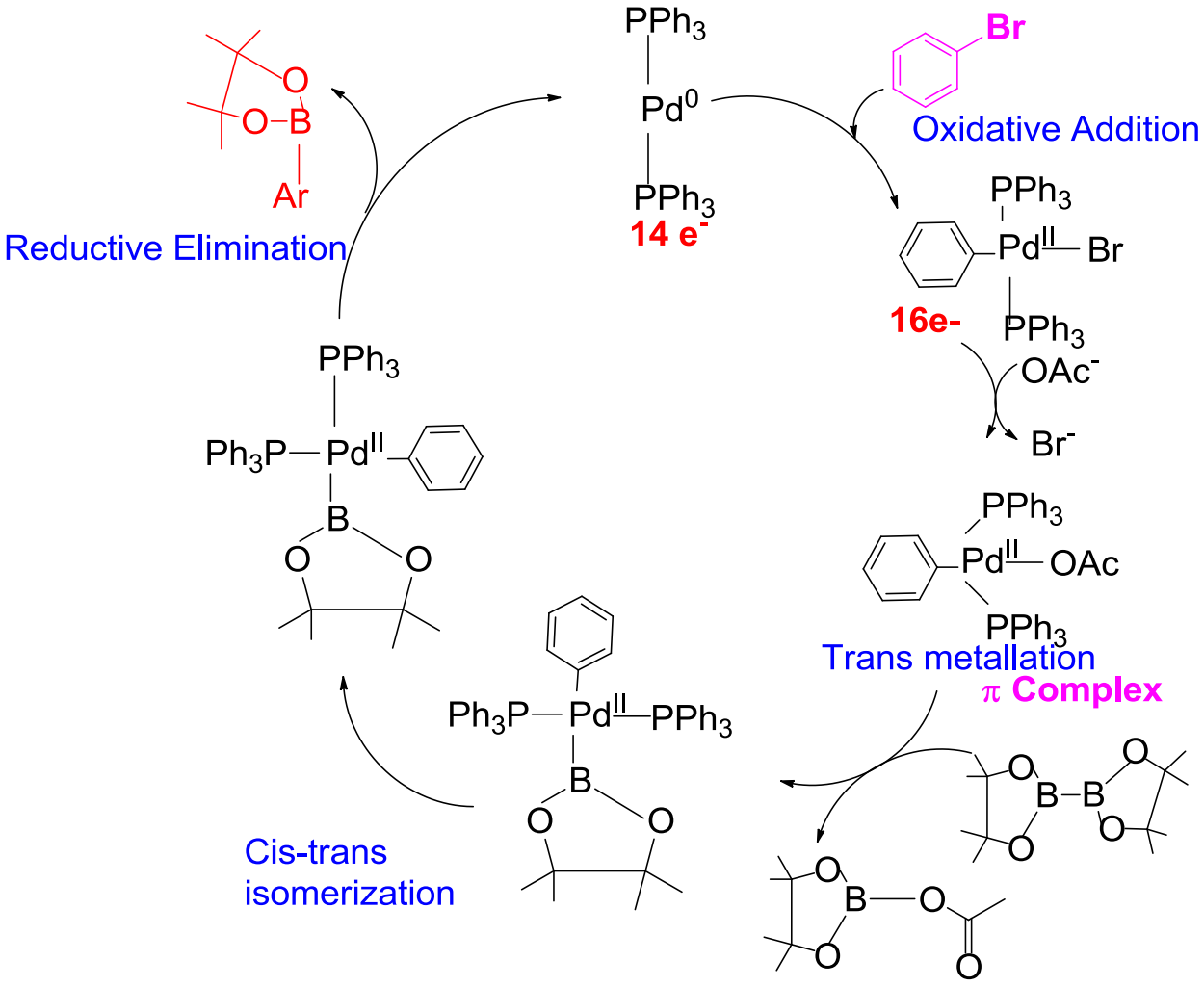


4.16 Miyaura borylation

The Miyaura borylation reaction enables the synthesis of boronates by cross-coupling of bis(pinacolato)diboron (B_2pin_2) with aryl halides and vinyl halides.



Mechanism:



Oxidative addition:

In this oxidation step, the electron count of central metal is increased, the oxidation state is increased and its coordination number is also increased.

Transmetallation:

Occurs when an organo boron reagent reacts with metal halide whose electronegativity is close to the metal. The groups exchanged are cis to each other.

Reductive elimination: In this step, the electron count of central metal is decreased, the oxidation state is decreased and its coordination number is also decreased. Ligands (organo boron) undergoing elimination must be cis to each other. The products formed in elimination must be stable.

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SCHOOL OF SCIENCE AND HUMANITIES

DEPARTMENT OF CHEMISTRY

UNIT –V - MOLECULAR REARRANGEMENTS – SCYA5101

UNIT-5

MOLECULAR REARRANGEMENTS

5.0 INTRODUCTION

Rearrangement: Reactions in which the carbon skeleton of the molecule is rearranged to give a structural isomer of the original molecule.

Sequence of steps involving substitution, elimination and addition reactions.

Atom or group which is migrates- Migrating Group.

Atom which is initially attached – Migration origin

Atom or group which it finally joins- Migration terminus.

Intermolecular Rearrangement:

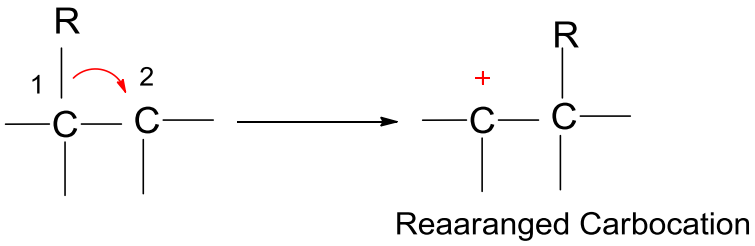
When the migratory group is completely detached from the molecule and go the migration terminus of the other molecule.

Intramolecular rearrangement:

When the migratory group remains attached to the molecule in some or the other way throughout the process of rearrangement.

1. Anionotropic Migration:

If the migratory atoms or groups may occur with the pair of electrons.

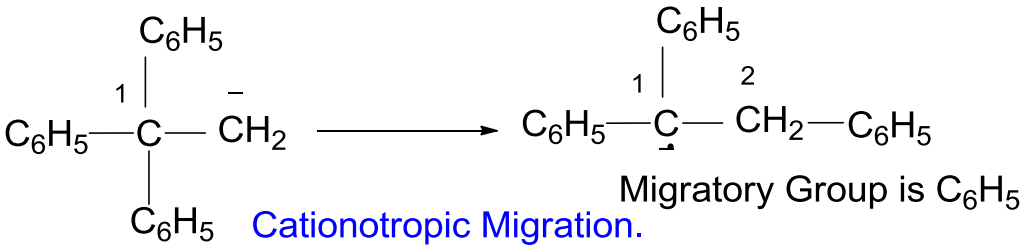


Reaaranged Carbocation

(C1= Migration Origin, C2- Migration Terminus)

2. Cationotropic Migration:

If the migratory atoms or groups may occur without this pair of electrons.

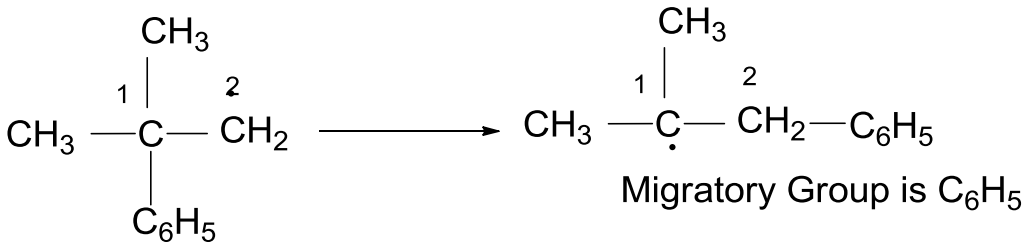


Migratory Group is C_6H_5

Cationotropic Migration.

3. Free Radical Migration:

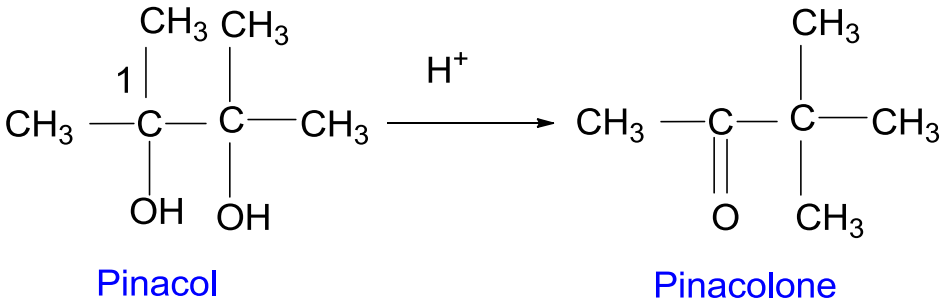
If the migratory group moves with one unpaired electron.



