Reagents in Organic Synthesis [Oxidation]

Chromium Trioxide (CrO_3)

- Chromium trioxide is a strong oxidizing agent that is not soluble in most organic solvents and tends to explode in the presence of organic compounds and solvents.

- In water, it forms chromic acid and anhydrides, from which salts such as sodium dichromate ($Na_2Cr_2O_7$) and pyridinium dichromate are commercially available.

- Chromium trioxide is soluble in *tert*-butyl alcohol, pyridine and acetic anhydride, although care must be taken to follow the given procedures, because these solutions tend to explode.

Production, structure, and basic reactions

- Chromium trioxide is generated by treating sodium chromate or the corresponding sodium dichromate with sulfuric acid.

$$H_2SO_4 + Na_2Cr_2O_7 \rightarrow 2\ CrO_3 + Na_2SO_4 + H_2O$$

- The structure of monomeric CrO_3 has been calculated using density functional theory, and is predicted to be pyramidal (point group C_{3v}) rather than planar (point group D_{3h}).
- Chromium trioxide decomposes above 197 °C, liberating oxygen and eventually giving Cr_2O_3:

$$4\ CrO_3 \rightarrow 2\ Cr_2O_3 + 3\ O_2$$

Production, structure, and basic reactions

- It is used in organic synthesis as an oxidant, often as a solution in acetic acid, or acetone in the case of the Jones oxidation. In these oxidations, the Cr(VI) converts primary alcohols to the corresponding carboxylic acids and secondary alcohols to ketones. The reactions are shown below:
- Primary alcohols

$$4\ CrO_3 + 3\ RCH_2OH + 12\ H^+ \rightarrow 3\ RCOOH + 4\ Cr^{3+} + 9\ H_2O$$

Secondary alcohols

$$2\ CrO_3 + 3\ R_2CHOH + 6\ H^+ \rightarrow 3\ R_2C{=}O + 2\ Cr^{3+} + 6\ H_2O$$

Applications

- Chromium trioxide is mainly used in chrome plating.
- The trioxide reacts with cadmium, zinc, and other metals to generate passivating chromate films that resist corrosion.
- It is also used in the production of synthetic rubies.
- Chromic acid solution is also used in applying types of anodic coating to aluminum, which are primarily used in aerospace applications.
- A chromic acid/phosphoric acid solution is also the preferred stripping agent of anodic coatings of all types.

Safety

- Chromium trioxide is highly toxic, corrosive, and carcinogenic.
- It is the main example of hexavalent chromium, an environmental hazard.
- The related chromium(III) derivatives are not particularly dangerous; thus, reductants are used to destroy chromium(VI) samples.
- Chromium trioxide, being a powerful oxidizer, will ignite organic materials such as alcohols on contact.

MnO_2

- **Manganese(II) oxide** is the inorganic compound with the formula MnO_2. This blackish or brown solid occurs naturally as the mineral pyrolusite, which is the main ore of manganese and a component of manganese nodules.
- The principal use for MnO_2 is for dry-cell batteries, such as the alkaline battery and the zinc-carbon battery.
- MnO_2 is also used as a pigment and as a precursor to other manganese compounds, such as $KMnO_4$.
- MnO_2 is characteristically nonstoichiometric, being deficient in oxygen.

Reactions of MnO_2

- The important reactions of MnO_2 are associated with its redox, both oxidation and reduction.
- **Oxidation**
- Heating a mixture of KOH and MnO_2 in air gives green potassium permanganate;

$$2\ MnO_2 + 4\ KOH + O_2 \rightarrow 2\ K_2MnO_4 + 2\ H_2O$$

- Potassium manganate is the precursor to potassium permanganate, a common oxidant.

- MnO_2 oxidizes allylic alcohols to the corresponding aldehydes or ketones.

cis-$RCH{=}CHCH_2OH$ + MnO_2 → cis-$RCH{=}CHCHO$ + MnO + H_2O

Reactions of MnO_2

- **Reduction**
- MnO_2 is the principal precursor to ferromanganese and related alloys, which are widely used in the steel industry. The conversions involve carbothermal reduction using coke.

$$MnO_2 + 2\ C \rightarrow Mn + 2\ CO$$

- The key reactions of MnO_2 in batteries is the one-electron reduction:

$$MnO_2 + e^- + H^+ \rightarrow MnO(OH)$$

- Manganese dioxide also catalyses the decomposition of hydrogen peroxide to oxygen and water:

$$2H_2O_2 \rightarrow 2\ H_2O + O_2$$

- Hot concentrated sulfuric acid reduces the MnO_2 to manganese(II) sulfate

$$2\ MnO_2 + 2\ H_2SO_4 \rightarrow 2\ MnSO_4 + O_2 + 2\ H_2O$$

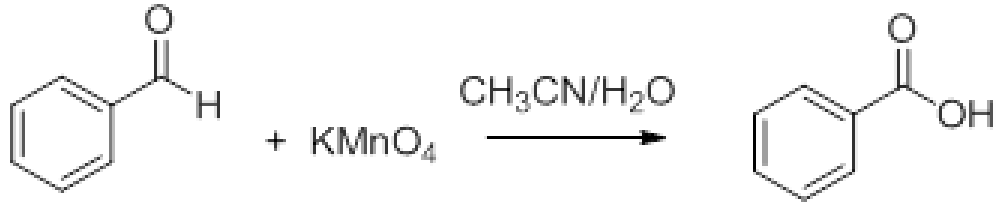
Potassium permanganate, $KMnO_4$

- Of all the oxidizing agents discussed in organic chemistry textbooks, potassium permanganate, $KMnO_4$, is probably the most common, and also the most applicable.
- As will be shown below, $KMnO_4$ can be utilized to oxidize a wide range of organic molecules. The products that are obtained can vary depending on the conditions, but because $KMnO_4$ is such a strong oxidizing agent, the final products are often carboxylic acids.

- $KMnO_4$ is able to oxidize carbon atoms if they contain sufficiently weak bonds, including
- Carbon atoms with π bonds, as in alkenes and alkynes
- Carbon atoms with weak C-H bonds, such as
  - C-H bonds in the alpha-positions of substituted aromatic rings
  - C-H bonds in carbon atoms containing C-O bonds, including alcohols and aldehydes
- Carbons with exceptionally weak C-C bonds such as
  - C-C bonds in a glycol
  - C-C bonds next to an aromatic ring AND an oxygen
  - $KMnO_4$ also oxidizes phenol to para-benzoquinone.

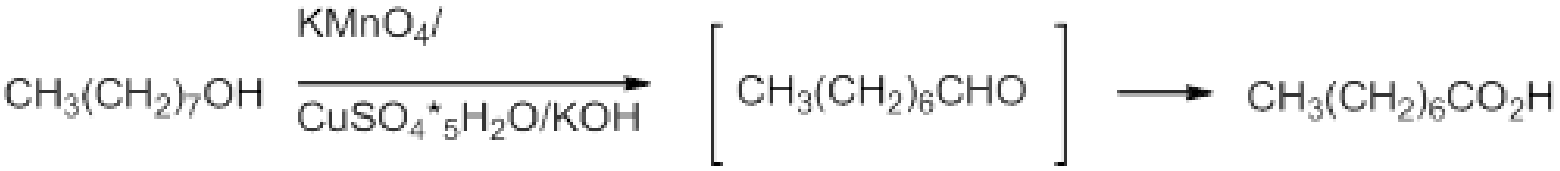
Reactions with Specific Functional Groups

- Exhaustive oxidation of organic molecules by $KMnO_4$ will proceed until the formation of carboxylic acids. Therefore, alcohols will be oxidized to carbonyls (aldehydes and ketones), and aldehydes (and some ketones) will be oxidized to carboxylic acids.
- **Aldehydes**
- Aldehydes RCHO are readily oxidized to carboxylic acids.



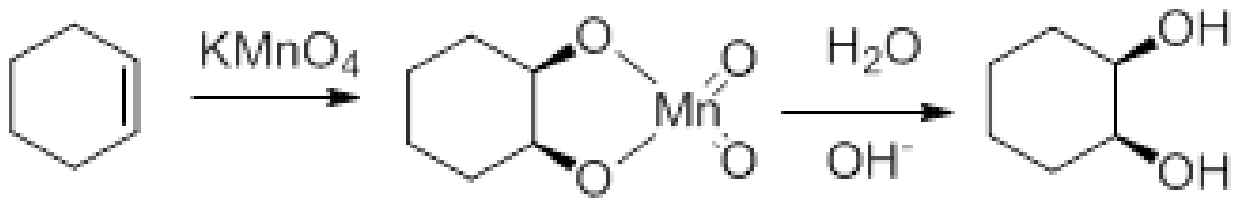
- Unless great efforts are taken to maintain a neutral pH, $KMnO_4$ oxidations tend to occur under basic conditions.

- **Alcohols**
- Primary alcohols such as octan-1-ol can be oxidized efficiently by $KMnO_4$, in the presence of basic copper salts. However, the product is predominantly octanoic acid, with only a small amount of aldehyde, resulting from over oxidation.

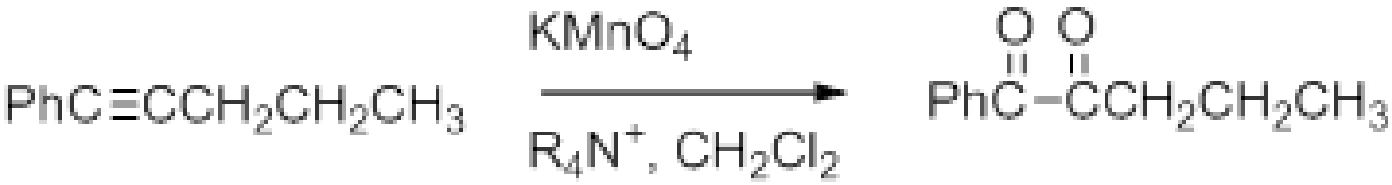


Although over oxidation is less of a problem with secondary alcohols, $KMnO_4$ is still not considered generally well-suited for conversions of alcohols to aldehydes or ketones.

- **Alkenes**
- Under mild conditions, potassium permanganate can effect conversion of alkenes to glycols. It is, however, capable of further oxidizing the glycol with cleavage of the carbon-carbon bond, so careful control of the reaction conditions is necessary. A cyclic manganese diester is an intermediate in these oxidations, which results in glycols formed by *syn* addition.



- **Alkynes**
- Instead of bis-hydroxylation that occurs with alkenes, permanganate oxidation of alkynes initially leads to the formation of diones.



Selenium Dioxide (SeO_2)

- Selenium dioxide is an important oxidizing agent, specific for oxidation of reactive methylene and methyl groups.
- It is prepared by the direct oxidation of metallic selenium. Selenium burns with a blue flame in air producing selenium dioxide. The oxidation is catalyzed by nitrogen peroxide.

$$Se + O_2\,(air) \longrightarrow SeO_2$$

- It is a white crystalline solid, dissolves in water forming selenious acid (H_2SeO_3) and it is highly toxic.

- The SeO_2 in general, oxidizes active methylene and methyl group to ketonic and aldehydic group.
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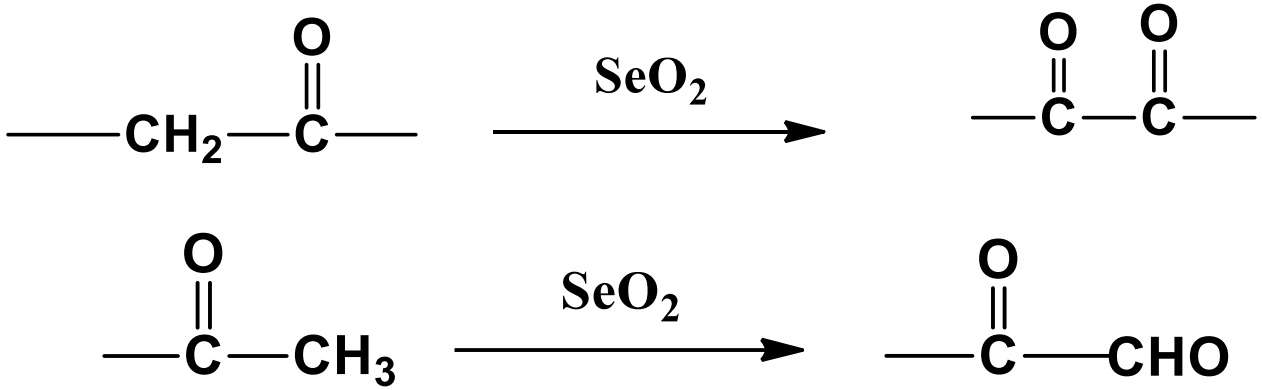
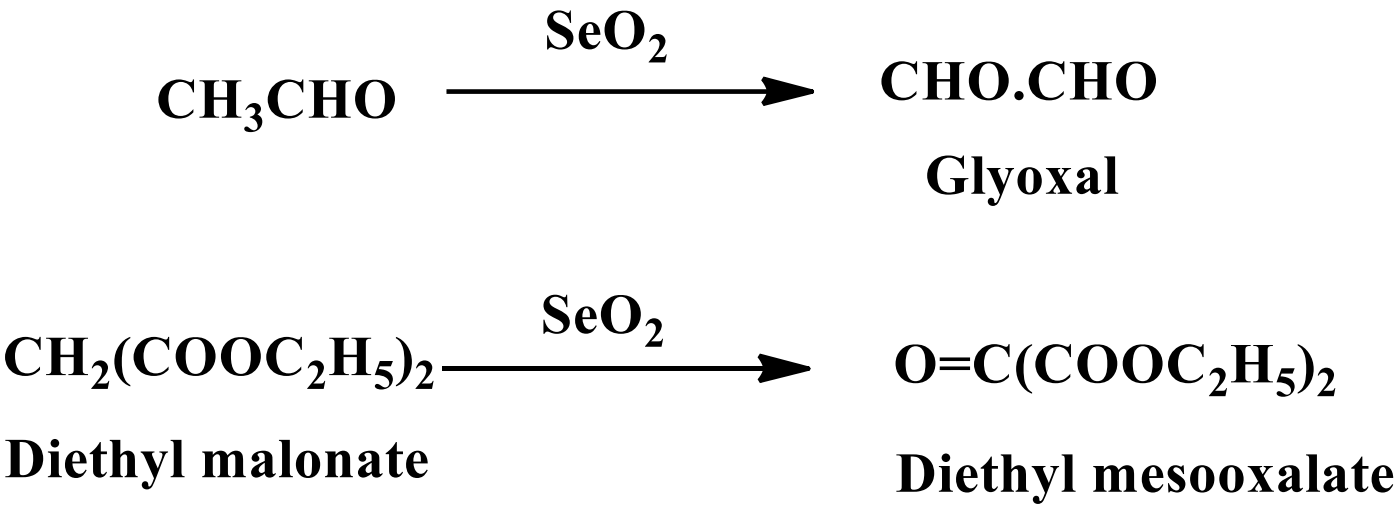


• Double bonds, triple bonds and aromatic rings may also activate the methylene group. The reaction is usually carried out in acetic medium or acetic anhydride at a temperature between 100-140 ˚C. Alcohol or dioxan may also be used as diluents.

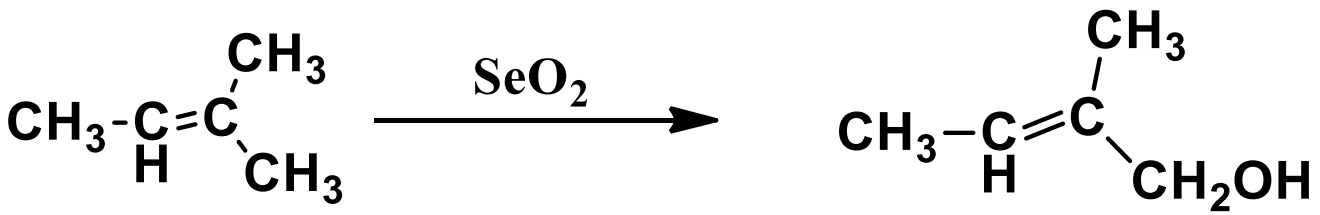
Uses of Selenium Dioxide (SeO_2)

- Oxidation of reactive methyl and methylene groups



Uses of Selenium Dioxide (SeO_2)

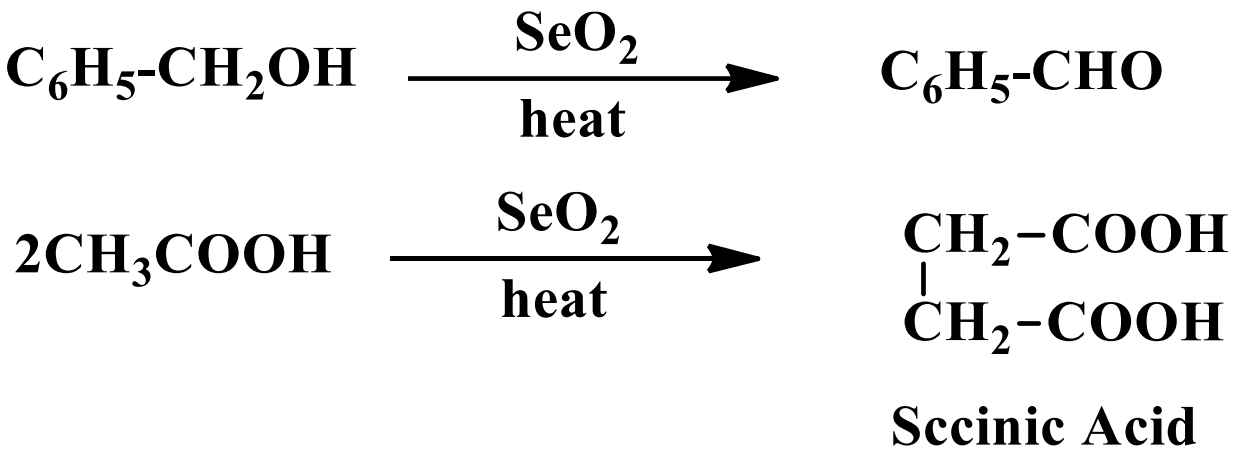
- Allylic hydroxylation
- In the methyl group alpha to the most highly substituted end of the of the double bond is hydroxylated according to the order of preference of oxidation CH_2 > CH_3 > CH groups.



2-Methyl-2-butene **2-methyl butanol**

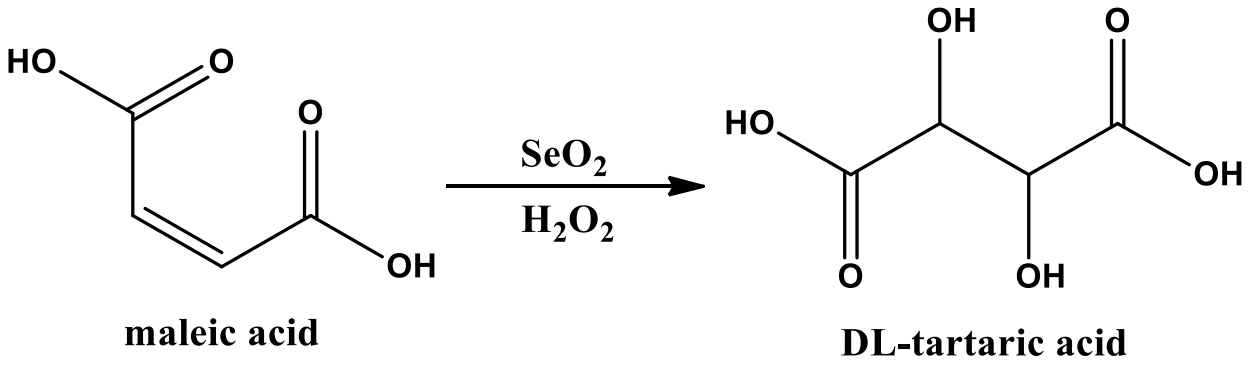
Uses of Selenium Dioxide (SeO_2)

- Dehydrogenation
- Selenium dioxide has been used for dehydrogenation at elevated temperature.



Uses of Selenium Dioxide (SeO_2)

- As a Catalyst
- It catalyses the trans–hydroxylation of some unsaturated compounds by hydrogen peroxide



maleic acid

DL-tartaric acid

Lead(IV) Acetate

- $C_8H_{12}O_8Pb$ · Lead(IV) Acetate · (MW 443.37)
- Oxidizing agent for different functional groups,

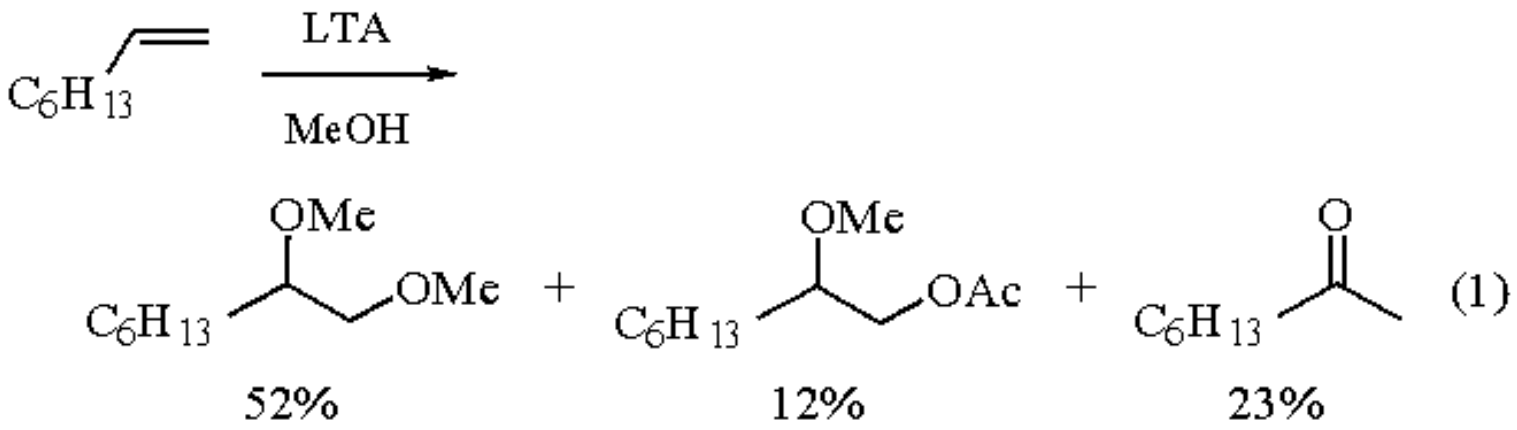
  such as, oxidation of unsaturated and aromatic hydrocarbons, oxidation of monohydroxylic alcohols to cyclic ethers, 1,2-glycol cleavage, acetoxylation of ketones, decarboxylation of acids, oxidative transformations of nitrogen-containing compounds.
- *Alternate Name:* lead tetraacetate; LTA.
- *Physical Data:* mp 175-180 °C; *d* 2.228 g cm^{-3}.
- *Solubility:* sol hot acetic acid, benzene, Cyclohexane, chloroform, carbon tetrachloride, methylene chloride; reacts rapidly with water.

Lead(IV) Acetate

- *Handling, Storage, and Precautions:* the solid reagent is very hygroscopic and must be stored in the absence of moisture. Bottles of lead tetraacetate should be kept tightly sealed and stored under 10 °C in the dark and in the presence of about 5% of glacial acetic acid.

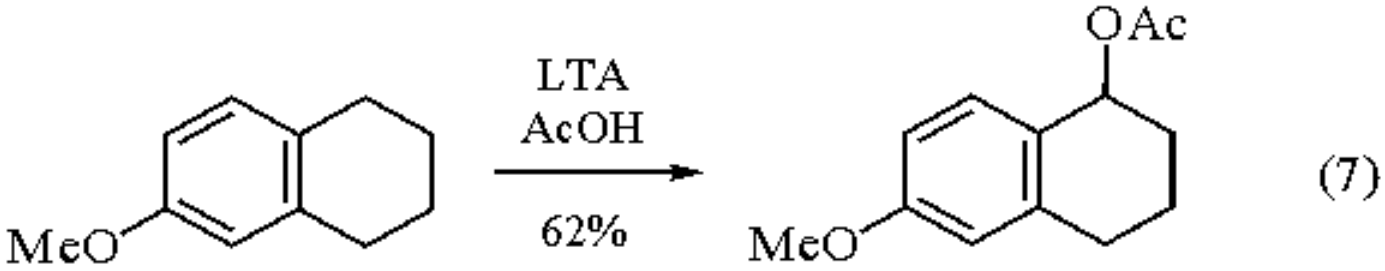
Oxidations of Alkenic and Aromatic Hydrocarbons

- Lead tetraacetate reacts with alkenes in two ways: addition of an oxygen functional group on the double bond and substitution for hydrogen at the allylic position.
- In addition to these two general reactions, depending on the structure of the alkene, other reactions such as skeletal rearrangement, double bond migration, and C-C bond cleavage can occur, leading to complex mixtures of products, and these reactions therefore have little synthetic value.



Oxidations of Alkenic and Aromatic Hydrocarbons

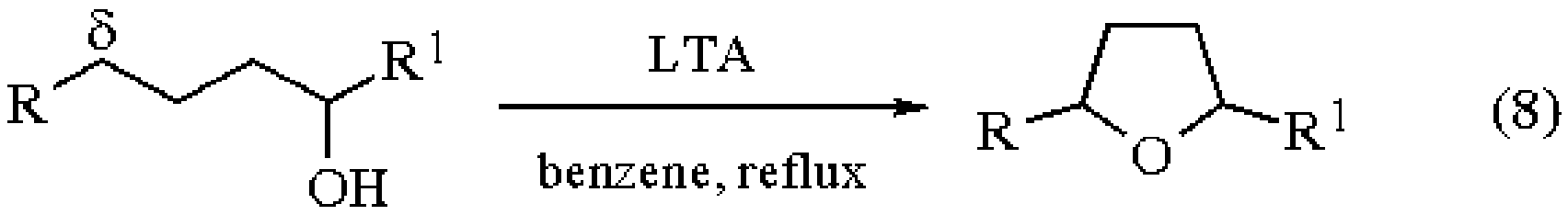
- Aromatic compounds possessing a C-H group at the benzylic position are readily oxidized by LTA to the corresponding benzyl acetates. Benzylic acetoxylation is preferably performed in refluxing acetic acid.
- Acetoxylation at the benzylic position can be accompanied by methylation of the aromatic ring, followed sometimes by acetoxylation of the newly introduced methyl group.



(7)

Oxidative Cyclization of Alcohols to Cyclic ethers

- The LTA oxidation of saturated alcohols, containing at least four carbon atoms in an alkyl chain or an appropriate carbon skeleton, to five-membered cyclic ethers represents a convenient synthetic method for intramolecular introduction of an ether oxygen function at the nonactivated d-carbon atom of a methyl, methylene, or methine group.
- The reactions are carried out in nonpolar solvents, such as benzene, cyclohexane, heptane, and carbon tetrachloride, either at reflux temperature or by UV irradiation at rt.



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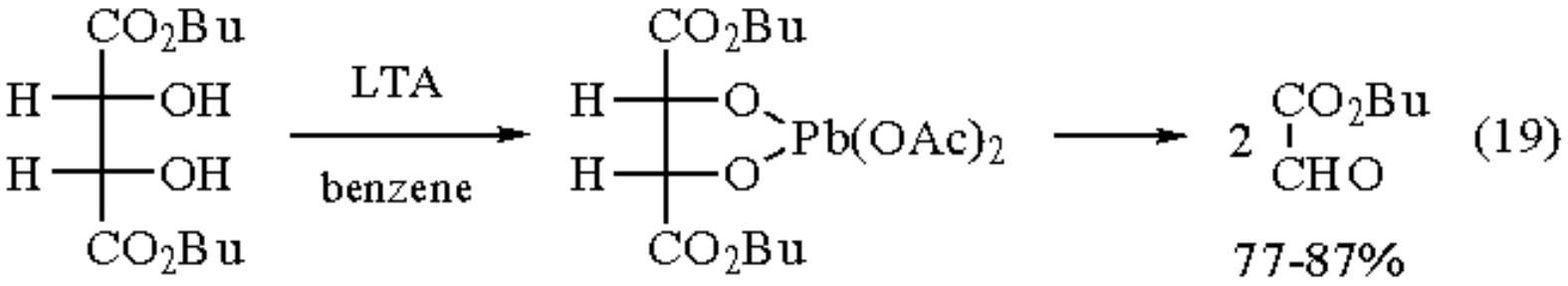
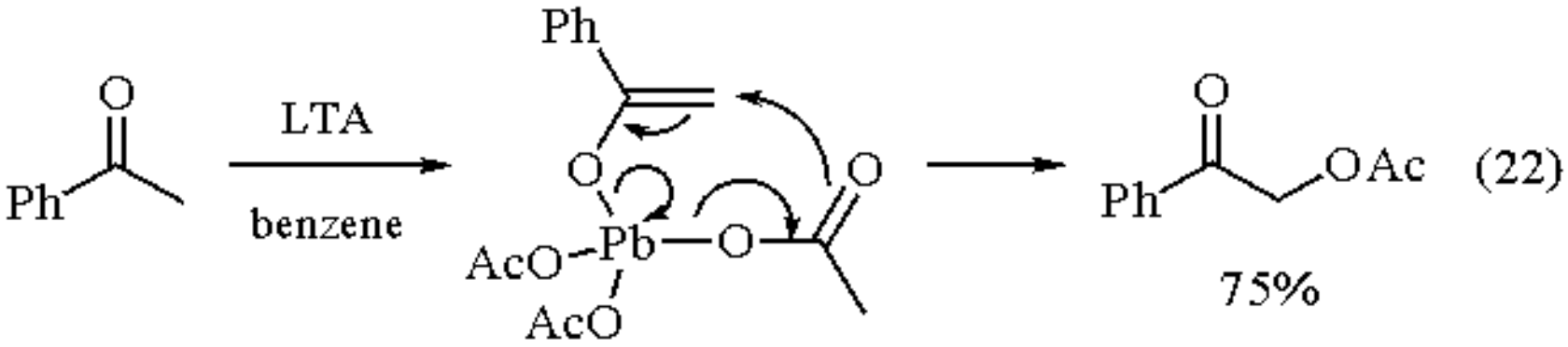
1,2-Glycol Cleavage

- LTA is one of the most frequently used reagents for the cleavage of 1,2-glycols and the preparation of the resulting carbonyl compounds.



Acetoxylation of Ketones

- The reaction of enolizable ketones with LTA is a standard method for α-acetoxylation. Enol ethers, enol esters, enamines, β-dicarbonyl compounds, β-keto esters, and malonic esters are also acetoxylated by LTA.



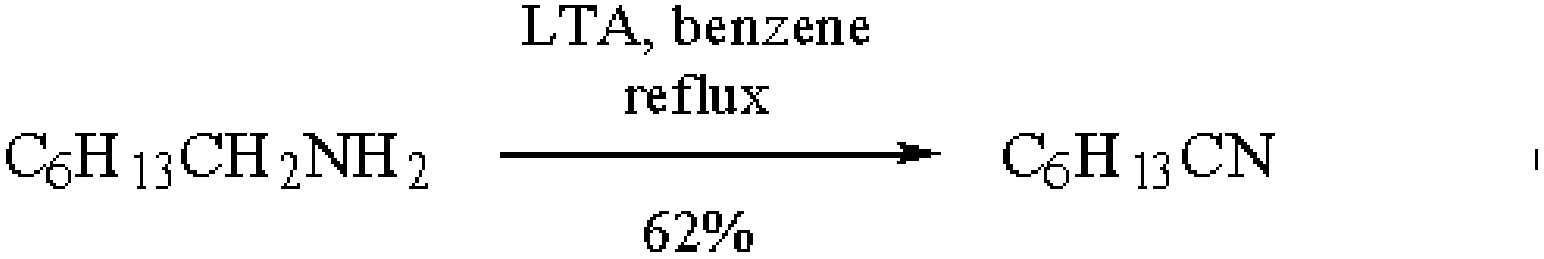
Decarboxylation of Acids

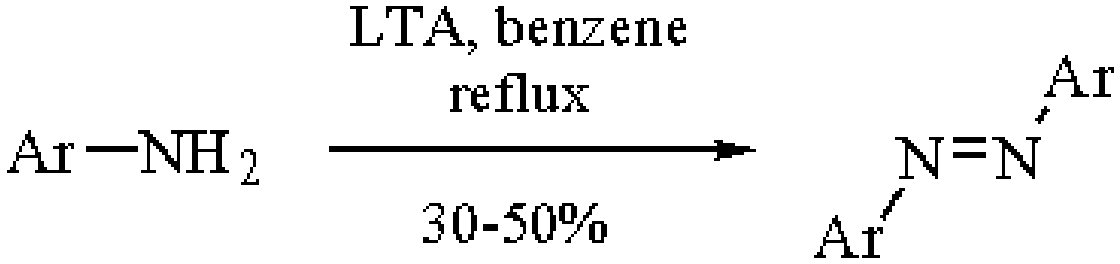
- Oxidative decarboxylation of carboxylic acids by LTA depends on the reaction conditions, coreagents, and structure of acids.
- The reactions are performed in nonpolar solvents (benzene, carbon tetrachloride) or polar solvents (acetic acid, pyridine).
- Thermal or photolytic decomposition decarboxylation occurs and alkyl radicals are formed.

$$n\,\text{R-CO}_2\text{H} + \text{Pb(OAc)}_4 \rightleftharpoons (\text{RCO}_2)_n\text{Pb(OAc)}_{4-n} \xrightarrow[(\text{or } h\nu)]{\Delta} n\,\text{R}\cdot + \text{CO}_2 + \text{Pb(OAc)}_2 \quad (23)$$

Oxidative Transformations of Nitrogen-Containing Compounds

- The LTA oxidation of aliphatic primary amines containing an α-methylene group results in dehydrogenation to alkyl cyanides (eq 1).
- However, aromatic primary amines give symmetrical azo compounds in varying yield (eq 2).





OsO4 (Osmium Tetroxide)

- **OsO4 (Osmium Tetroxide) As A Reagent For the Dihydroxylation Of Alkenes.**

- *Today's reagent is among one of the best and most useful at what it does in all of organic chemistry. It's blindingly good, in fact. So blinding, I don't know if I've ever seen an example of it being used in an undergraduate teaching lab. It's not a reagent for rookies: it's genuinely dangerous, and should be handled with extreme care.*

- **OsO_4 For The Formation Of Vicinal Diols From Alkenes**

- Osmium tetroxide (OsO_4) is a volatile liquid that is most useful for the synthesis of 1,2 diols from alkenes.

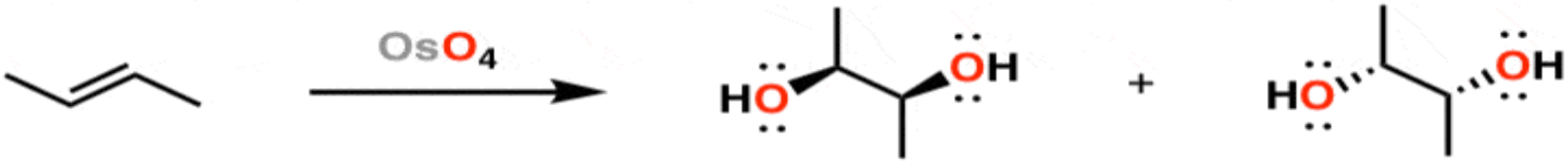
- (Side note: another name for 1,2 diols is vicinal diols, or *vic*-diols). The reaction is very mild, and usefully leads to the formation of *syn* diols.

- Another side note: **this reaction doesn't work with alkynes.**

Osmium Tetroxide, OsO_4

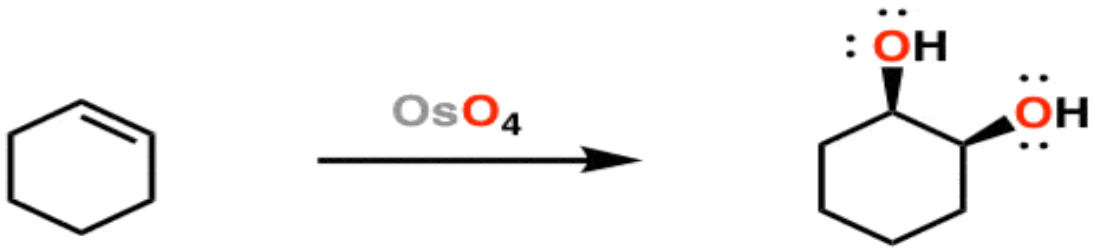
- Used for dihydroxylation of alkenes
- Always gives 1,2-diols (vicinal diols)
- Stereochemistry is always *syn*

Example 1:

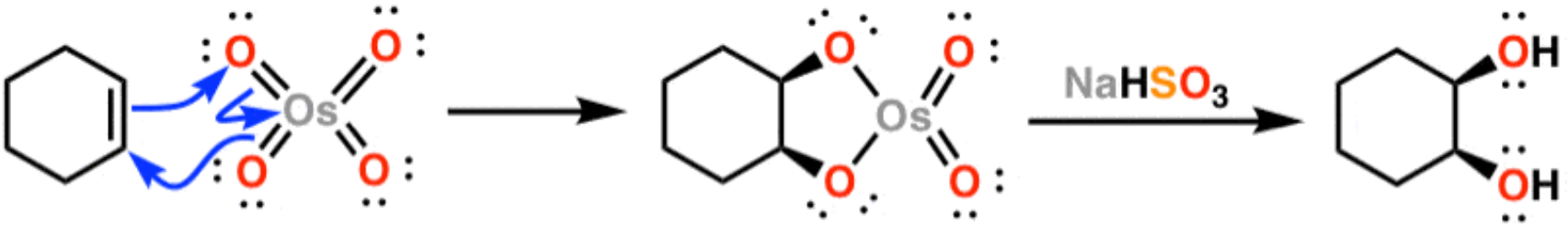


(enantiomer)

Example 2:



How it works: Dihydroxylation of alkenes



The oxygens both approach from the same side of the alkene

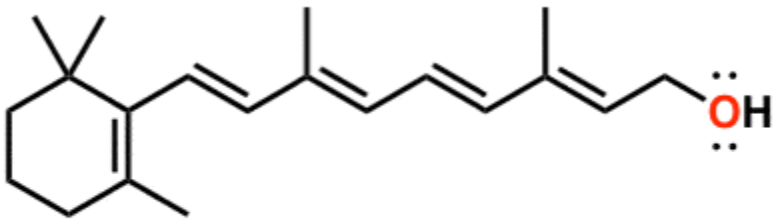
Sometimes NaHSO$_3$ (sodium bisulfite) is shown as a co-reactant. Its purpose is to break down the resulting cyclic Os compound into the diol and an osmium salt.

The reaction works through a concerted process whereby two oxygens from the osmium interact with one face of the double bond. This results in a 5-membered ring (called an osmate ester) and generates the *syn* stereochemistry. The osmate ester is broken up into the 1,2-diol by use of an aqueous solution of a reducing agent such as potassium bisulfite, KHSO$_3$. This is frequently omitted in textbooks (the mechanism is tedious to write out), but is worth mentioning just in case.

- By the way, dihydroxylation of alkenes can also be performed with cold, dilute potassium permanganate ($KMnO_4$).
- One advantage of OsO_4 is that it is much more compatible with other functional groups than KMnO4, which is kind of a ravenous beast.
- Why is osmium "blindingly good"? One of the molecules required for vision is retinol:

What do you think would happen if the vapors from OsO_4 reached your eyes? Everything would go dark, let me tell you.

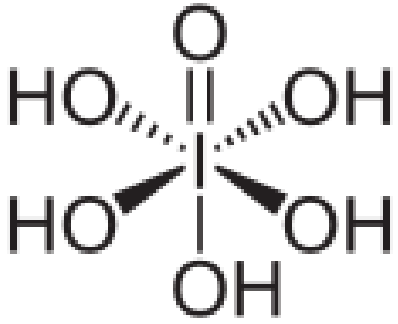
The good news is that apparently the blindness wears off after several months.

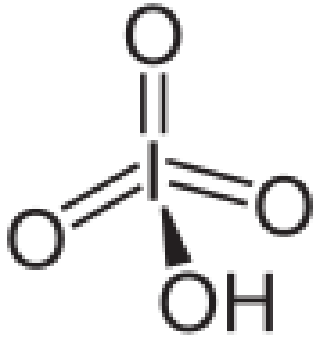


Retinol

Periodic Acid

- Periodic acid is the highest oxoacid of iodine, in which the iodine exists in oxidation state VII.
- Like all periodates it can exist in two forms: orthoperiodic acid, with the chemical formula H_5IO_6 and metaperiodic acid, which has the formula HIO_4.





- Periodic acid was discovered by Heinrich Gustav Magnus and C. F. Ammermüller in 1833

Periodic Acid

- In dilute aqueous solution, periodic acid exists as discrete hydronium and metaperiodate ions.
- When more concentrated, orthoperiodic acid, H_5IO_6, is formed; this dissociates into hydronium and orthoperiodate ions.
- In practice, the metaperiodate and orthoperiodate ions co-exist in a pH-dependent chemical equilibrium Orthoperiodic acid can be obtained as a crystalline solid that can be dehydrated to metaperiodic acid, HIO4.

Periodic Acid

Synthesis

✓Modern industrial scale production involves the electrochemical oxidation of iodic acid, on a PbO2anode, with the following standard electrode potential:

$$H_5IO_6 + H^+ + 2\ e^- \rightarrow IO^{-3} + 3\ H_2O\ E° = 1.6\ V$$

✓Orthoperiodic acid can be dehydrated to give metaperiodic acid by heating to 100 °C

$$HIO_4 + 2\ H_2O \rightleftharpoons H_5IO_6$$

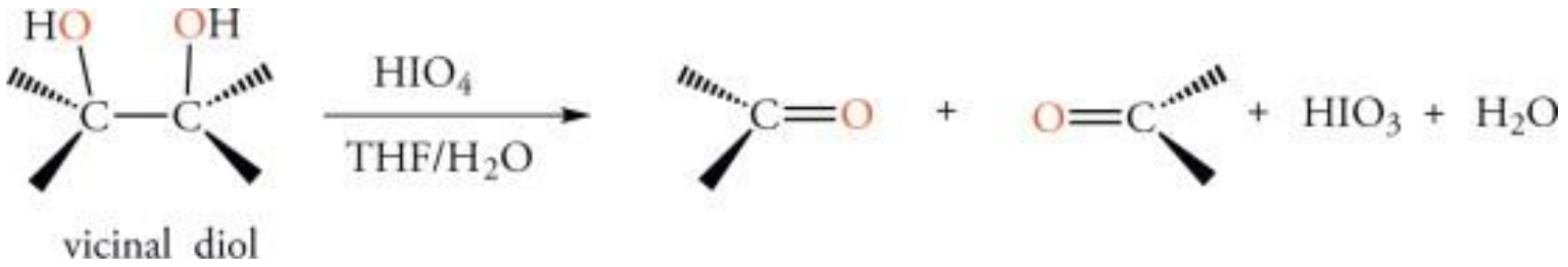
- Further heating to around 150 °C gives iodine pentoxide (I_2O_5) rather than the expected anhydride diiodine heptoxide (I_2O_7).
- Metaperiodic acid can also be prepared by from various orthoperiodates by treatment with dilute nitric acid.

$$H_5IO_6 \rightarrow HIO_4 + 2\ H_2O$$

Periodic acid is also used in as an oxidising agent of moderate strength.