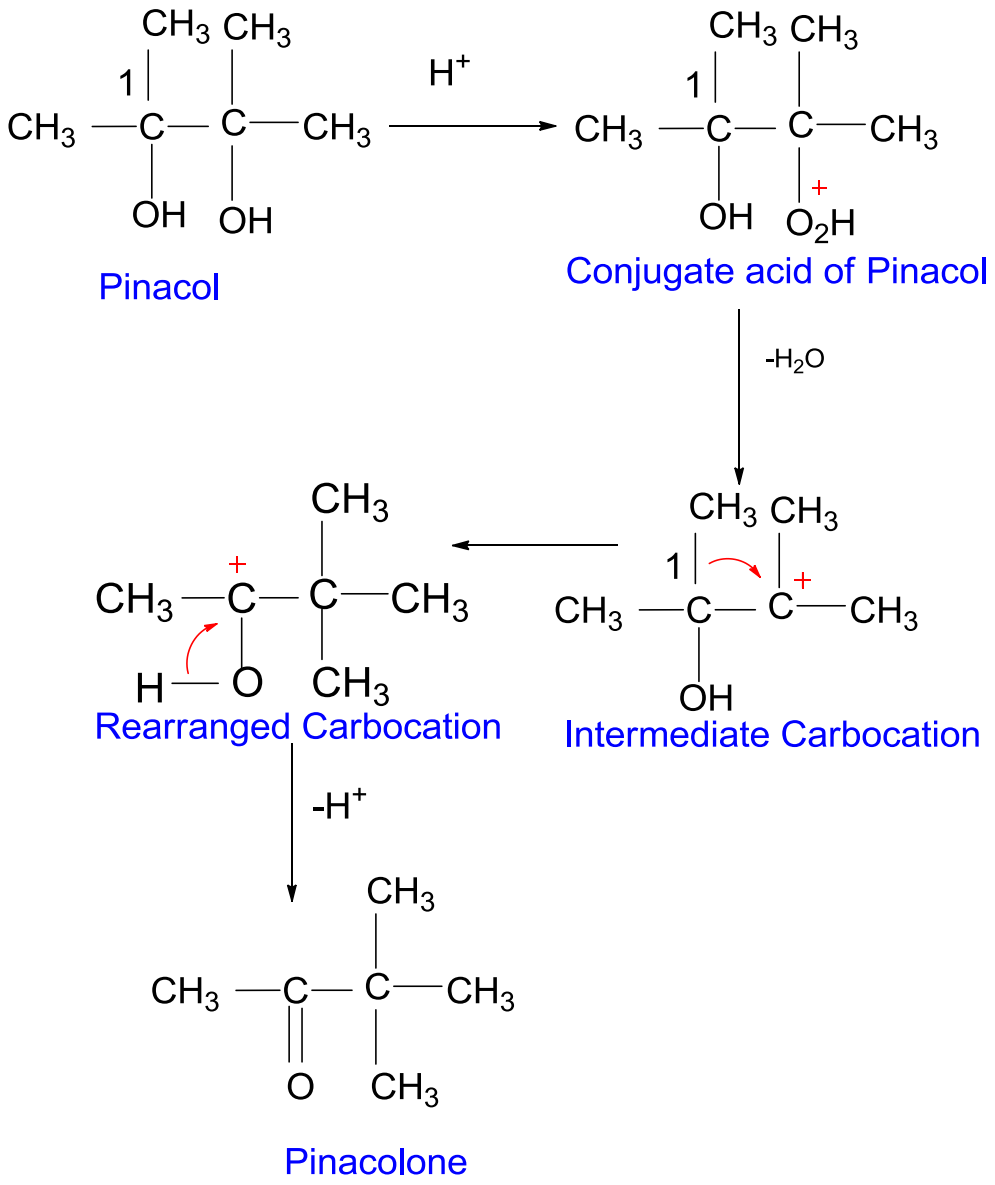
5.1 C-C Migration-

5.1.1Pinacol-Pinacolone Rearrangement

The acid-catalyzed elimination of water from pinacol gives *t*-butyl methyl ketone.

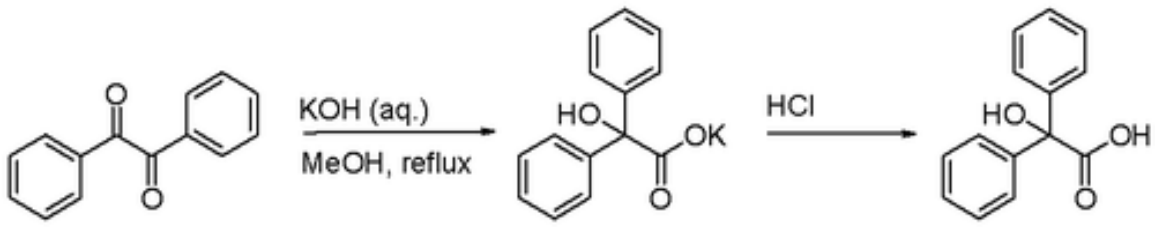


Mechanism: This reaction occurs with a variety of fully substituted 1,2-diols, and can be understood to involve the formation of a carbenium ion intermediate that subsequently undergoes a rearrangement. The first generated intermediate, an α-hydroxycarbenium ion, rearranges through a 1,2-alkyl shift to produce the carbonyl compound. If two of the substituents form a ring, the Pinacol Rearrangement can constitute a ring-expansion or ring-contraction reaction



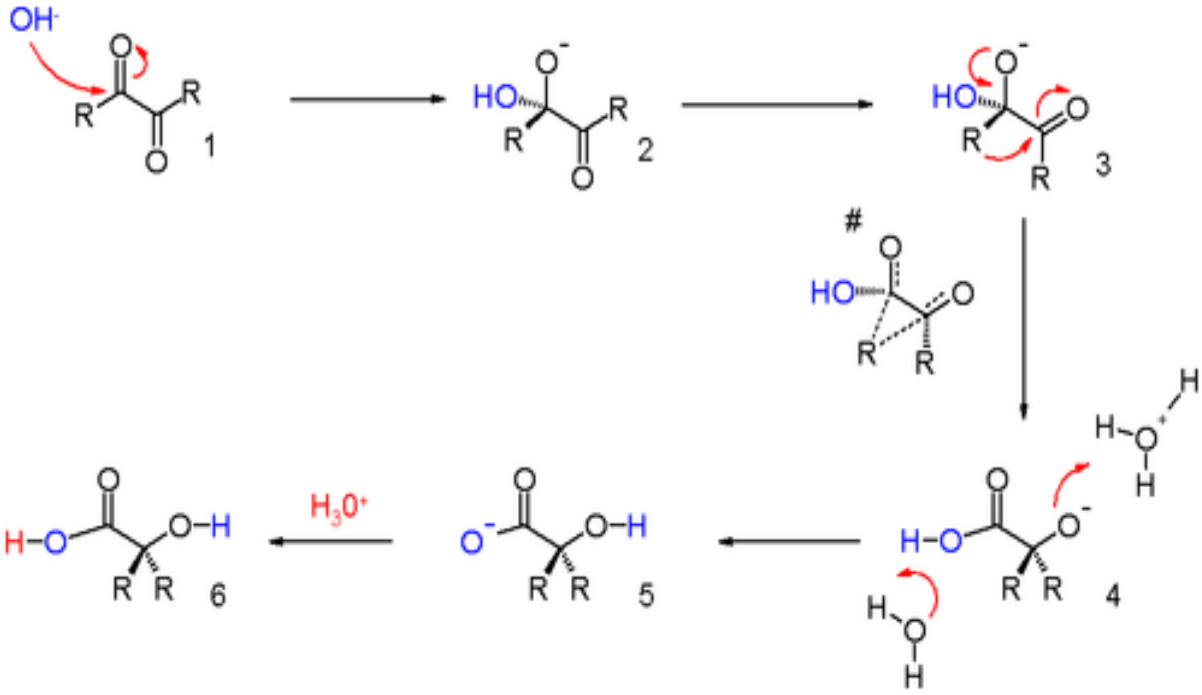
5.1.2 Benzil-Benzilic Rearrangement

The **benzilic acid rearrangement** is the rearrangement reaction of benzil with potassium hydroxide to benzilic acid.



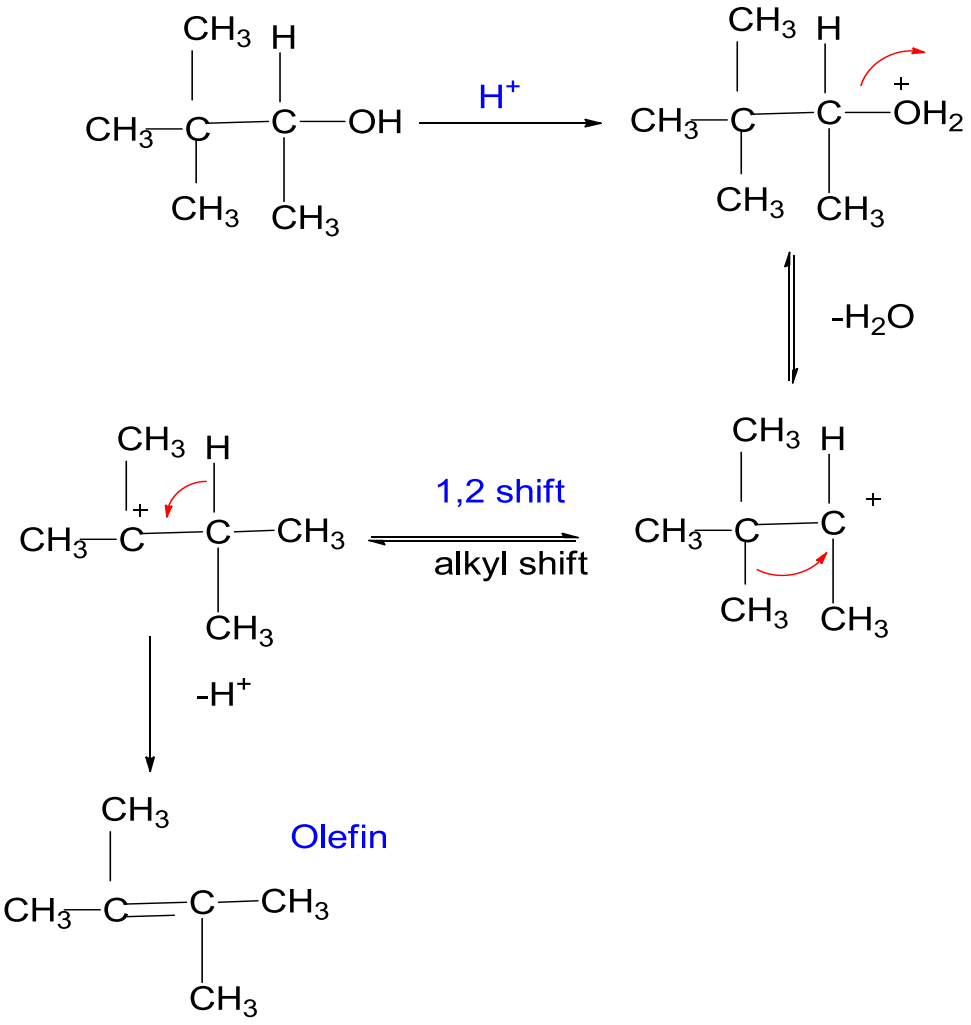
Mechanism:

A hydroxide anion attacks one of the ketone groups in **1** in a nucleophilic addition to the hydroxyl anion **2**. The next step requires a bond rotation to conformer **3** which places the migrating group R in position for attack on the second carbonyl group in a concerted step with reversion of the hydroxyl group back to the carbonyl group. This sequence resembles a nucleophilic acyl substitution.



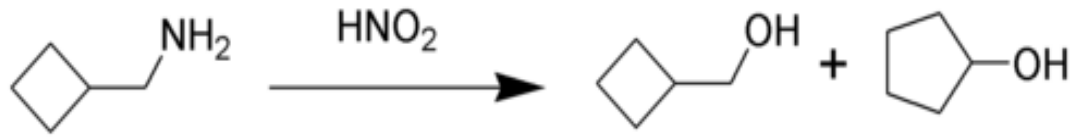
5.1.3 Wagner-Meerwein rearrangement

The Wagner-Meerwein rearrangement is an organic reaction used to convert an alcohol to an olefin using an acid catalyst. The mechanism begins with protonation of the alcohol by the acid which is then released as water to forms a carbocation. A 1,2-shift then occurs to form a more substituted and stabilized carbo-cation. A final deprotonation with water produces the final olefin product and regenerates the acid catalyst



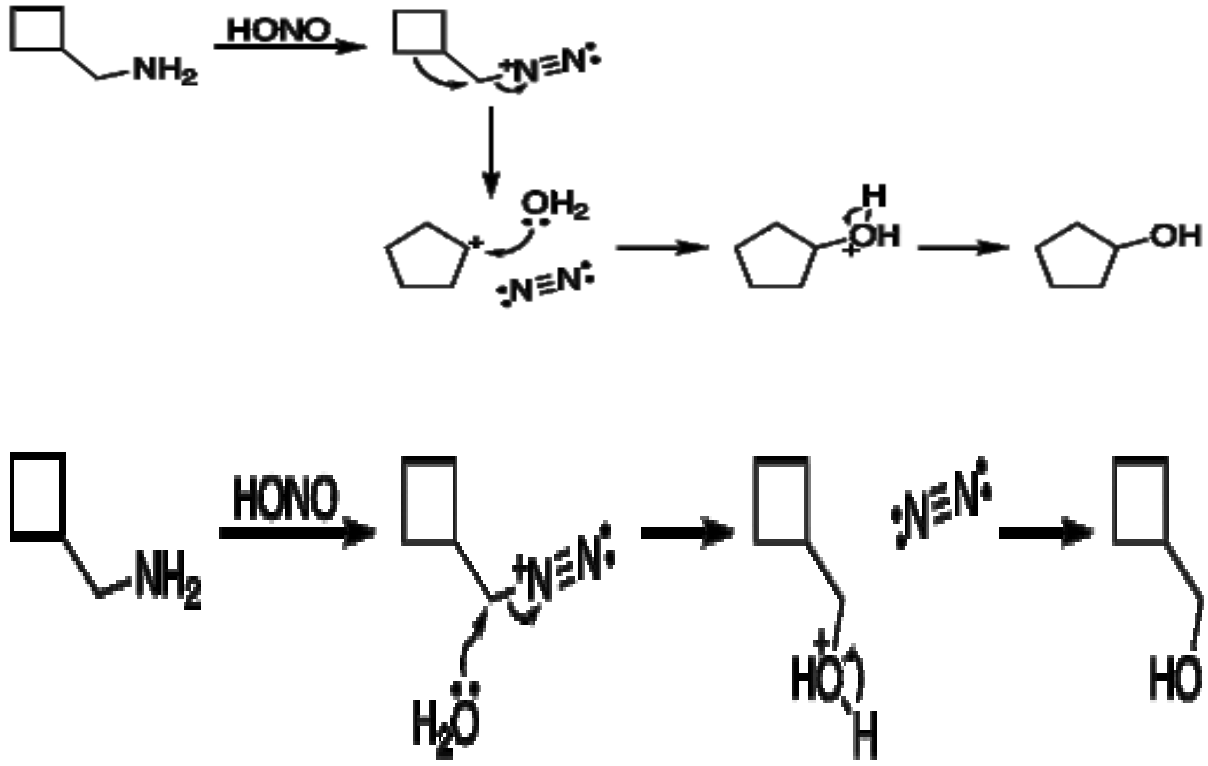
5.1.4 Demjanov Rearrangement

The **Demjanov rearrangement** is the chemical reaction of primary amines with nitrous acid to give rearranged alcohols.



The reaction process begins with diazotization of the amine by nitrous acid. The diazonium group is a good leaving group, forming nitrogen gas when displaced from the organic structure. This displacement can occur via a rearrangement (path A), in which one of the sigma bonds adjacent to the diazo group migrates. This migration results in an expansion of the ring. The resulting carbocation is then attacked by a molecule of water. Alternately, the diazo group can be displaced directly by a molecule of water in an S_N2 reaction (path B). Both routes lead to formation of an alcohol.

Mechanism-Demjanov Rearrangement

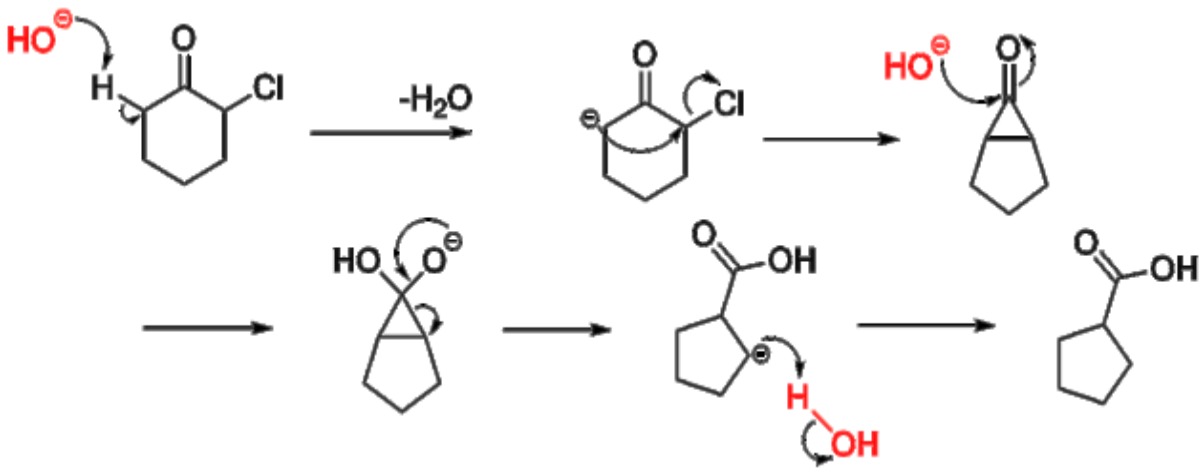


5.1.5 Favorskii rearrangement

Favorskii rearrangement, is most principally a rearrangement of cyclopropanones and α-halo ketones which leads to carboxylic acid derivatives. In the case of cyclic α-halo ketones, the Favorski rearrangement constitutes a ring contraction. This rearrangement takes place in the presence of a base, sometimes hydroxide, to yield a carboxylic acid but most of the time either an alkoxide base or an amine to yield an ester or an amide, respectively. α,α'-Dihaloketones eliminate HX under the reaction conditions to give α,β-unsaturated carbonyl compounds.

Mechanism-Favorskii rearrangement

It involve the formation of an enolate on the side of the ketone away from the chlorine atom. This enolate cyclizes to a cyclopropanone intermediate which is then attacked by the hydroxide nucleophile.



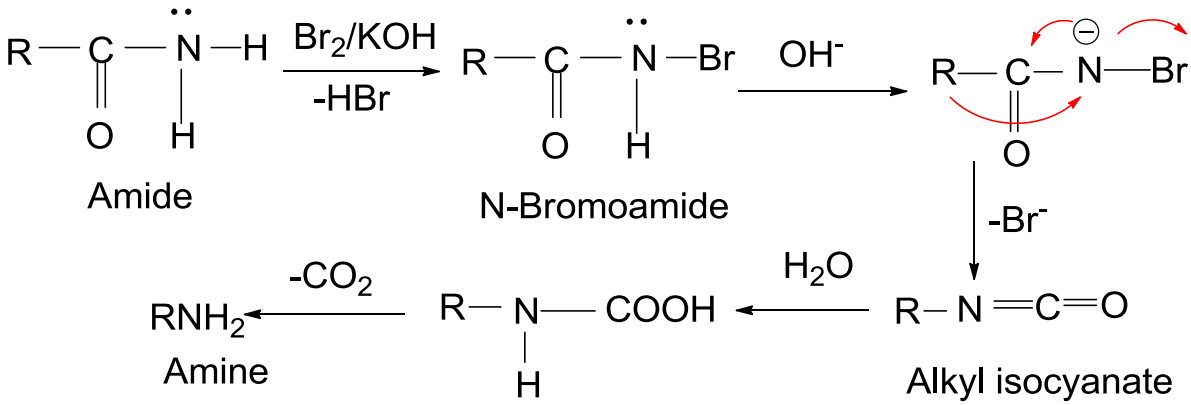
5.2 C-N Migration

5.2.1 Hoffmann Reaction:

The **Hofmann rearrangement** (**Hofmann degradation**) is the organic reaction of a primary amide to a primary amine with one fewer carbon atom.The reaction involves oxidation of the nitrogen followed by rearrangement of the carbonyl and nitrogen to give an isocyanate intermediate.

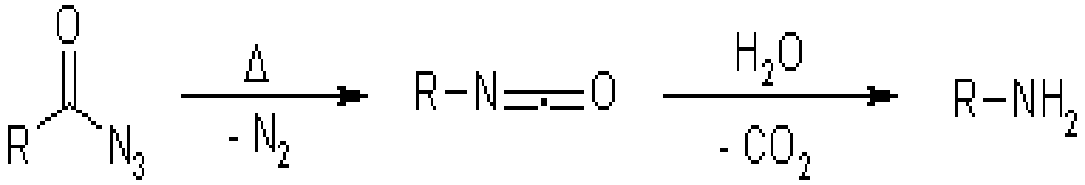
$$CH_3CH_2CONH_2 + Br_2 + 4KOH \longrightarrow CH_3CH_2NH_2 + 2KBr + K_2CO_3 + 2H_2O$$

Mechanism: The reaction involves the migration of aryl or aryl group from adjacent carbon atom to electron deficient nitrogen atom forming isocyanates.