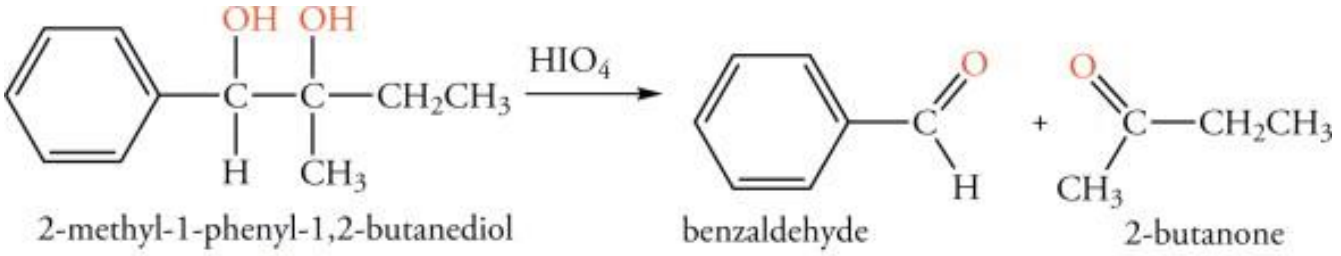
Periodic Acid

- Vicinal diols are cleaved by periodic acid to yield aldehydes or ketones, depending on the number of substituents on the carbon atoms bearing the hydroxyl groups. The periodic acid is reduced to iodic acid (HIO_3).

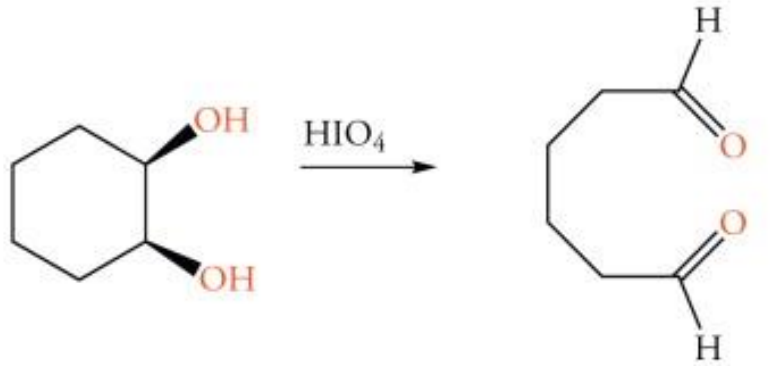


Periodic Acid

- If the vicinal diol is contained in an acyclic portion of a molecule, two carbonyl compounds result—unless the vicinal diol is a symmetrical molecule, in which case it yields two equivalents of a carbonyl compound. If the two hydroxyl groups are on a ring, a ring-opened product containing two carbonyl groups forms.



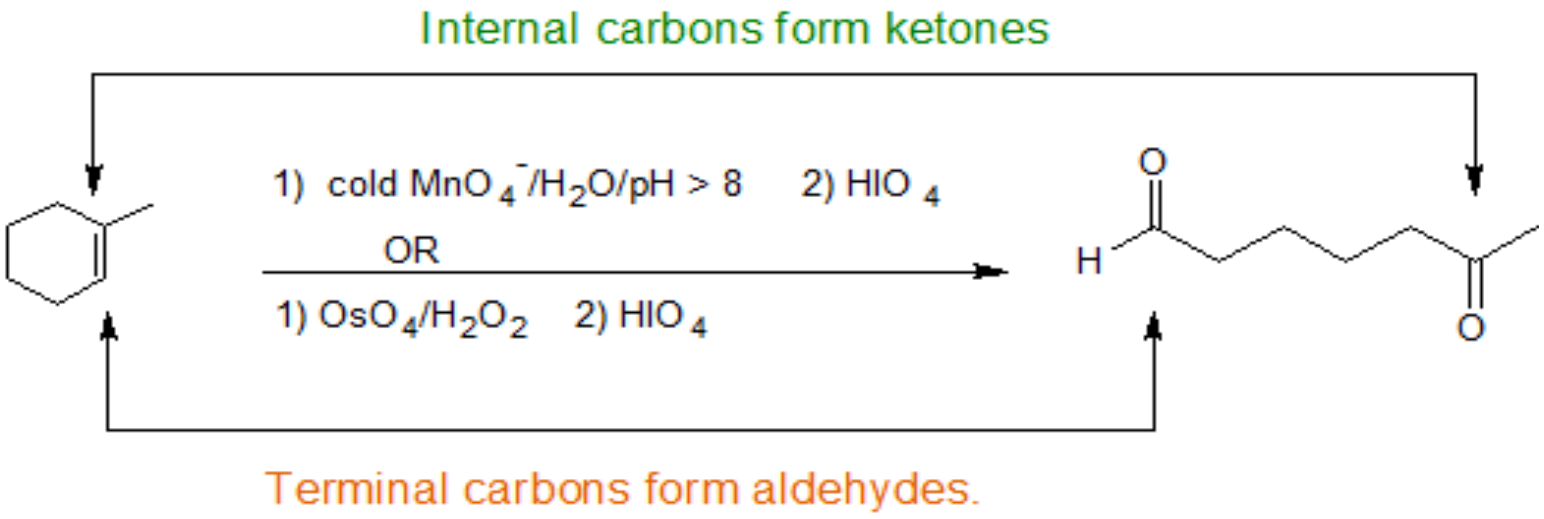
2-methyl-1-phenyl-1,2-butanediol benzaldehyde 2-butanone



cis-1,2-cyclohexanediol 6-oxohexanal

Oxidation of Alkenes

- Alkenes can also be gently cleavage in a two-step reaction sequence in which the alkene first undergoes syn-dihydroxylation using cold, slightly basic $KMnO_4$ or OsO_4/H_2O_2 followed by oxidation with periodic acid (HIO_4).
- Both reaction sequences are shown below using 1-methylcyclohexene as an example.



Dimethyl Sulfoxide (DMSO)

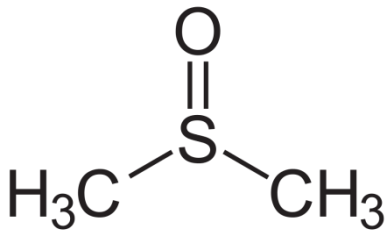
- Dimethyl Sulfoxide (DMSO) is a highly polar and water miscible organic liquid.
- It is essentially odorless, and has a low level of toxicity.
- DMSO is a dipolar aprotic solvent, and has a relatively high boiling point.
- Further below is a compilation of Physical Properties data for this useful solvent.
- DMSO, or dimethyl sulfoxide, is a by-product of paper making. It comes from a substance found in wood.
- DMSO has been used as an industrial solvent since the mid-1800s. From about the mid-20th century, researchers have explored its use as an anti-inflammatory agent.

Dimethyl Sulfoxide (DMSO)

- The FDA has approved DMSO as a prescription medication for treating symptoms of painful bladder syndrome.
- It's also used under medical supervision to treat several other conditions, including shingles.
- DMSO is available without a prescription most often in gel or cream form. It can be purchased in health food stores, by mail order, and on the Internet.
- While it can sometimes be found as an oral supplement, its safety is unclear. DMSO is primarily used by applying it to the skin.

Dimethyl Sulfoxide (DMSO)

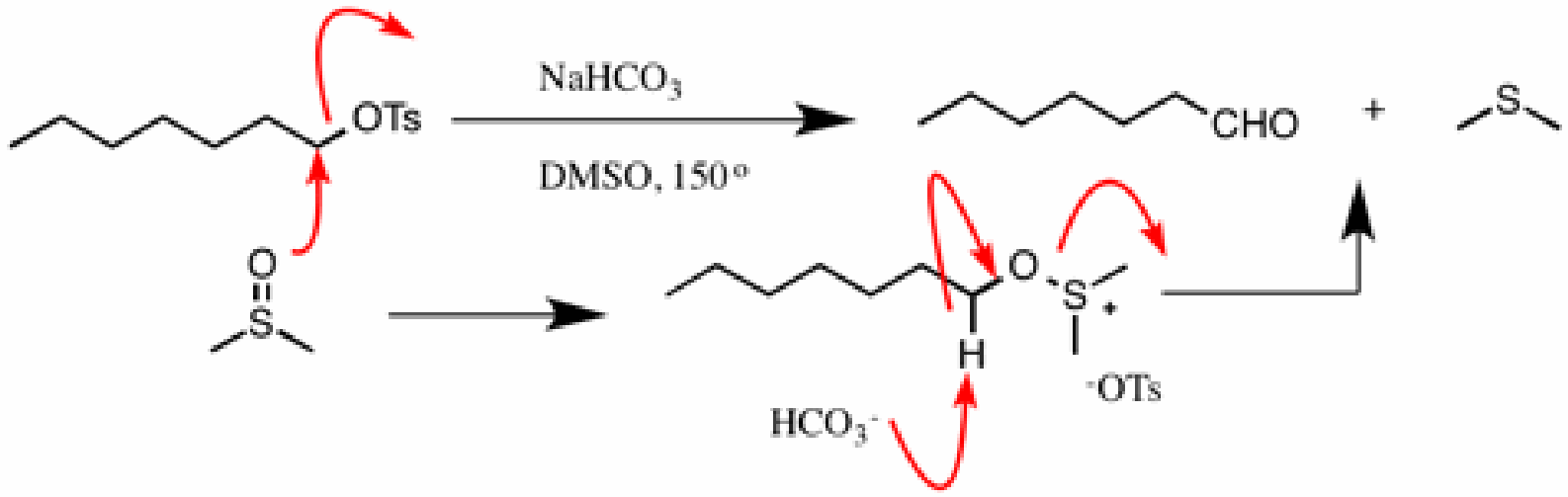
- In terms of chemical structure, the molecule has idealized C_s symmetry. It has a trigonal pyramidal molecular geometry.



It was first synthesized in 1866 by the Russian scientist Alexander Zaytsev, who reported his findings in 1867. Dimethyl sulfoxide is produced industrially from dimethyl sulfide, a by-product of the Kraft process, by oxidation with oxygen or nitrogen dioxide.

Dimethyl Sulfoxide (DMSO)

- **Kornblum Oxidation:** (1959) A primary tosylate is heated at 150° to cause S_N2 displacement by the oxygen of dimethyl sulfoxide (DMSO) in the presence of $NaHCO_3$.
- The accepted mechanism at the time was an E2 elimination as shown. Dimethyl sulfide (DMS) is the reduction product of the reaction. This work formed the tosylate from the alkyl iodide with silver tosylate.

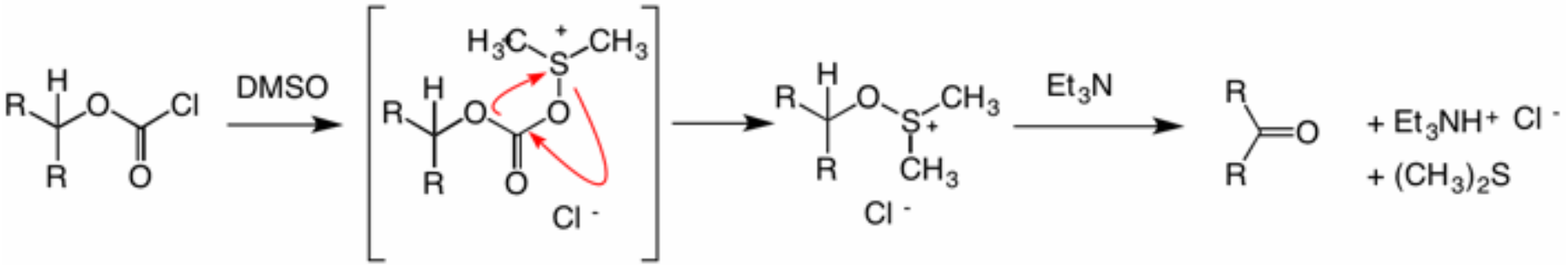


Dimethyl Sulfoxide (DMSO)

Barton Modification: (1964) Barton and coworkers were able to generate sulfenate salts by treating alkyl chloroformates with DMSO with loss of CO_2.

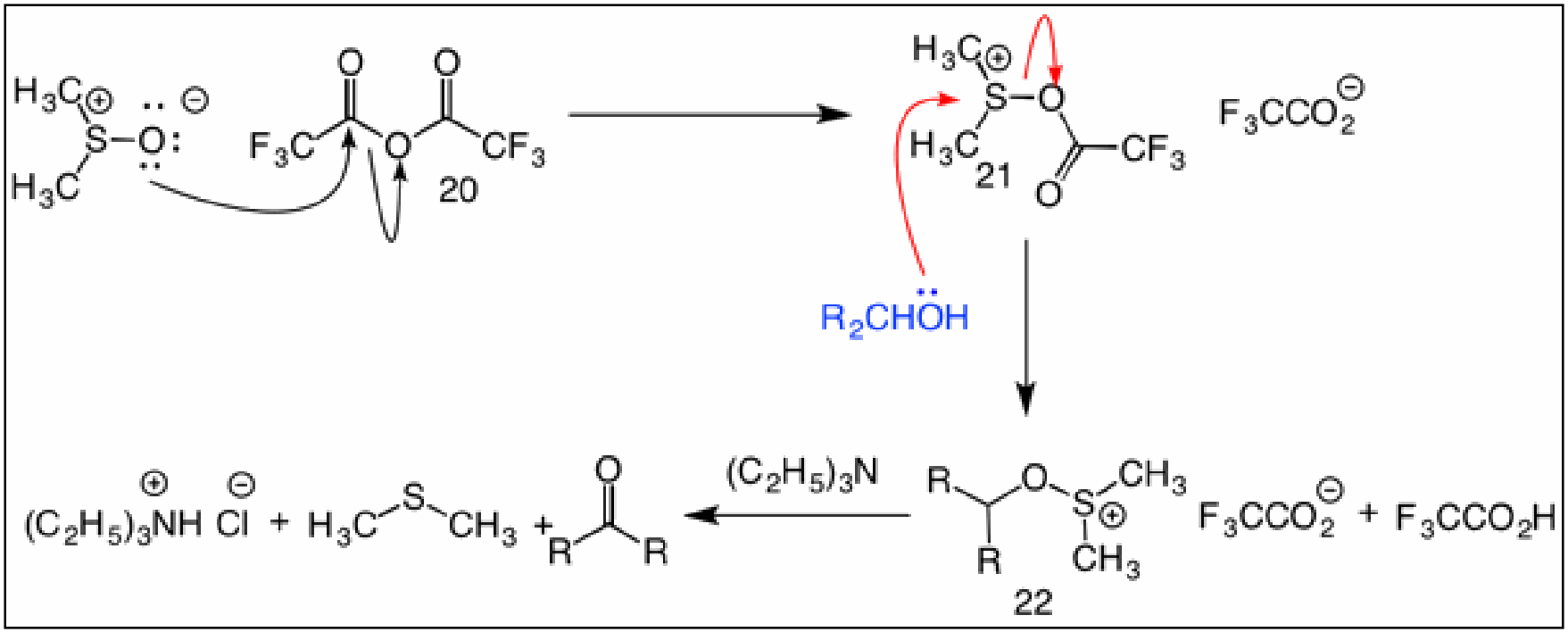
❖Addition of triethylamine generates the oxidation product. This procedure ameliorated the harsh conditions of the Kornblum procedure.

❖Moreover, the chloroformate is readily available by treatment of the alcohol to be oxidized with excess phosgene.

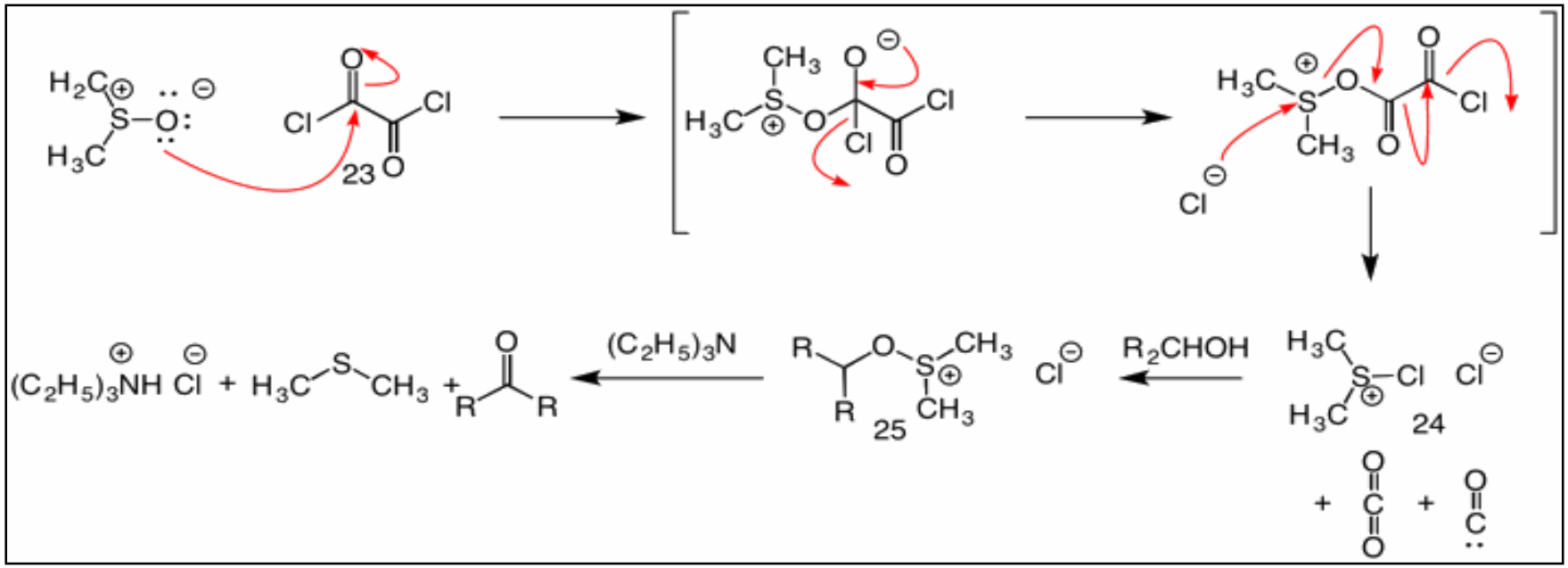


Dimethyl Sulfoxide (DMSO)

- **Swern Oxidation:** (1976) This early Swern oxidation employs trifluoroacetic anhydride (**20**) at -50°C to activate dimethyl sulfoxide. Addition of the alcohol to intermediate **21** yields the desired sulfenate **22**. The ketone or aldehyde is produced in the usual fashion with triethylamine.



- **Swern Oxidation:** (1978) This later Swern procedure is a convenient method for the production of reagent **24** without using dimethyl sulfide and chlorine. Dimethyl sulfoxide, which is at the same oxidation level as salt **24**, reacts with oxalyl chloride (**23**) to liberate carbon monoxide, carbon dioxide and reagent **24**. Addition of the primary or secondary alcohol followed by deprotonation of sulfenate **25** with triethylamine leads to the desired aldehyde or ketone, respectively.



Ozone

- 1856 Thomas Andrews showed that the ozone was formed only by oxygen,
- and in 1863 Soret established the relationship between oxygen and ozone by finding that
- *three volumes of oxygen produce two volumes of ozone.*
- Formation of ozone is endothermic:

  $3\ O2 \rightarrow 2\ O3\ \Delta H$ at 1 atm = +284.5 $kJ.mol^{-1}$
- Ozone is thermodynamically is unstable and spontaneously reverts back into oxygen.

Ozone

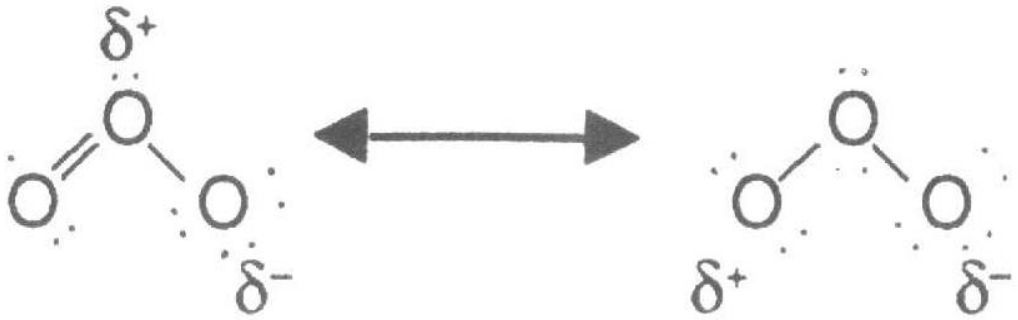
- Ozone is a strong oxidizing agent, capable of participating in many chemical reactions with inorganic and organic substances.
- Comercially, ozone has been applied as a chemical reagent in synthesis, used for potable water purification, as a disinfectant in sewage treatment, and for the bleaching of natural fibers (Ullmann's, 1991).

Physical properties of ozone

- Ozone is an irritating pale blue gas, heavier than the air, very reactive and unstable, which cannot be stored and transported, so it has to be generated “in situ”.
- It is explosive and toxic, even at low concentrations. In the Earth’s stratosphere, it occurs naturally (with concentrations between 5 and 10 ppm).
- Protecting the planet and its inhabitants by absorbing ultraviolet radiation of wavelength 290-320 nm (Ullmann’s, 1991).

Physical properties of ozone

- By analysis of the electronic structure, the molecule is considered to have the following resonant structure;

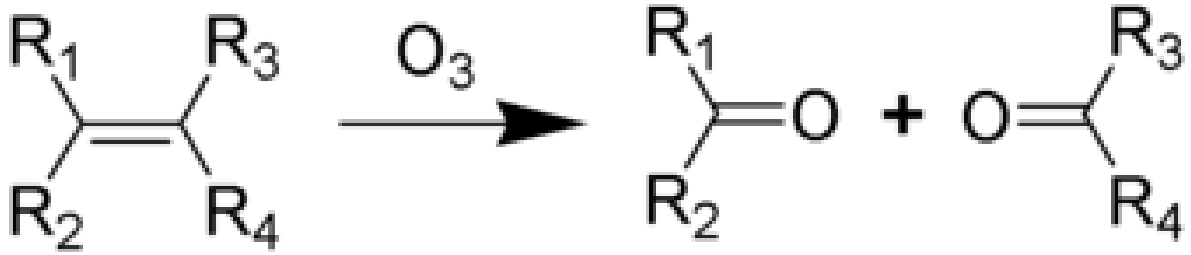


Résonance structure of ozone (Langlais et al., 1991)

The chemistry of ozone is largely governed by its strongly electrophilic nature.

Ozonolysis

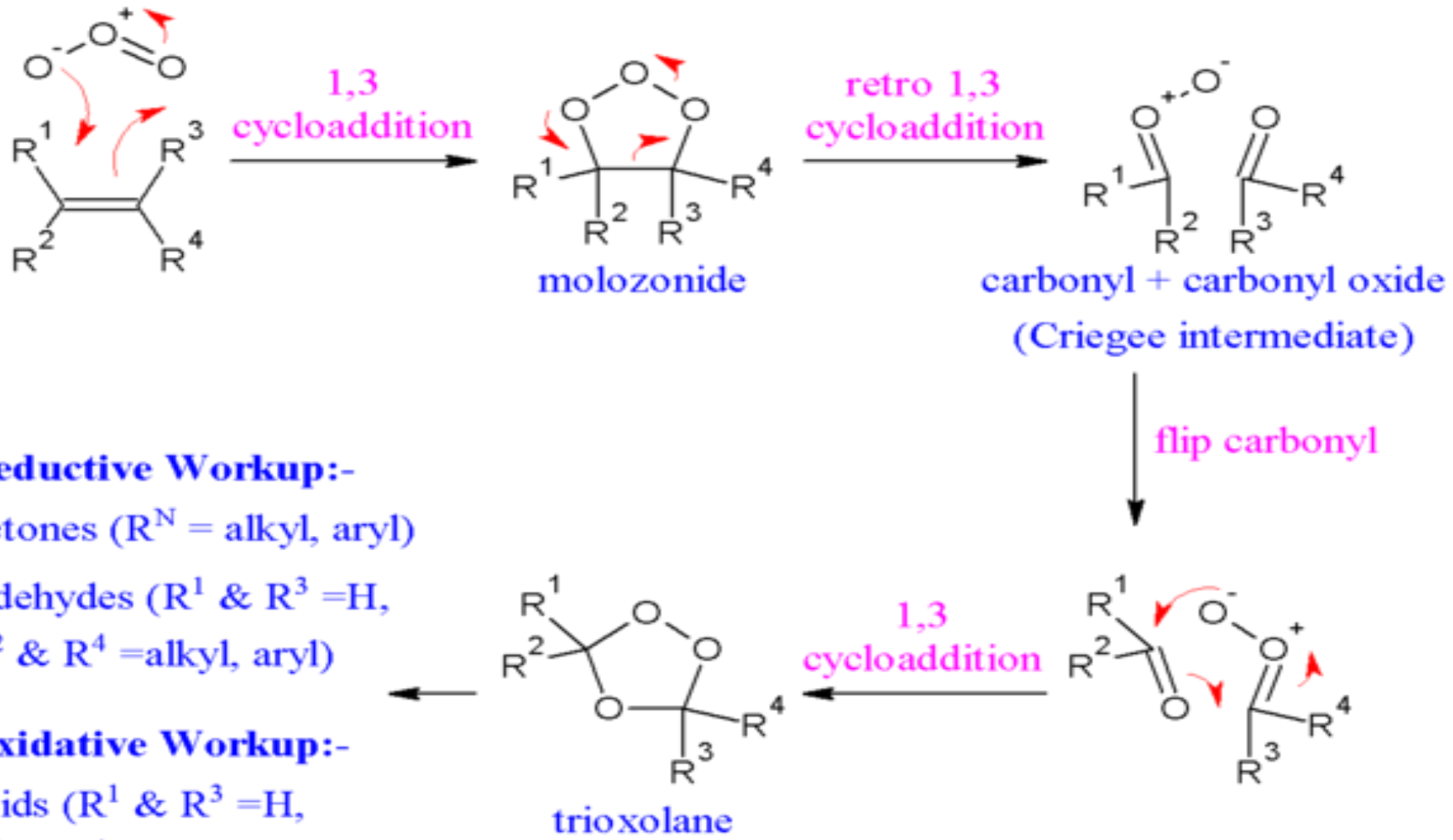
- **Ozonolysis** is an organic reaction where the unsaturated bonds of alkenes, alkynes, or azo compounds are cleaved with ozone. Alkenes and alkynes form organic compounds in which the multiple carbon–carbon bond has been replaced by a carbonyl group.
- Alkenes can be oxidized with ozone to form alcohols, aldehydes or ketones, or carboxylic acids.
- In a typical procedure, ozone is bubbled through a solution of the alkene in methanol at −78 °C until the solution takes on a characteristic blue color, which is due to unreacted ozone.



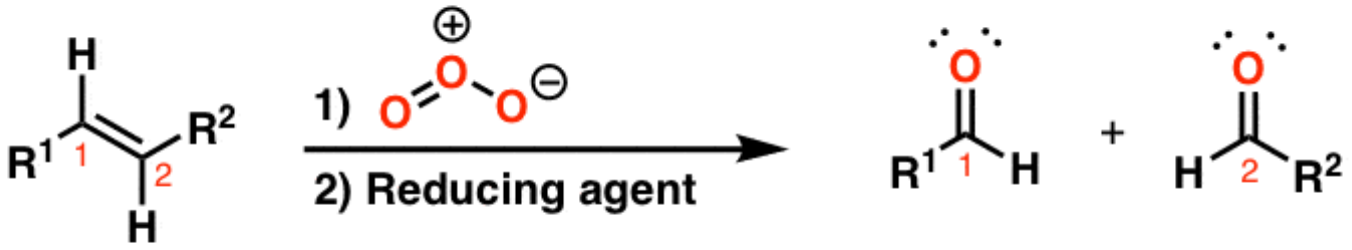
Ozonolysis

- n the generally accepted mechanism proposed by Rudolf Criegee in 1953, the alkene and ozone form an intermediate molozonide in a 1,3-dipolar cycloaddition.
- Next, the molozonide reverts to its corresponding **carbonyl oxide** (also called the Criegee intermediate or Criegee zwitterion) and aldehyde or ketone in a retro-1,3-dipolar cycloaddition.
- The oxide and aldehyde or ketone react again in a 1,3-dipolar cycloaddition or produce a relatively stable ozonide intermediate (a trioxolane).

Ozonolysis

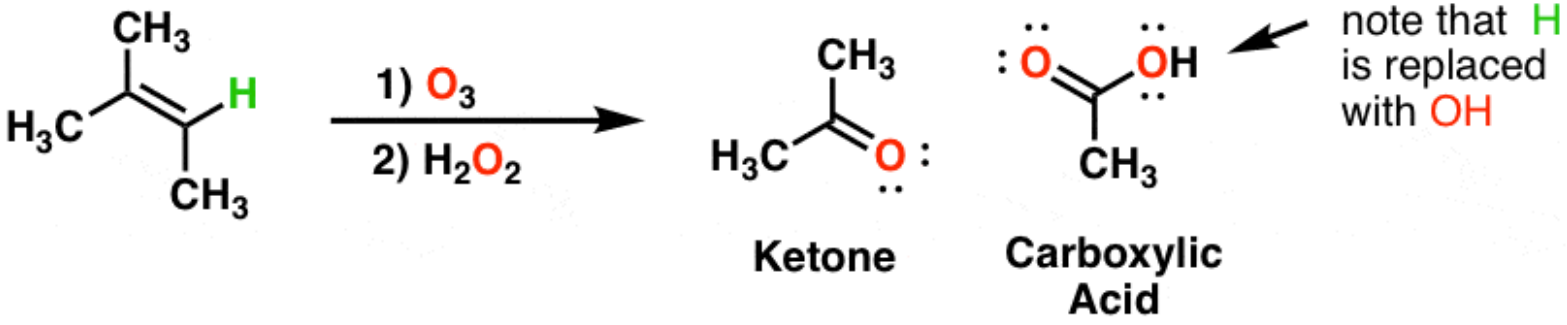

1,3
cycloaddition
molozonide
retro 1,3
cycloaddition
carbonyl + carbonyl oxide
(Criegee intermediate)
flip carbonyl
1,3
cycloaddition
trioxolane
Reductive Workup:-
ketones (R^N = alkyl, aryl)
aldehydes (R^1 & R^3 =H,
R^2 & R^4 =alkyl, aryl)
Oxidative Workup:-
acids (R^1 & R^3 =H,
R^2 & R^4 =alkyl, aryl)

Ozonolysis of alkenes with reductive workup



(common reducing agents are zinc (Zn) or dimethyl sulfide $(CH_3)_2S$)

"Oxidative workup" oxidizes sp^2 hybridized C–H bonds to C–OH as well as cleaving C=C



Typical oxidant used for "oxidative workup" is H_2O_2 ; this oxidizes any aldehydes to carboxylic acids

The same process can be performed by replacing O_3 with hot, acidic $KMnO_4$

Mercury(II) oxide

- **Mercury(II) oxide**, also called **mercuric oxide** or simply **mercury oxide**, has a formula of HgO.
- It has a red or orange color. Mercury(II) oxide is a solid at room temperature and pressure. The mineral form montroydite is very rarely found.
- The red form of HgO can be made by heating Hg in oxygen at roughly 350 °C, or by pyrolysis of $Hg(NO_3)_2$.
- The yellow form can be obtained by precipitation of aqueous Hg^{2+} with alkali.
- The difference in color is due to particle size, both forms have the same structure consisting of near linear O-Hg-O units linked in zigzag chains with an Hg-O-Hg angle of 108°

Mercury(II) oxide

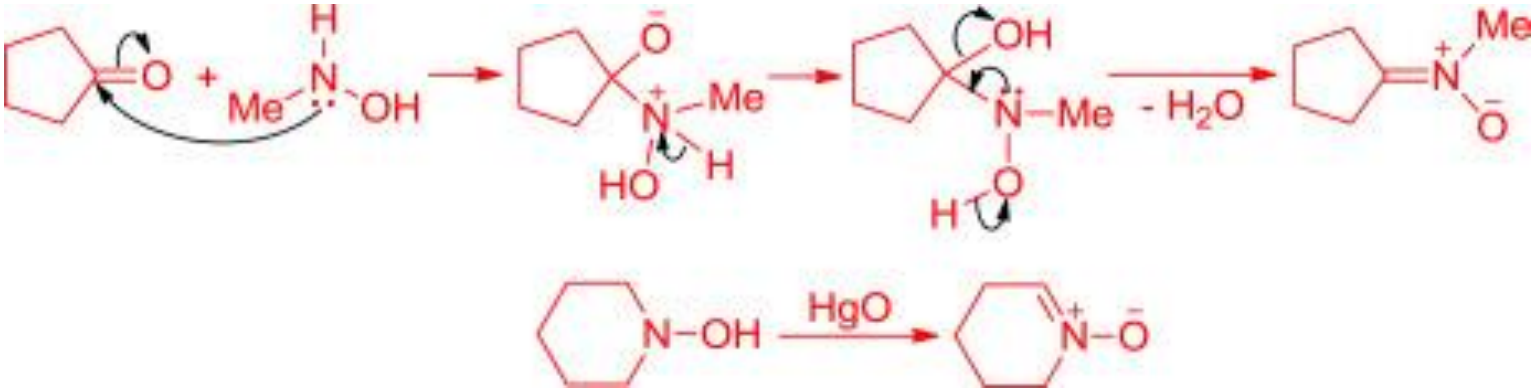
- **Mercury (II) oxide reference electrode (Hg/HgO)**
- $HgO + 2e^- + H_2O \rightleftharpoons Hg + 2OH^-$, $EHg|HgOo = 0.098V$

- **Condensation of alcohols with acetylenes**
- Acetylene reacts with alcohols in the presence of boron trifluoride and mercuric oxide to afford acetals. Substituted acetylenes react with alcohols to give ketals. The reaction probably proceeds via the intermediate vinyl ether as shown in Eq.

$$ROH + HC{\equiv}CH \xrightarrow{HgO\text{-}BF_3} ROCH{=}CH_2 \xrightarrow{ROH} (RO)_2CH{-}CH_3$$

Mercury(II) oxide

- **Cycloaddition with Nitrones**
- Nitrones are stable compounds and thus do not require in situ generation. The two commonly employed methods for the preparation of nitrones are: (1) reaction of an aldehyde or ketone with a monosubstituted hydroxylamine and (2) oxidation of a hydroxylamine with yellow mercuric oxide



Potassium ferricyanide ($K_3Fe(CN)_6$)

- **Potassium ferricyanide** is the chemical compound with the formula $K_3[Fe(CN)_6]$. This bright red salt contains the octahedrally coordinated $[Fe(CN)_6]^{3-}$ ion.
- It is soluble in water and its solution shows some green-yellow fluorescence. It was discovered in 1822 by Leopold Gmelin, and was initially used in the production of ultramarine dyes.

- Potassium ferricyanide is manufactured by passing chlorine through a solution of potassium ferrocyanide. Potassium ferricyanide separates from the solution:

- $2\ K_4[Fe(CN)_6] + Cl_2 \rightarrow 2\ K_3[Fe(CN)_6] + 2\ KCl$

Potassium ferricyanide ($K_3Fe(CN)_6$)

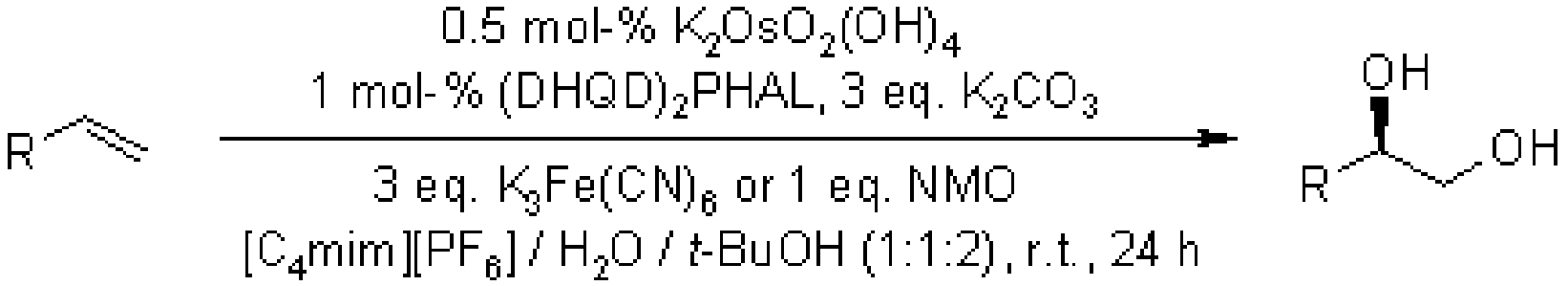
- Potassium ferricyanide was used as an oxidizing agent to remove silver from color negatives and positives during processing, a process called bleaching.
- Because potassium ferricyanide bleaches are environmentally unfriendly, short-lived and capable of releasing hydrogen cyanide gas if mixed with acid, bleaches using ferric EDTA have been used in color processing since the 1972 introduction of the Kodak C-41 process.
- The compound is also used to harden iron and steel, in electroplating, dyeing wool, as a laboratory reagent, and as a mild oxidizing agent in organic chemistry.

Potassium ferricyanide ($K_3Fe(CN)_6$)

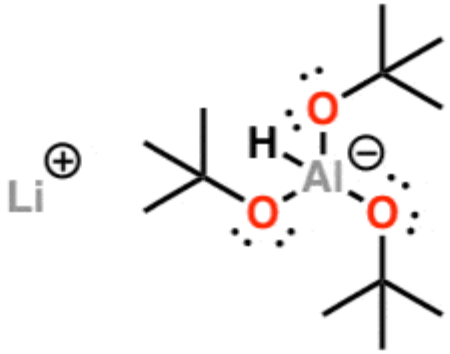
- **Recent Literature**

  The ionic liquids [C_4mim][PF_6] and [C_8mim][PF_6] as cosolvents in asymmetric dihydroxylation give yields and enantioselectivity comparable or higher than those of the conventional H_2O/*tert*-BuOH solvent system. After extraction of the reaction mixture with diethyl ether, the contamination of the product by osmium was remarkably low. The reuse of ionic liquid and catalyst is possible.

  L. C. Branco, C. A. M. Afonso, *J. Org. Chem.*, **2004**, *69*, 4381-4389.



Lithium Tri-*tert*-butoxyaluminum Hydride ($LiAlH(Ot\text{-}Bu)_3$)



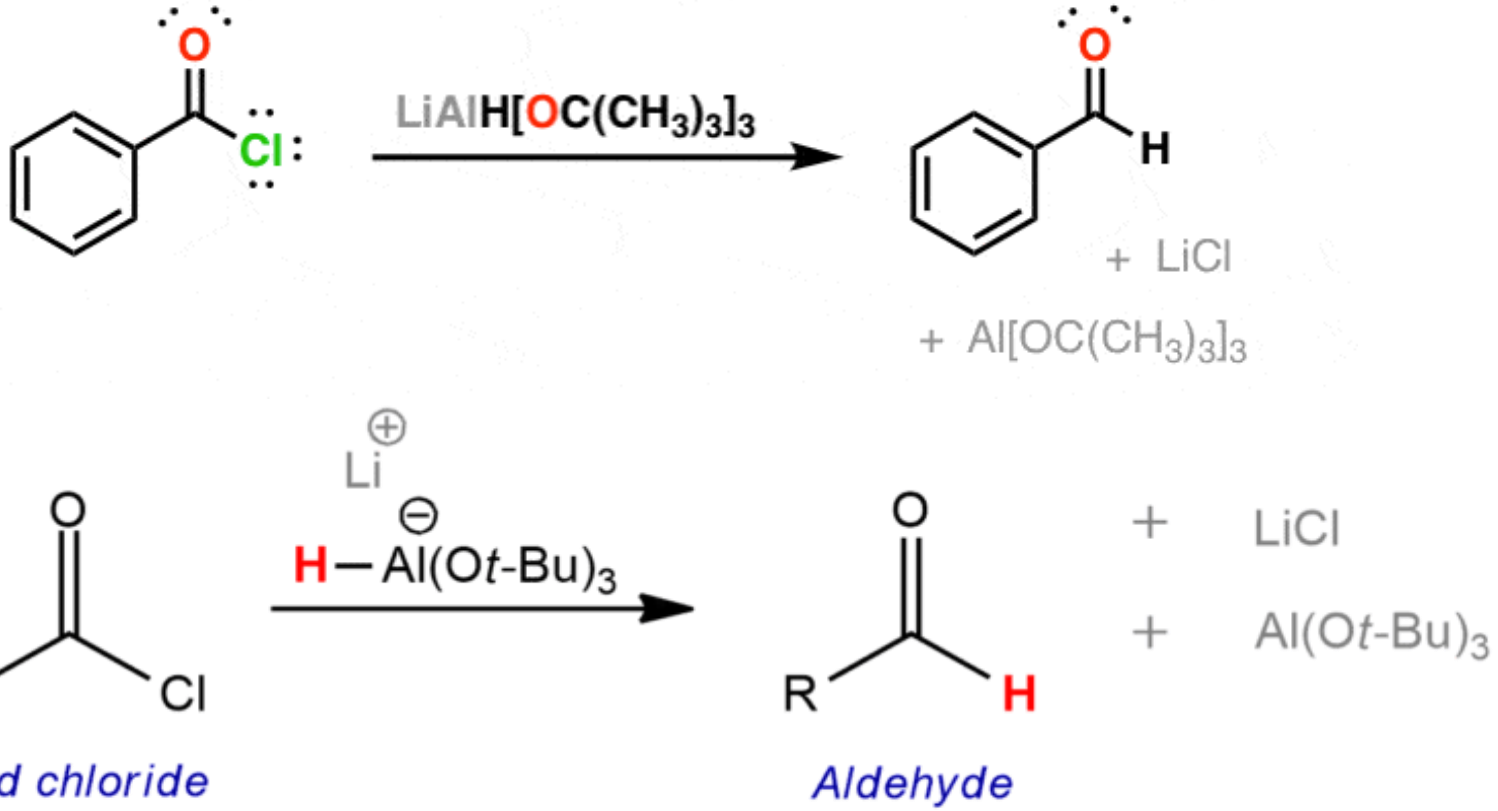
Lithium tri-t-butoxy aluminum hydride

Lithium tri *tert*-butoxy aluminum hydride is lot like lithium aluminum hydride, but with a difference. Like lithium aluminum hydride, it's a reducing agent. As a source of hydride, it will form carbon-hydrogen bonds.