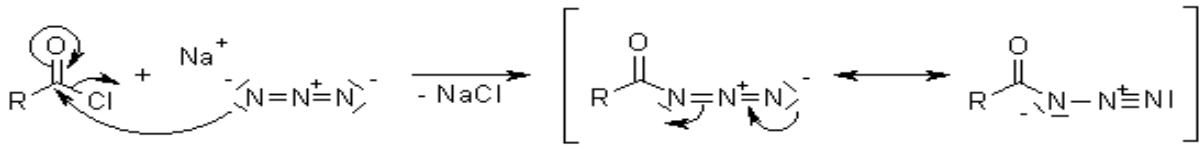


5.2.2 Curtius Rearrangement

The Curtius Rearrangement is the thermal decomposition of carboxylic azides to produce an isocyanate. These intermediates may be isolated, or their corresponding reaction or hydrolysis products may be obtained.

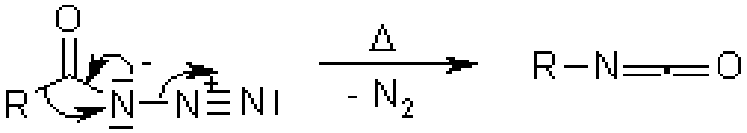


Preparation of azides:

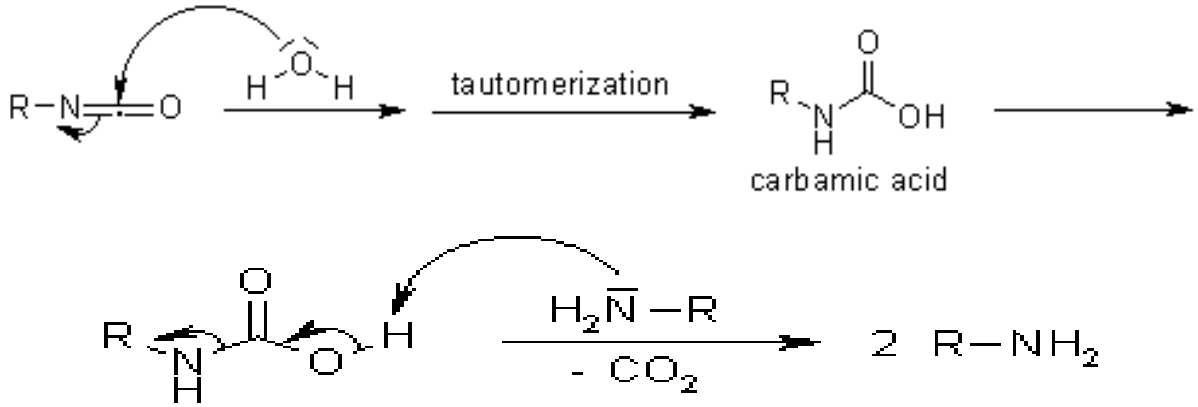


Mechanism-Curtius Rearrangement

Decomposition:

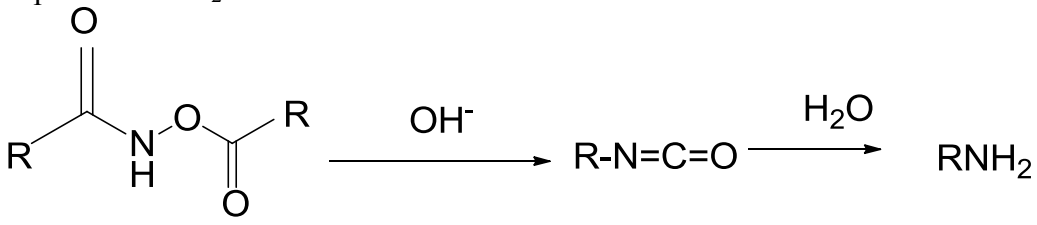


Reaction with water to the unstable carbamic acid derivative which will undergo spontaneous decarboxylation:



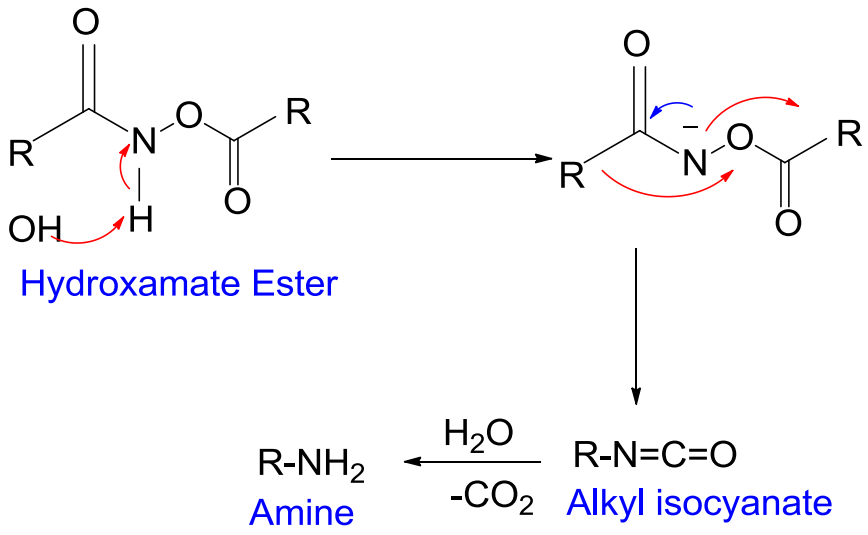
5.2.3 Lossen rearrangement

The **Lossen rearrangement** is the conversion of a hydroxamate ester to an isocyanate. Typically O-acyl, sulfonyl, or phosphoryl O-derivative are employed. The isocyanate can be used further to generate ureas in the presence of amines or generate amines in the presence of H_2O.



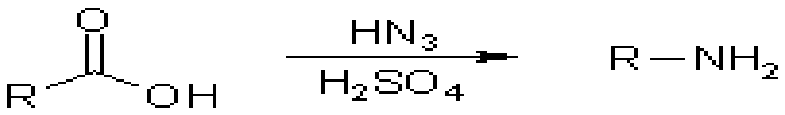
Hydroxamate Ester

Mechanism:

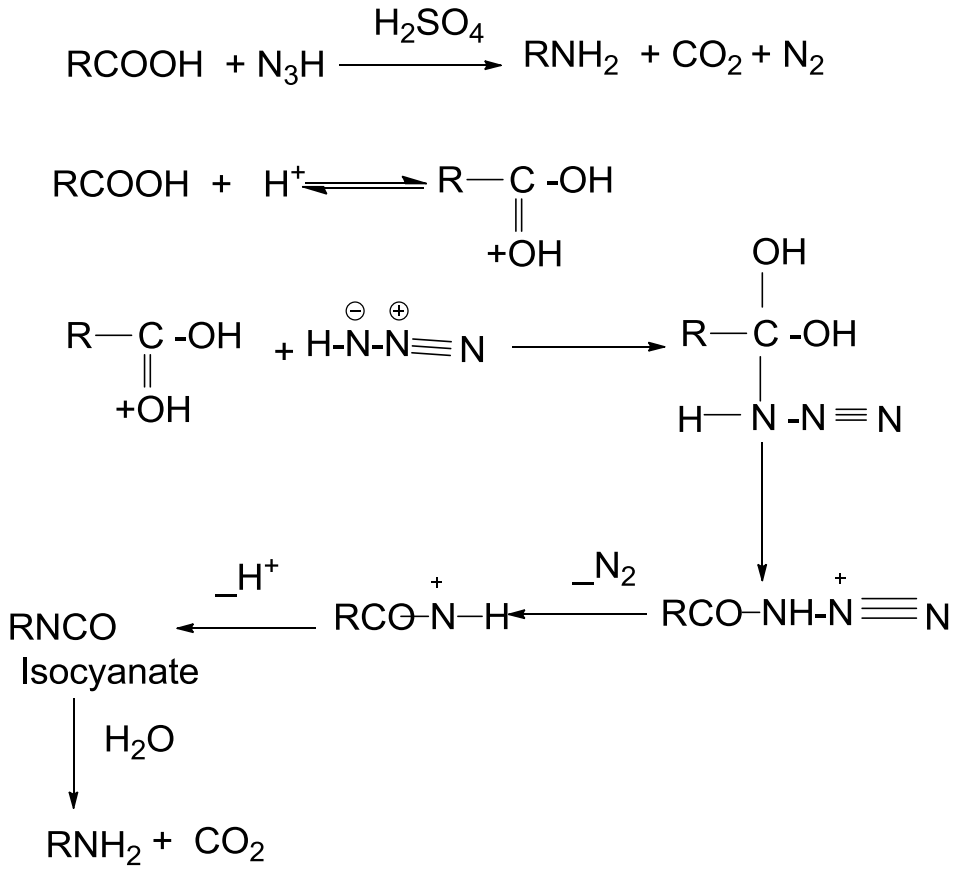


5.2.4 Schmidt Reaction

The acid-catalysed reaction of hydrogen azide with electrophiles, such as carbonyl compounds, tertiary alcohols or alkenes. After a rearrangement and extrusion of N_2, amines, nitriles, amides or imines are produced.

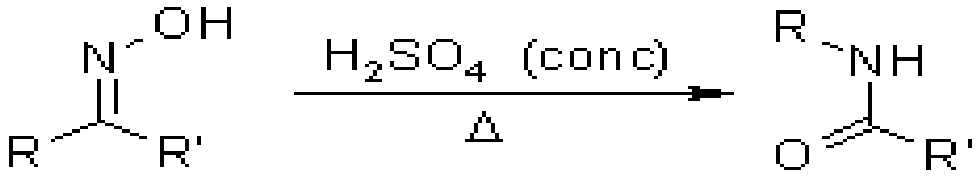


Mechanism Reaction of carboxylic acids gives acyl azides, which rearrange to isocyanates, and these may be hydrolyzed to carbamic acid or solvolysed to carbamates. Decarboxylation leads to amines.