- Unlike lithium aluminum hydride, which is kind of a raging beast, reducing everything in sight, $LiAlH[OC(CH_3)_3]_3$ is a lot more controlled.
- First of all, it only has one hydride to give, unlike $LiAlH_4$, so it's a lot easier to control the reaction using stoichiometry.
- Secondly, those big bulky tert-butoxy groups (that's $-OC(CH_3)_3$) help to modulate (i.e. slow down) the reactivity of the reagent. They're kind of like a fat suit around aluminum that ensure that the hydride can't fit into tight spaces.

Reduction Of Acid Chlorides To Aldehydes ByLiAlH(Ot-Bu)3

Example 1: Reduction of acyl chlorides to give aldehydes



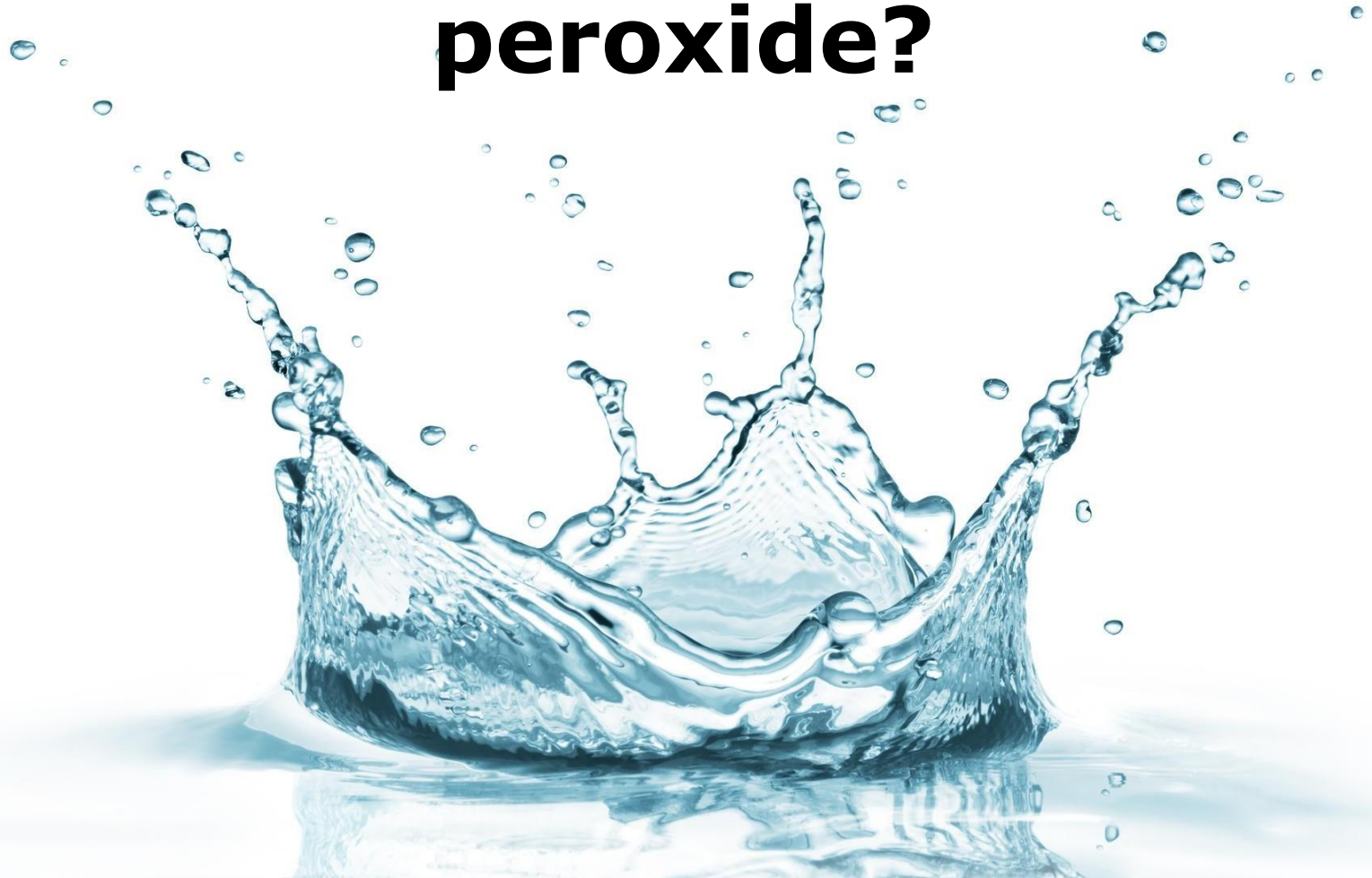
Tributyltin hydride (TBTH)

- **Tributyltin hydride** is an organotin compound with the formula $(C_4H_9)_3SnH$.
- It is a colorless liquid that is soluble in organic solvents.
- The compound is used as a source of hydrogen atoms in organic synthesis.
- It is a useful reagent in organic synthesis. Combined with azobisisobutyronitrile (AIBN) or by irradiation with light, tributyltin hydride converts organic halides (and related groups) to the corresponding hydrocarbon.
- This process occurs via a radical chain mechanism involving the radical $Bu_3Sn\bullet$.
- The radical abstracts a H• from another equivalent of tributyltin hydride, propagating the chain

Tributyltin hydride (TBTH)

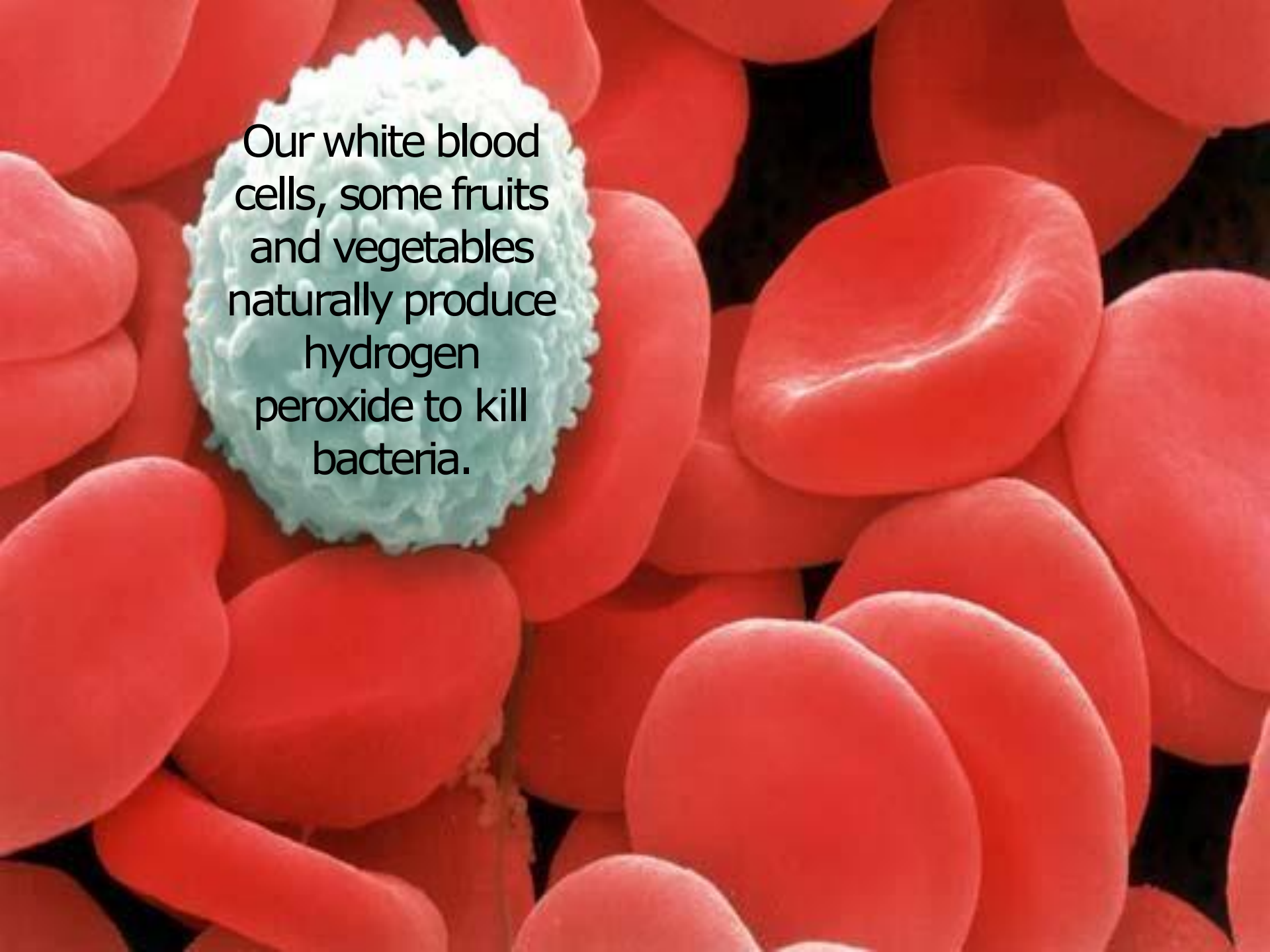
- Tributyltin hydride's utility as a H• donor can be attributed to its relatively weak bond strength (78 kcal/mol).
- It is the reagent of choice for hydrostannylation reactions:
- $RC_2R' + HSnBu_3 \rightarrow RC(H)=C(SnBu_3)R'$

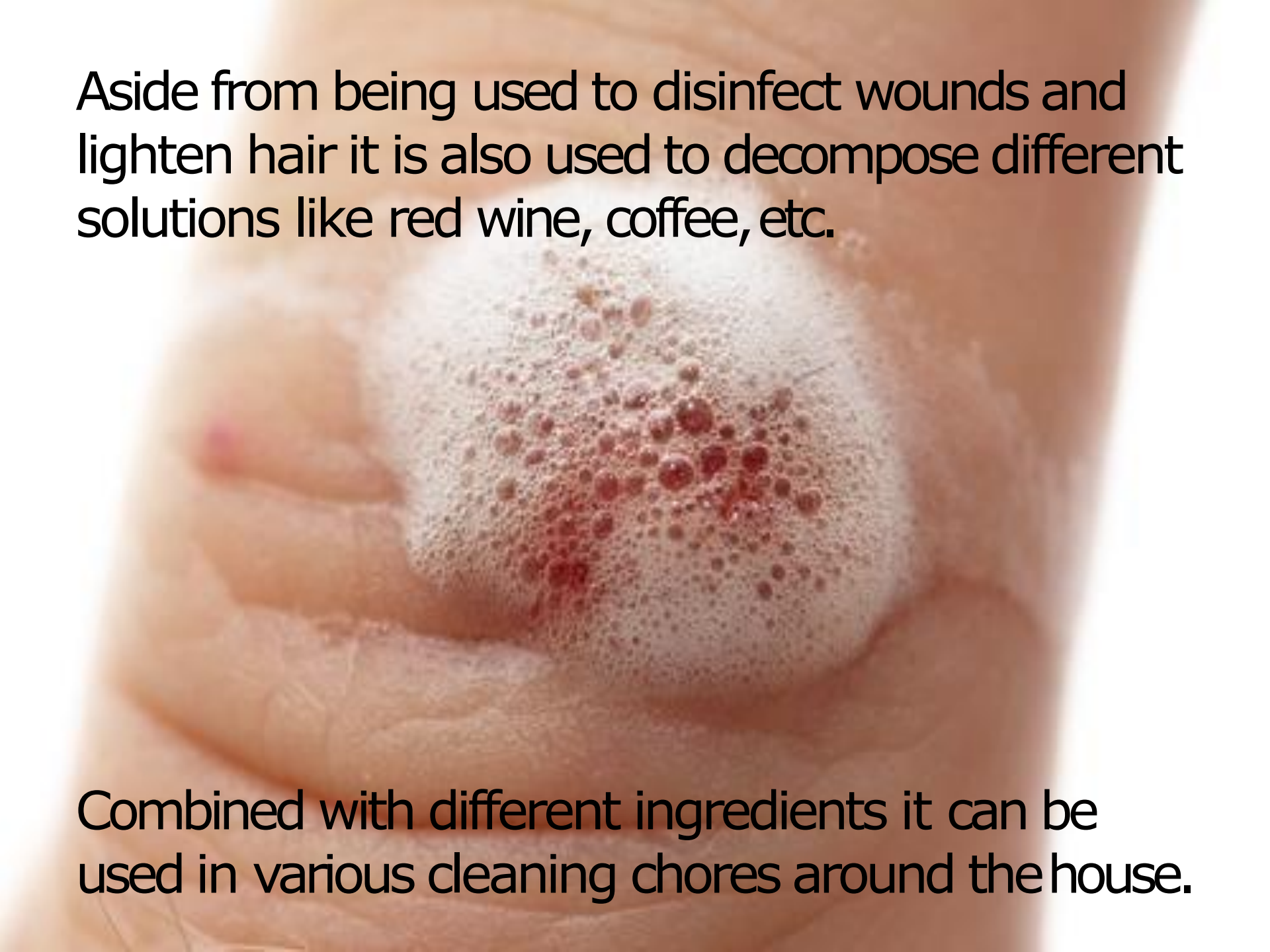
What is hydrogen peroxide?



Composed by hydrogen and oxygen, it is colourless, weak acid which has many uses.

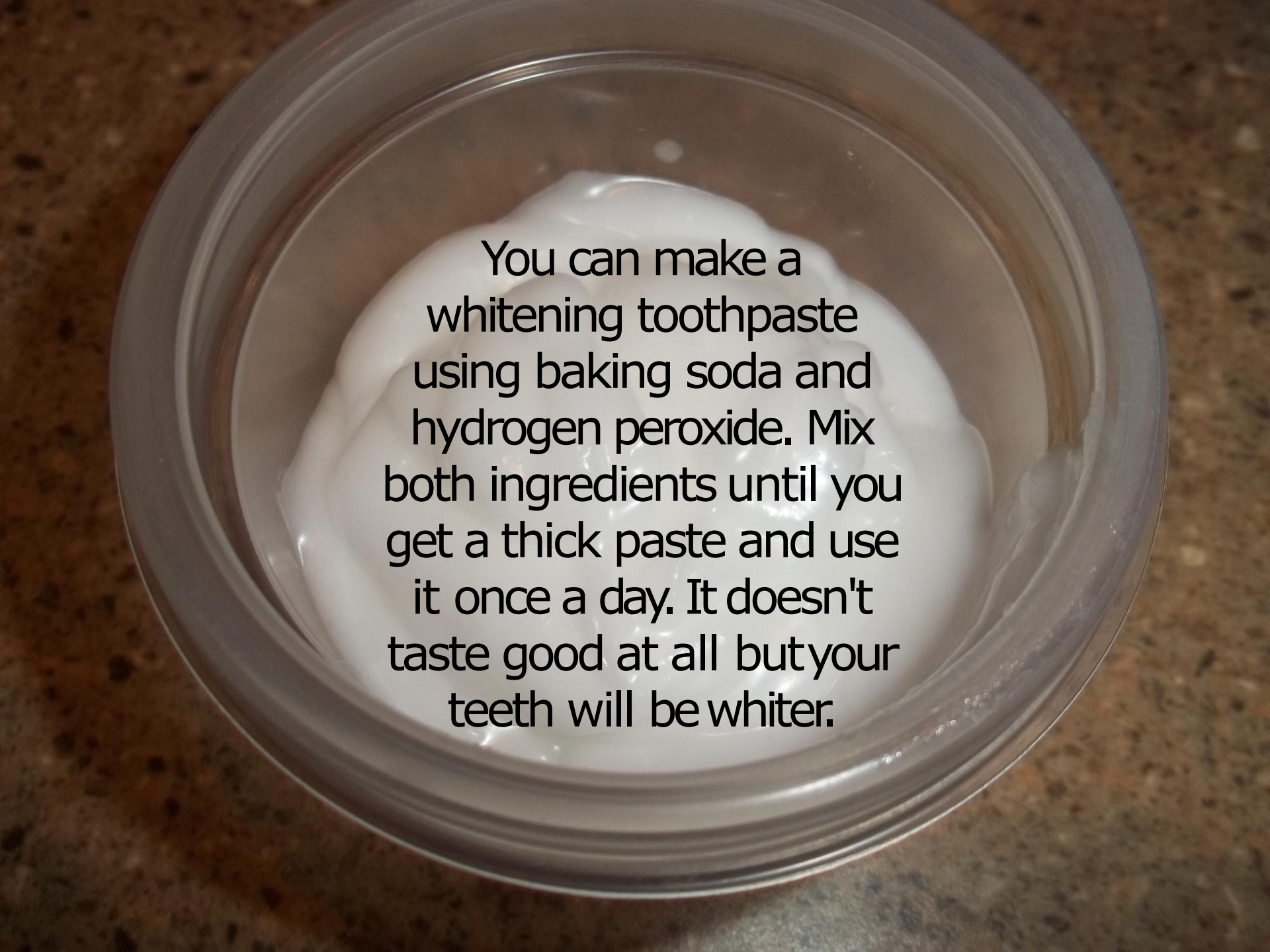
In addition to its disinfecting qualities hydrogen peroxide also has bleaching properties. Being 100% degradable H2O2 is preferred cleaner by most homemakers. Moreover it doesn't leave any residue.


Our white blood cells, some fruits and vegetables naturally produce hydrogen peroxide to kill bacteria.



Aside from being used to disinfect wounds and lighten hair it is also used to decompose different solutions like red wine, coffee, etc.

Combined with different ingredients it can be used in various cleaning chores around the house.


You can make a whitening toothpaste using baking soda and hydrogen peroxide. Mix both ingredients until you get a thick paste and use it once a day. It doesn't taste good at all but your teeth will be whiter.

The same paste can be used to clean different surfaces including moisture sensitive fabrics and clothes.


Kill fungus with a solution of water and 3% hydrogen peroxide mixed together in equal quantities. Soak your feet fifteen minutes a day for a week and you'll get rid of fungus.

Sustain plant growth by sprinkling it with a 50/50 solution of hydrogen peroxide and tap water.

90% solution of hydrogen peroxide is used as rocket fuel

During the London bombings in 2005 homemade hydrogen peroxide bombs are used.

INTRODUCTION

- Hydrogen Peroxide was discovered by a French chemist J.L. Thenard in 1818.
- Its molecular formula is **H_2O_2**

PREPARATION OF H_2O_2

- **H_2O_2** can be prepared in laboratory by:

1. The action of cold, dilute sulphuric acid on sodium.
2. The action of cold, dilute sulphuric acid on barium peroxide.

PREPARATION OF H_2O_2

1. **FROM SODIUM PEROXIDE[MERCK'S PROCESS]**

Hydrogen peroxide is prepared by adding calculated amount of sodium peroxide to ice cold dilute solution of sulphuric acid. The addition is carried out slowly in small amounts with constant stirring.

$$Na_2O_2+H_2SO_4 \rightarrow Na_2SO_4+H_2O_2$$

upon cooling, crystals of $Na_2SO_4.10H_2O$ separate out. The crystals of $Na_2SO_4.10H_2O$ are decanted leaving behind solution of hydrogen peroxide.

PREPARATION OF H_2O_2

2. FROM BARIUM PEROXIDE

In this method, a paste of hydrated barium peroxide is prepared in ice cold water and is treated with about 20% ice cold solution of sulphuric acid.

$$BaO_2.8H_2O + H_2SO_4 \rightarrow BaSO_4 + H_2O_2 + 8H_2O$$

The white precipitate of $BaSO_4$ is removed by filtration leaving behind about 5% solution of H_2O_2.

MANUFACTURE OF H_2O_2

1. BY ELECTROLYSIS OF 50% H_2SO_4 SOLUTION

In this method, a 50 % solution of sulphuric acid is electrolysed at high current density in an electrolytic cell when peroxodisulphuric acid is formed at the anode.

$$2H_2SO_4 \rightarrow H_2S_2O_8 + H_2$$

peroxodisulphuric acid is drawn off from the cell and hydrolysed with water to give H_2O_2. The resulting solution is distilled under low pressure when H_2O_2 gets distilled while H_2SO_4 with high boiling point, remains undistilled.

MANUFACTURE OF H_2O_2

2. FROM 2 ETHYLANTHRAQUINOL

The method involves the following steps:

i. 2 ethyl anthraquinone is dissolved in benzene and hydrogen gas is passed through the solution in the presence of paladium catalyst.

ii. The reduced product is dissolved in a mixture of benzene and cyclohexanol and upon passing air, it is oxidised back to 2 ethyl anthraquinone and **H_2O_2** is produced.

CONCENTRATION OF H_2O_2

The **H_2O_2** obtained by the mentioned method is extracted with water and the aqueous solution is concentrated. Concentration of the solution cannot be done by simple boiling because, **H_2O_2** decomposes below its boiling point.

Further , the decomposition of **H_2O_2** is catalysed by presence of heavy metal ion impurities, dust and rough and uneven surfaces.

CONCENTRATION OF H_2O_2

The concentration can be done by the following steps:

i. EVAPORATION ON A WATER BATH

The dilute solution of **H_2O_2 is** transferred to an evaporating dish and warmed carefully on a water bath. In this process 30 **%H_2O_2** of is obtained.

ii. DEHYDRATION IN A VACUUM DESICCATOR

The above solution of **H_2O_2** is placed over concentrated **H_2SO_4** in a vacuum condenser . The water vapours are absorbed by concentrated **H_2SO_4** and thus about 90 **%** solution of **H_2O_2** is obtained.

CONCENTRATION OF H_2O_2

iii. DISTILLATION UNDER REDUCED PRESSURE

The 90 **%** solution of **H_2O_2** is then distilled under reduced pressure. During this process, water distills over 303 to 313K and 99 **%** pure **H_2O_2** is left behind.

iv. REMOVAL OF LAST TRACES OF WATER

The 99 **%** solution of **H_2O_2** is cooled in a freezing mixture of solid **CO_2** and ether. As a result, crystals of **H_2O_2** separate out which are removed and, dried and remelted. This gives completely pure **H_2O_2 .**

STORAGE OF H_2O_2

THE FOLLOWING PRECAUTIONS MUST BE TAKEN WHILE STORING **H_2O_2 :**

i. It must be kept in wax lined colored bottles because the rough glass surface causes its decomposition.

ii. A small amount of phosphoric acid, glycerol or acetanilide is generally added which retard the decomposition of **H_2O_2** . These are also called negative catalysts.

PROPERTIES OF H_2O_2

PHYSICAL PROPERTIES:

i. Pure **H_2O_2** is a thick syrupy liquid with pale blue color.

ii. It is more viscous, less volatile and dense than water.

iii. Its density is 1.44**g/cm^3**

iv. Its melting point is 272.4K and boiling point is 358K at 68mm of Hg pressure.

v. It is completely miscible with water, alcohol and ether in all proportions. It forms a hydrate with water as **H_2O_2**. H_2O[m.p.221K]

PROPERTIES OF H_2O_2

CHEMICAL PROPERTIES:

H_2O_2 behaves as an oxidising agent as well as reducing agent in both acidic and alkaline solution. The oxidation state of oxygen in is -1. It can therefore be oxidised to O_2. However, it is a powerful oxidising agent but a weak reducing agent.

i. **Oxidising action in acidic medium**

In the presence of an acid, **H_2O_2** can accept electrons and, thus acts as an oxidising agent. **H_2O_2 o**xides ferrous sulphate to ferric sulphate.

$$2Fe+2H+H_2O_2 \rightarrow 2Fe+2H_2O_2$$

PROPERTIES OF H_2O_2

ii. **Reducing action in acidic medium**

$2MnO_4+6H+5H_2O_2 \rightarrow PbSO_4+4H_2O$

$HOCl+H_2O_2 \rightarrow H_3O+Cl+O_2$

iii. **Oxidising action in basic medium**

$2Fe+H_2O_2 \rightarrow 2Fe+2OH$

$2MNO_4+3H_20_2 \rightarrow 2MNO_2+3O_2+2H_2O+2OH$

PROPERTIES OF H_2O_2

iv. **Reducing action in basic medium**

$$I_2 + H_2O_2 + 2OH \rightarrow 2I + 2H_2O + O_2$$

$$2MNO_4 + 3H_20_2 \rightarrow 2MNO_2 + 3O_2 + 2H_2O + 2OH$$

USES OF H_2O_2

i. It is used in industry as a bleaching agent for textiles, paper, pulp, straw, leather, oils, fats etc.

ii. Domestically, it is used as a hair bleach and as a mild disinfectant.

iii. It is used in the manufacture of many inorganic compounds such as sodium perborates and percarbonates which are important constituent of high quality detergents.

iv. It is used as an antiseptic for washing wounds, teeth and ears under the name perhydrol.

v. It is used for the production of epioxides, propylene oxide and polyurethanes.

USES OF H_2O_2

vi. It is used for the synthesis of hydroquinone, pharmaceuticals, food products like tartaric acid.

vii. It is used as an antichlor in bleaching.

viii. It is used for restoring the color of lead paintings.

ix. It is used for preserving milk and wines.

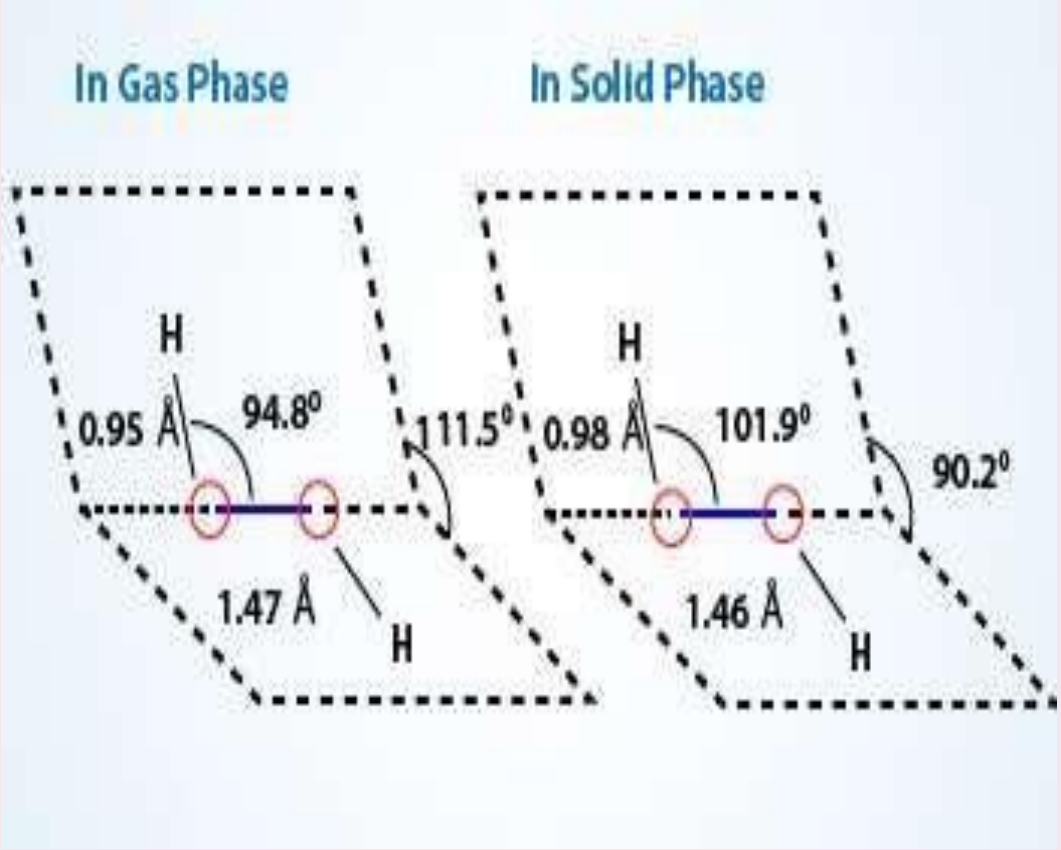
x. Recently **H_2O_2** is used in environmental chemistry such as in pollution control treatment of domestic and industrial effluents, oxidation of cyanides and restoration of aerobic conditions to sewage waste.

STRUCTURE OF H_2O_2

H_2O_2 has a none planar structure in which two H atoms are arranged in two directions almost perpendicular to each other and to the axis joining the two oxygen atoms.

The O—O linkage is called peroxide linkage. In the solid phase, the dihedral angle is reduced to 90.2 degree from 111.5 degrees in the gas phase.

STRUCTURE OF H_2O_2



STRENGTH OF H_2O_2

The strength of H_2O_2 is expressed in terms of weight or volume as:

i. AS WEIGHT PERCENTAGE The

weight percentage of H_2O_2 gives the weight of H_2O_2 in 100g of solution.

ii. AS VOLUME

The strength of H_2O_2 is commonly expressed as volume. This commonly refers to the volume of oxygen which a solution of H_2O_2 will give.

H_2O_2 REACTIONS

INTRODUCTION

What is oxidation?

Oxidation is nothing but a process in which either;

- Addition of oxygen.
- Removal of hydrogen.
- Loss of an electron.
- Increase in oxidation number takes place.

EXAMPLE

- Ethanol can be oxidized to ethanal:

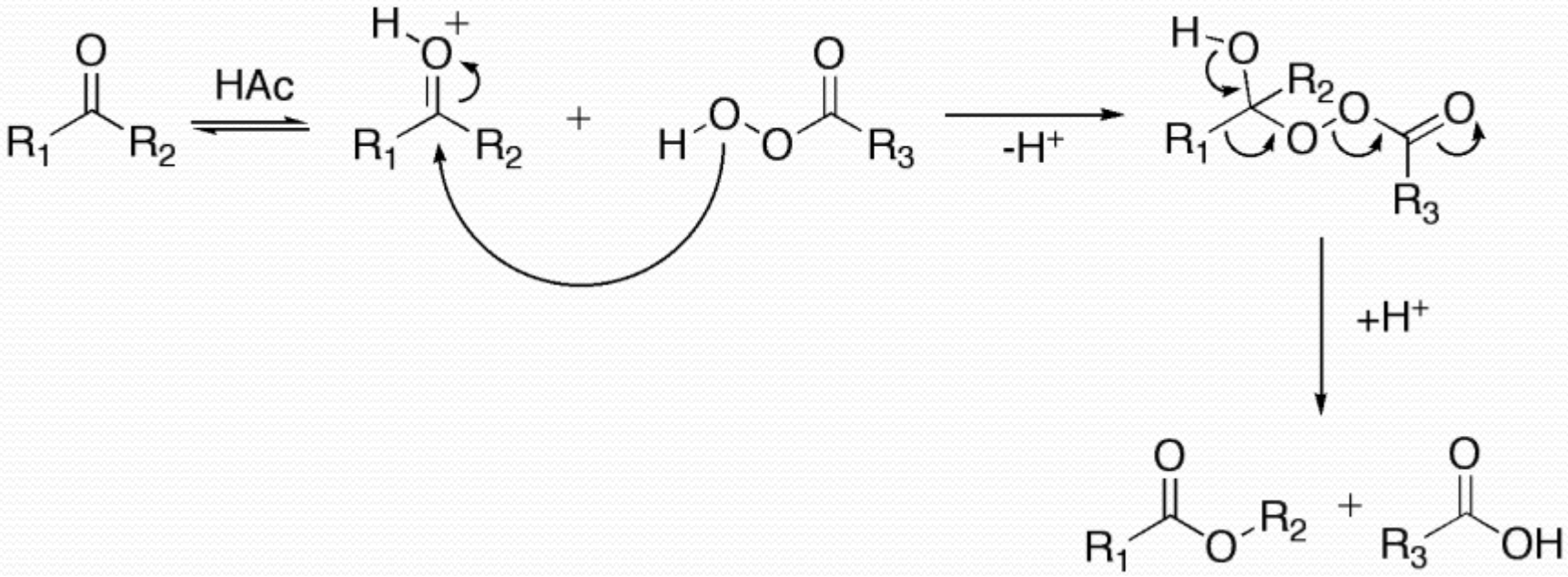
- We would need to use an oxidizing agent to remove the hydrogen from ethanol.
- The commonly used oxidizing agent is Potassium Dichromate(VI) Solution acified with dil.H_2SO_4.

BAEYER-VILLIGER OXIDATION

- The transformation for ketones into esters and cyclic ketones into lactones or hydroxy acid by peroxy acid was discovered as early as 1899 by A.Baeyer and Villiger.
- A wide range of oxidizing agents can be used to perform the Baeyer-Villiger oxidations.
- Reagents typically used to carryout this rearrangement are m-CPBA,peraceticacids,etc.
- Reactive or strained ketones react with hydrogen peroxide to form lactones.

MECHANISM

- The mechanism of Baeyer-Villiger rearrangement is not clear, however it is believed the reaction proceed as follows:



- Initial protonation of the carbonyl oxygen is followed by addition of peracid to yield an adduct which undergoes rearrangement where the R group migrates to the electron deficient oxygen. This is followed by deprotonation.
- Salient points are retention of stereochemistry by the migrating group, migration concerted with departure of leaving group and increased migratory aptitude of groups possessing greater electron donating power.

- Retention of stereochemistry by the migrating group.
- Migration is concerted with the departure of the leaving group. The concerted step is rate determining.
- Migrating groups with greater electron donating power have correspondingly greater migratory aptitude because of the increased ability to stabilize a positive charge in the transition state. This renders stereoselectivity to the oxidation of *unsymmetrical* ketones.
- Migration is favored when the migrating group is antiperiplanar to the O-O bond of the leaving group; this is known as the primary stereoelectronic effect.

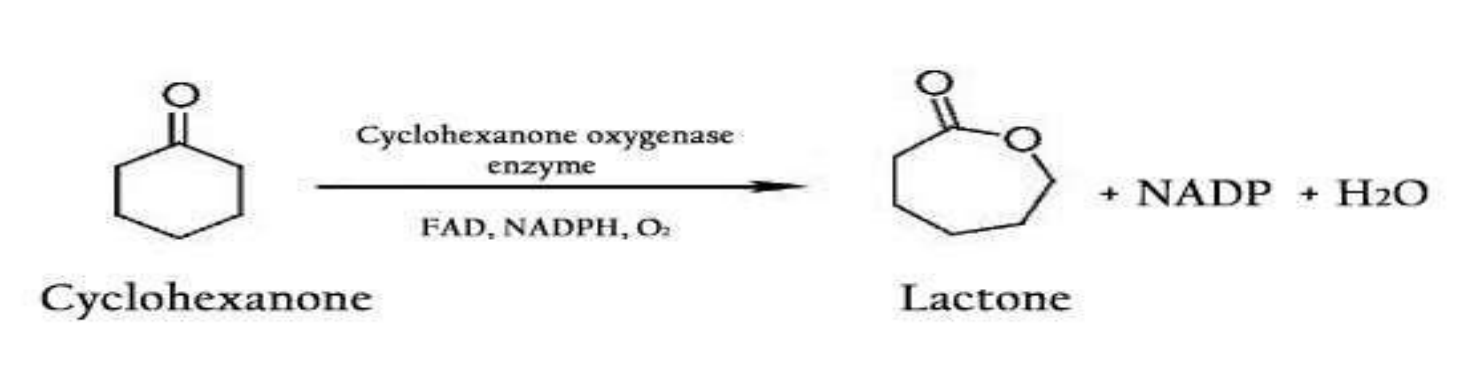
MIGRATING APTITUDE

- The order of preference for migration among alkyl group is, **Tertiary > Secondary > Primary > Methyl.**
- Aryl group migrates in preference to methyl and primary alkyl groups.
- In aryl series, migration is facilitated by electron **para** position.

APPLICATION

- Baeyer-Villiger oxidation has great synthesis utility as it permits the transformation of ketones into esters. An oxygen atom is inserted next to the carbonyl group. This reaction is applicable to both acyclic ketones and cyclic ketones. Oxidation of cyclic ketones occurs with ring expansion and form lactones as illustrated in the conversion of Cyclohexanone to lactone by this method.

- Baeyer-Villiger oxidation is also possible by the action of enzymes. For eg. Cyclohexanone is converted into lactone by using purified cyclohexanone oxygenase enzyme.



- Aldehydes also undergo Baeyer-Villiger oxidation to usually give carboxylic acids. The reaction involves either migration of hydrogen of fragmentation of the intermediate.

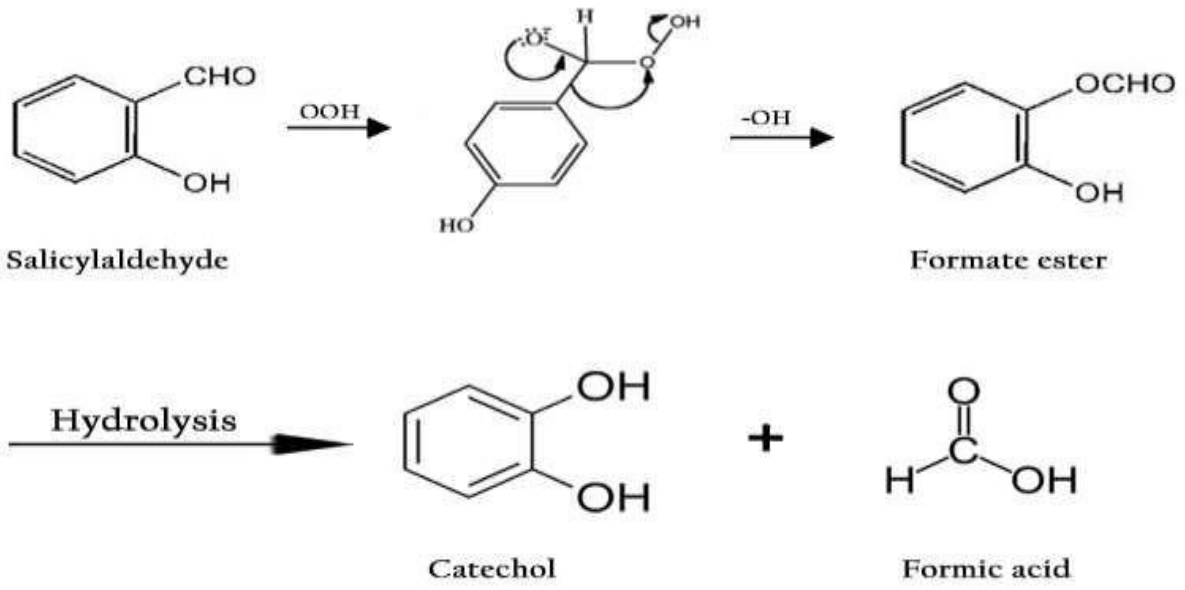
DAKIN REACTION

- The oxidation of aldehydes and ketones to the corresponding phenols is known as **Dakin reaction**.
- The reaction works best if the aromatic aldehyde or ketone is electron rich.
- The reagents used in **Dakin reaction** are;

  Alkaline H_2O_2, Acidic H_2O_2, Peroxybenzoic acid($C_7H_6O_3$), Peroxyacetic acid($C_2H_4O_3$), Sodium percarbonate, 30% H_2O_2 with aryl selenium compounds as activators and Urea-H_2O_2 adduct.

MECHANISM

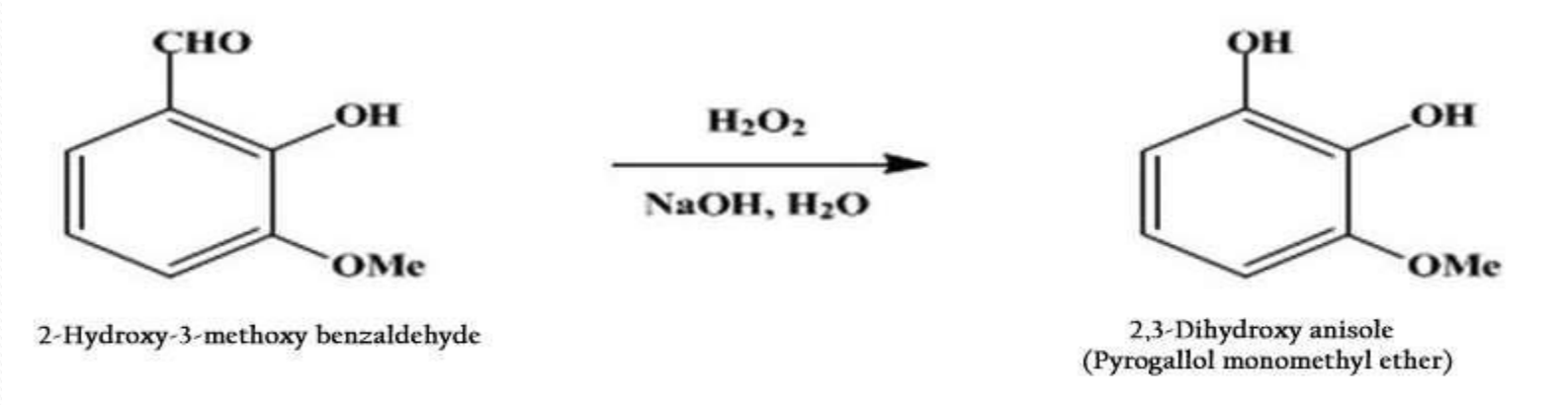
- The mechanism of **Dakin reaction** is very much similar to the mechanism of **Baeyer-Villiger reaction**.



The mechanism of **Dakin reaction** is not certain. However, a mechanism analogous to **Baeyer-Villiger oxidation** is suggested. The carbonyl carbon is attacked by the hydroperoxide anion. The resulting tetrahedral intermediate undergoes migration of aryl group with subsequent elimination of hydroxide ion to give an ester. An electron-releasing group is necessary for efficient migration of aryl group. The intermediate ester has been isolated and converted into catechol on hydrolysis under aqueous alkaline conditions of the reaction.

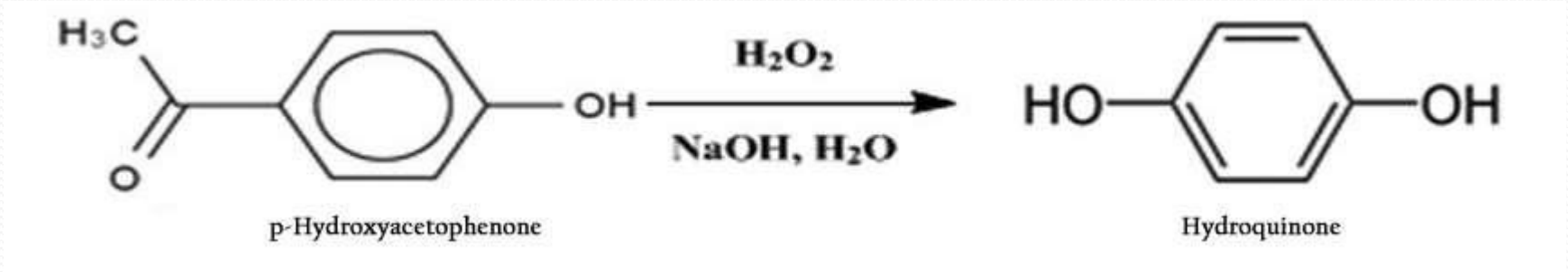
APPLICATION

- Dakin reaction has many useful synthetic application.



2-Hydroxy-3-methoxy benzaldehyde

2,3-Dihydroxy anisole
(Pyrogallol monomethyl ether)

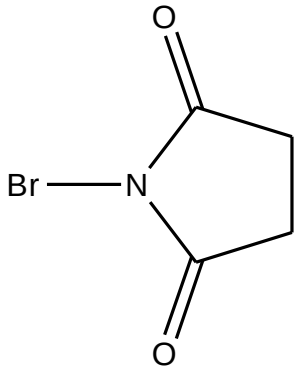


p-Hydroxyacetophenone

Hydroquinone

- The Dakin oxidation is most commonly used to synthesize benzenediols and alkoxyphenols.
- Catechol, for example, is synthesized from o-hydroxy and o-alkoxy phenyl aldehydes and ketones and is used as the starting material for synthesis of several compounds, including the catecholamines, catecholamine derivatives and 1,4-tertbutlycatechol a common antioxidant and polymerization inhibitor.
- Other synthetically useful products of the Dakin reaction include guaiacol, a precursor of several flavorants.
- Hydroquinone, a common photograph-developing agent; and 2-tertbutyl-4-hydrooxyanisole and 3-tertbutyl-4-hydrooxyanisole,two antioxidants commonly used to preserve packaged food.

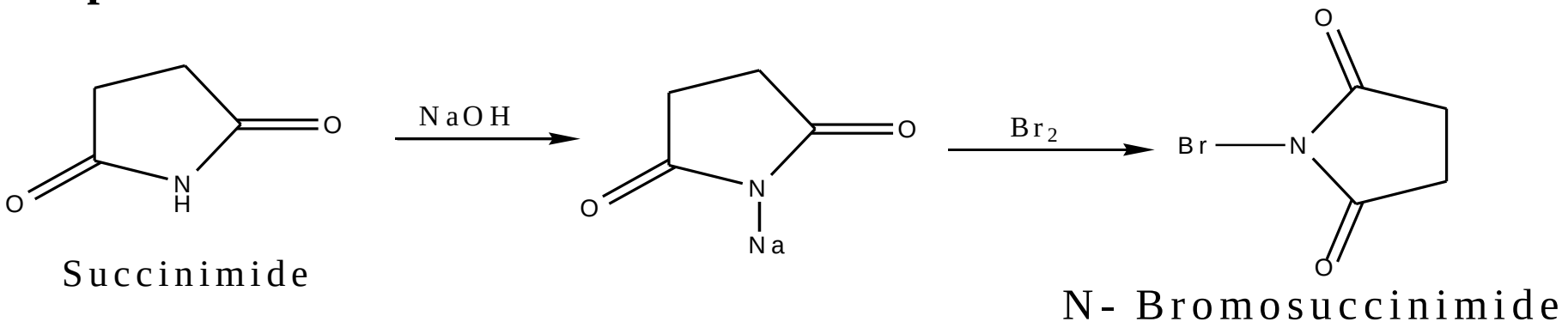
N-BROMO SUCCINIMIDE



PHYSICAL PROPERTIES:-

- It is a white solid.
- Moleculear formula of NBS is C4H4BrNo2.
- It is soluble in CCl4 and insoluble in water.
- The boiling point of NBS is 339^0 C and the melting point is 175-178^0 C.

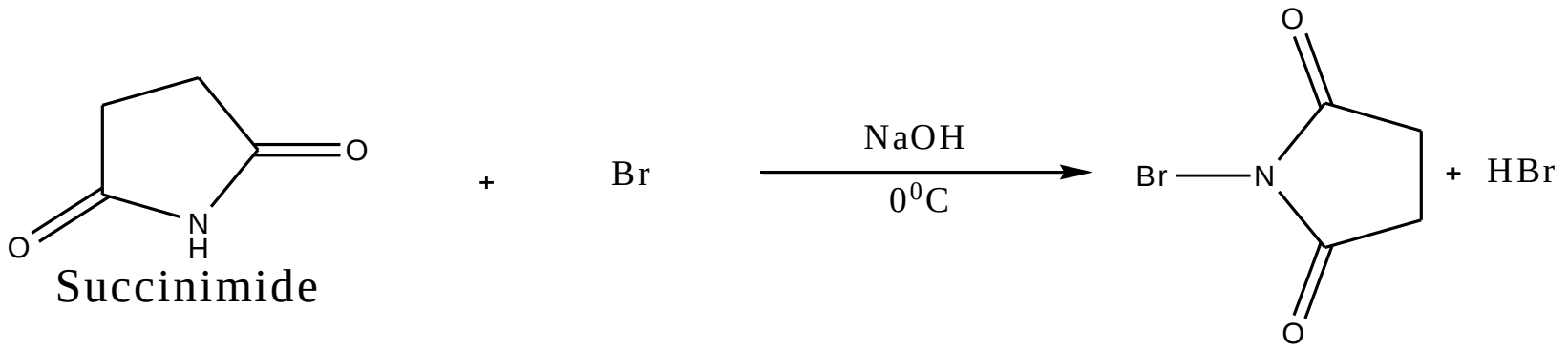
Preparation



Succinimide

N- Bromosuccinimide

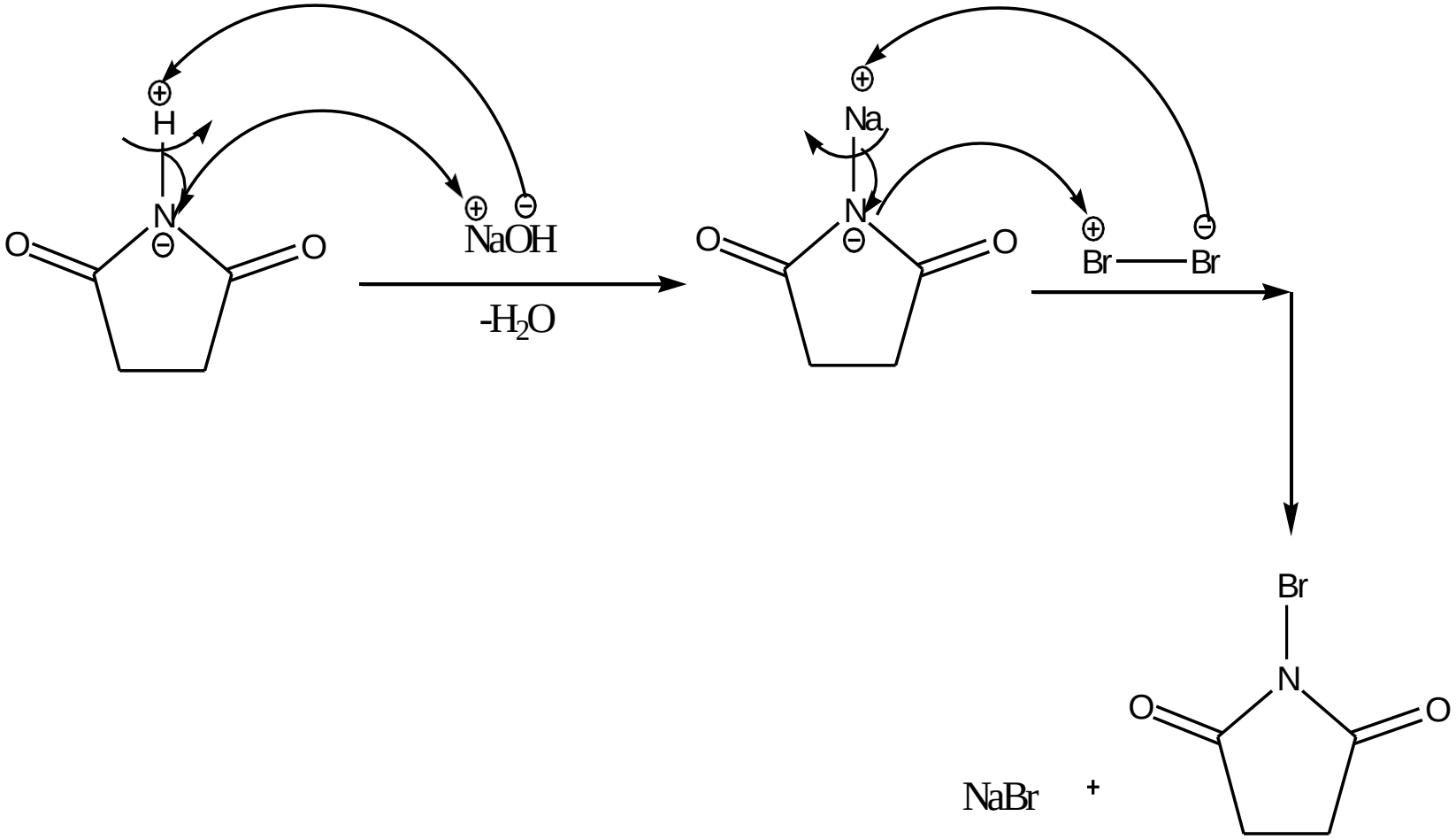
OR



Succinimide

N- Bromosuccinimide

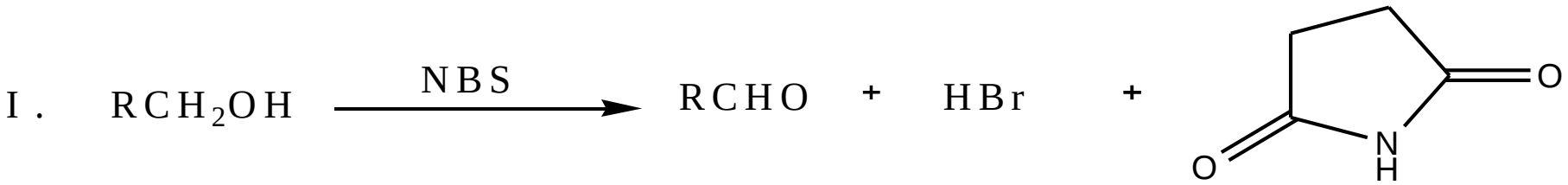
Mechanism:



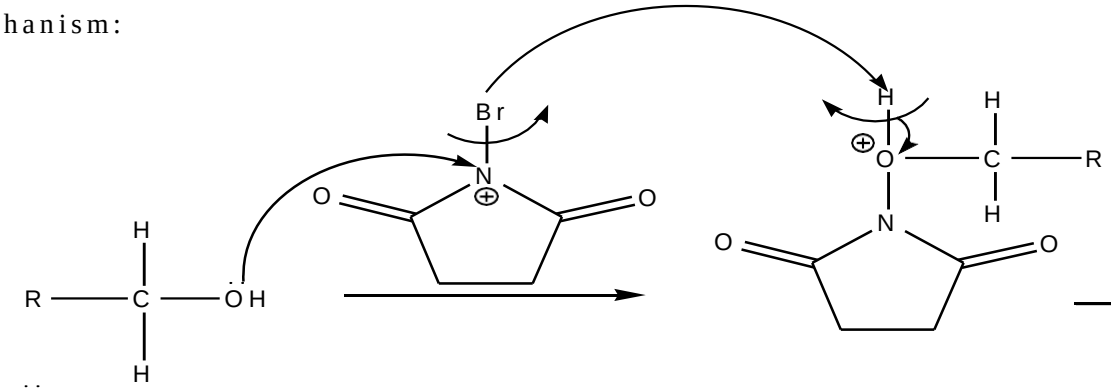
APPLICATIONS:-

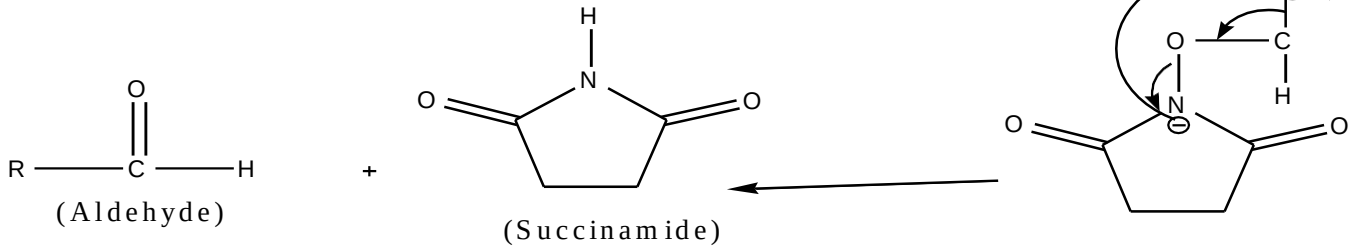
1.Oxidising agent

- It oxidizes primary alcohols and primary amine to aldehydes and secondary alcohols and ketones

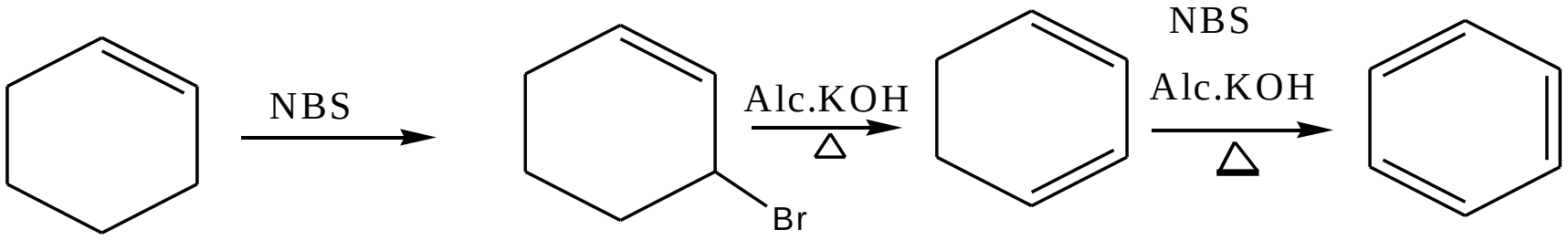


Mechanism:

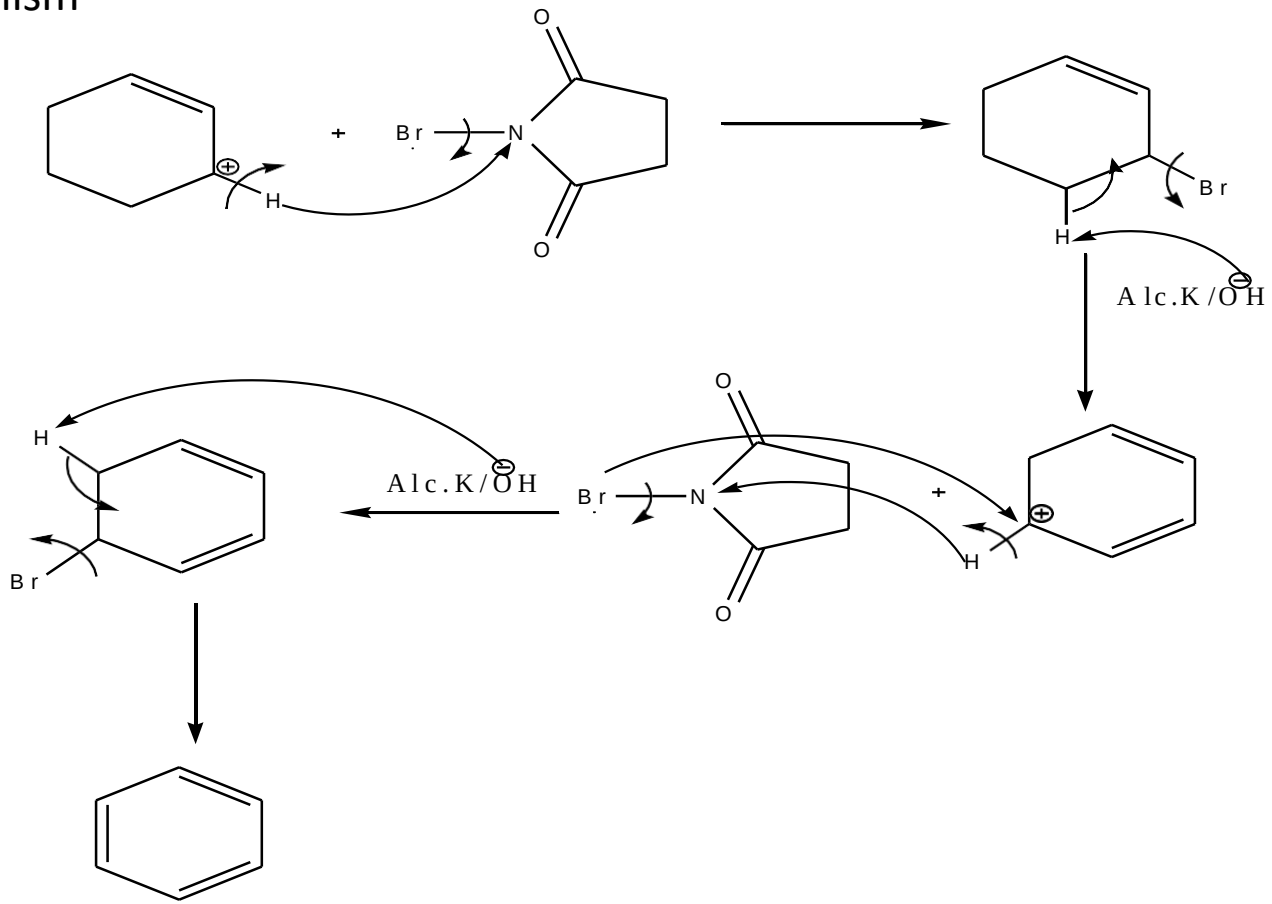




II. Conversion of monoenes to dienes to trienes

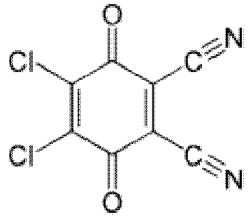


Mechanism



DDQ

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone



2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (or **DDQ**) is the chemical reagent with formula $C_8Cl_2N_2O_2$. This oxidant is useful for the dehydrogenation of alcohols, phenols, and steroid ketones in organic chemistry. DDQ decomposes in water, but is stable in aqueous mineral acid.

Preparation

Synthesis of DDQ involves cyanation and chlorination of 1,4-benzoquinone. Thiele and Günther first reported a 6-step preparation in 1906. The substance did not receive interest until its potential as a dehydrogenation agent was discovered. A single-step chlorination from 2,3-dicyanohydroquinone was reported in 1965.

Stability

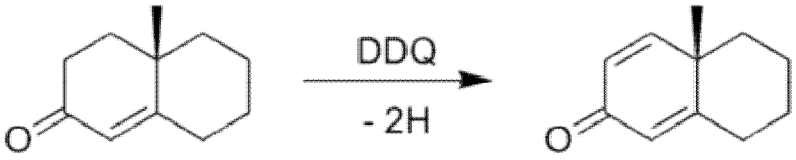
DDQ can react with water and give off hydrogen cyanide (**HCN**), which is highly toxic. Storage should be in dry area. A low-temperature and weakly acidic environment increases the stability of DDQ.

Uses

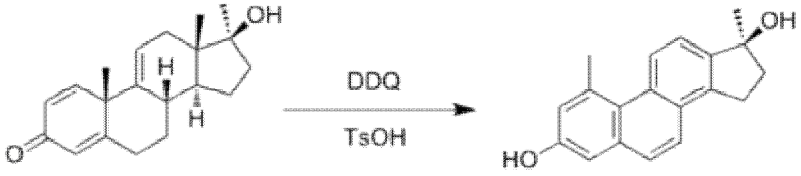
It is used as a reagent in organic chemistry, a mild oxidizing agent as well as a radical receptor.

Reactions

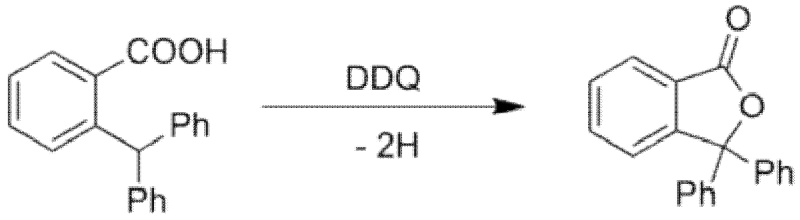
1.Dehydrogenation



2.Aromatization



3.Oxidative Coupling



ALUMINIUM ISOPROPOXIDE

$[\ (CH_3)_2\ CHO]_3Al$

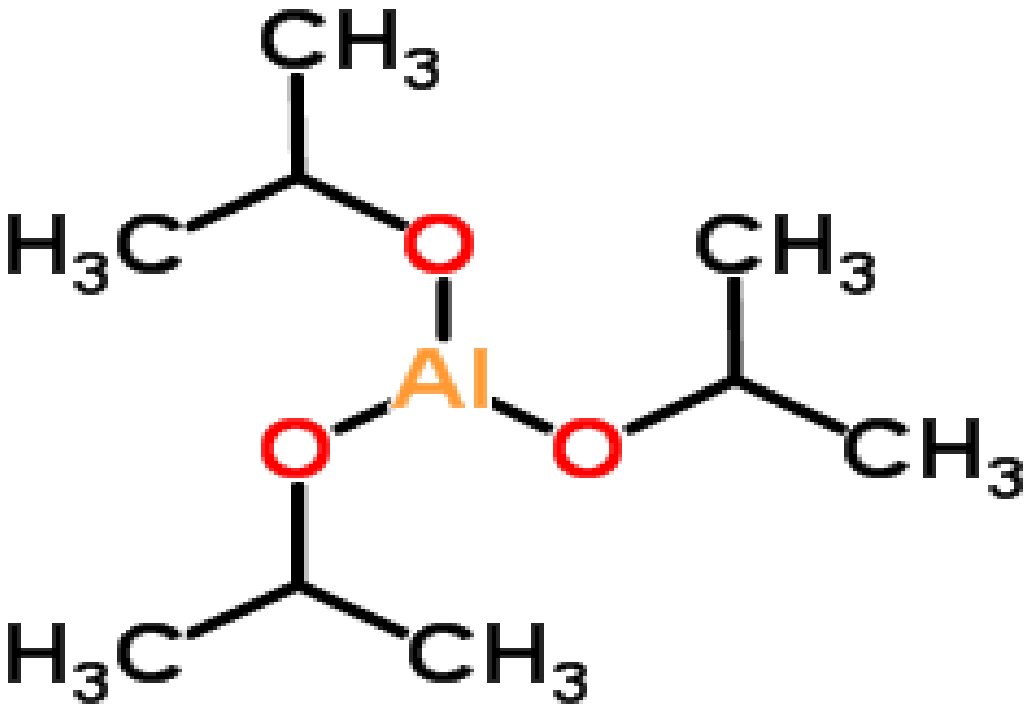
- It is used as catalysts and an intermediates in a different reaction.
- They belong to aluminum alkoxides groups.
- Widely used as a selective reducing agent for aldehydes and ketones.
- It is an inexpensive and also easy to handle among the other aluminum alkoxides.

ALTERNATIVE NAMES

- Triisopropoxyaluminium
- Aluminiumisopropanolate
- 2-Propanol aluminium salt
- AIP

STRUCTURE OF ALUMINIUM ISOPROPOXIDE

- The central Aluminium is octahedral surrounded by three bidentate $(O\text{-}i\text{-}Pr)_4$ ligands, each featuring tetrahedral Al.



PHYSICAL PROPERTY

- More soluble in benzene and less soluble in alcohols
- White solid
- Boiling point : 140.5^0C
- Melting point : $128\text{-}133^0C$
- It decomposes in presence of water

HANDLING, STORAGE, AND PRECAUTIONS

- The dry solid is corrosive
- Moisture sensitive
- Flammable
- An irritant
- Used in a fume hood.

PREPARATION

- It is prepared by the reaction between isopropyl alcohol and aluminium metal, or aluminium trichloride:

- $2\,Al + 6\,i\text{PrOH} \rightarrow 2\,Al(O\text{-}i\text{-}Pr)_3 + 3\,H_2$

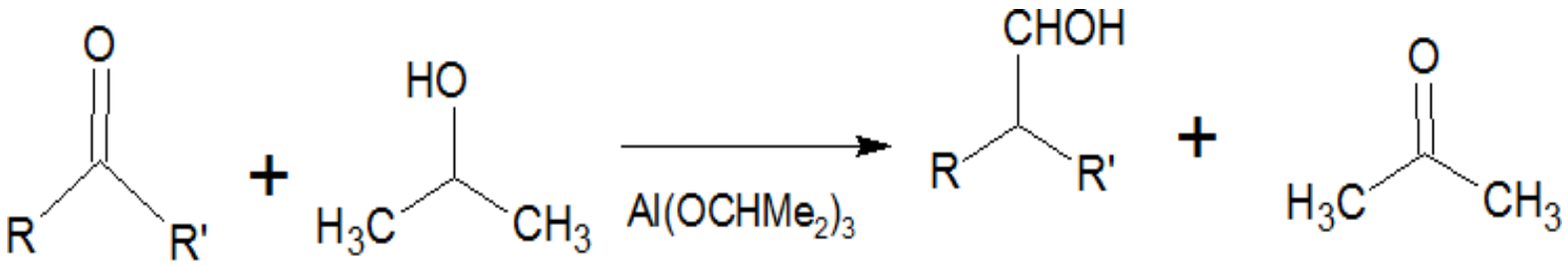
- $AlCl_3 + 3\,i\text{PrOH} \rightarrow Al(O\text{-}i\text{-}Pr)_3 + 3\,HCl$

SYNTHETIC APPLICATION

1) MEERWEIN-PONNDORF-VERLEY (MPV) REDUCTIONS

- Carbonyl compound are reduced to the respective alcohol in the presence of aluminium isopropoxide solution.

- The acetone, so formed, is removed by slow distillation and hence the reaction proceeds only in the desired direction.



Ketone Isopropanol Alcohol Acetone

Mechanism

STEP (1)

- The aluminium alkoxide 1, reacted with a carbonyl oxygen to form tetra coordinated aluminium intermediate 2.

STEP (2)

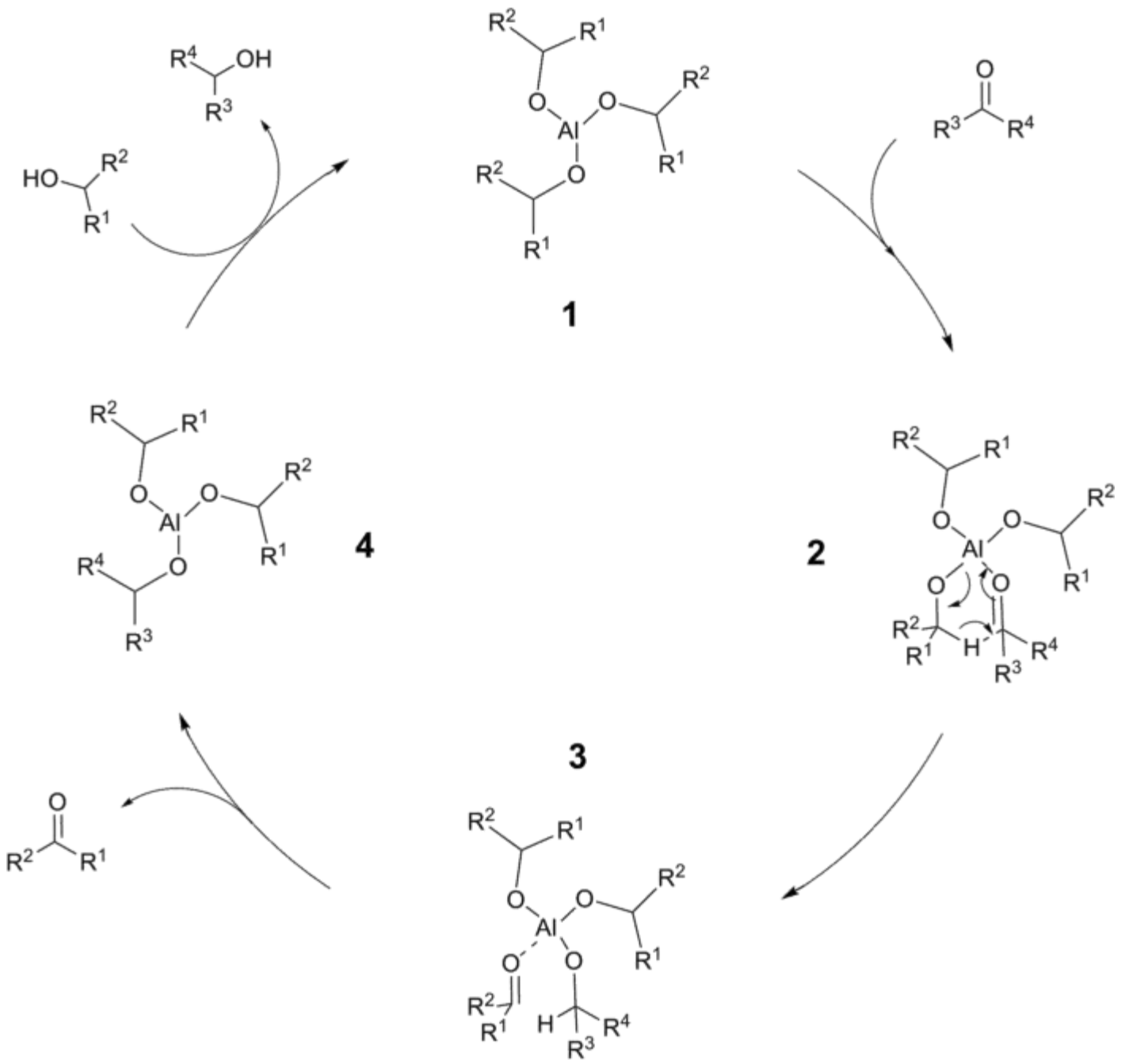
- The intermediates 2 transfer hydride to the carbonyl group from the alkoxy ligand to form an another intermediate 3.

STEP (3)

- The intermediate 3 eliminate a new carbonyl group and gives a tricoordinated aluminium species 4.

STEP (4)

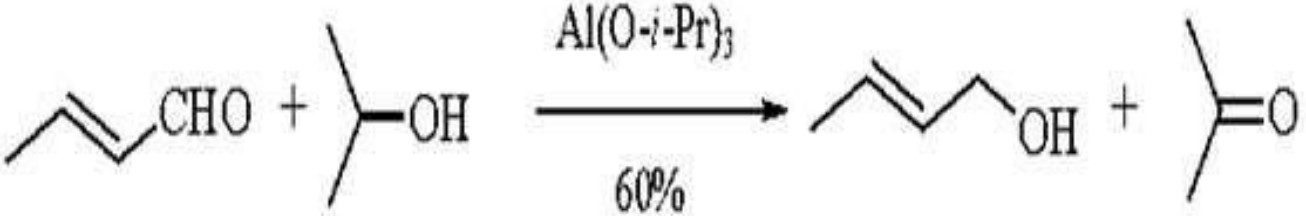
- Alcohol is formed and the catalyst 1 is regenerated.


1
2
3
4

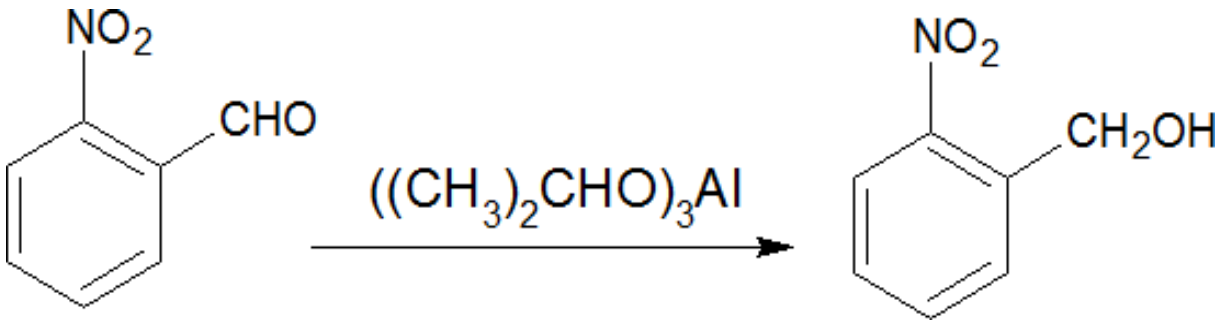
Example:

a) Reduction of aldehyde

i) Reduction of crotonaldehyde to crotyl alcohol

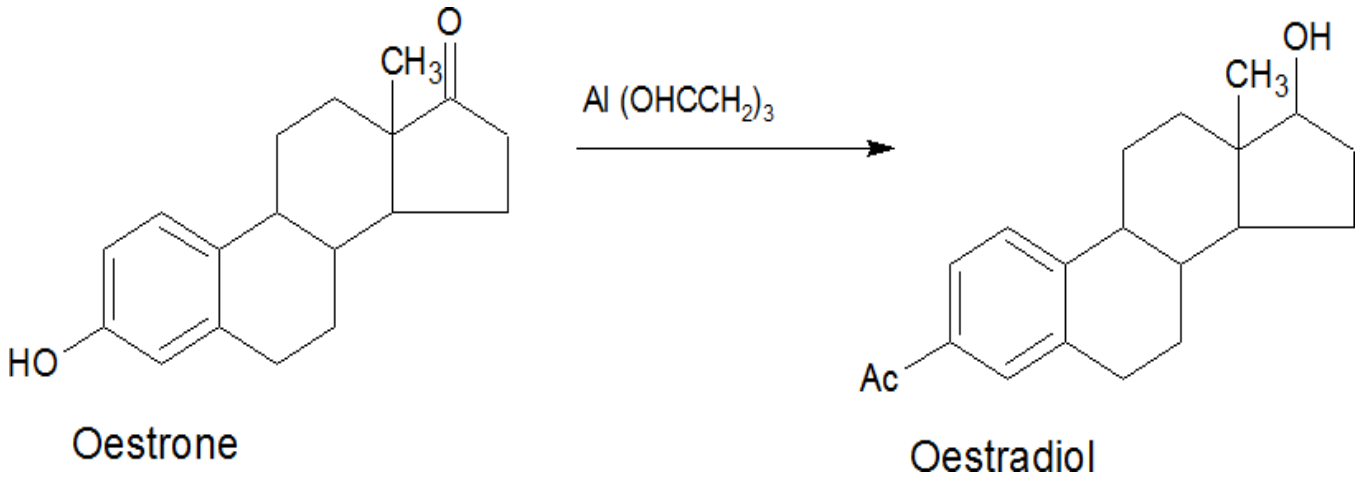


ii) Reduction of o-nitrobenzaldehyde to o-nitrobenzyl alcohol



b) Reduction of ketone

i) Synthesis of oestradiol from oestrone

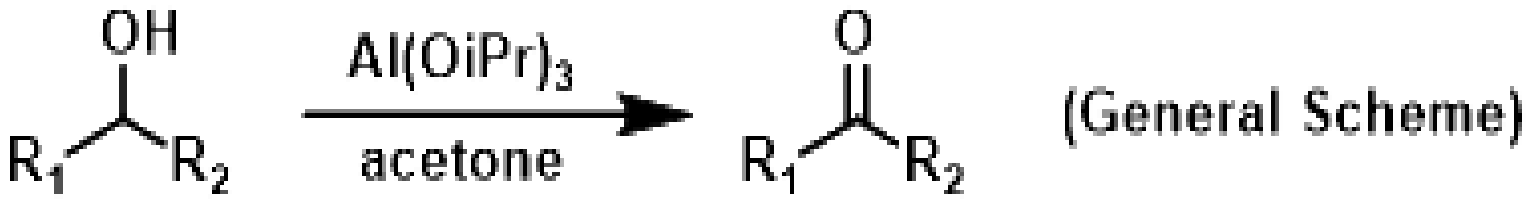


Oestrone

Oestradiol

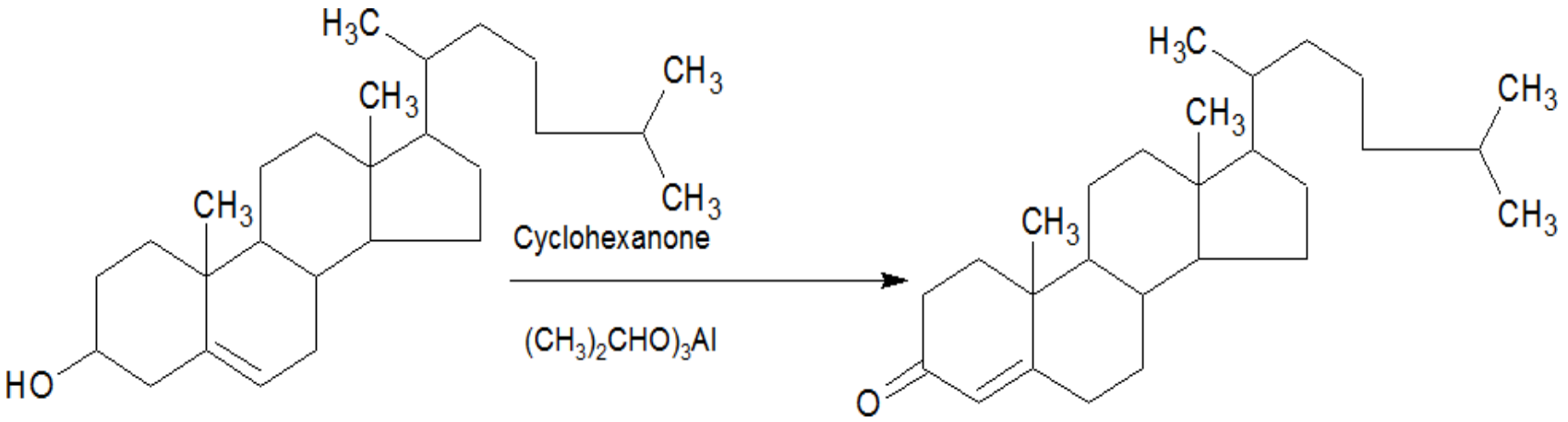
2) OPPENAUER OXIDATION

- It is an oxidation reaction of alcohol to ketone in presence of aluminium isopropoxide.

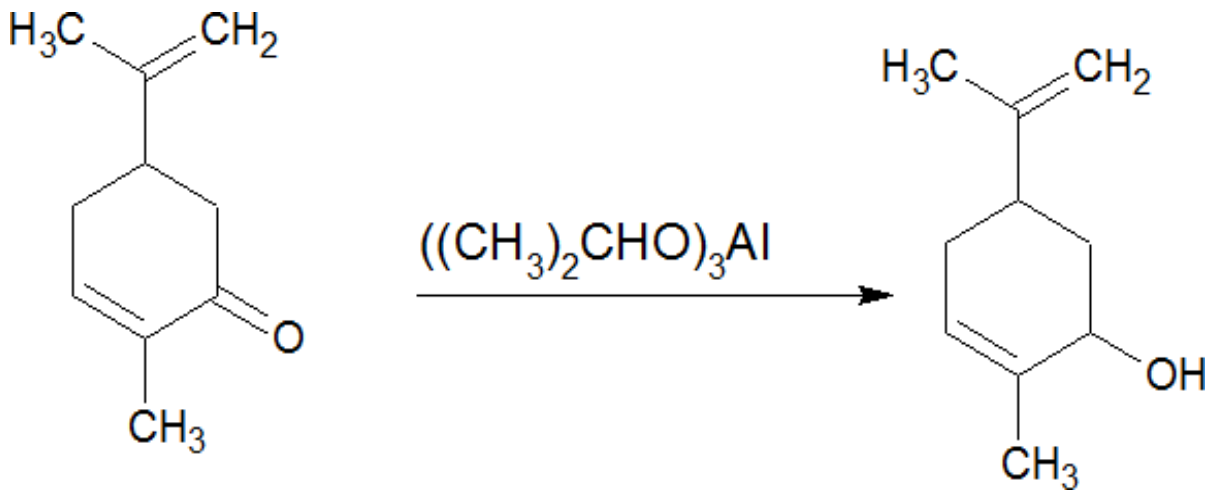


(General Scheme)

Eg: Cholestenone is prepared by oxidation of cholesterol in toluene solution with aluminum isopropoxide as catalyst and cyclohexanone as hydrogen acceptor.

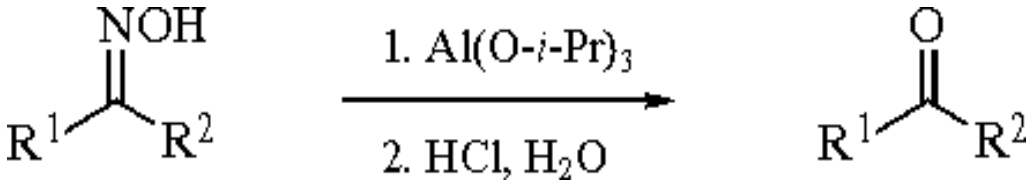


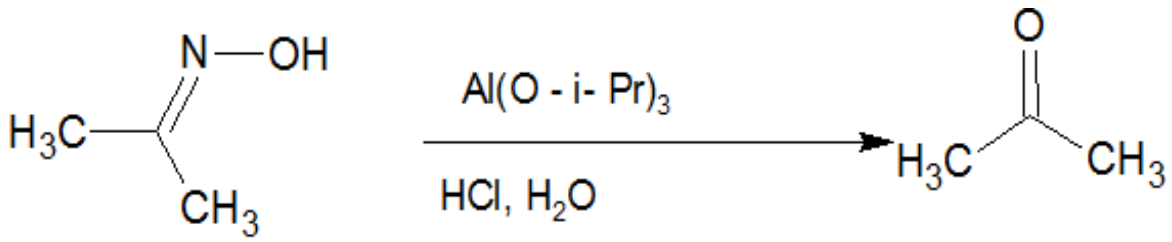
- Conversion of carvone to carveol



3) HYDROLYSIS OF OXIMES

- Oximes can be converted into parent carbonyl compounds by aluminum isopropoxide followed by acid hydrolysis.