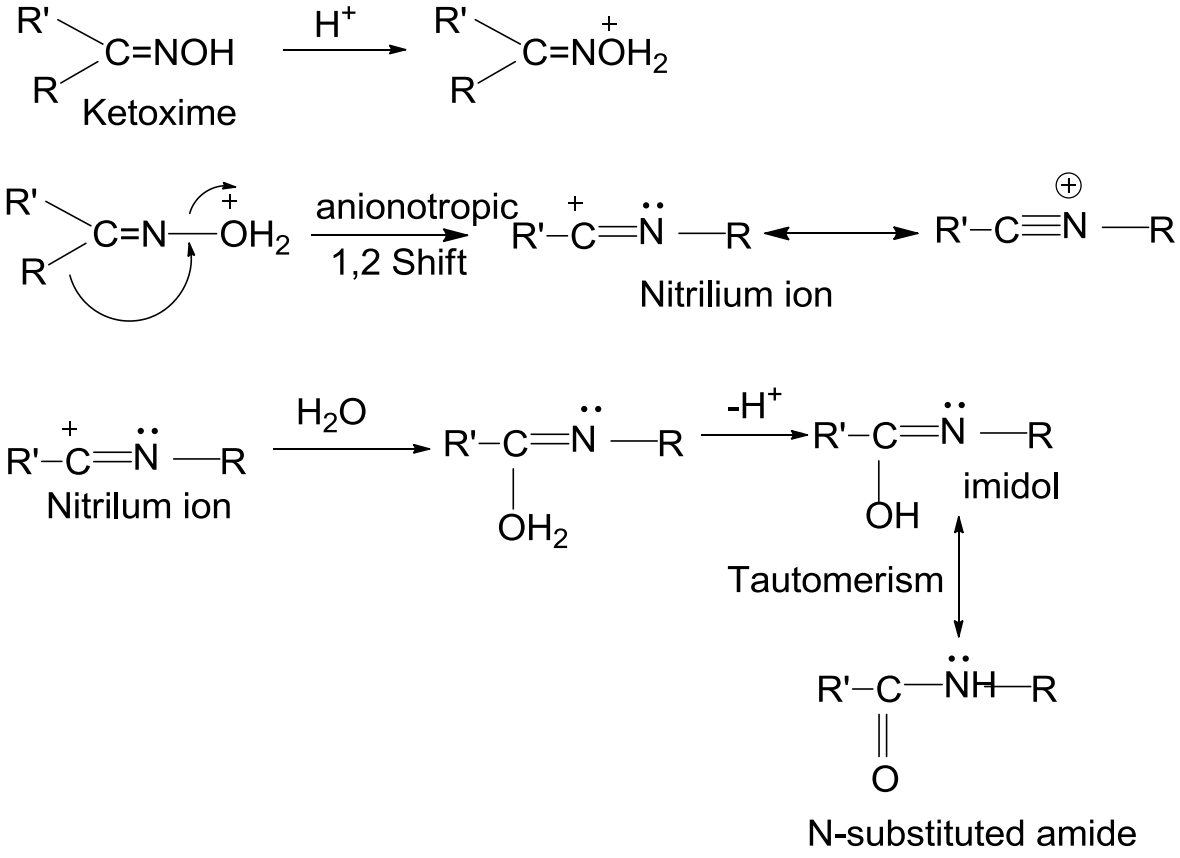
5.2. 5 Beckmann Rearrangement

An acid-induced rearrangement of oximes to give amides.

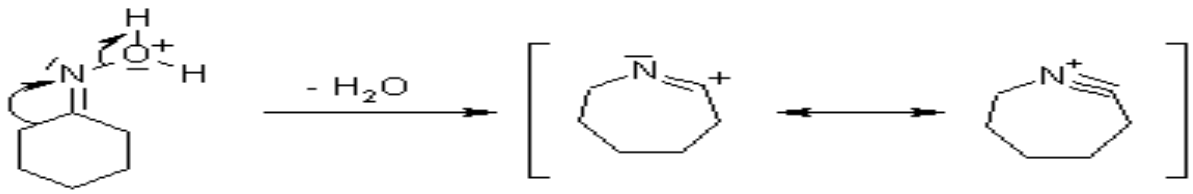


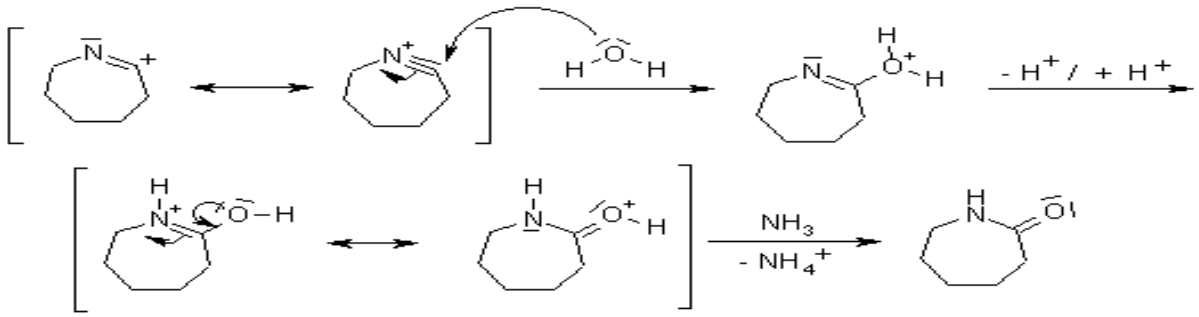
Mechanism:

Conversion of ketoxime to better leaving group in the presence of H^{+}.



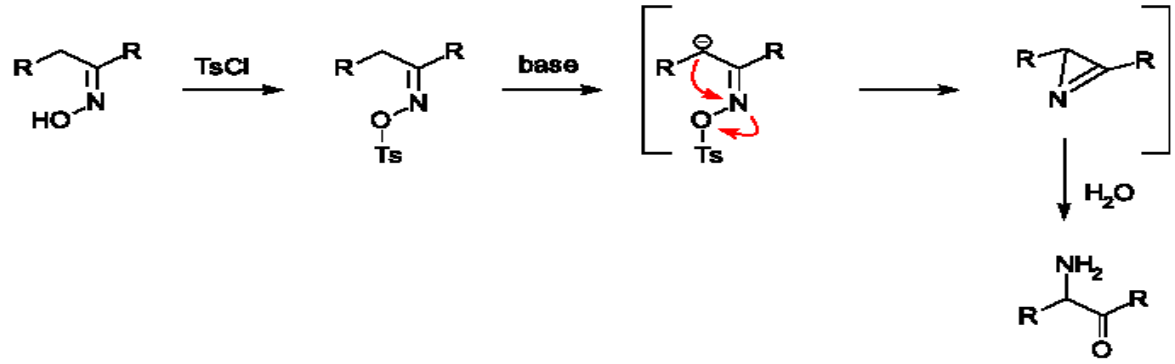
Mechanism:





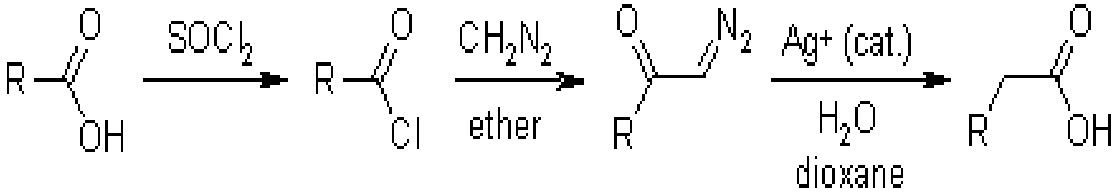
5.2.6 Neber Rearrangement

The **Neber rearrangement** in which an oxime is converted into an alpha-aminoketone in a rearrangement reaction. The oxime is first converted to a ketoxime tosylate by reaction with tosyl chloride. Added base forms a carbanion which displaces the tosylate group in a nucleophilic displacement to an azirine and added water subsequently hydrolyses it to the aminoketone



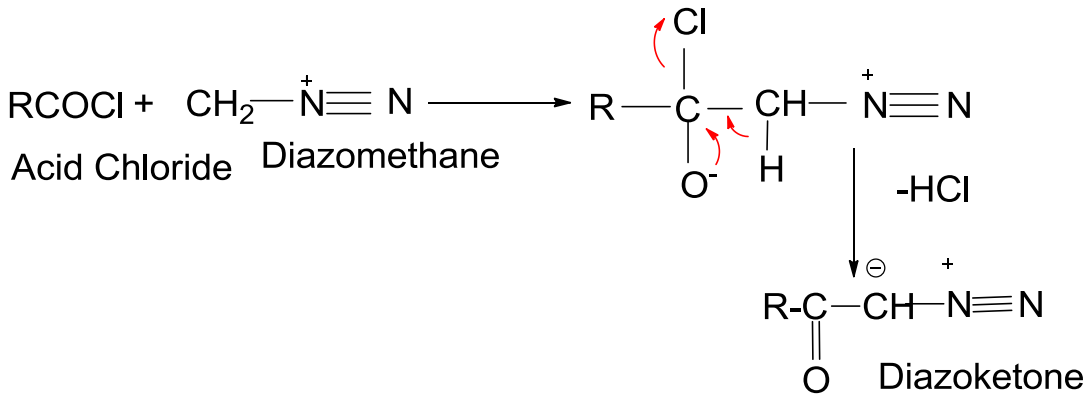
5.2.7Arndt-Eistert Synthesis

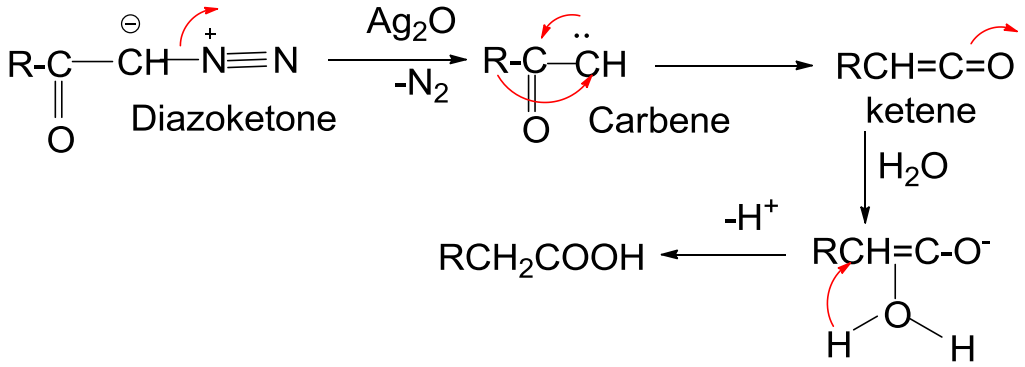
The Arndt-Eistert Synthesis allows the formation of homologated carboxylic acids or their derivatives by reaction of the activated carboxylic acids with diazomethane and subsequent Wolff-Rearrangement of the intermediate diazoketones in the presence of nucleophiles such as water, alcohols, or amines.