N-propan-2-ylidenehydroxylamine

Acetone

DICYCLOHEXYLCARBODIIMIDE ($C_{13}H_{22}N_2$)

- *N*,*N'*-Dicyclohexylcarbodiimide is an organic compound.
- The important use is to couple amino acids during artificial peptide synthesis
- The compound is abbreviated as DCC, DCCD or DCCI

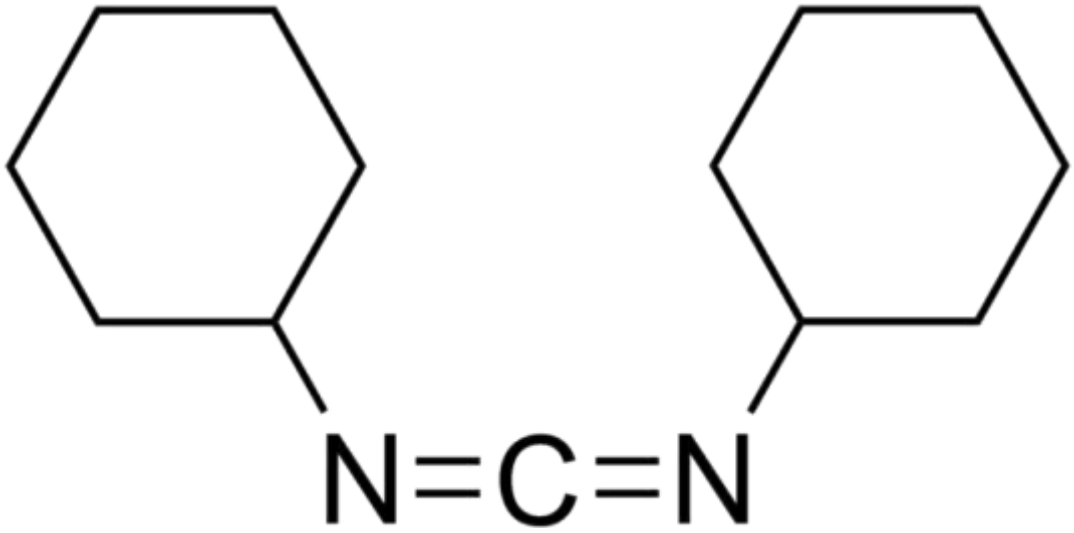
PROPERTIES

- Under standard conditions, it exists in the form of white crystals with a heavy, sweet odor.
- The low melting point (30- 35^{0}C)
- Boiling point 122- 124^{0}C
- Soluble in tetrahydrofuran , acetonitrile and dimethylformamide , dichloromethane, but insoluble in water Stable, but moisture sensitive.

SAFETY PRECAUTION

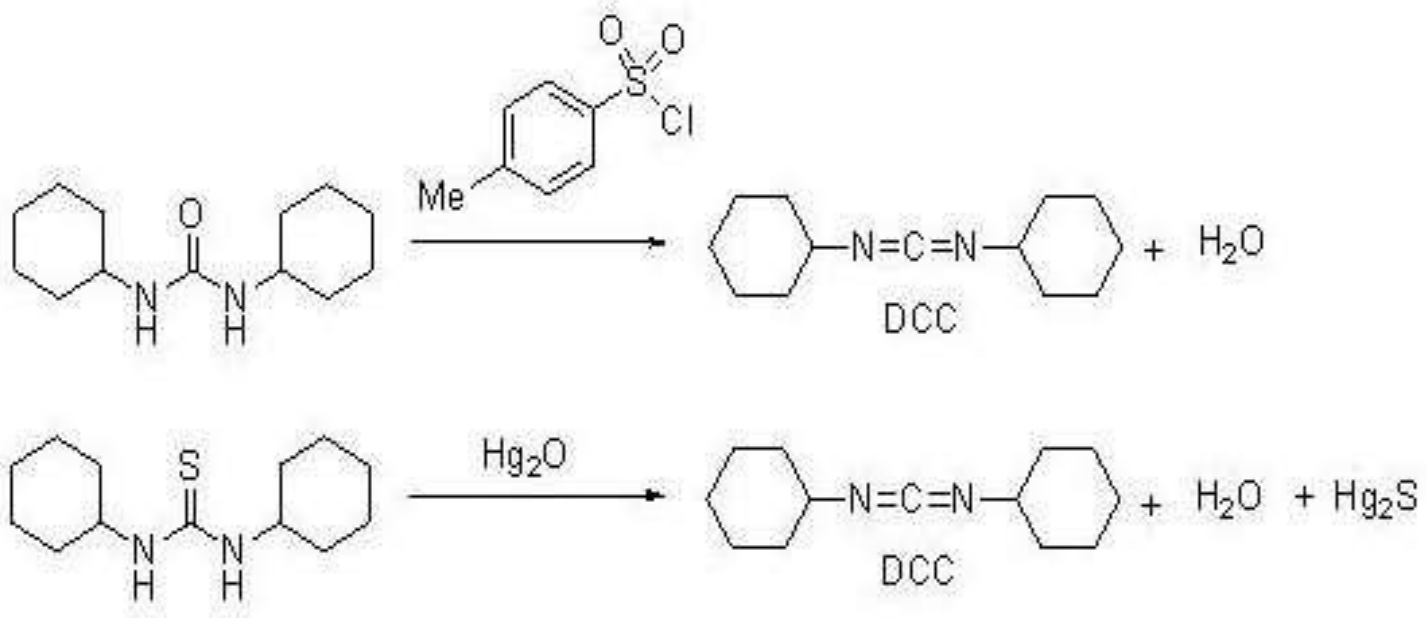
- DCC is a potent allergen and a sensitizer, and causing skin rashes.

STRUCTURE



SYNTHESIS

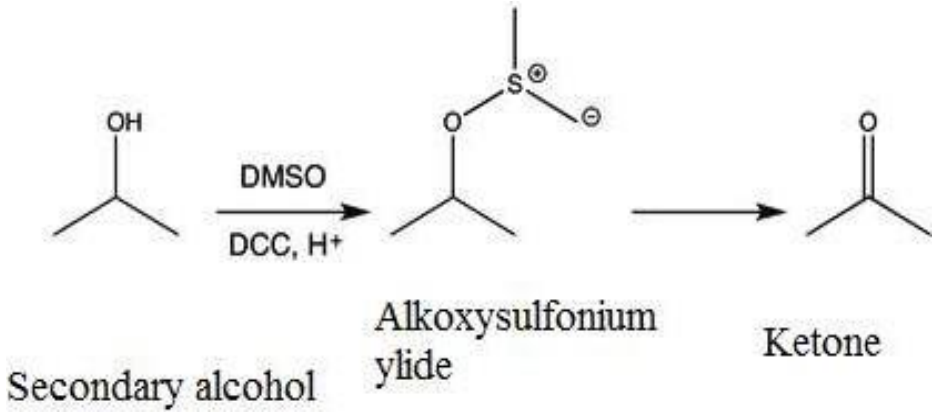
- It can also be prepared by oxidation of dicyclohexylurea with *p* - toluene sulfonyl chloride in hot pyridine or by heating dicyclohexylthiourea with yellow mercuric oxide.



APPLICATIONS

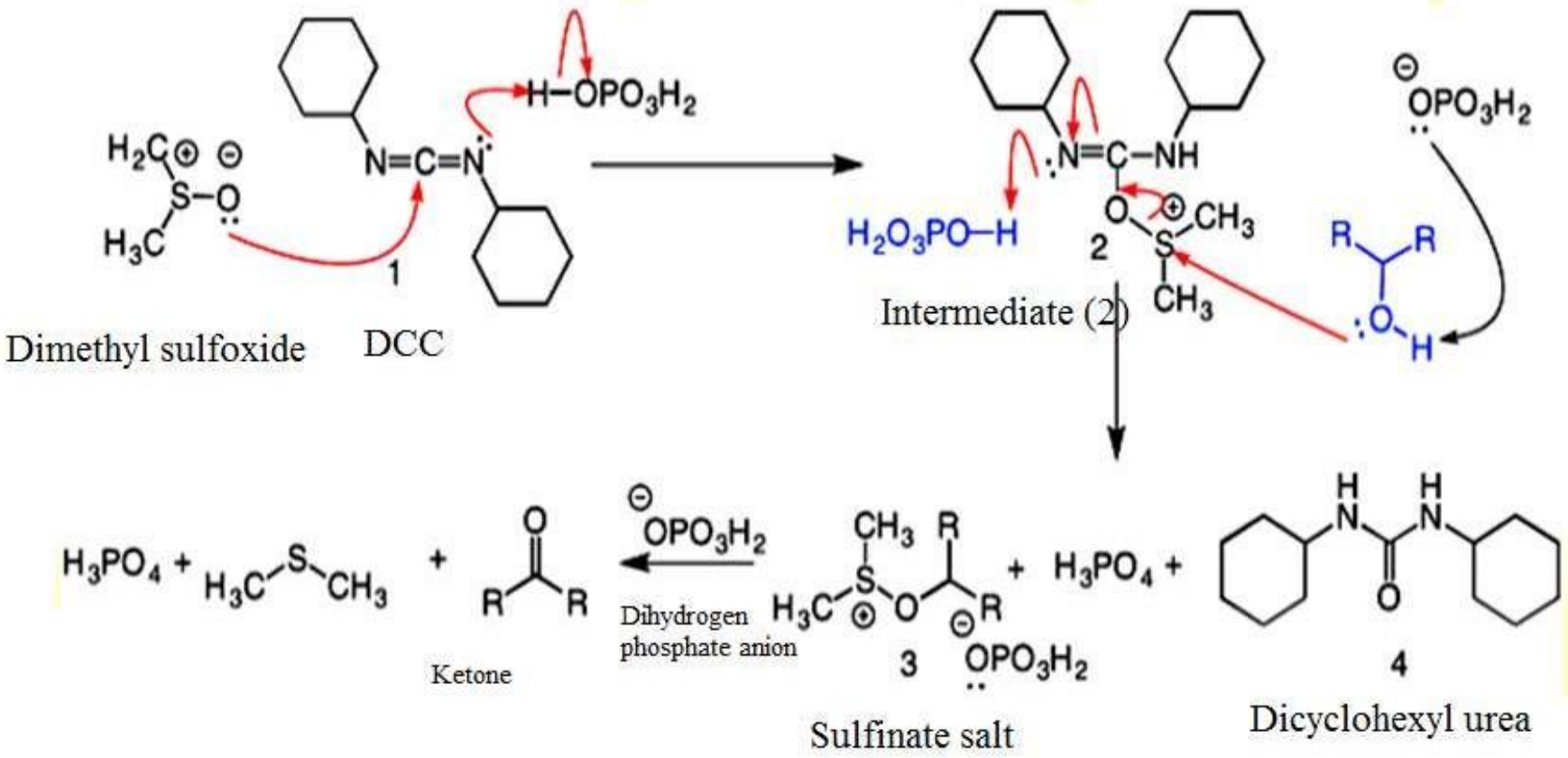
1) MOFFATT OXIDATION

- Moffatt oxidation is the oxidation of primary and secondary alcohols in presence of dimethyl sulfoxide (DMSO) and dicyclohexylcarbodiimide (DCC) to form a alkoxysulfonium ylide intermediate, which rearranges to form aldehydes and ketones.



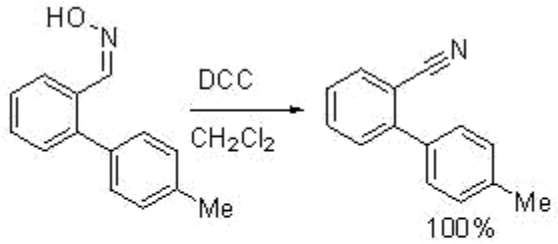
MECHANISM

- Dicyclohexyl carbodiimide (**1)** is attacked by dimethyl sulfoxide to form an intermediate **(2).**
- **It** is then protonated by the addition of the alcohol oxygen on the sulfur atom.
- Then a stable dicyclohexyl urea **(4)** is formed along with sulfenate salt **(3)**.
- It then react with a dihydrogen phosphate anion to form ketones.


Dimethyl sulfoxide
DCC
1
Intermediate (2)
2
Ketone
Dihydrogen phosphate anion
Sulfinate salt
3
Dicyclohexyl urea
4

2) SYNTHESIS OF NITRILE

- The oximes undergo dehydration in the presence of DCC to nitriles.

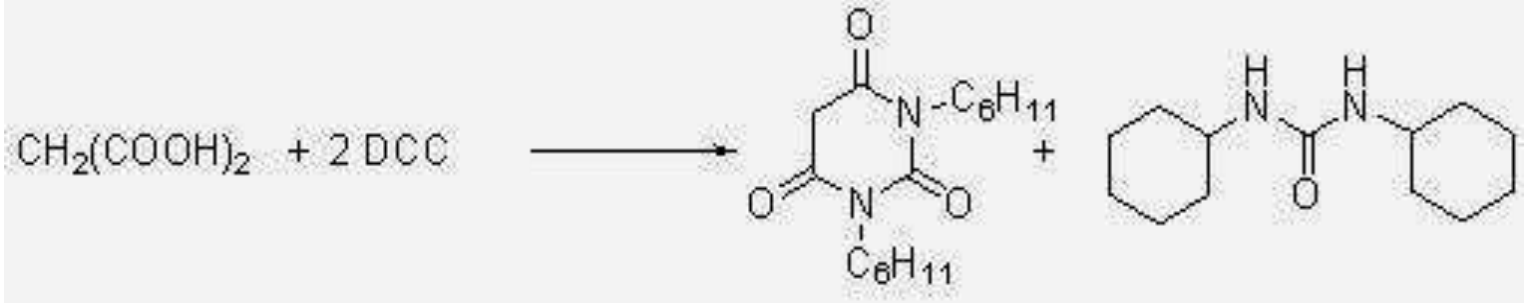


4'-methyl,1,1'-biphenyl,2-methylidene hydroxylamine

4-methyl, 1,1'-biphenyl 2-carbo nitrile

3) SYNTHESIS OF BARBITURIC ACID

- Barbituric acid and its derivatives can be prepared by the reaction of malonic acid with DCC.



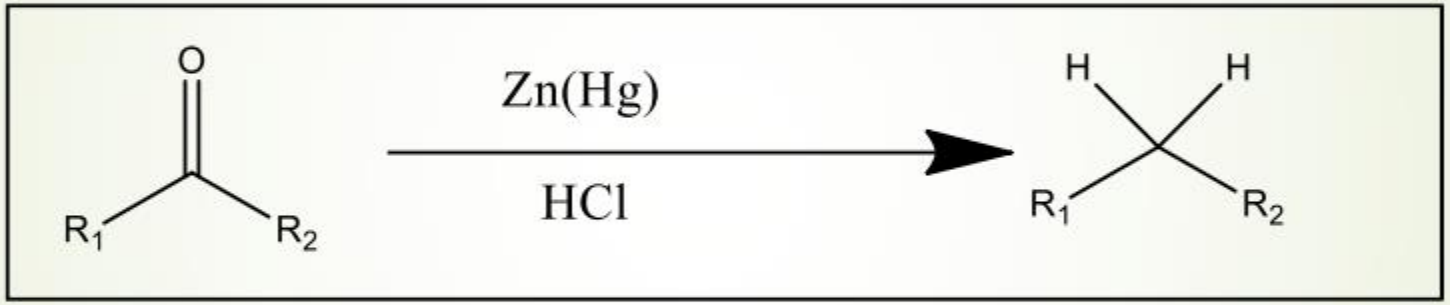
INDEX

CLEMMENSEN REDUCTION

INTRODUCTION

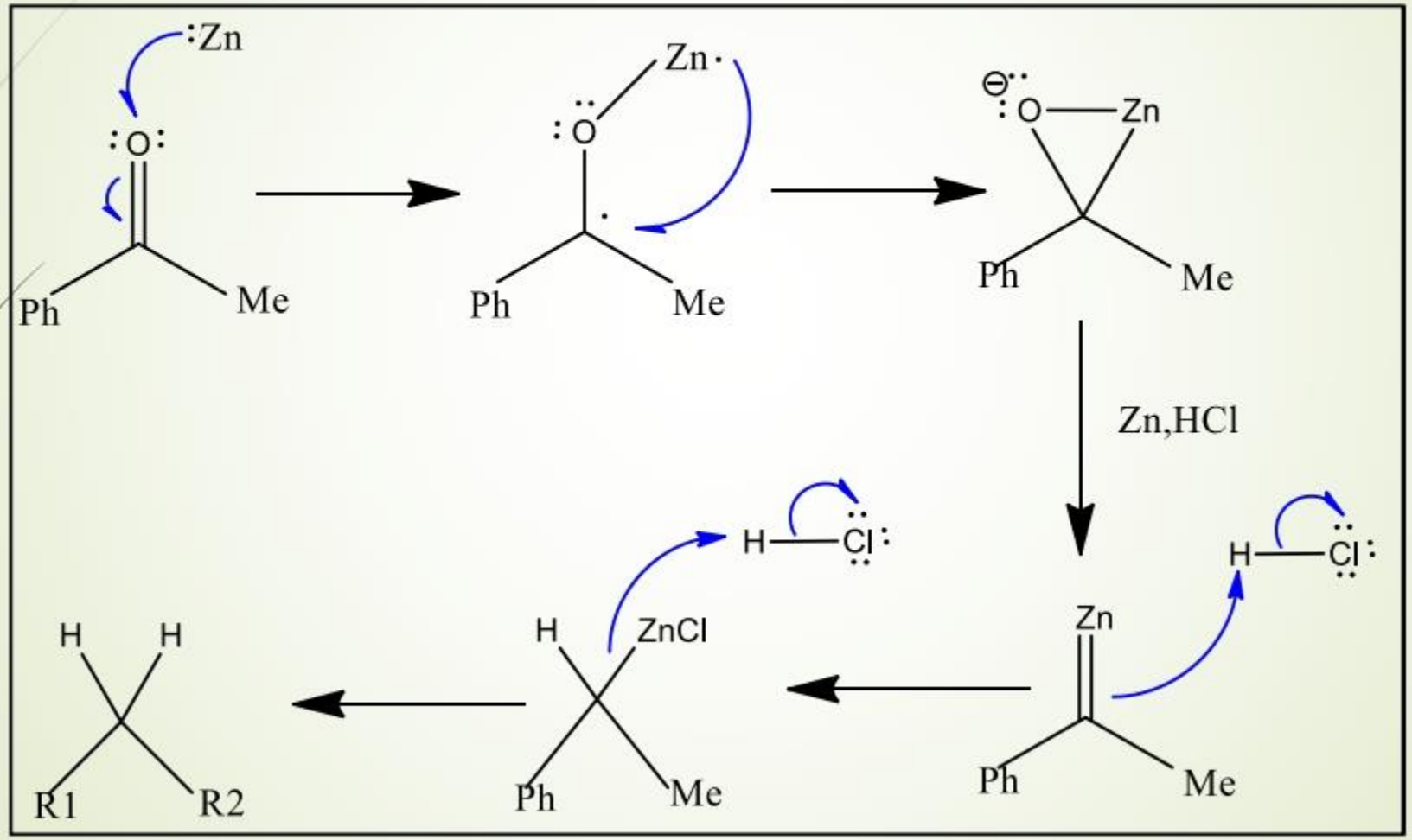
- This reaction was first reported by Clemmensen of Park Davis in 1913.
- It is the reduction of carbonyl groups (in aldehyde and ketone) to methylene group.
- This reaction done with zinc amalgam and hydrochloric acid and it is generally known as Clemmensen reduction.
- The Clemmensen reduction is particularly effective at reducing aryl-alkyl ketones,such as those formed in a Friedel-Crafts acylation.

GENERAL REACTION

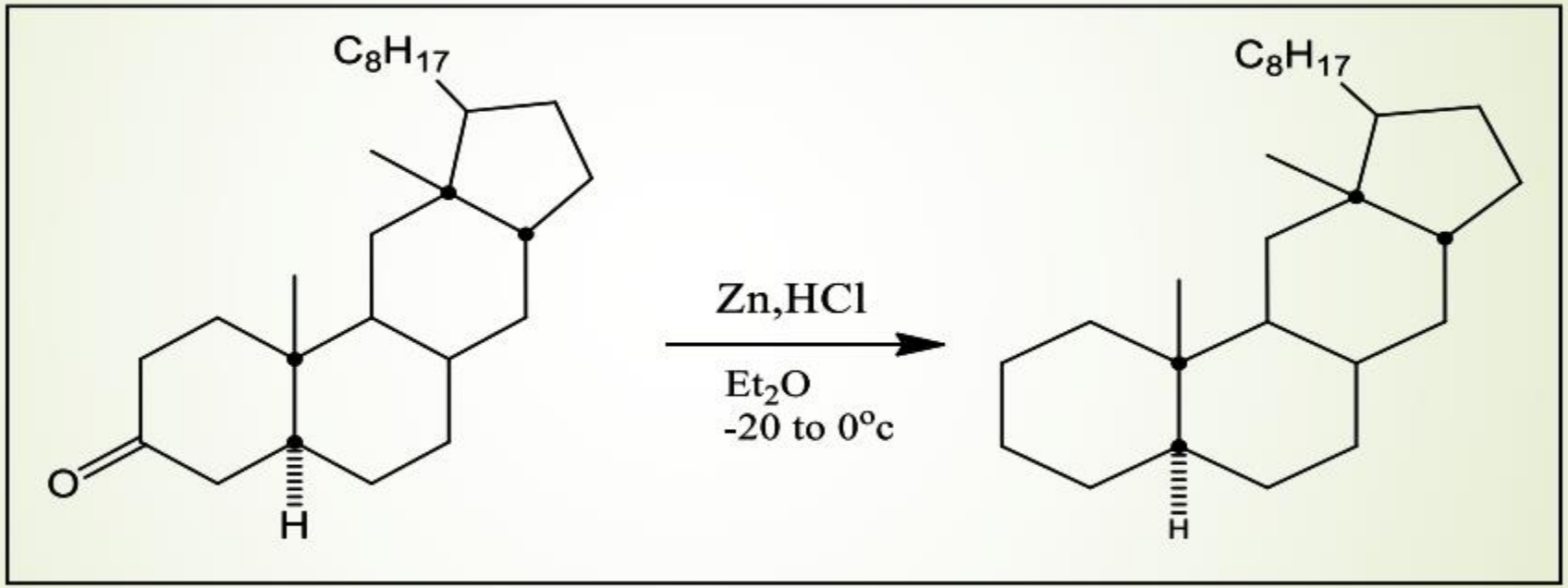


R_1=Alkyl, Aryl
R_2= H, Alkyl, Aryl

MECHANISM


:Zn
:O:
Ph
Me
Zn·
:O
Ph
Me
Θ
O
Zn
Ph
Me
Zn,HCl
H
Cl:
Zn
Ph
Me
H
Cl:
H
ZnCl
Ph
Me
H
H
R1
R2

MODIFICATION

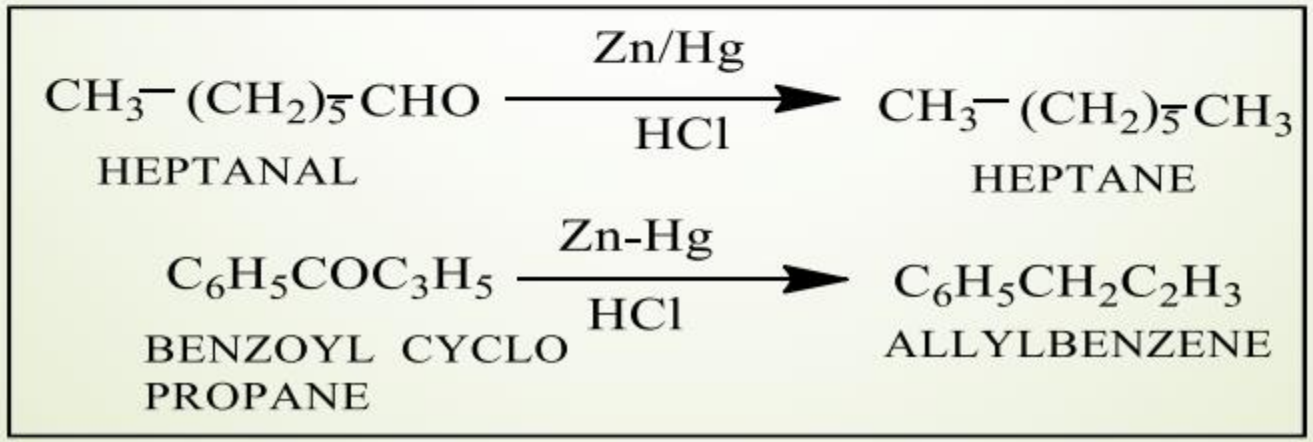


CHOLESTANE-3-ONE

CHOLESTANE

APPLICATIONS

- This reaction has widely used to convert a carbonyl group into a methylene group.
- Also important application in the preparation of polycyclic aromatics and aromatics containing unbranched side hydrocarbon chains.
- To reduce aliphatic and mixed aliphatic-aromatic carbonyl compounds

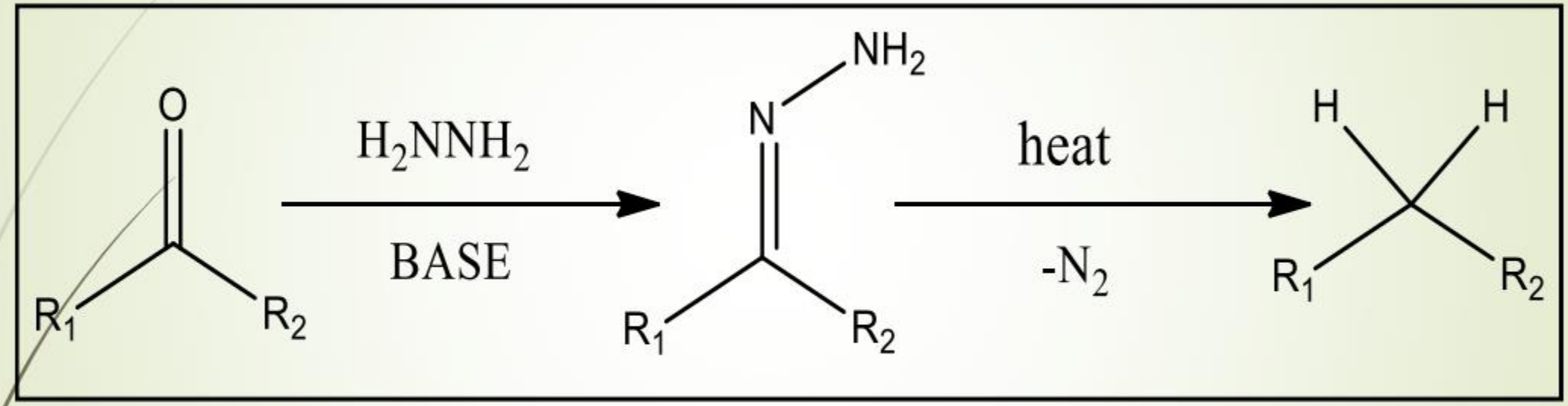


WOLFF–KISHNER REACTION

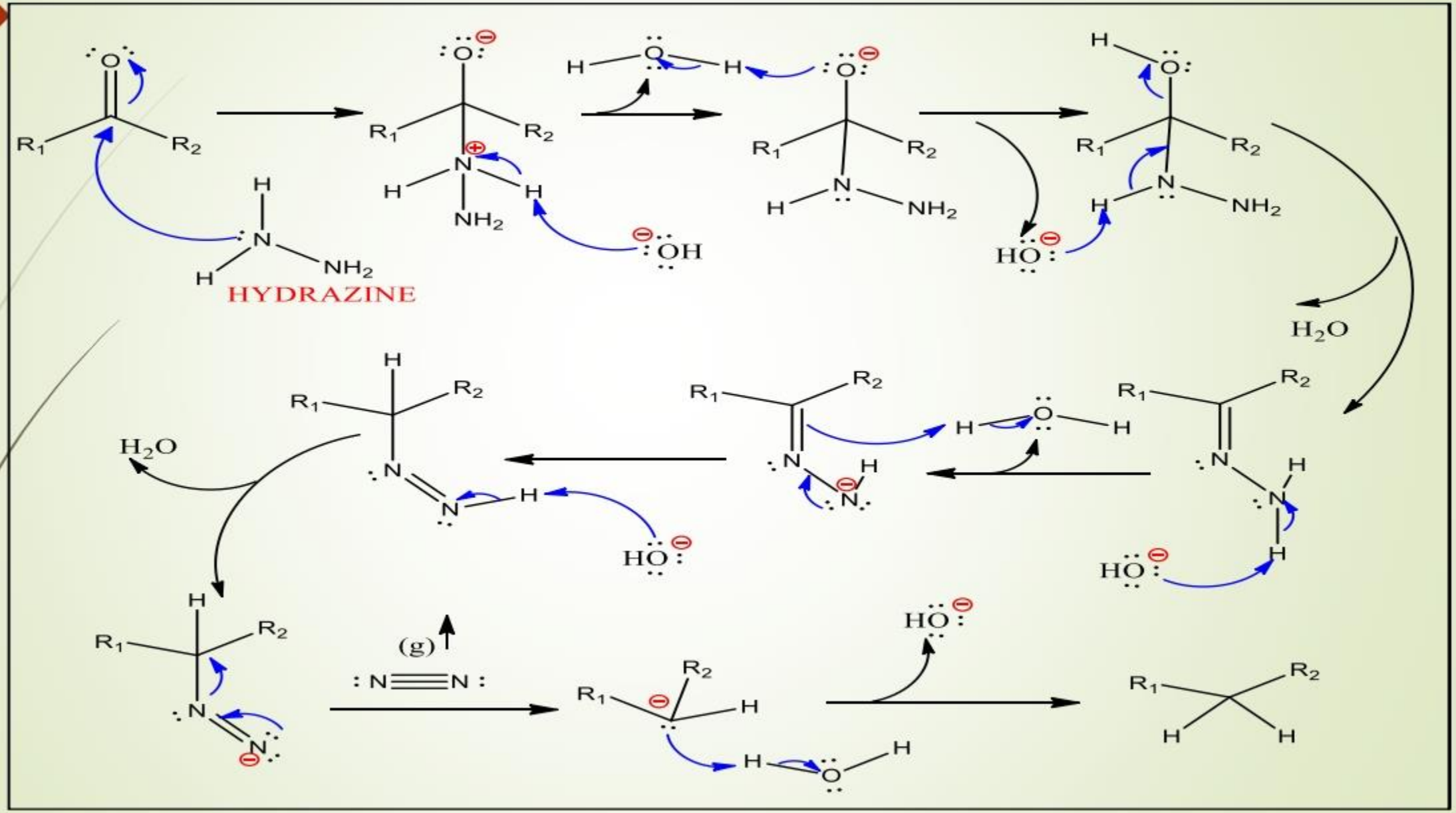
INTRODUCTION

- The Wolff– Kishner reduction was discovered independently by N. Kishner in 1911 and L. Wolff in 1912.
- The Wolff– Kishner reduction is a reaction used in organic chemistry to convert carbonyl functionalities into methylene groups.
- The Wolff-Kishner reduction is an organic reaction used to convert an aldehyde or ketone to an alkane using hydrazine, base, and thermal conditions.
- Because the Wolff–Kishner reduction requires highly basic conditions, it is unsuitable for base-sensitive substrates.

GENERAL REACTION



MECHANISM



MODIFICATION

- The reaction has been extensively modified.
- One of the modification uses the Huang Minlon modification using distillation to remove excess water and also used 85% hydrazine and solvent used is ethylene glycol.
- In addition, the Wolff- kishner reduction has been carried out in DMSO instead of hydroxylic solvent by addition of hydrazones into anhydrous DMSO containing freshly sublimed potassium tert-butoxide at 25^0C.
- Moreover,it has been reported that the Wolff-Kishner reduction can occur in a very short period of time in a microwave irradiation, affording product with high purity.

APPLICATIONS

- This reaction has very broad application in organic synthesis, especially for the multiwalled carbon nanotubes.
- In 2011, Pettus and Green reduced a tricyclic carbonyl compound using the Huang Minlon modification of the Wolff–Kishner reduction.Several attempts towards decarbonylation of tricyclic allylic acetate containing ketone failed and the acetate functionality had to be removed to allow successful Wolff–Kishner reduction. Finally, the allylic alcohol was installed via oxyplumbation.
- The Wolff–Kishner reduction has also been used on kilogram scale for the synthesis of a functionalized imidazole substrate.

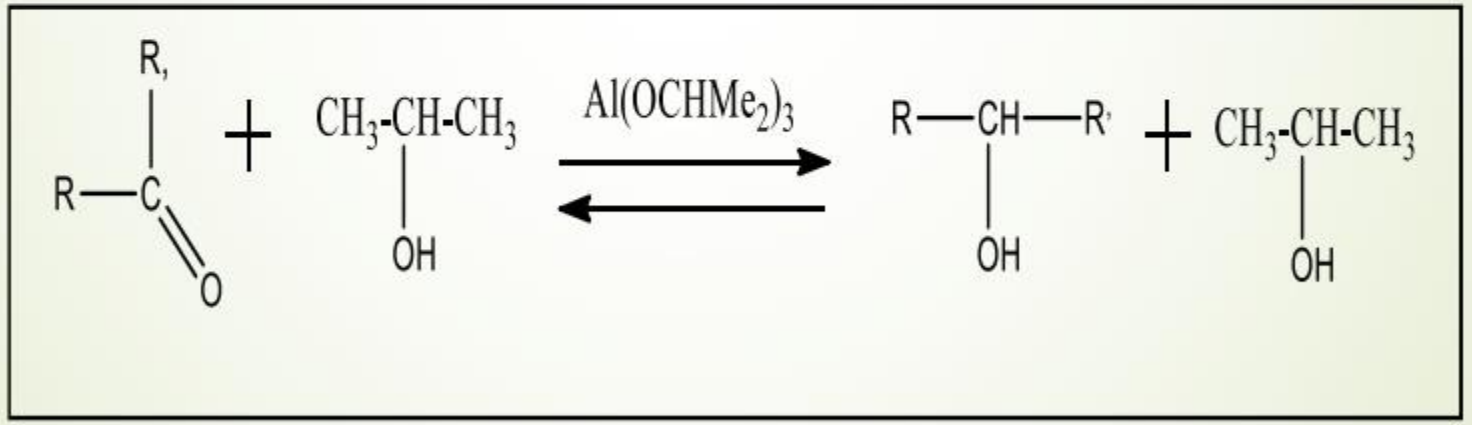
MEERWEIN-PONNDORF-VERLEY REDUCTION (MPV)

INTRODUCTION

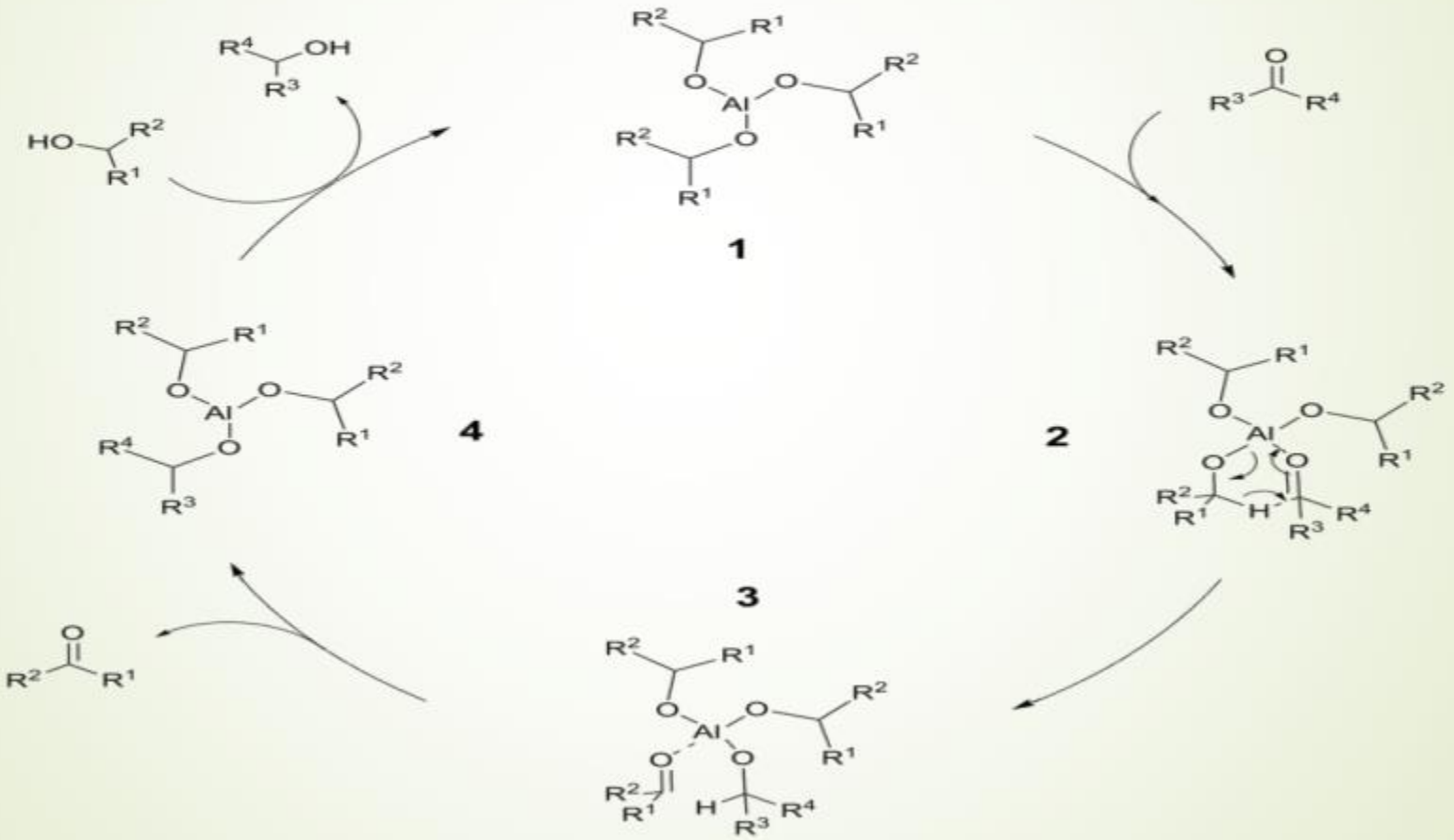
- MPV reduction is the reduction of aldehyde and ketones to their corresponding alcohols utilizing Aluminium oxide catalysis in the presence of sacrificial alcohol.
- MPV reduction was discovered by Meerwein and Schmidt and separated by Verley in 1925.They found that the mixture of aluminium oxide and ethanol could reduce aldehyde to alcohols.
- Pondroff applied the reaction to ketones and upgraded the catalyst to aluminium isopropoxide in isopropanol.

GENERAL REACTION

- Conversion of aldehyde or ketone in to corresponding alcohol by treatment with Aluminium isopropoxide in isopropanol solution.
- This reaction is reversible and is called Oppenauer oxidation.

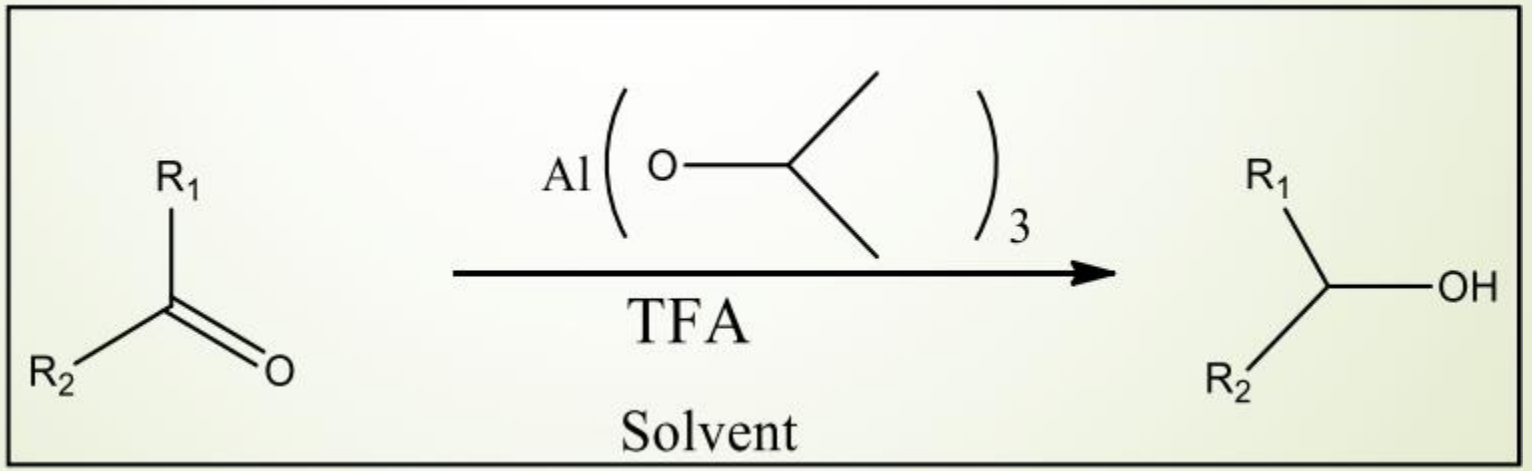


MECHANISM



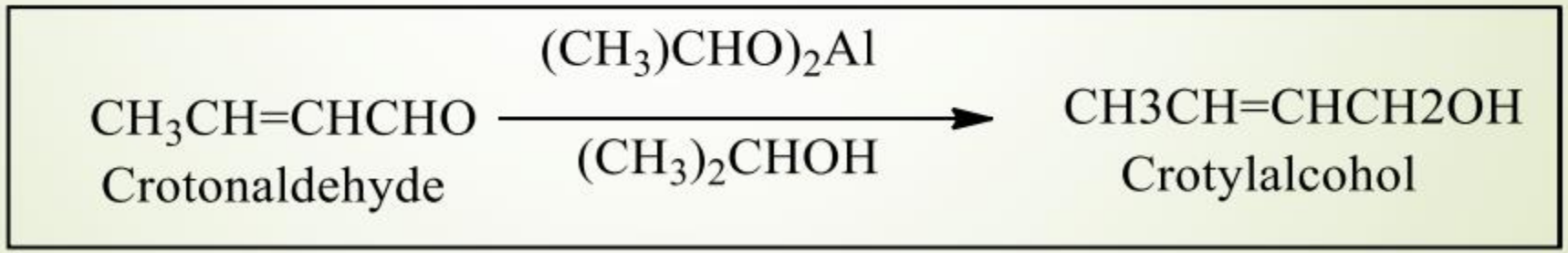
MODIFICATION

- A modified MPV reduction has been developed which results in extremely rapid conversion of aldehyde and ketones to corresponding carbinols at room temperature by adding TFA (TrifluroAceticacid) to Aluminium isopropoxide (AIP).



APPLICATIONS

- This method of reduction is specific for carbonyl group and therefore it can be used for reducing aldehydes and ketones containing some other reducible group, such as, a double bond, a nitro or an ester group, which are not reduced under these conditions.



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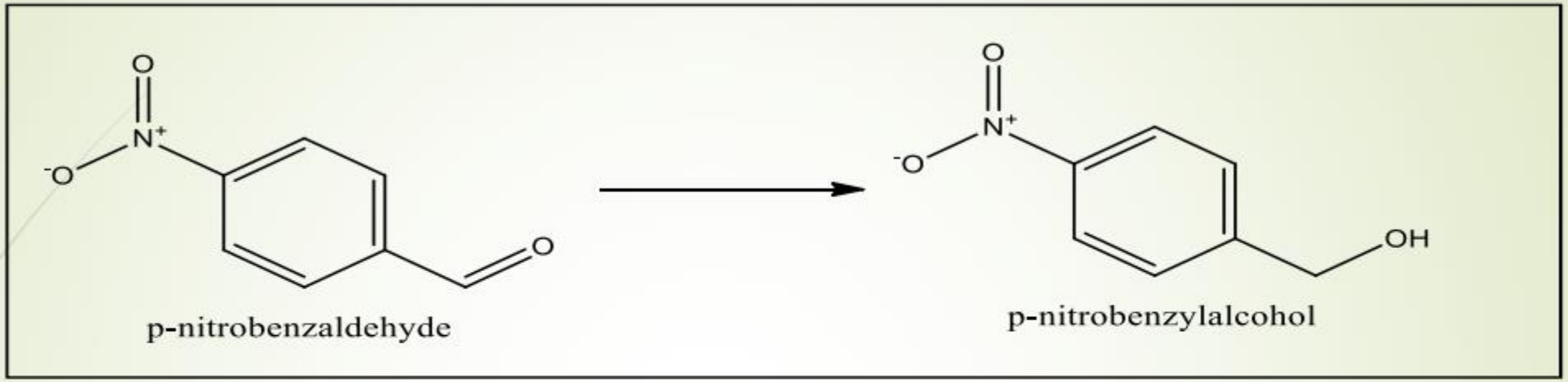
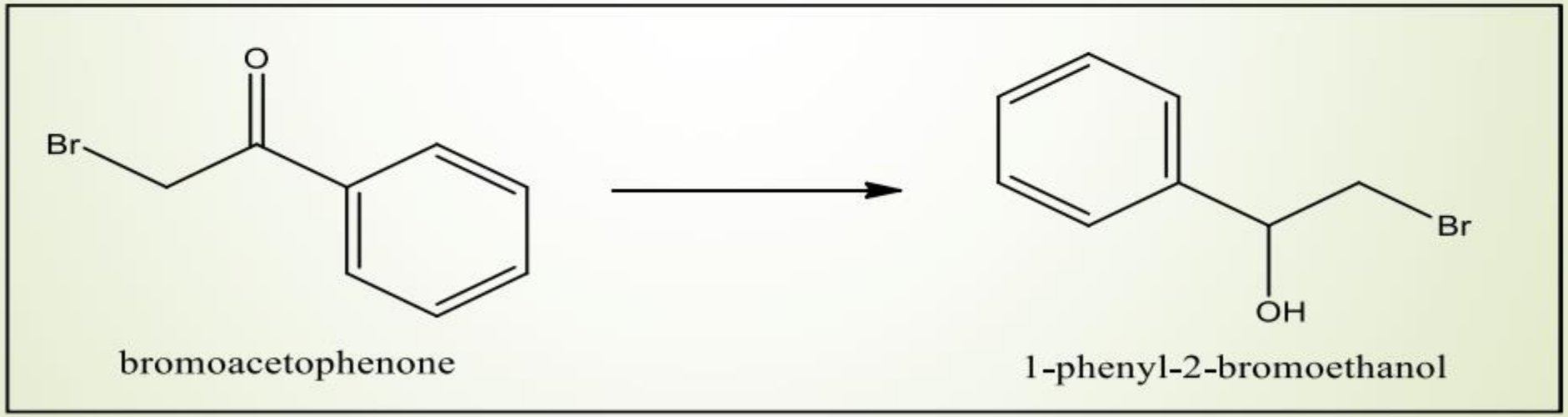
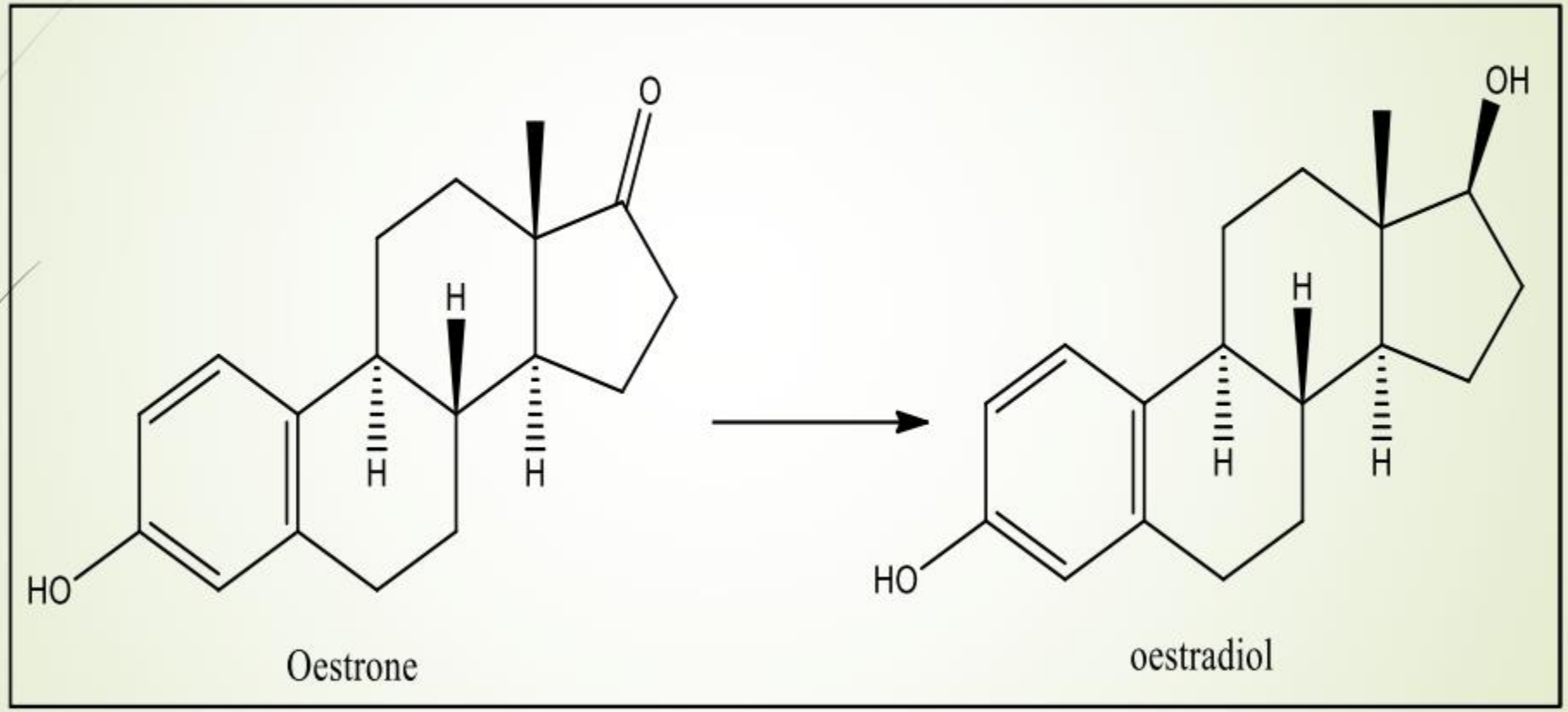

O
N+
-O
O
p-nitrobenzaldehyde
O
N+
-O
OH
p-nitrobenzylalcohol


O
Br
bromoacetophenone
Br
OH
1-phenyl-2-bromoethanol

Cont……

- Used in synthesis of oestradiol



OPPENAUER OXIDATION

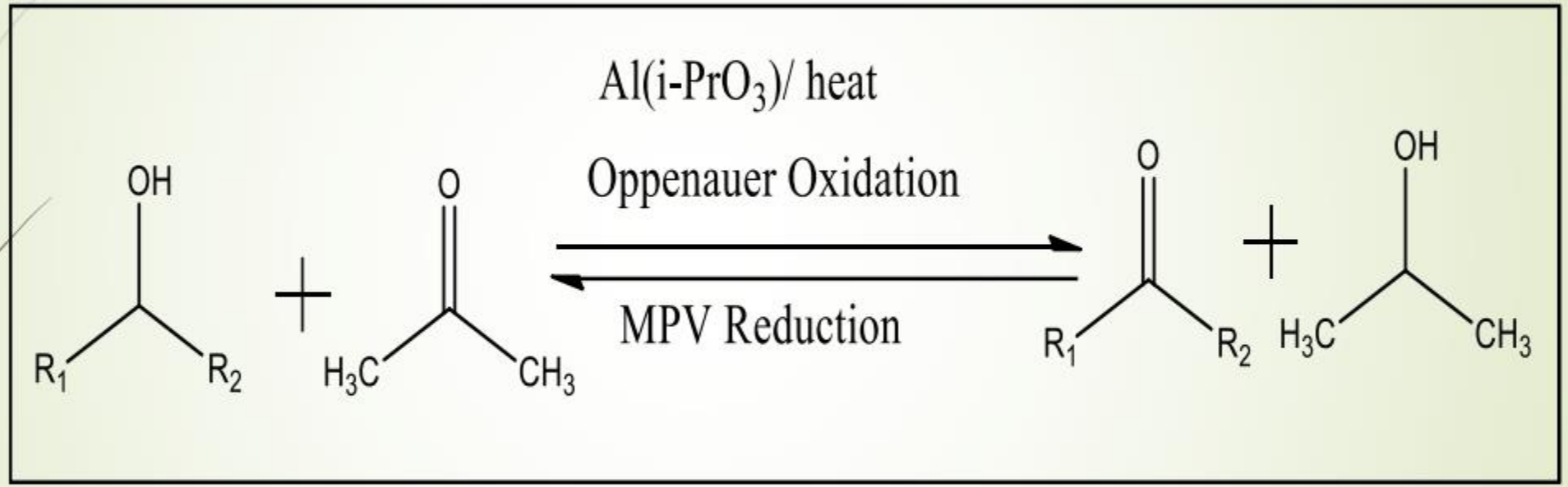
INTRODUCTION

- Named after Rupert Viktor Oppenauer.
- It is a gentle method for selectively oxidizing secondary alcohols to ketones.
- The reaction is the opposite of Meerwein– Ponndorf –Verley reduction.
- The alcohol is oxidized with aluminium isopropoxide in excess acetone.
- This shifts the equilibrium toward the product side.

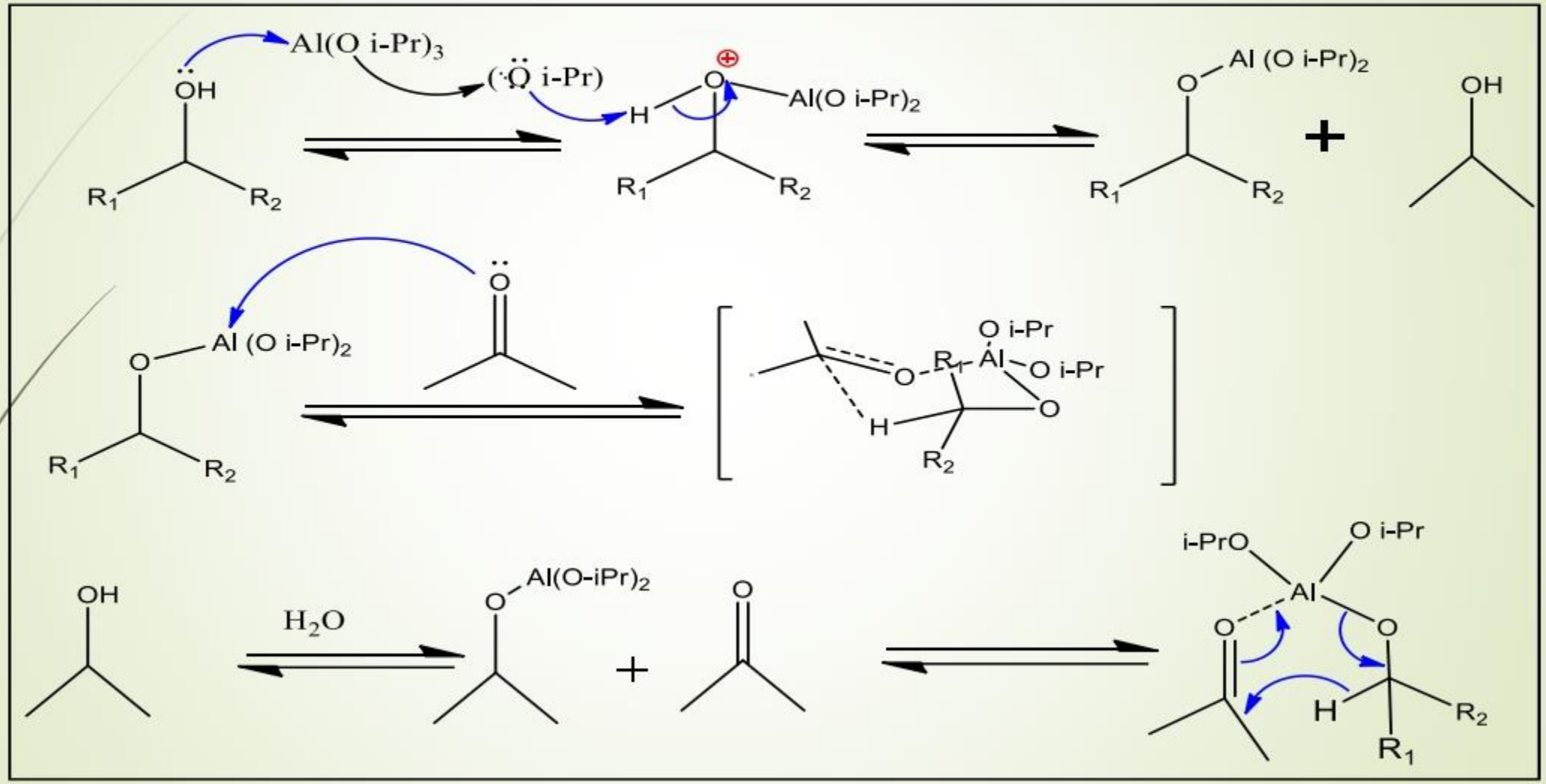
Cont……

- The oxidation is highly selective for secondary alcohols and does not oxidize other sensitive functional groups such as amines and sulfides,
- Though primary alcohols can be oxidized under Oppenauer conditions, primary alcohols are seldom oxidized by this method due to the competing aldol condensation of aldehyde products.
- The Oppenauer oxidation is still used for the oxidation of acid labile substrates.

GENERAL REACTION



MECHANISM

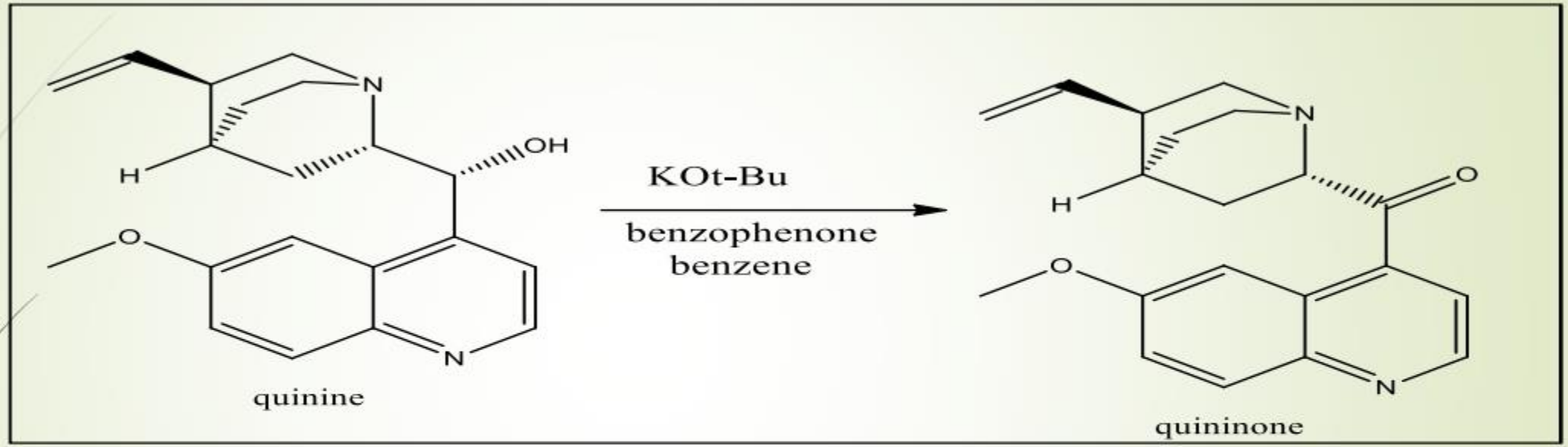


MODIFICATION

Woodward modification

- In the Woodward modification, Woodward substituted potassium tert-butoxide for the aluminium alkoxide.
- The Woodward modification of the Oppenauer oxidation is used when certain alcohol groups do not oxidize under the standard Oppenauer reaction conditions.
- For example, Woodward used potassium tert-butoxide and benzophenone for the oxidation of quinine to quininone, as the traditional aluminium catalytic system failed to oxidize quinine due to the complex formed by coordination of the Lewis-basic nitrogen to the aluminium centre.

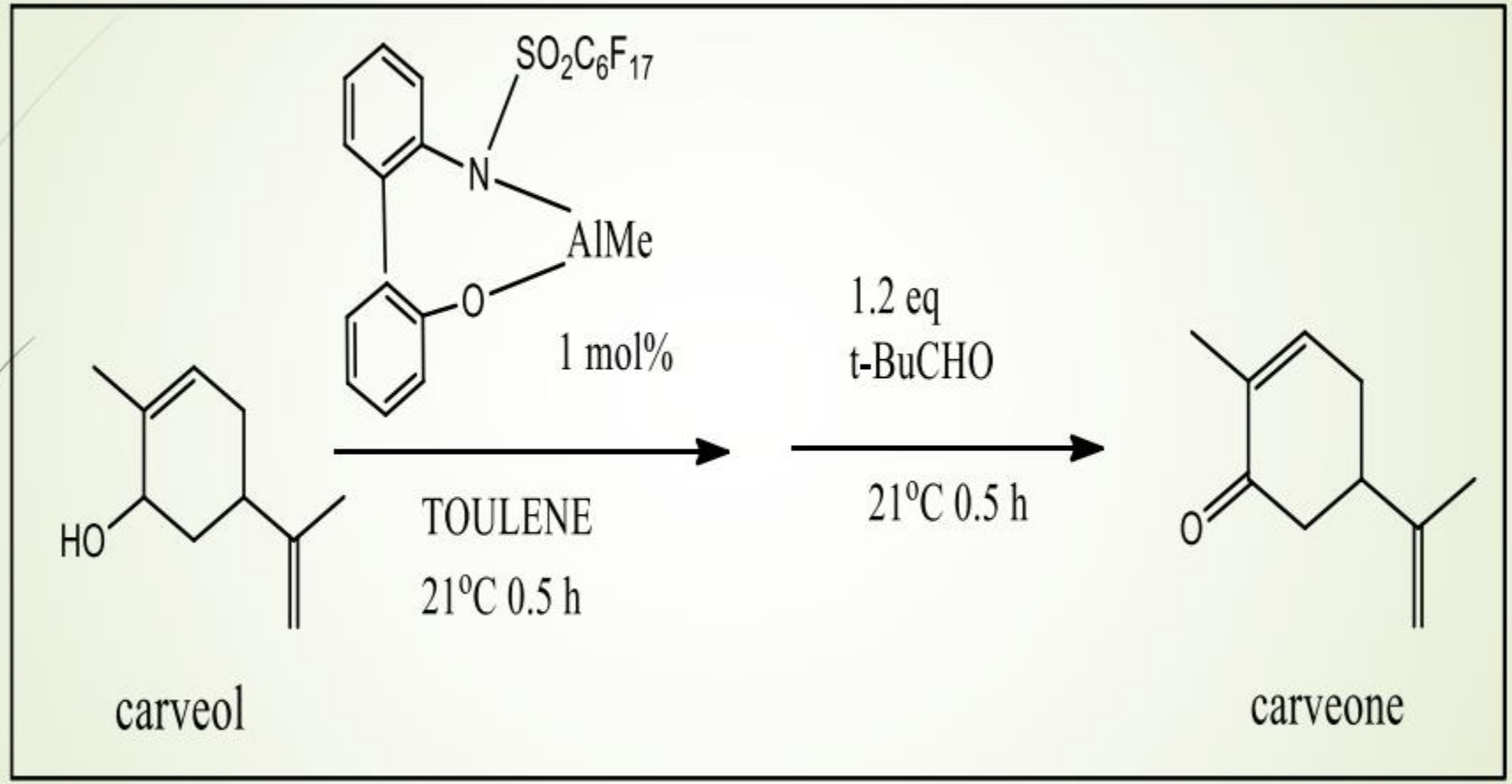
Cont……



Other modifications

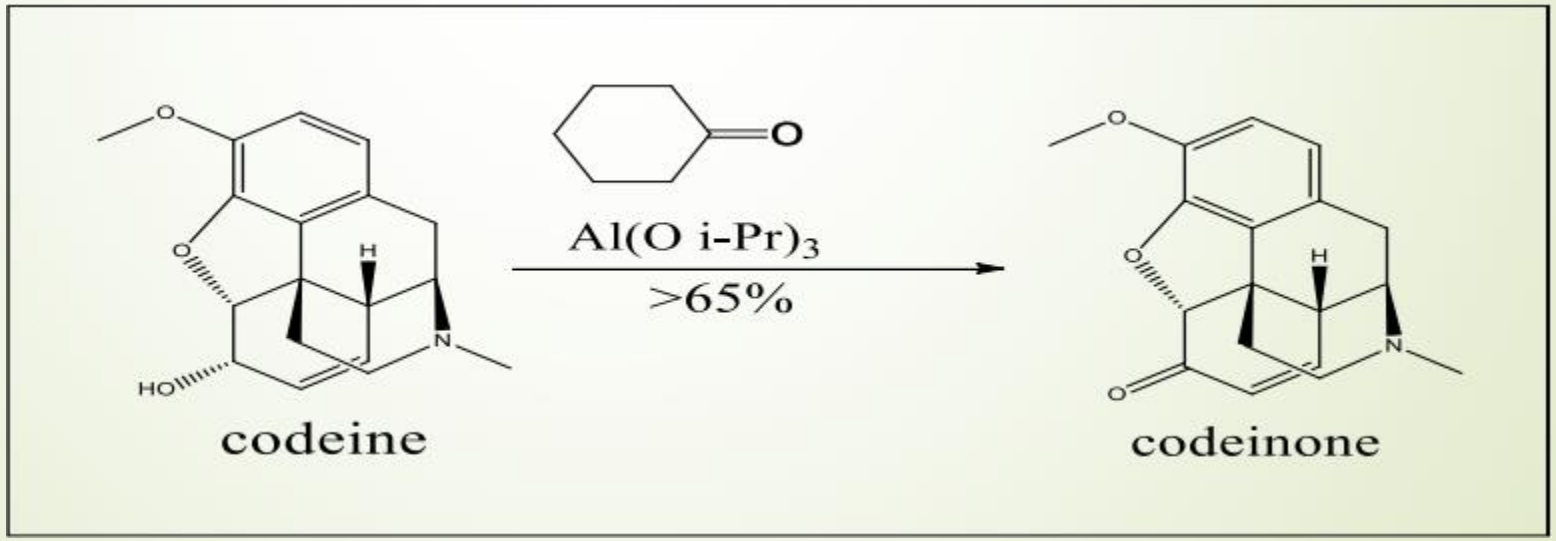
- Several modified aluminium alkoxide catalysts have been also reported
- For example, a highly active aluminium catalyst was reported by Maruoka and co-workers which was utilized in the oxidation of carveol to carvone (a member of a family of chemicals called terpenoids) in excellent yield (94%)

Cont……


SO2C6F17
N
AlMe
O
1 mol%
1.2 eq
t-BuCHO
HO
TOULENE
21°C 0.5 h
21°C 0.5 h
O
carveol
carveone

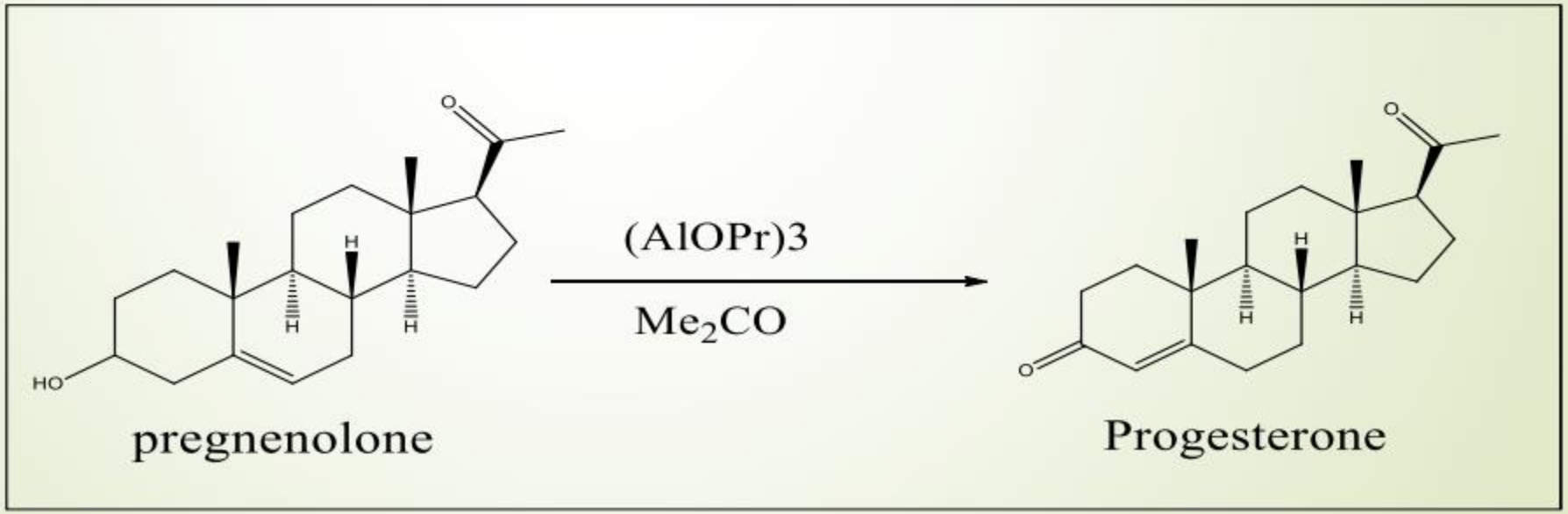
APPLICATIONS

- The Oppenauer oxidation is used to prepare analgesics in the pharmaceutical industry such as morphine and codeine. For instance, codeinone is prepared by the Oppenauer oxidation of codeine.



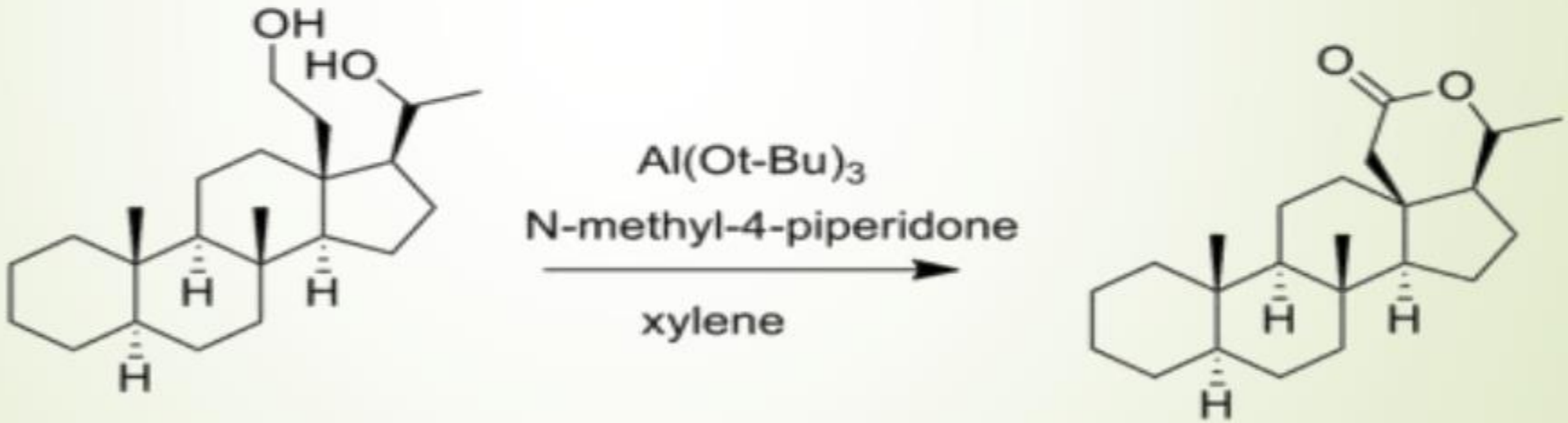
Cont……

- The Oppenauer oxidation is also used to synthesize hormones.
- Progesterone is prepared by the Oppenauer oxidation of pregnenolone.



Cont……

- The Oppenauer oxidation is also used in the synthesis of lactones from 1,4 and 1,5 diols.



10.3.4 REDUCTION REACTIONS

Reduction of aldehydes, ketones and carboxylic acids

- Common reducing agents are :

*lithium aluminium hydride ($LiAlH_4$)

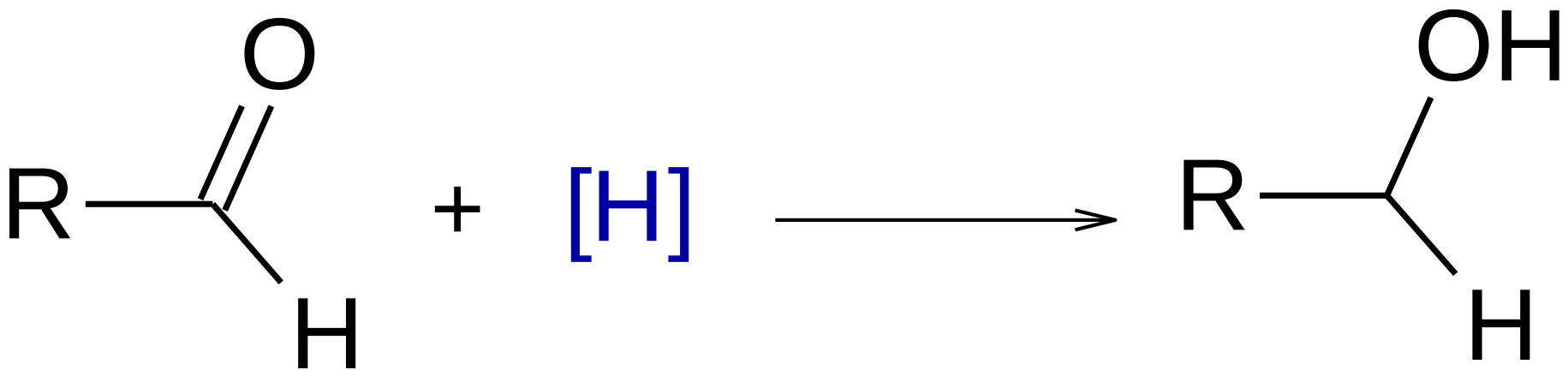
*Sodium borohydride ($NaBH_4$)

- $LiAlH_4$ are the stronger reducing agent
- Can be used to reduce carboxylic acids, aldehydes and ketones
- $NaBH_4$ only strong enough to reduce aldehydes and ketones
- $NaBH_4$ is much easier to use than $LiAlH_4$ and usually preferred for the reduction of aldehydes and ketones

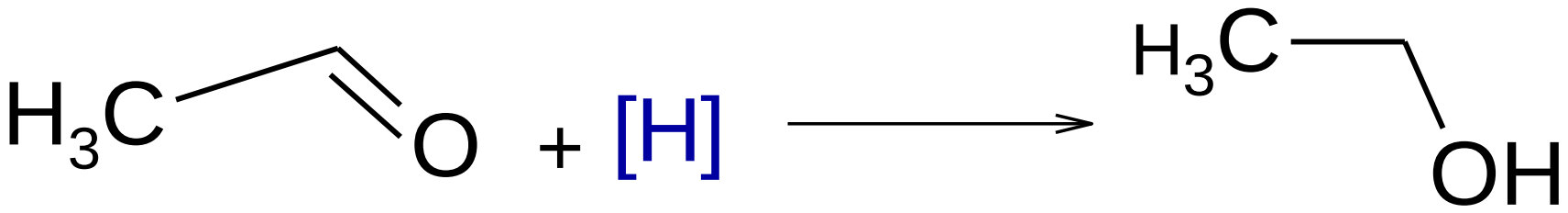
ALDEHYDES

BASIC REACTION :

Aldehydes $\xrightarrow[\text{methanol}]{NaBH_4}$ primary alcohol

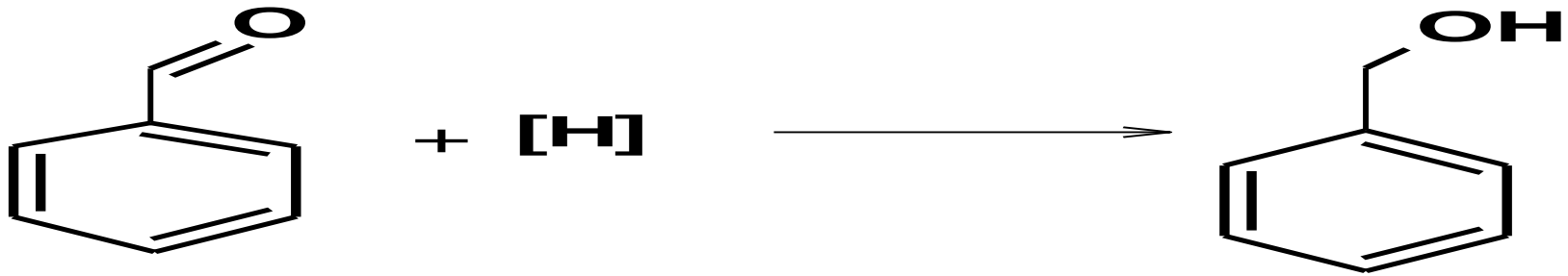


Examples



Ethanal

Ethanol



benzaldehyde

benzylalcohol

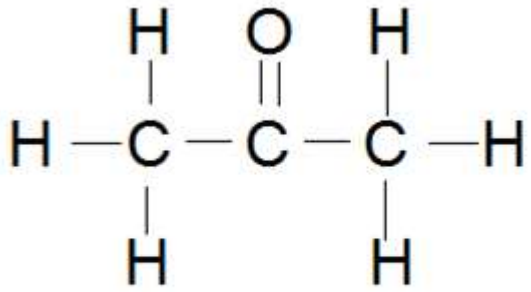
- A balanced equation for the reaction can be written using [H] to represent hydrogen from reducing agent:

$$CH_3CHO + 2[H] \rightarrow CH_3CH_2OH$$

Ketones

BASIC REACTION :

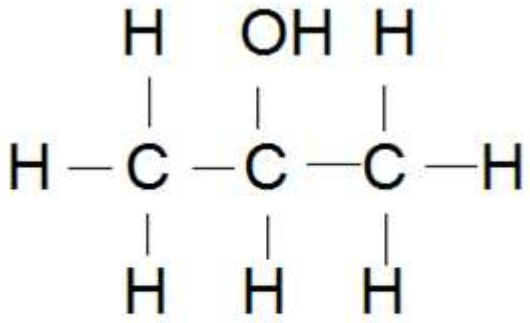
ketone $\xrightarrow[\text{methanol}]{NaBH_4}$ secondary alcohol



propanone

$NaBH_4$

methanol

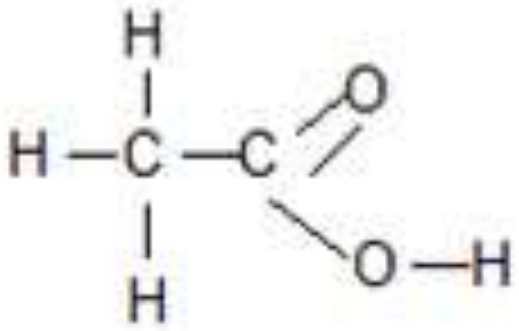


propan-2-ol

Carboxylic acids

BASIC REACTION :

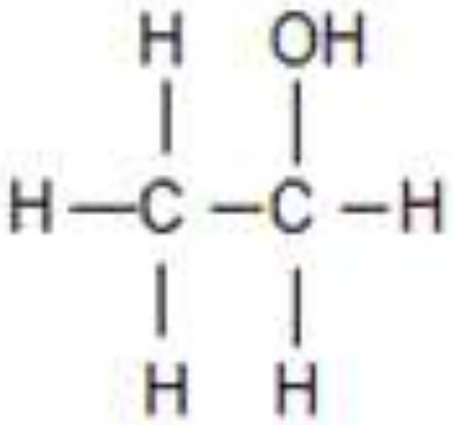
Carboxylic acids —(i) $LiAlH_4$ in ethoxyethane; (ii) H^+/H_2O→ primary alcohol



Ethanoic acid

(i) $LiAlH_4$ in ethoxyethane

(ii) H^+/H_2O



Ethanol

- This can also be written as a balanced equation using [H] to represent hydrogen from the reducing agent:
- $CH_3COOH + 4[H] \rightarrow CH_3CH_2OH + H_2O$

If you need to make an aldehyde from a carboxylic acids, the carboxylic acids must be reduced to a primary alcohol using $LiAlH_4$ and then the primary alcohol must be oxidised back to an aldehyde . (partial oxidation with distillation)

Reduction of nitrobenzene

BASIC REACTION :

Nitrobenzene + 6[H] —(i) Sn/ conc. HCl HEAT; (ii) NaOH→ phenylamine aniline

- First step could be written as :

$C_6H_5NO_2 + 6[H] + H^+ \rightarrow C_6H_5NH_3^+ + 2H_2O$

- And the second as :

$C_6H_5NH_3^+ + OH^- \rightarrow C_6H_5NH_2 + H_2O$

Reduction Reactions

Classification of reduction reactions

- Catalytic hyrdogenation (H_2 with metals)
- Hydride transfer reactions, using hydride sources such as $LiAlH_4$, $NaBH_4$,..
- Dissolving metal reductions (Na, Li in ammonia solution) (Birch reduction)

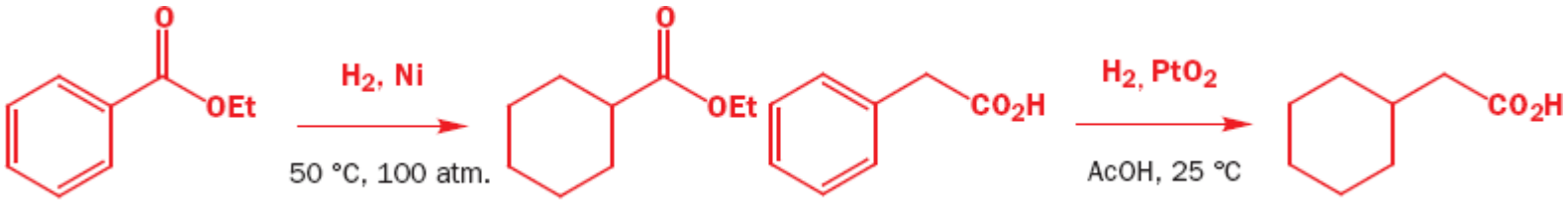
Classification of reduction reactions

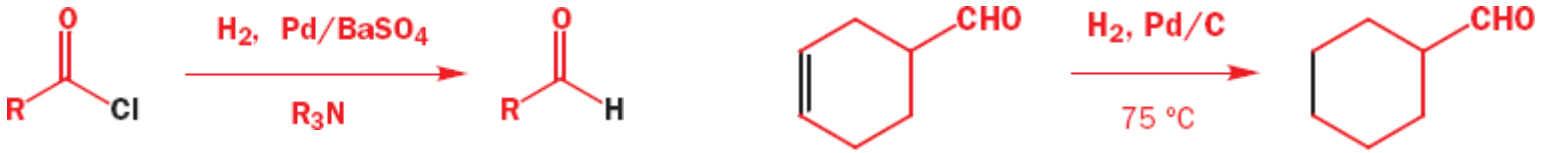
- Replacement of oxygen by hydrogen
- Removing oxygen from the substrate
- Reduction with cleavage
- Reductive coupling

Catalytic Hydrogenation

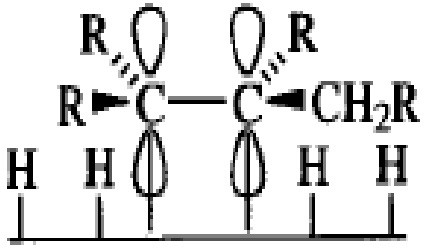
- Addition of H_2 to unsat. bond (double , triple bonds, NO_2, CN,..
- Without catalysts ,it needs 480°c
- Pt group metals (Pd, Ni ,Ru and Rh) used as catalysts
- Can be selective reduction, depends on conditions