Mechanism of the Arndt-Eistert Synthesis

In the first step of this one-carbon homologation, the diazomethane carbon is acylated by an acid chloride or mixed anhydride, to give an α-diazoketone. Formation of diazoketone,on warmed with Ag_2O loses N_2 to form carbene where alkyl group migrates to form ketene which reacts with water to form acids.

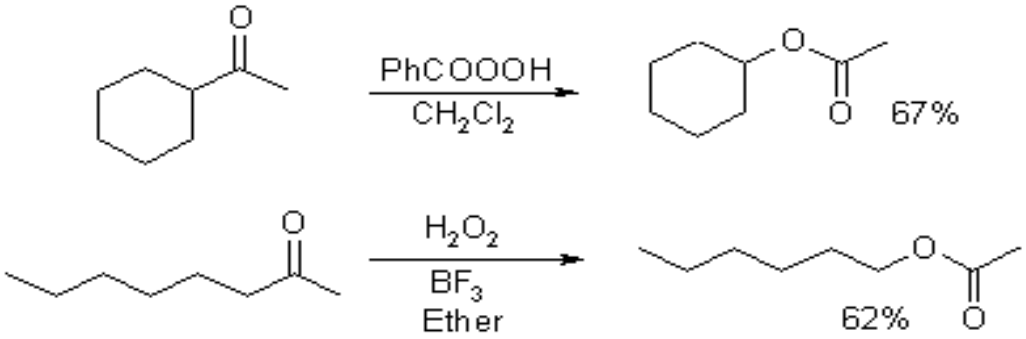




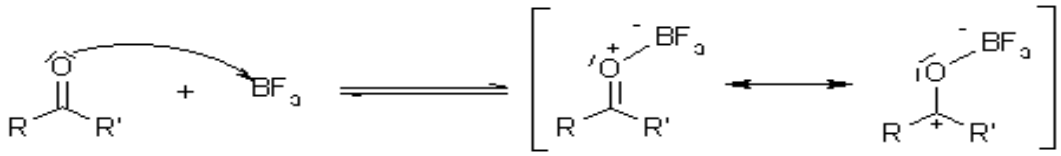
5.3 C-O Migration

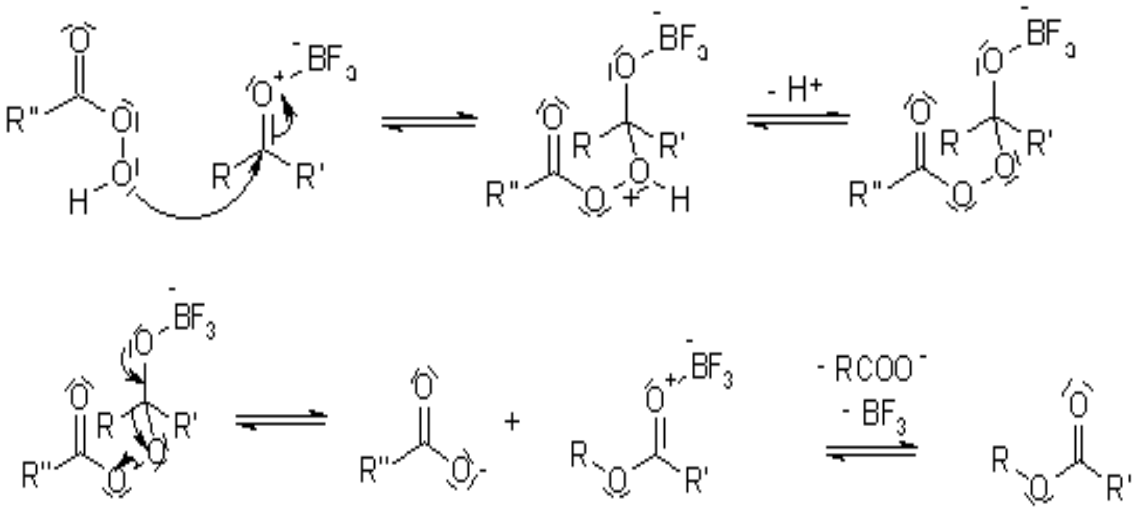
5.3.1 Baeyer-Villiger Oxidation

The Baeyer-Villiger Oxidation is the oxidative cleavage of a carbon-carbon bond adjacent to a carbonyl, which converts ketones to esters and cyclic ketones to lactones. It is carried out with peracids, such as MCBPA, or with hydrogen peroxide and a Lewis acid.



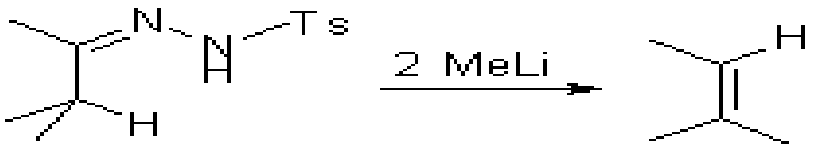
Mechanism-Baeyer-Villiger Oxidation



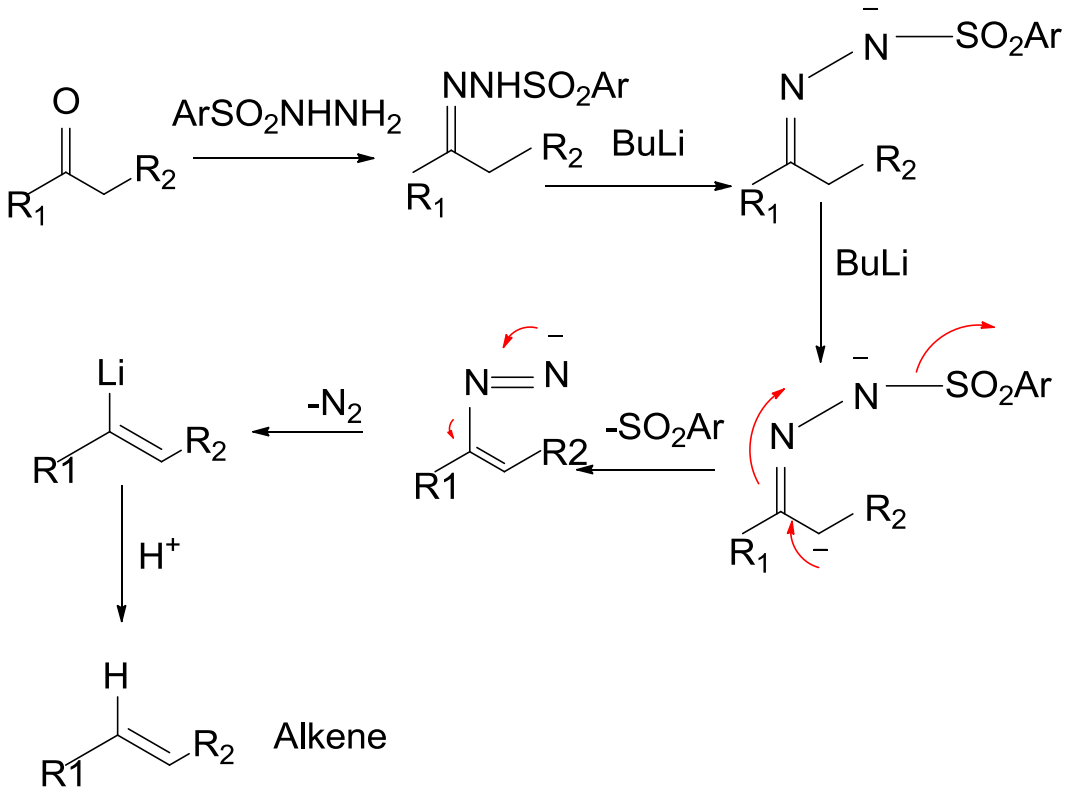


5.3.2 Shapiro Reaction

The Shapiro Reaction, a variation on the Bamford-Stevens_Reaction, is the base-induced reaction of tosylhydrazones to afford alkenes. This reaction is carried out with two equivalents of an organolithium compound.



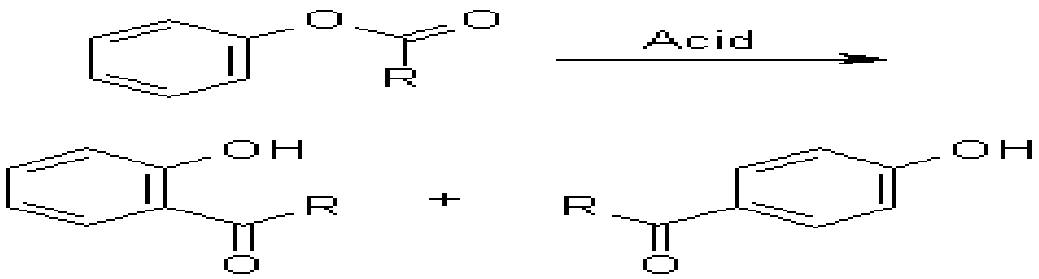
Mechanism: The resulting dianion does not tend to rearrange, which can occur with intermediate carbenes and carbenium ions.



5.4 Miscellaneous Rearrangements:

5.4.1 Fries Rearrangement

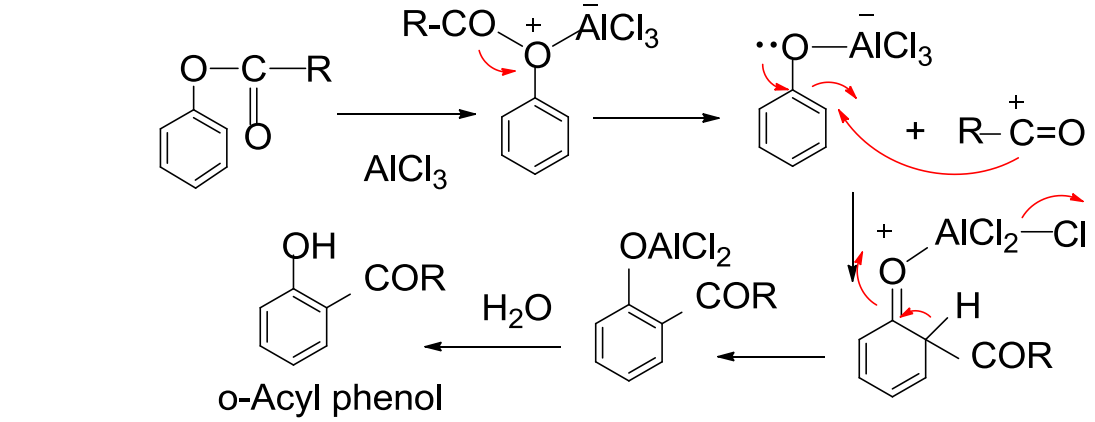
The Fries Rearrangement enables the preparation of acyl phenols

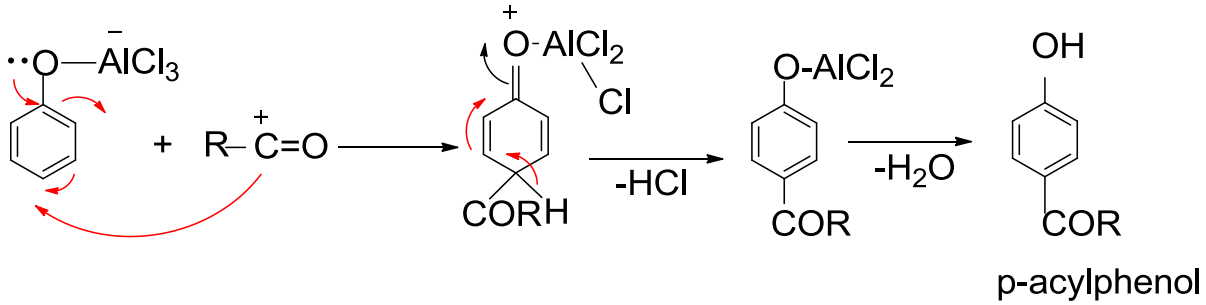


Mechanism of the Fries Rearrangement

The reaction is catalyzed by Brønsted or Lewis acids such as HF, $AlCl_3$, BF_3, $TiCl_4$ or $SnCl_4$. The acids are used in excess of the stoichiometric amount, especially the Lewis acids, since they form complexes with both the starting materials and products. The complex can dissociate to form an acylium ion. Depending on the solvent, an ion pair can form, and the ionic species can react with each other within the solvent cage

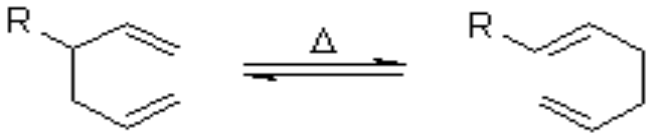
After hydrolysis, the product o and p acyl phenol is liberated



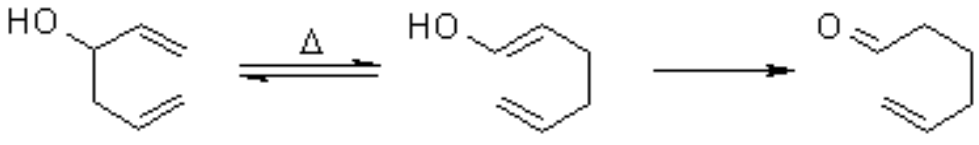


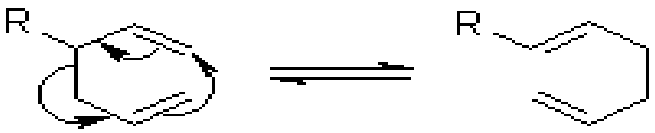
5.4.2 Cope Rearrangement (Anionic) Oxy-Cope Rearrangement

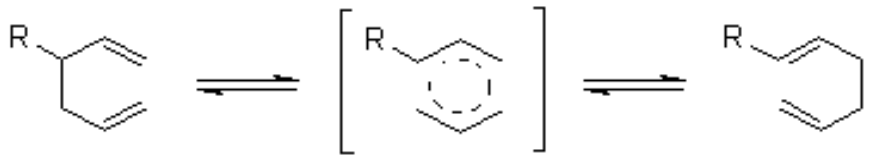
The Cope Rearrangement is the thermal isomerization of a 1,5-diene leading to a regioisomeric 1,5-diene. The main product is the thermodynamically more stable regioisomer. The Oxy-Cope has a hydroxyl substituent on an sp^3-hybridized carbon of the starting isomer.

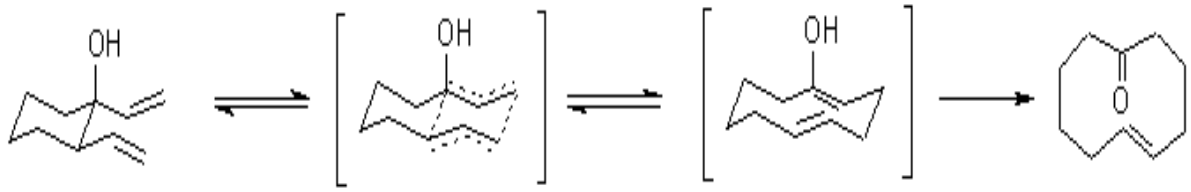


The driving force for the neutral or anionic Oxy-Cope Rearrangement is that the product is an enol or enolate (resp.), which can tautomerize to the corresponding carbonyl compound. This product will not equilibrate back to the other regioisomer.



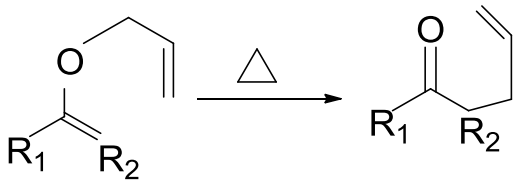






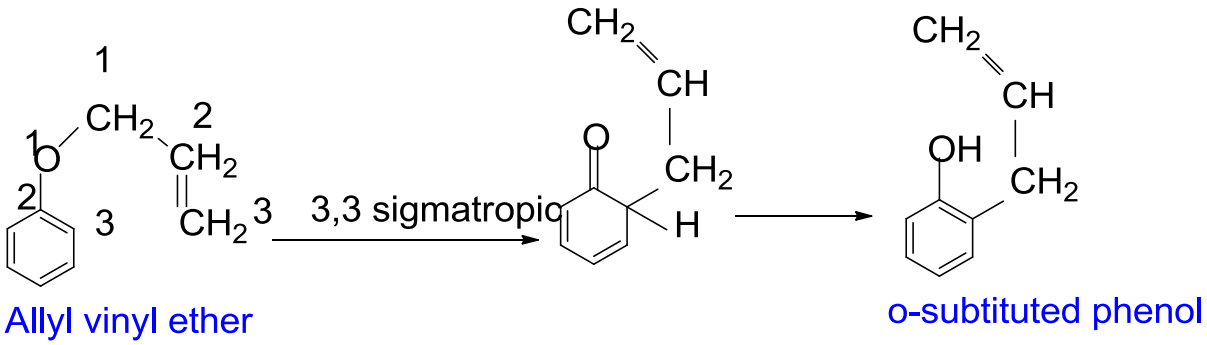
5.4.3 Claisen Rearrangement:

The **Claisen rearrangement** is a powerful carbon–carbon bond-forming chemical reaction discovered by Rainer Ludwig Claisen. The heating of an allyl vinyl ether will initiate a [3,3]-sigmatropic rearrangement to give a γ,δ-unsaturated carbonyl.



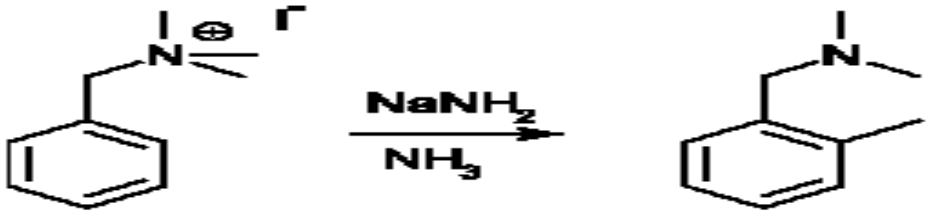
Reaction:

The [3,3]-sigmatropic rearrangement of an allyl phenyl ether to intermediate 1, which quickly tautomerizes to an ortho-substituted phenol.