Catalytic Hydrogenation

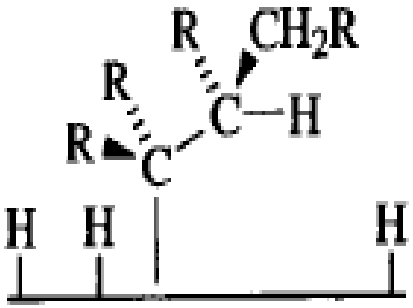




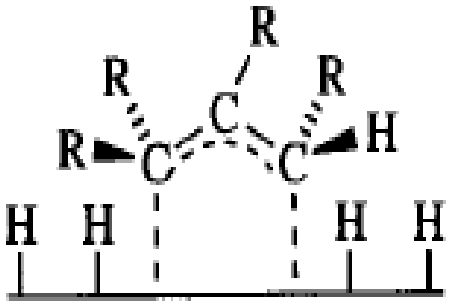
Catalytic Hydrogenation



A π-complex



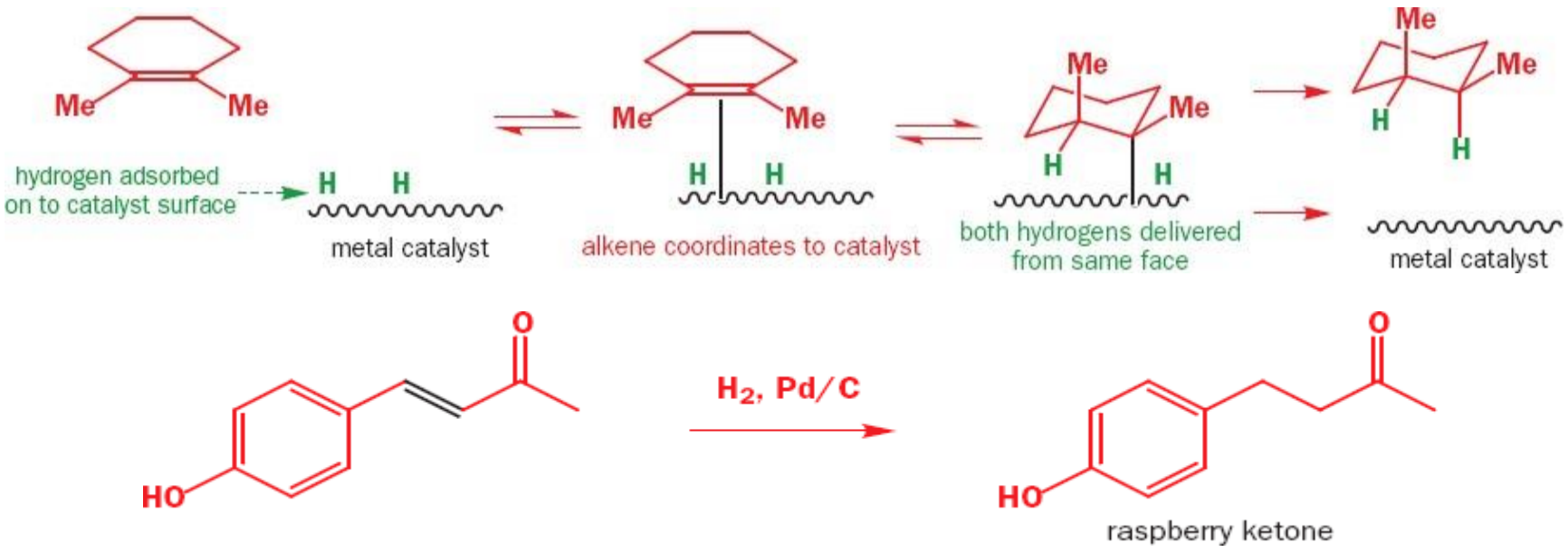
B σ-bond



C π-allyl complex

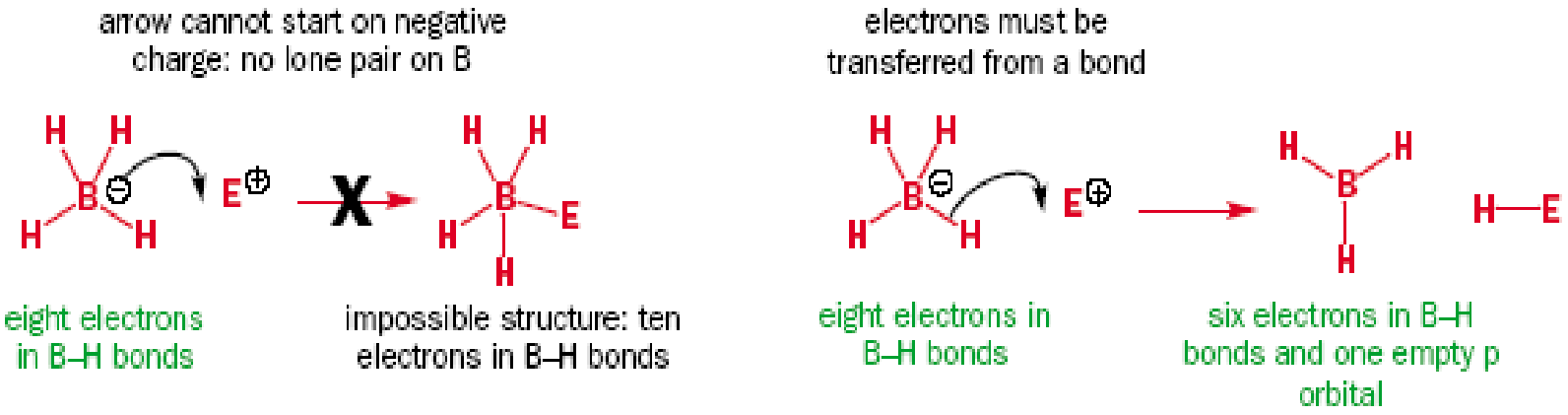
Pd/C reduction

- Pd powder spread on charcoal after reduction of $PdCl_2$ with H_2
- Homogenous catalyst, can be recovered by filtration



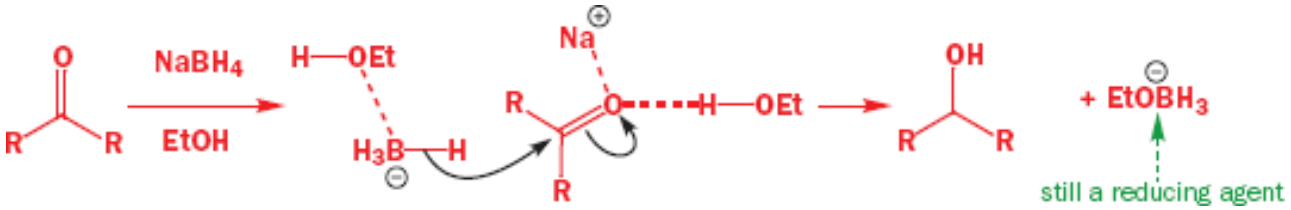
$NaBH_4$

- Selective (chemoselectivity) reagent
- White crystals, safe and easy to handle
- Reduces aldehydes, ketones.
- Can`t reduce esters ,acids, amides

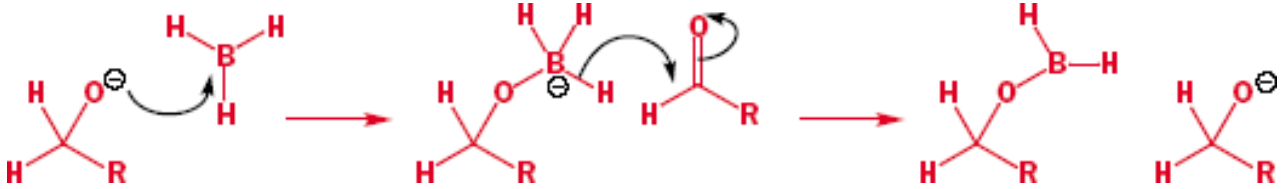


$NaBH_4$

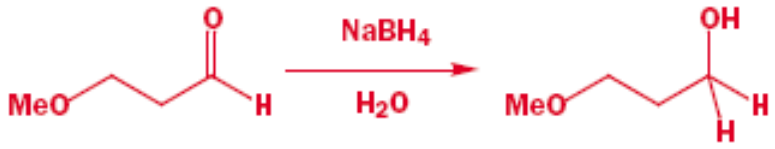
Generally

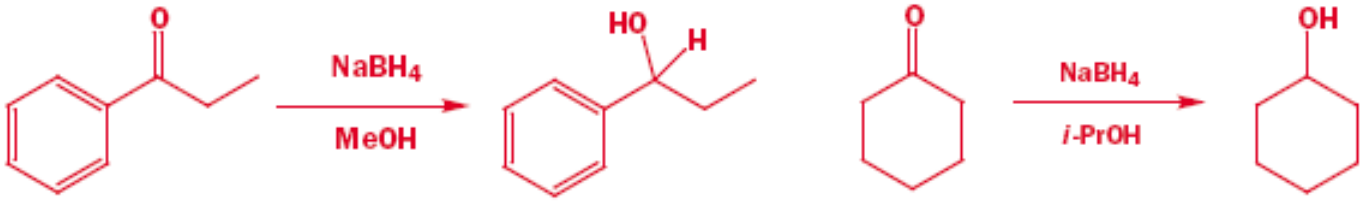


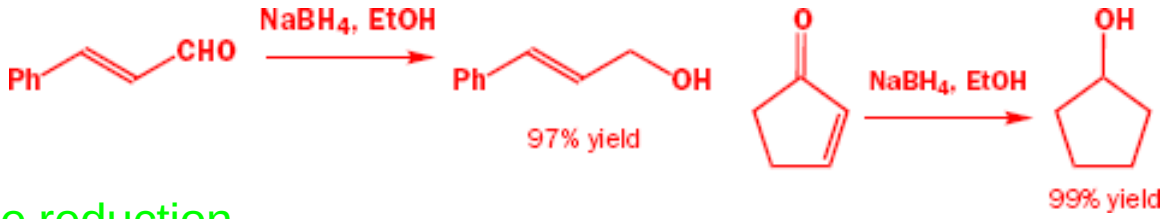
Still reducing agent



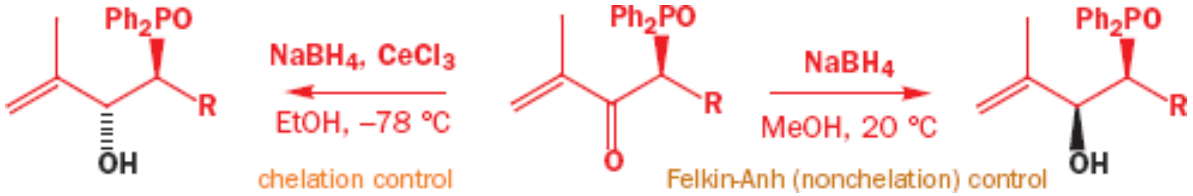
$NaBH_4$







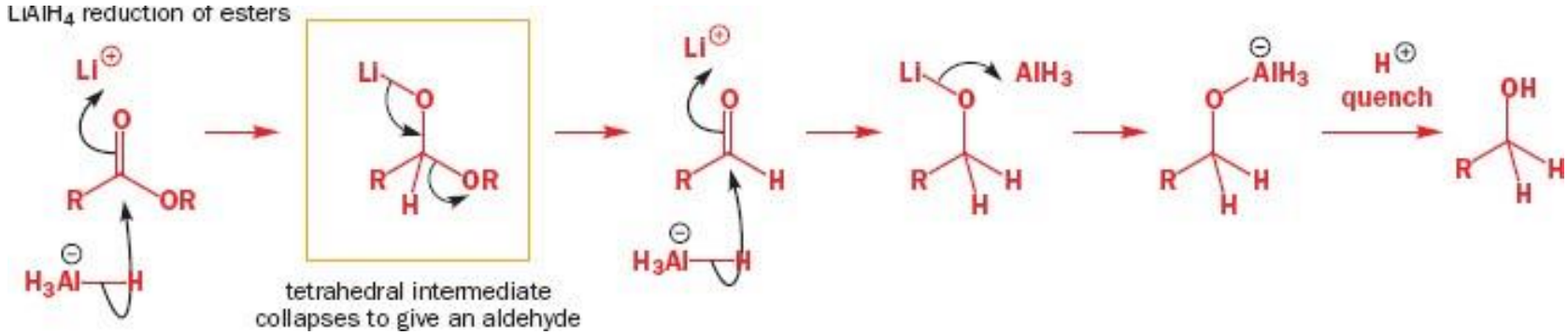
Luche reduction

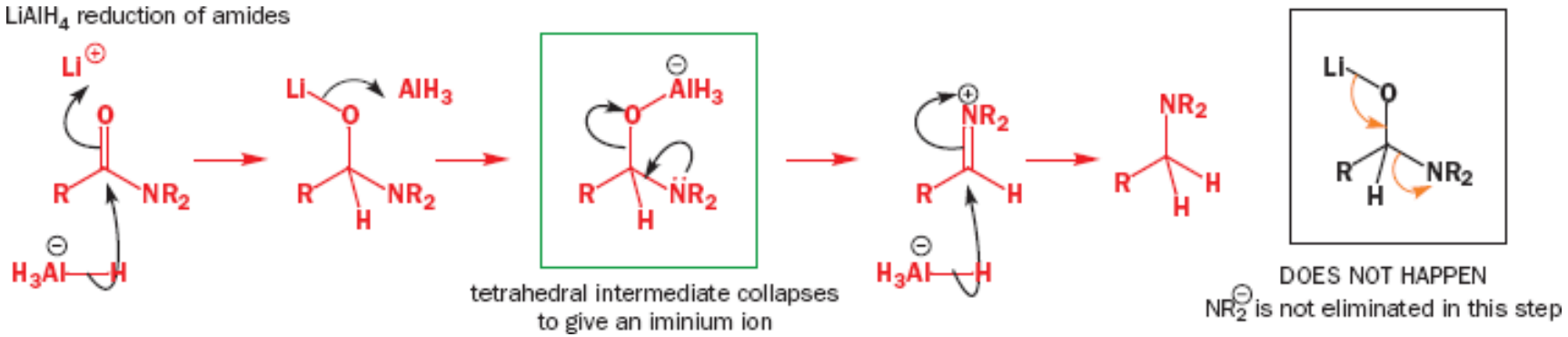


$LiAlH_4$

- Powerful reducing agent compared to $NaBH_4$ due to weaker Al-H bond.
- Pure sample is white but commercially is grey????
- Dangerous, reacts violently with water
- Reduce aldehyde, ketones, esters, amides and nitro compounds.

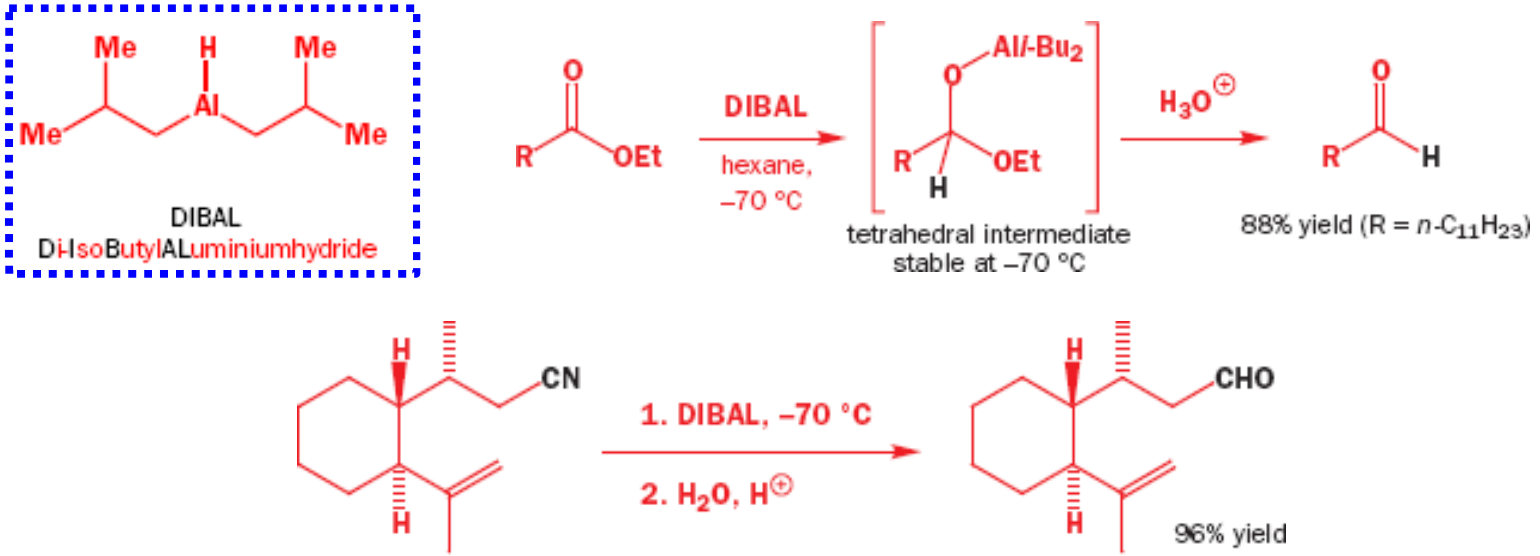
$LiAlH_4$


LiAlH4 reduction of esters
Li
O
R
OR
H3Al
H
tetrahedral intermediate
collapses to give an aldehyde
AlH3
H
quench
OH


LiAlH4 reduction of amides
Li
O
R
NR2
H3Al
H
AlH3
tetrahedral intermediate collapses
to give an iminium ion
DOES NOT HAPPEN
NR2 is not eliminated in this step

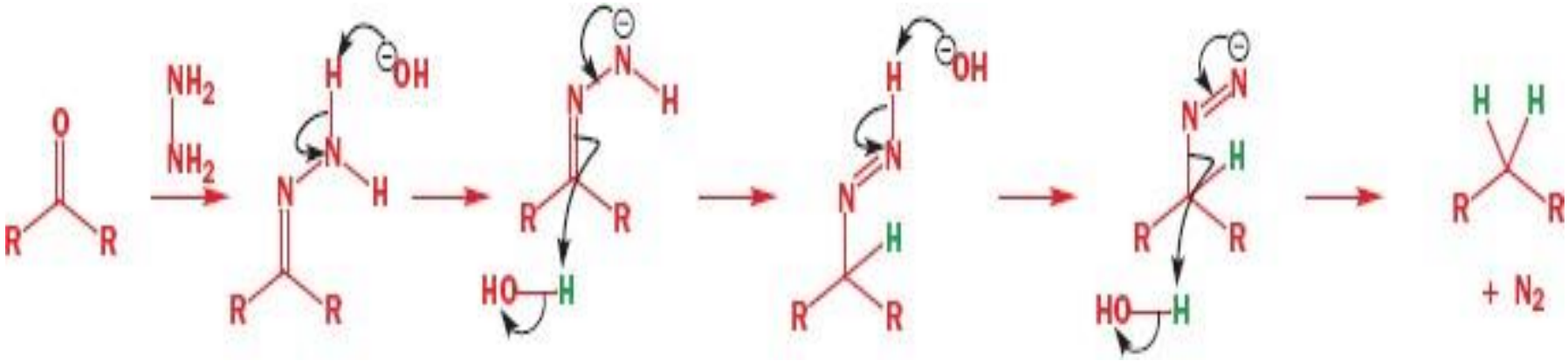
DIBAL

- Selective reagent (alkyne to alkene, ester or ketone to aldehyde).
- Specialist reductant of nitrile to aldehyde



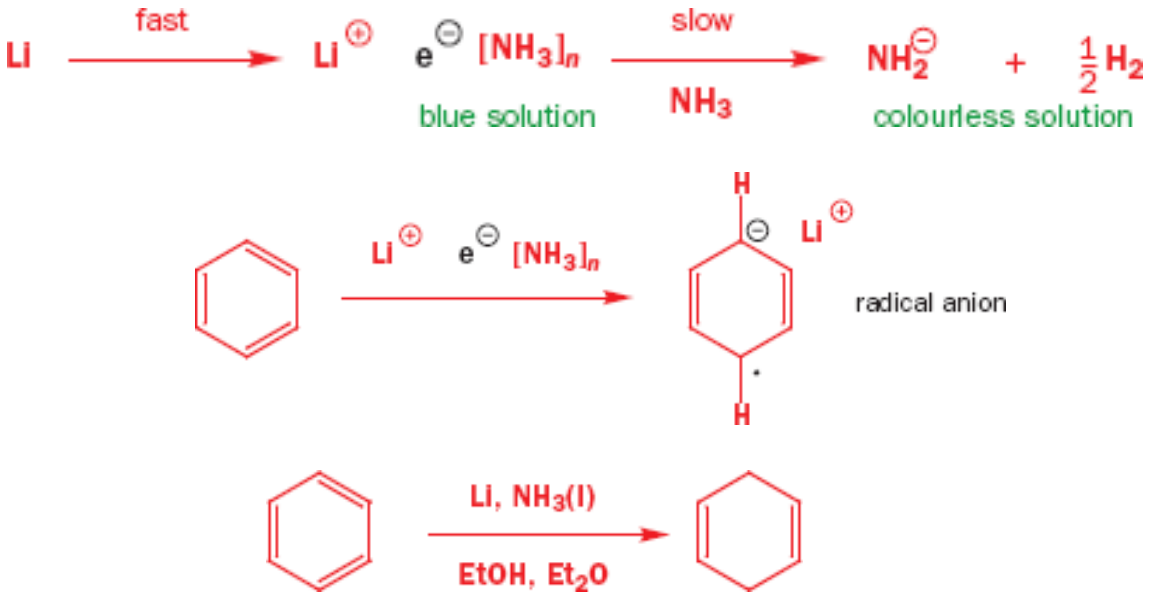
Wolff-Kishner reduction

- Reduction of aldehydes, ketones to alkane
- Using hydrazine in basic media



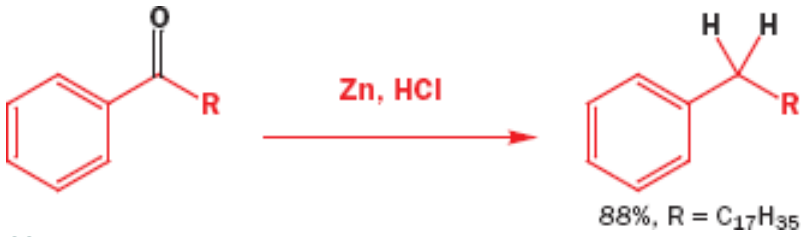
Metal dissolving reduction

- Dissolving Li or Na in NH_3 solution
- Birch reduction in case of aromatics
- Good access to cyclohexadienes

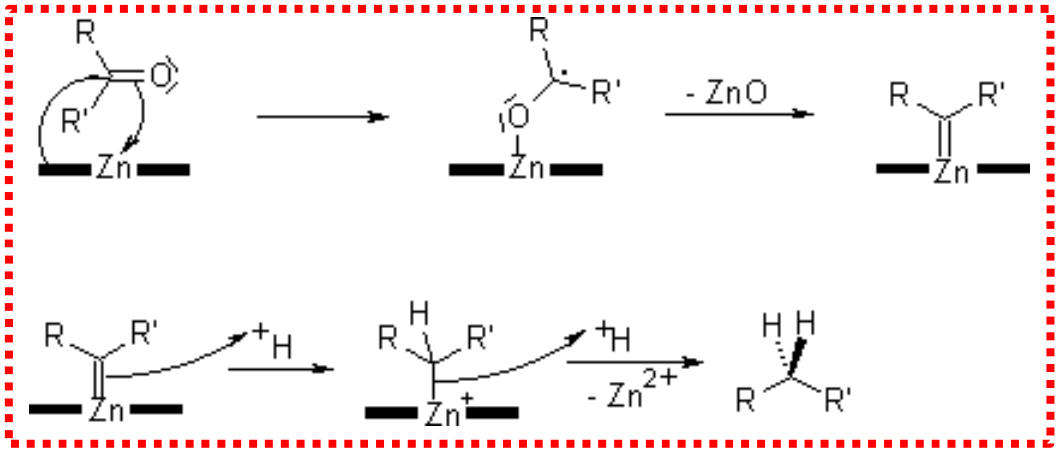


Clemmensen reduction

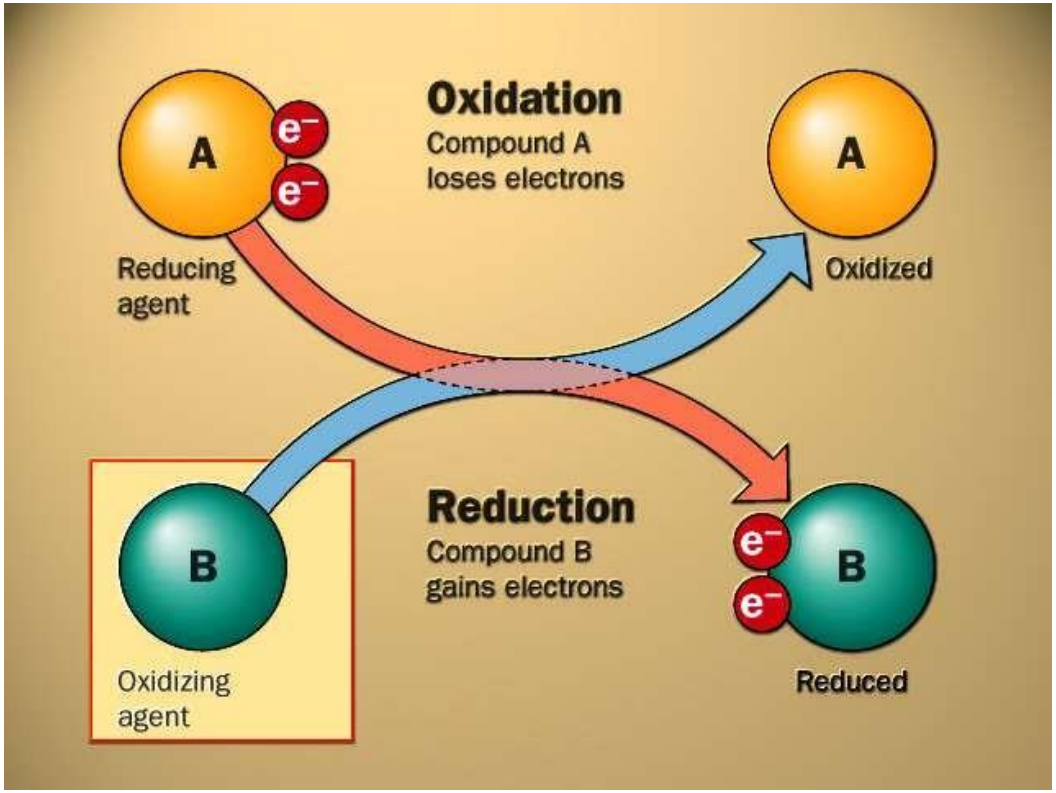
- Kind of electron reduction reactions
- Zinc metal in Conc. HCl
- Carbonyl to alkane (CH_2)



Carbenoid mechanism



Birch reduction



Reduction :-

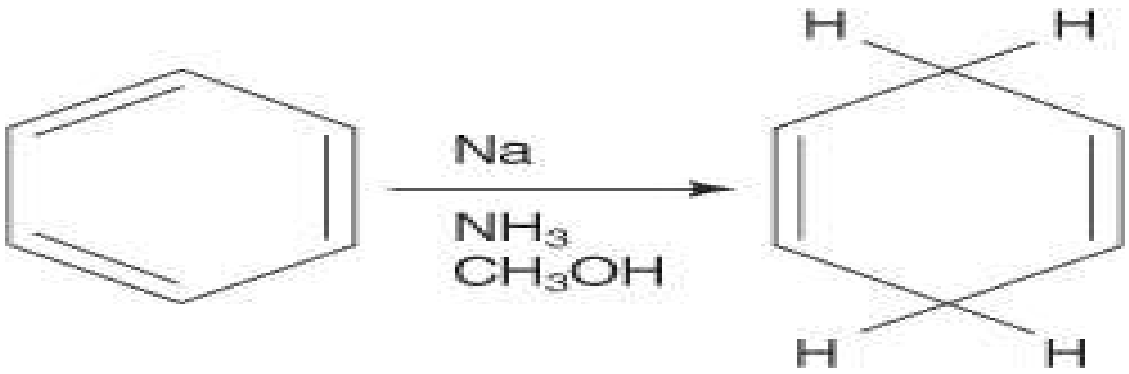
- Addition of hydrogen or removal of oxygen is called as reduction.
- In this the addition of electropositive element takesplase.
- It may also be defined as the process in which an atom or group of atoms taking part in a chemical reaction' gain one or more electrons.

Birch reduction :-

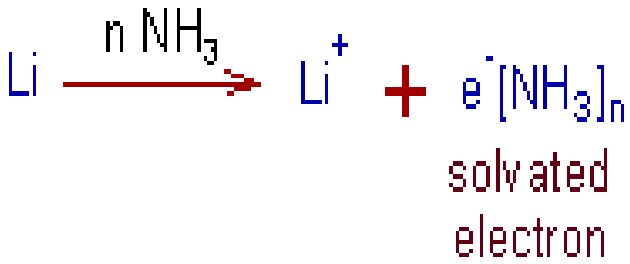
Principle:-

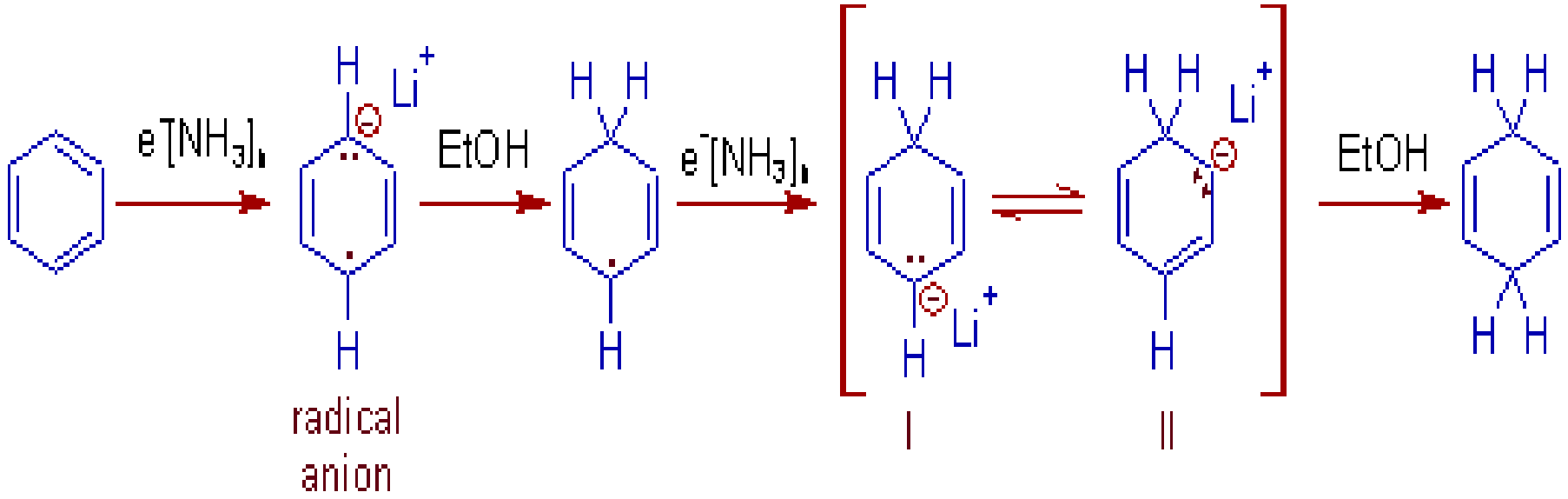
Reduction of aromatic rings by means of alkali metals (Li or Na) in liquid ammonia or amines with ethanol as proton donar,to give mainaly unconjugated dihydroderivatives is known as birch reduction.

General reaction:-

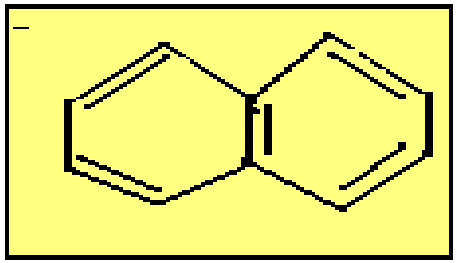


Mechanism:-

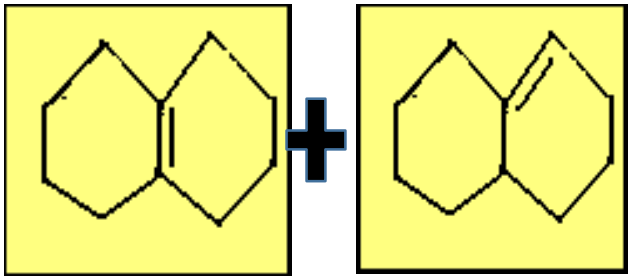

Li
n NH3
Li+
+
e-[NH3]n
solvated
electron

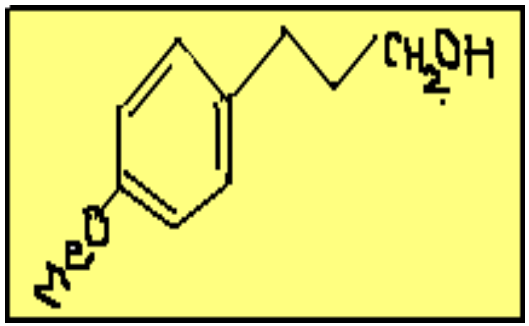

e-[NH3]n
H
Li+
radical
anion
EtOH
H H
H
e-[NH3]n
H H
H
Li+
I
H H
Li+
H
II
EtOH
H H
H H

APPLICATIONS :



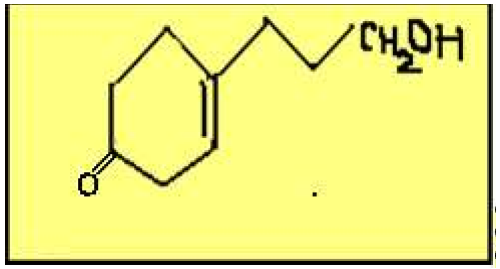
Li/ Et_2 NH ,Me_2NH





Li ,NH_3

$(COOH)_2$, H_2O ‘
t- Bu OH.



Oxidation :-

- Addition of oxygen or removal of hydrogen is called as oxidation.
- In this the addition of electronegative element takes place.
- It may be also defined as the process in which an atom or group of atoms, taking part in a chemical reaction, loses one or more electrons.

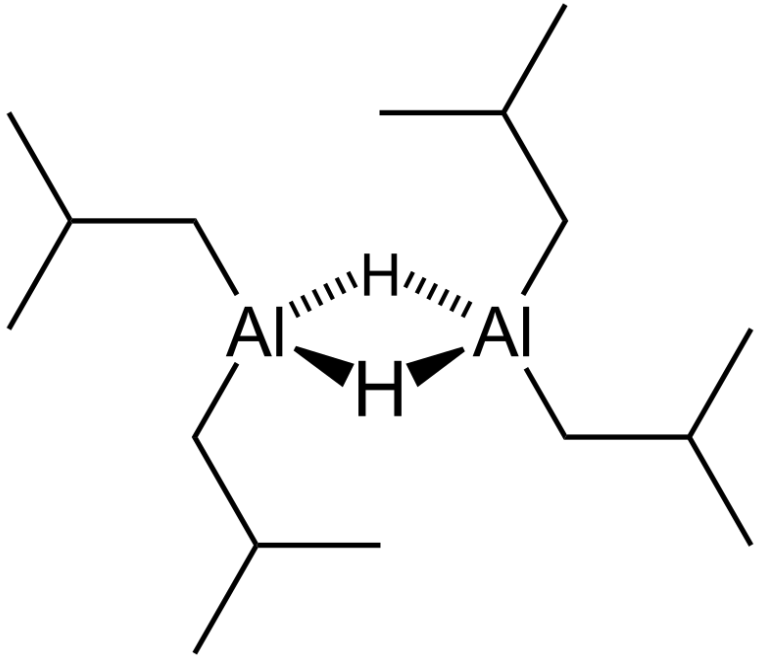
Complex Hydrides

- Hydrides such as sodium borohydride, lithium aluminium hydride, diisobutylaluminium hydride (DIBAL) and super hydride, are commonly used as reducing agents in chemical synthesis.
- The hydride adds to an electrophilic center, typically unsaturated carbon.
- **Diisobutylaluminium hydride (DIBAL)**
- is a reducing agent with the formula $(i\text{-}Bu_2AlH)_2$, where *i*-Bu represents isobutyl ($-CH_2CH(CH_3)_2$).
- This organoaluminium compound was investigated originally as a co-catalyst for the polymerization of alkenes.

Diisobutylaluminium hydride

✓DIBAL is useful in organic synthesis for a variety of reductions, including converting carboxylic acids, their derivatives, and nitriles to aldehydes.

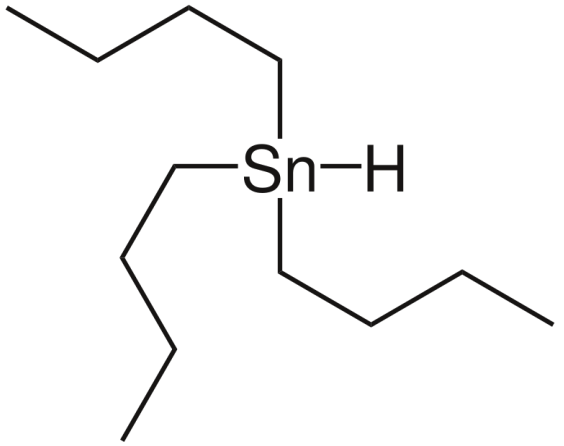
✓DIBAL efficiently reduces α-β unsaturated esters to the corresponding allylic alcohol



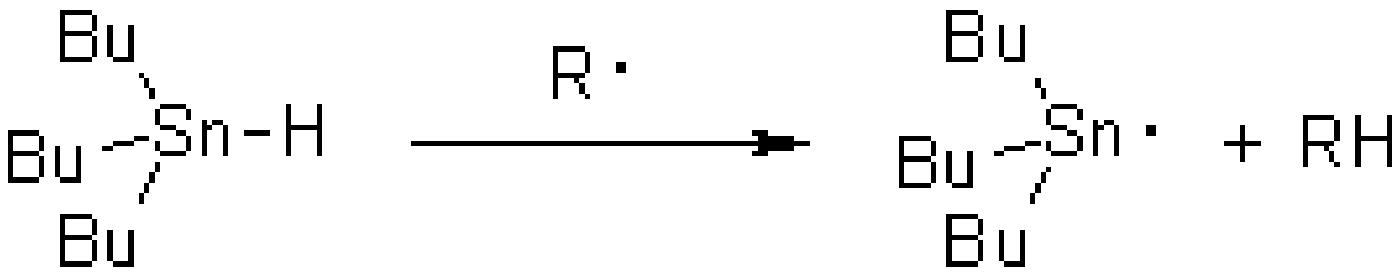
Tributyltin hydride (TBTH)

- **Tributyltin hydride** is an organotin compound with the formula $(C_4H_9)_3SnH$.
- It is a colorless liquid that is soluble in organic solvents. The compound is used as a source of hydrogen atoms in organic synthesis.
- Organotin hydrides are very good radical reducing agents due to the relatively weak, nonionic bond between tin and hydrogen (Bu_3SnH 74 kcal/mol) that can cleave homolytically.

Organotin hydrides are very good radical reducing agents due to the relatively weak, nonionic bond between tin and hydrogen (Bu_3SnH 74 kcal/mol) that can cleave homolytically.



Tributyltin hydride (TBTH)



- However, these compounds are plagued by their high toxicity and high fat solubility (lipophilicity).
- Therefore, with few exceptions, the use of tin hydrides should be avoided.
- The catalytic use of this reagents with a suitable second reducing agent, or the use of radical H-donors such as indium hydrides and silanes [especially tris(trimethylsilyl)silane] are possible alternatives.

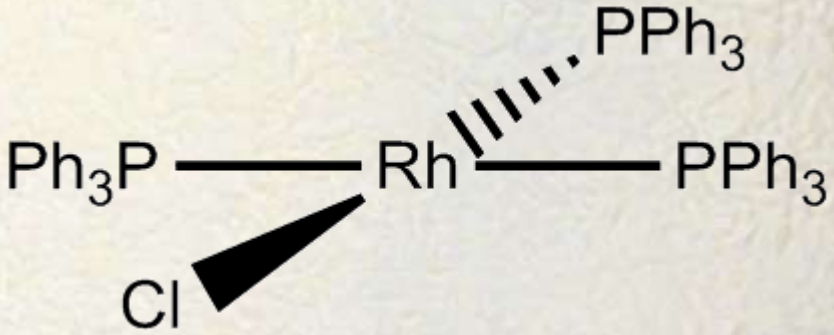
Organometallic catalysts

- In chemistry, homogeneous catalysis is catalysis in a solution by a soluble catalyst.
- Homogeneous catalysis refers to catalytic reactions where the catalyst is in the same phase as the reactants.
- The term is used almost exclusively to describe solutions and often implies catalysis by organometallic compounds.