5.4.4 Sommelet–Hauser rearrangement

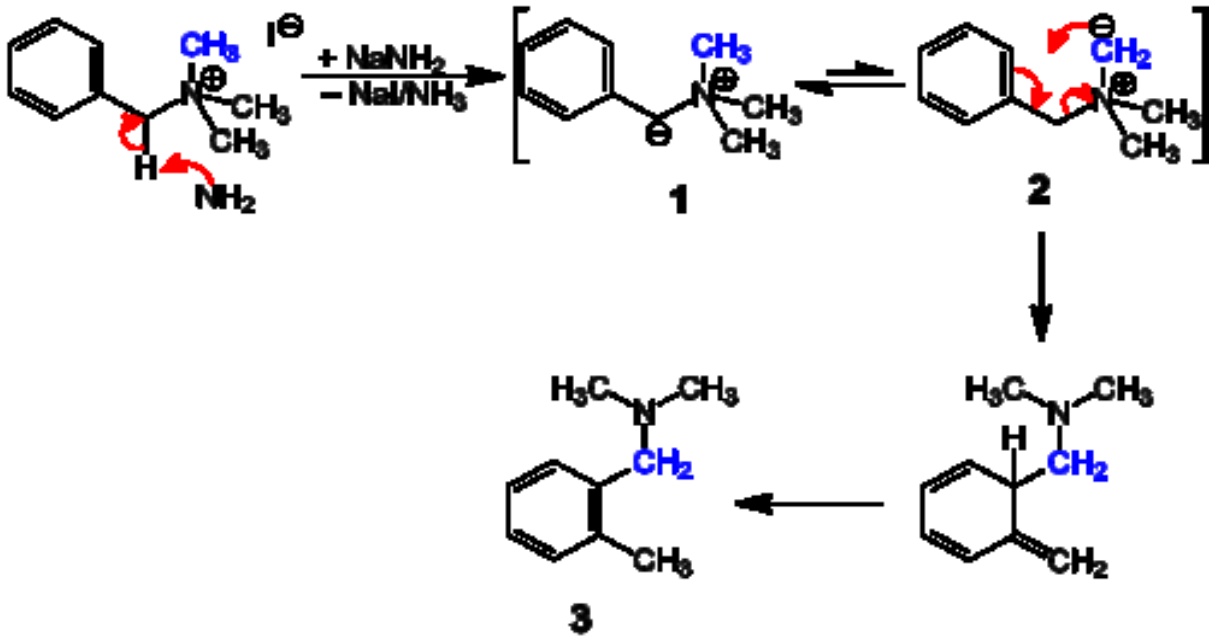
The **Sommelet–Hauser rearrangement** is a rearrangement reaction of certain benzyl quaternary ammonium salts. The reagent is sodium amide or another alkali metal amide and the reaction product a N-dialkyl benzyl amine with a new alkyl group in the aromatic ortho position.



Mechanism

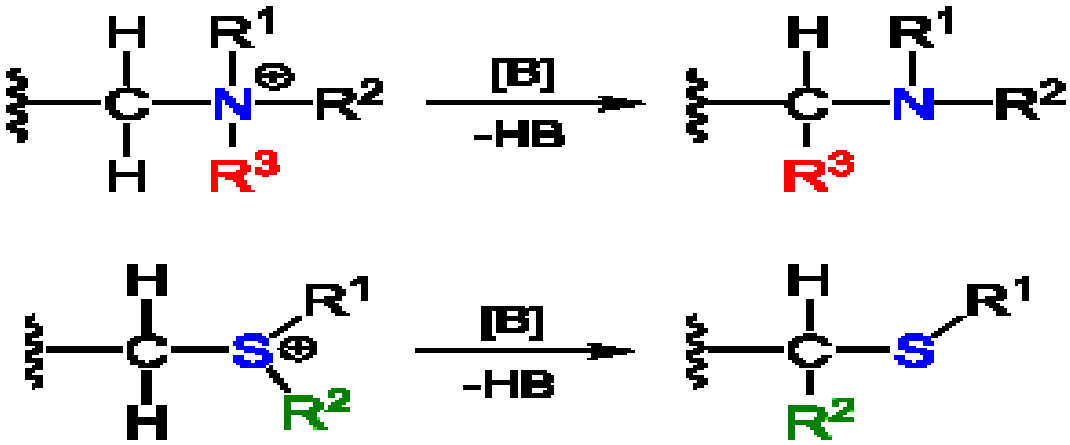
The benzylic methylene proton is acidic and deprotonation takes place to produce the benzylic ylide. This ylide is in equilibrium with a second ylide that is formed by deprotonation of one of the ammonium methyl groups Though the second ylide is present in much smaller amounts, it undergoes a 2,3-sigmatropic rearrangement and subsequent aromatization to form the final product

Mechanism-Sommelet–Hauser rearrangement



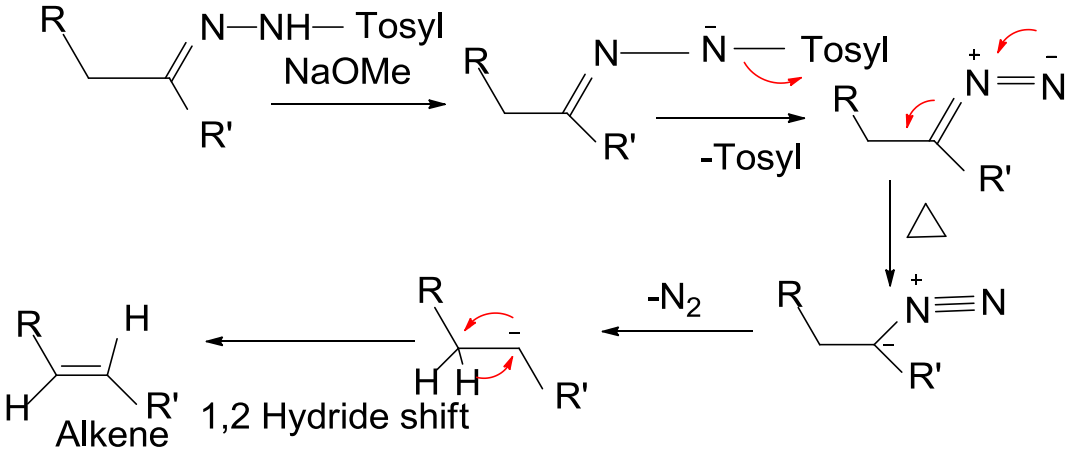
5.4.5 Stevens Rearrangement

The **Stevens rearrangement** is an organic reaction converting quaternary ammonium salts and sulfonium salts to the corresponding amines or sulfides in presence of a strong base in a 1,2-rearrangement.



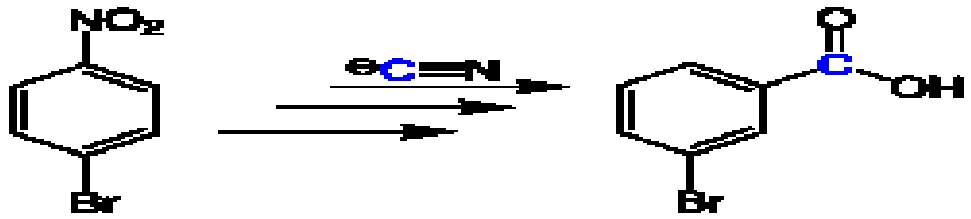
Mechanism-Stevens Rearrangement

Stevens Rearrangement involving 1,2 hydride shift:



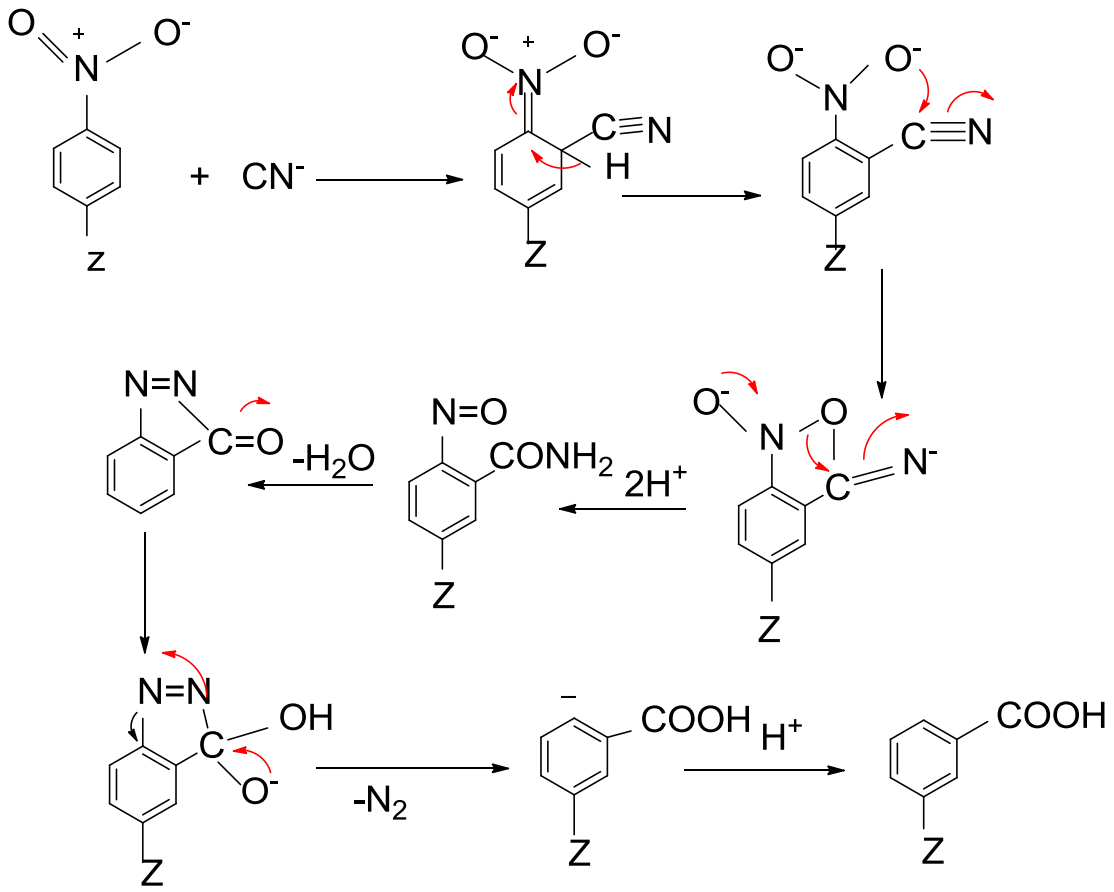
5.4.6 Von-Richter rearrangement

It is the chemical reaction of aromatic nitro compounds with potassium cyanide giving carboxylation ortho to the position of the former nitro group.



First, the cyanide attacks the carbon-atom in *ortho*-position to the nitro-group **1**. After this the compound is aromatic again **2**. In the next step, the negative charged oxygen-atom attacks the neighbor carbon-atom and an five-membered ring is build **3**. It opens under building a carconlylic-group **4**. Next, an other five-membered ring is built **5**. After acondensation, a double bond is build between the two nitrogen-atoms **6**. Elemental nitrogen is cut of for opening the ring **7**. In the last step, the compound is protonated and the 3-halogenbenzoic acid **8** is built.

Mechanism-Von-Richter rearrangement



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