- Polymer industry
- Pharma industry
- Petroleum industry
- Organic synthesis

Wilkinson's catalyst

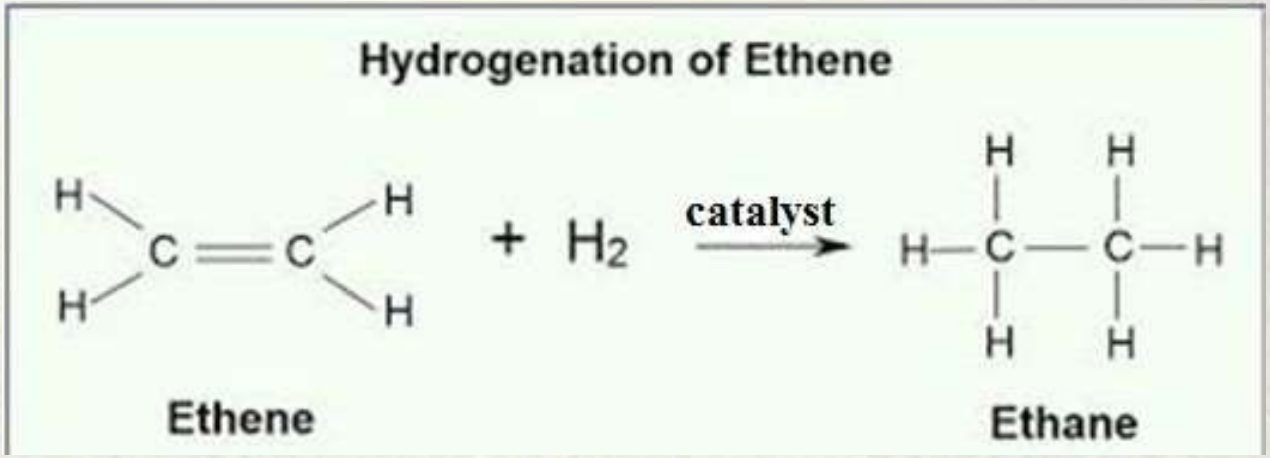
- **Chlorotris(triphenylphosphine)rhodium(I), [RhCl(PPh3)3]**



- Discovered accidentally by **Fred Jardine** ,(PhD scholor) working for Geoffrey Wilkinson was trying to make [RhCl3(PPh3)3], from the reaction of hydrated rhodium trichloride and excess triphenylphosphine in boiling ethanol.

$$[RhCl_3(H_2O)_3] + 4\ PPh_3 \longrightarrow [RhCl(PPh_3)_3] + Ph_3PO + 2\ HCl + 2\ H_2O$$

Hydrogenation of alkenes

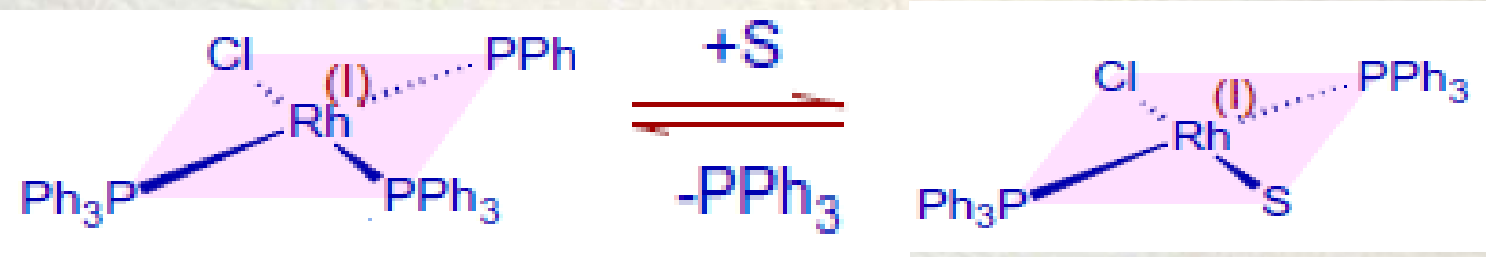


It is a very active catalyst for the rapid homogenous hydrogenation (i.e. in solution) of unsaturated compounds.

working rapidly at 25°C and 1 atm pressure of hydrogen gas

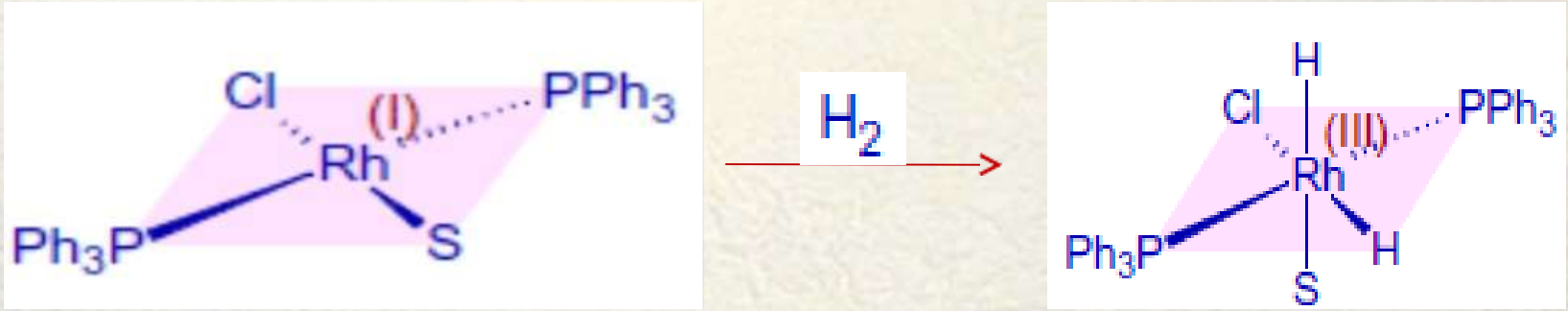
mechanism

- Mechanism involves 5 steps
- **Step (i) Dissociation of one ligand**

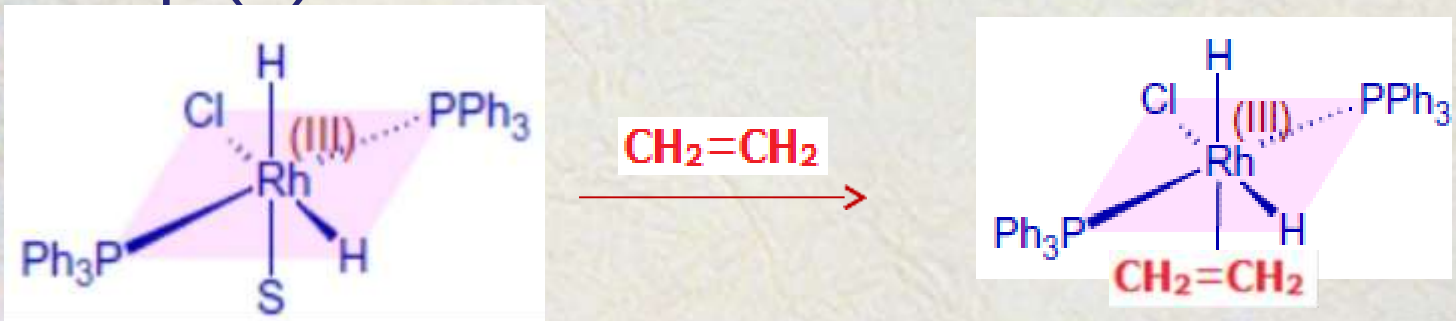


- One of the Ligand is lost replaced by the solvent S

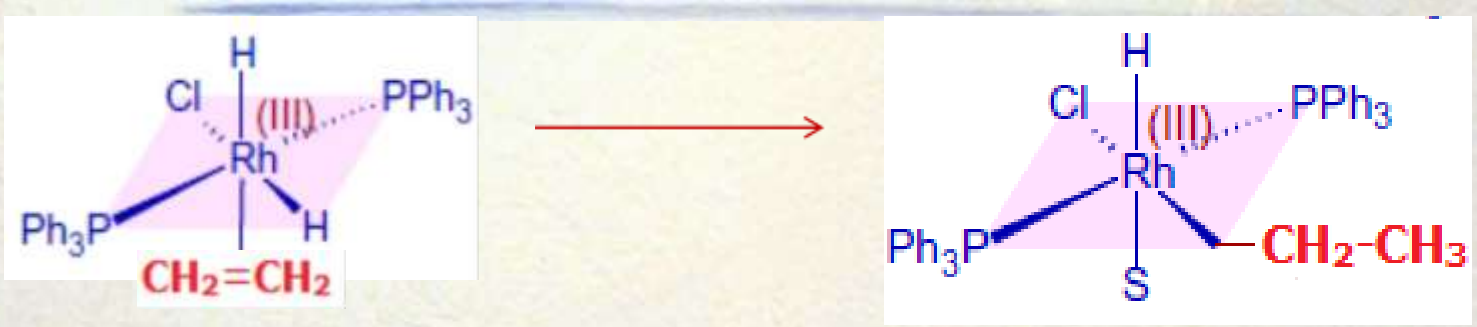
- Step (ii) Oxidative addition of Hydrogen



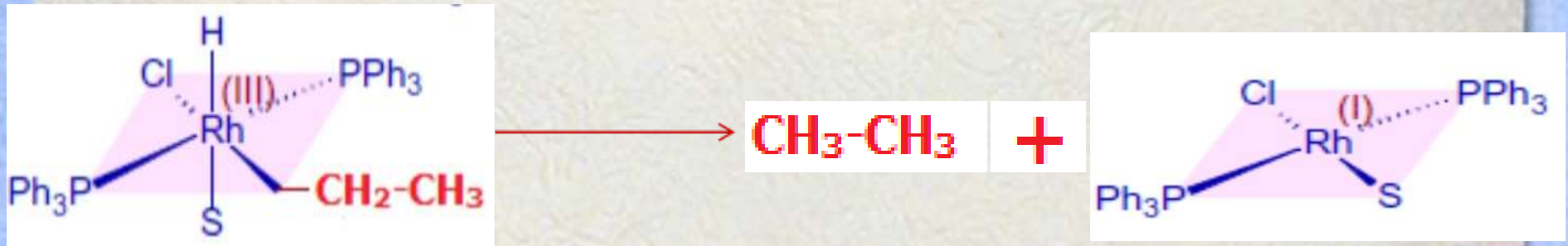
- Hydrogen is added to the metal leading to the increase in both oxidation number and coordination number.
- Step (iii) Co-ordination of alkene



- Step (iv) Migratory insertion



- One hydrogen migrates and inserted between carbon and hydrogen of alkene
- Step (v) Reductive elimination

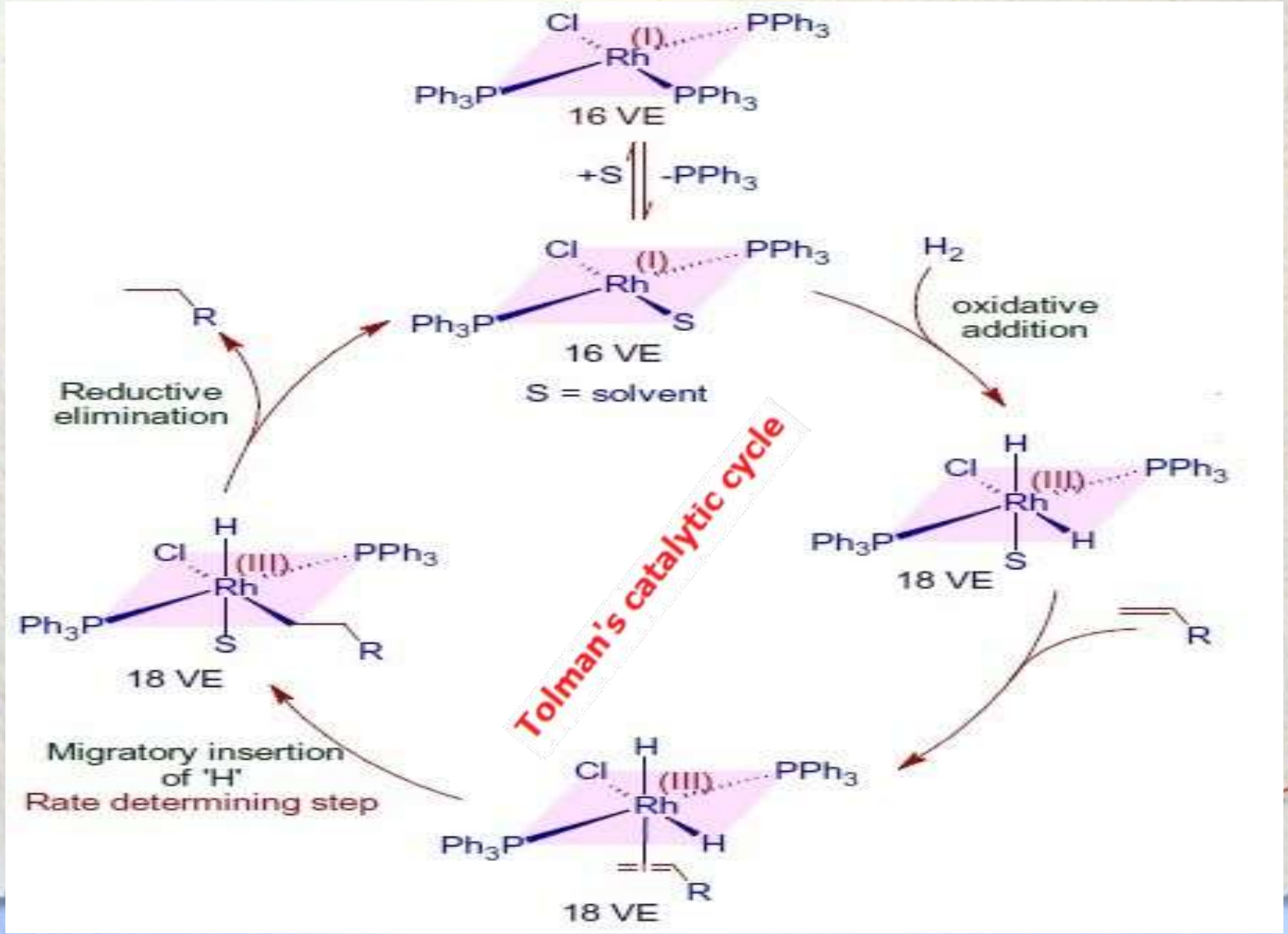


- **Release of the product with regeneration of the catalyst**

Tolman's catalytic cycle

- Hydrogenation of alkenes by Wilkinson's catalyst is called as Tolman's catalytic cycle or loop.
- It is an extended version of $18e^-$ rule.
- In reactions catalyzed by homogeneous organometallic catalysts, the intermediates obtained in different steps shuttle between 18 and 16^{e-}.
- The shifting of electrons are energetically favored hence allowed.

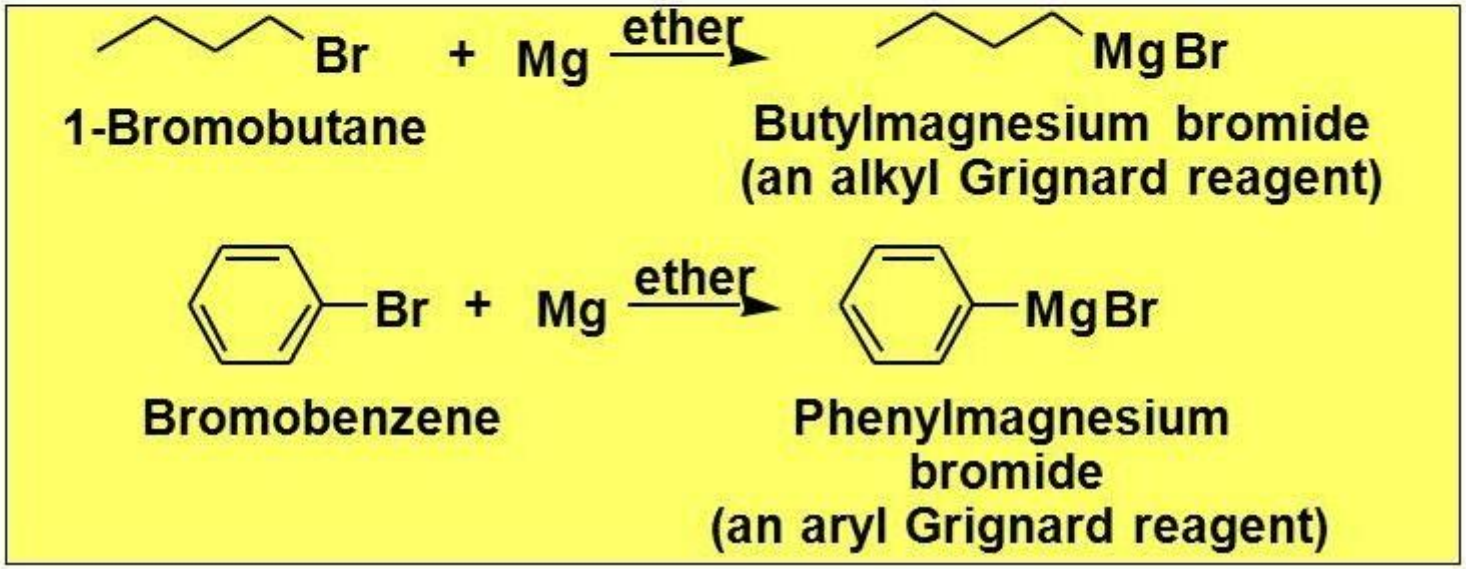
Hydrgenation of alkenes by Wilkinson's catalyst



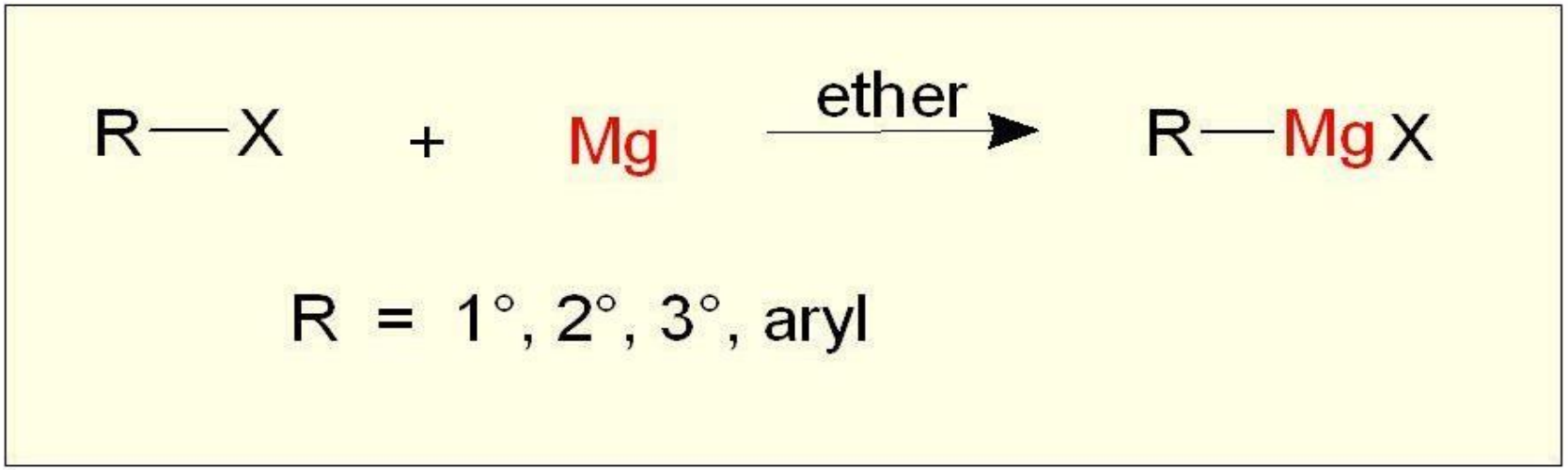
Grignard Reagents

Grignard Reagents

- Grignard reagent: an organomagnesium compound
  - prepared by addition of an alkyl, aryl, or alkenyl (vinylic) halide to Mg metal in diethyl ether or THF



Formation of Grignard Reagents



This reaction was discovered by the Frenchman, Victor Grignard -- Nobel Prize in 1912

Mechanism

The reaction proceeds through single electron transfer. In the Grignard formation reaction, radicals may be converted into carbanions through a second electron transfer.

$$R{-}X + Mg \rightarrow R{-}X^{\bullet -} + Mg^{\bullet +}$$

$$R{-}X^{\bullet -} \rightarrow R^{\bullet} + X^{-}$$

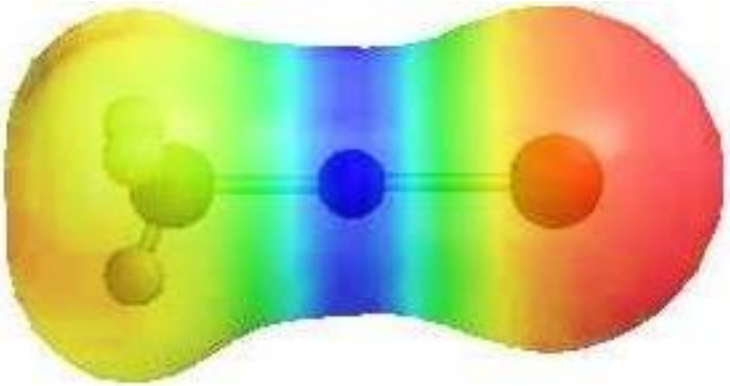
$$R^{\bullet} + Mg^{\bullet +} \rightarrow RMg^{+}$$

$$RMg^{+} + X^{-} \rightarrow RMgX$$

Nature of Grignard Reagent

$CH_4 \longrightarrow CH_3^-$

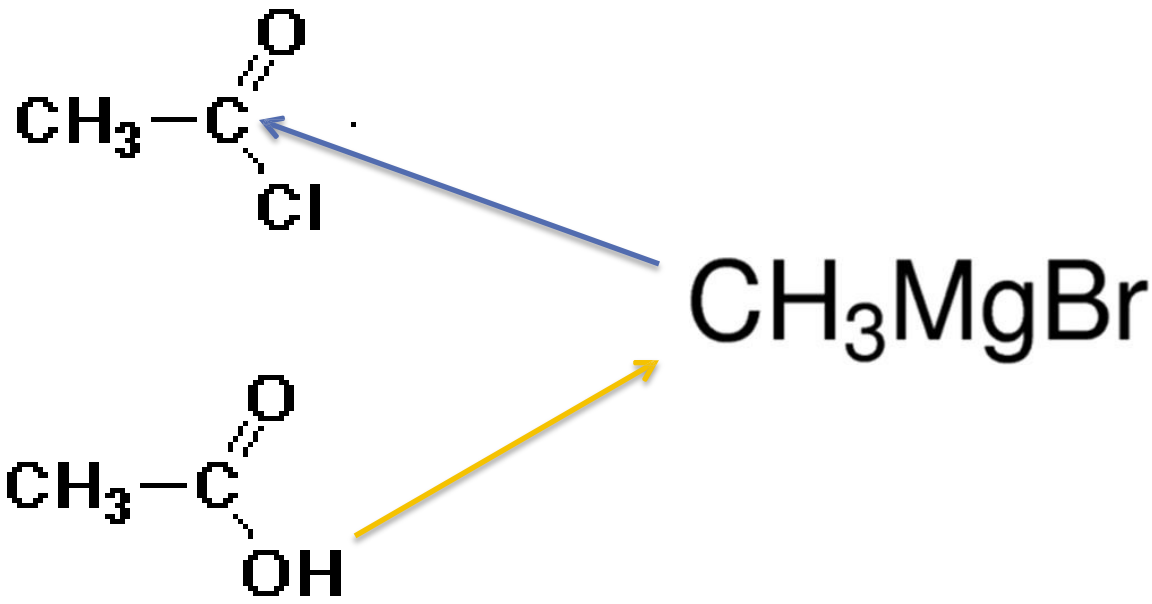
weak acid strong base



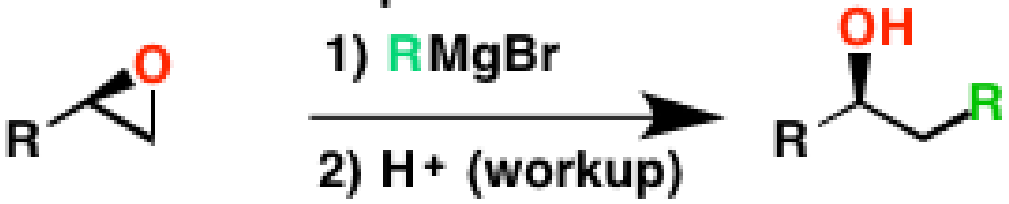
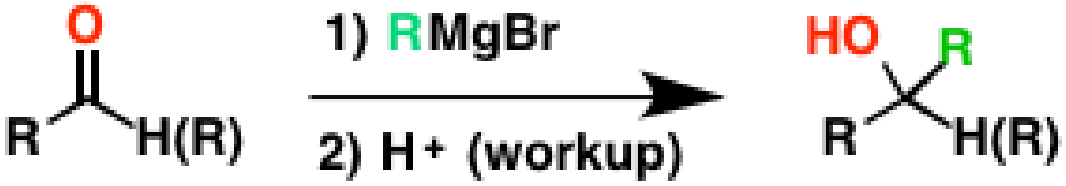
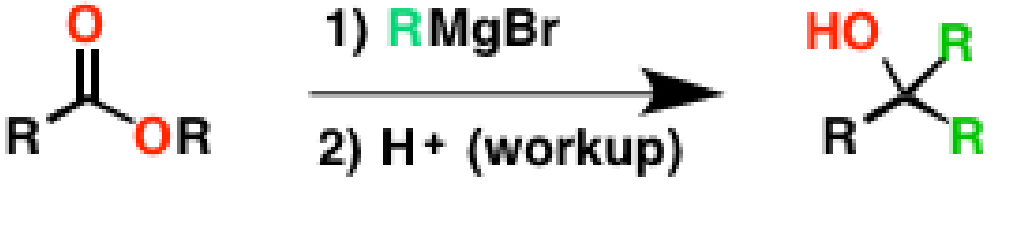
CH_3MgBr

It can take out H+ from C-H bonds

Grignard reagents are similar to organolithium reagents because both are strong nucleophiles that can form new carbon–carbon bonds.



Key Reactions of Grignard Reagents

	Form	Break	Notes
• Reaction with Epoxides			
	C–C O–H	C–O	Adds to least sub. carbon
• Reaction with Aldehydes & Ketones			
	C–C O–H	C–O(π)	
• Reaction with Esters			
	C–C C–C O–H	C–O(π) C–OR	Adds twice!

Organocopper Reagents (Gilman Reagent)

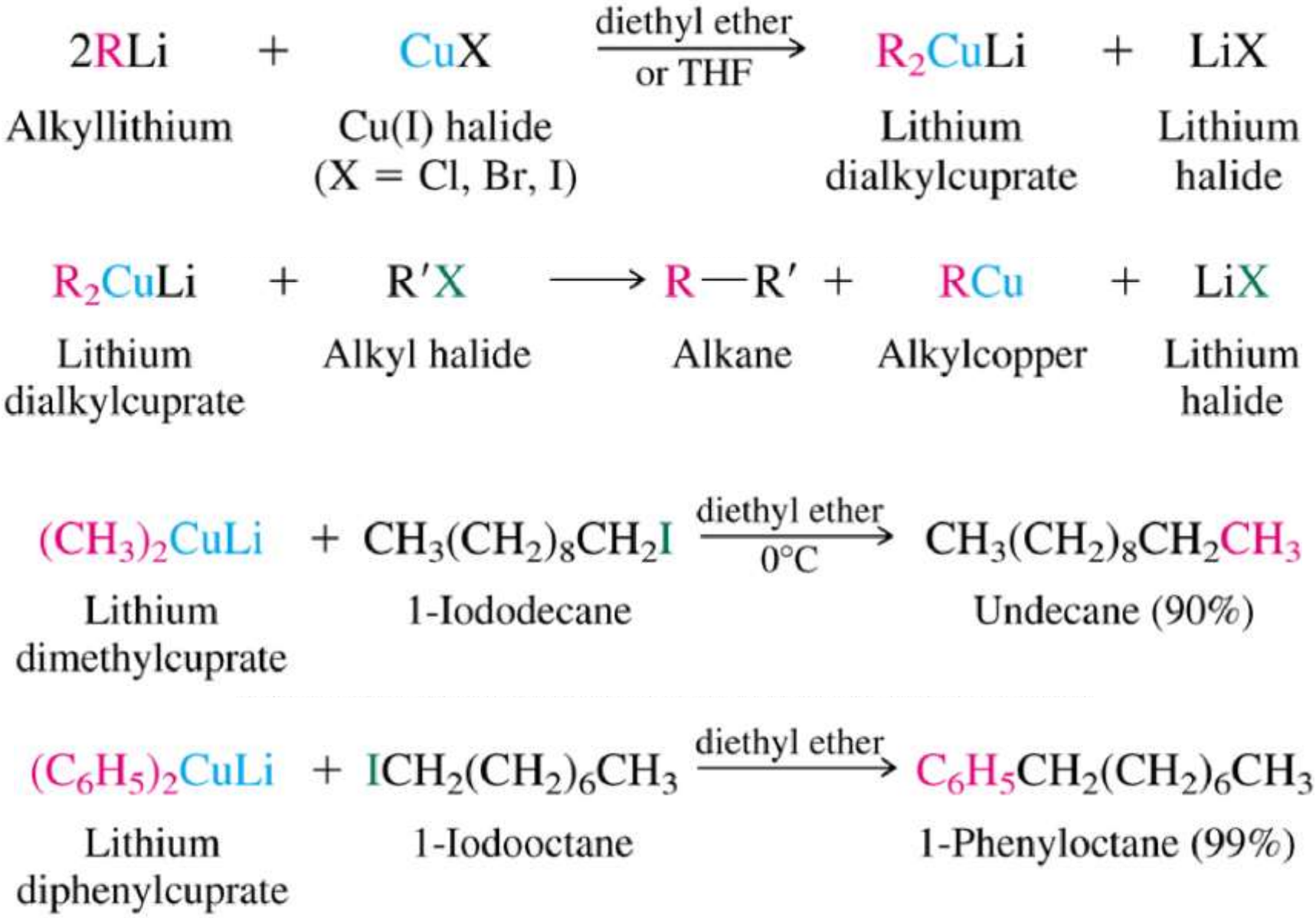
Organocopper compounds

Reviews

- **Most seen example: Lithium Dialkylcopper (organocuprate) $[(R)_2Cu]^-$ Li^+**
- **Cuprates are less reactive than organolithium**
- **R acts as a Nucleophile**
- **Oxidation state of copper is Cu(I).**
- **Nucleophile "R" will attack various organic electrophiles.**
- **Organocuprates are used in cross-coupling reactions to form higher alkanes.**

- **Cross-Coupling Reaction: coupling of two different alkyls R and R' to yield a new alkane (R-R'). This type of reaction is used to make new C-C between alkyl groups.**

Organocopper Reagents (Gilman Reagent)



Gilman Limitations

- Methyl and 1° R-X iodides work well
  - elimination occurs with 2° and 3 ° R-X
  - seems to follow S_N2 conditions
- also works for vinyl and aryl halides

Organocopper compounds

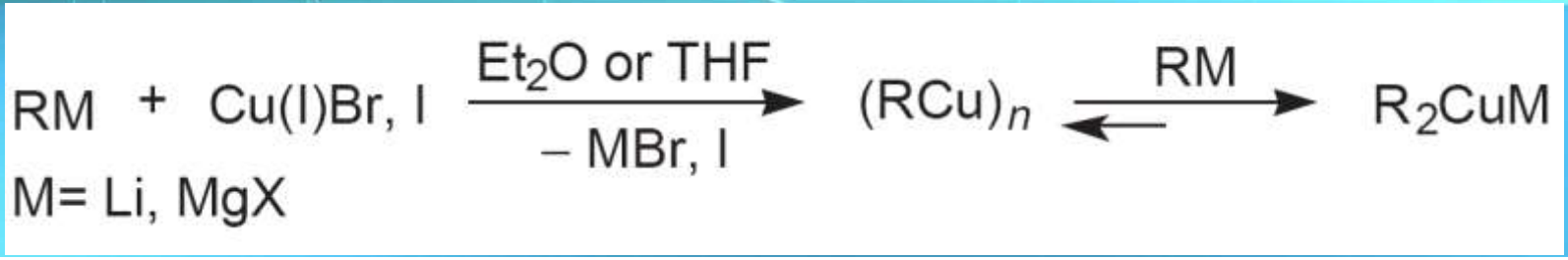
- Use of organocopper reagents offers a very efficient method for coupling of two different carbon moieties.
- Cu is **less electropositive than Li and Mg**, the *C–Cu bond is less polarized than the C–Li and C–Mg bonds*. This difference produces three useful changes in reactivity:
  - organocopper reagents react with **alkyl-**, **alkenyl-**, and **aryl halides** to give *alkylated products*.
  - organocopper reagents: **more selective** and *can be acylated with acid chlorides* without concomitant attack on ketones, alkyl halides, and esters.
  - Relative reactivity: RCOCl > RCHO > tosylates, iodides > epoxides > bromides >> ketones > esters > nitriles.
- In reactions with α,β-unsaturated carbonyl compounds, the organocopper reagents prefer **1,4-addition** over **1,2-addition**.

Preparations

Homocuprate reagents

(Gilman reagent: R_2CuLi, R_2CuMgX)

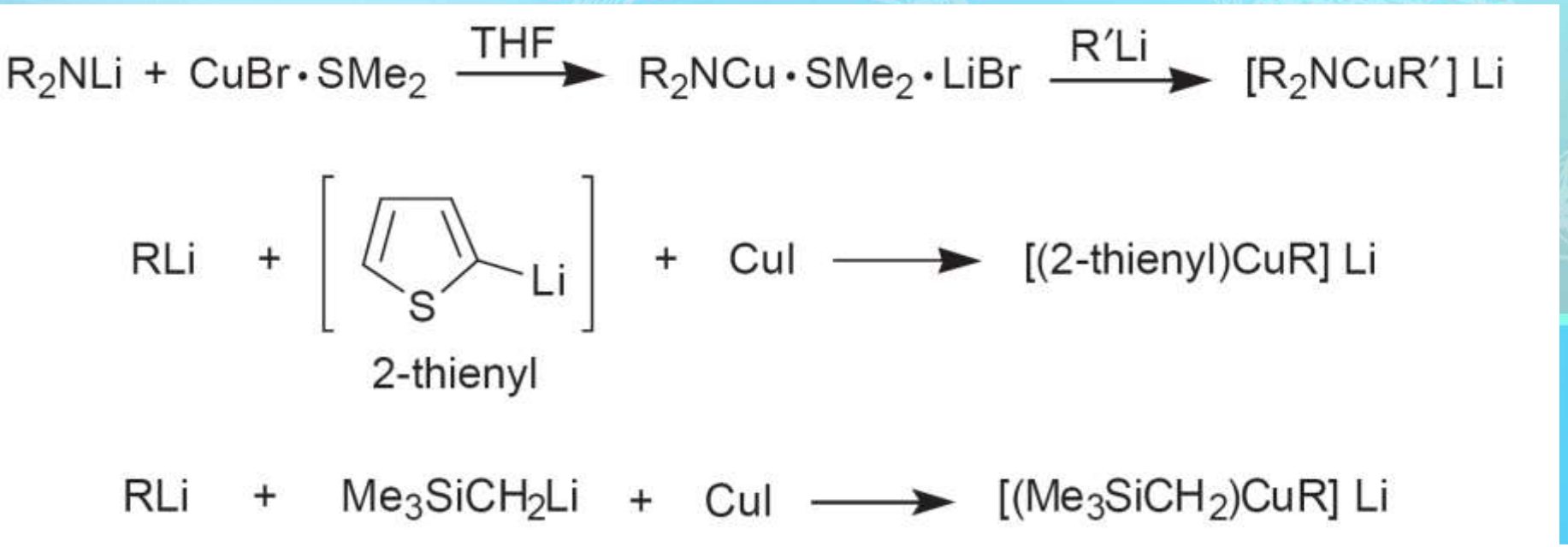
- widely used organocopper reagents.
- prepared by reaction of copper(I) bromide or preferably copper(I) iodide with 2 equivalents of appropriate lithium or Grignard reagents in ether or THF
- The initially formed **$(RCu)_n$** are polymeric and insoluble in Et_2O and THF but dissolve on addition of a second equivalent of RLi or RMgX.
- The resultant organocuprates are thermally labile and thus are prepared at low temperatures.



Preparations

Heterocuprate reagents

- Since only one of the organic groups of homocuprates is usually utilized, a non-transferable group bonded to copper, such as RC≡C, 2-thienyl, PhS, *t*-BuO, R_2N, Ph_2P, or Me_3SiCH_2, is employed for the preparation of heterocuprate reagents.
- These cuprates are usually thermally more stable (less prone toward β-elimination of Cu–H), and a smaller excess of the reagent may be used.



Phase-Transfer Catalyst

A phase-transfer catalyst or PTC is a catalyst that facilitates the migration of a reactant from one phase into another phase where reaction occurs

Phase-transfer catalysis is a special form of heterogeneous catalysis

Ionic reactants are insoluble in an organic phase in the absence of the phase-transfer catalyst but they are soluble in aq. phase

Phase-transfer catalysts are especially useful in green chemistry—by allowing the use of water, the need for organic solvents is reduced

TYPES OF PHASE-TRANSFER CATALYSTS

There are many types of phase transfer catalysts, such as quaternary ammonium and phosphonium salts, crown ethers, cryptands, etc.

Among these, the quaternary ammonium salts are the cheapest and hence the most widely used in the industry.

PRINCIPLE

The principle of PTC is based on the ability of certain phase-transfer agents (the PT catalysts) to facilitate the transport of one reagent from one phase into another (immiscible) phase wherein the other reagent exists

reaction is made possible by bringing together the reagents which are originally in different phases

it is also necessary that the transferred species is in an active state for effective PT catalytic action, and that it is regenerated during the organic reaction

MECHANISMS OF PTC

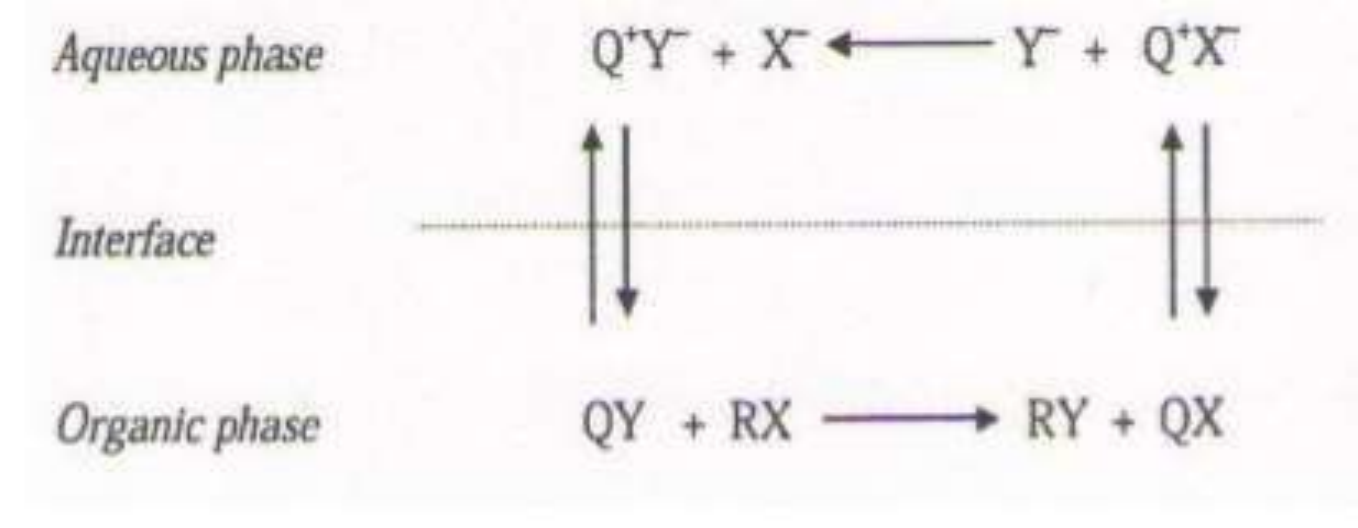
A quaternary ammonium halide dissolved in the aqueous phase (Q^+X^-) undergoes anion exchange with the anion of the reactant dissolved in the aqueous solution

The ion-pair formed (Q^+X^-) can cross the liquid-liquid interface due to its lipophilic nature and diffuses from the interface into the organic phase, this step being the phase-transfer

In the organic phase, the anion of the ion-pair being quite nucleophilic undergoes a nucleophilic substitution reaction with the organic reagent forming the desired product (RY)

The catalyst subsequently returns to the aqueous phase and the cycle continues.

An overview of PTC reactions is given in the scheme bellow:



APPLICATIONS OF PTC

PTC finds applications in a variety of reactions

- PTC is widely exploited industrially
- Applications involving the use of a co-catalyst include co-catalysis by surfactants, alcohols and other weak acids in hydroxide transfer reactions, use of iodide, or reactions carried out with dual PI catalysts have been also reported
- In nucleophilic substitution reactions and in reactions in the presence of bases involving the deprotonation of moderately and weakly acidic organic compounds
- PTC has made possible the use of cheaper and easily available alternative raw materials like potassium carbonate and aqueous NaOH solution, thereby obviating the need of severe anhydrous conditions, expensive solvents, and dangerous bases such as metal hydrides and organometallic reagents
- When any kind of chemical reactions are carried out in the presence of a PT catalyst in biphasic systems, simple, cheap and mild bases like NaOH and K2CO3 can be used instead of toxic alkali metal alkoxides, amides, and hydrides
- Perfumery and Fragrance Industry like Synthesis of phenylacetic acid, an intermediate in the perfumery industry

- In the field of Pharmaceuticals like Synthesis of various drugs like dicyclonine, phenoperidine, oxaladine, ritaline, etc.
- Polymeric bonded PTC for the determination of cyanide, iodide, nitrite, sulphide and thiocyanate, led to easy layer separation and PTC-free injection of the sample into the chromatograph
- However, the main disadvantages of PTC, especially in commercial applications, are the need to separate the catalyst from the product organic phase
- PTC can also be used for the synthesis process for fine chemicals manufacture industries
- Polyester polymers
  for example are prepared from acid chlorides and bisphenol-A
- Phosphothioate -based pesticides are generated by PTC-catalyzed alkylation of phosphothioates
- One of the more complex applications of PTC involves asymmetric alkylations, which are catalyzed by chiral quaternary ammonium salts derived from cinchona alkaloids

DICYCLOHEXYLCARBODIMIDE ($C_{13}H_{22}N_2$)

- N,N’-Dicyclohexylcarbodimide is an organic compound
- The important use to couple amino acids during artificial peptide synthesis
- The compound is abbreviated as DCC, DCCD or DCCI

PROPERTIES

- Under standard condition, it exists in the from of white crystals with a heavy, sweet odor.
- The low melting point (30-35^{0}C)
- Boiling point 122-124^{0}C
- Soluble in tetrahydrofuran, acetonitrile and dimethylformamide dichloromethane, but insoluble in water stable, but moisture sensitive.

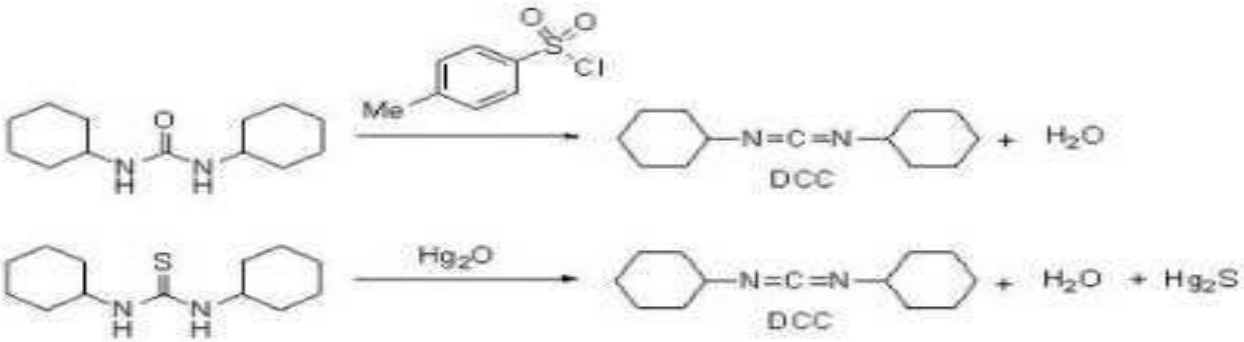
SAFETY PRECAUTION

- DCC is a potent allergen and a sensitizer, and causing skin rashes.

STRUCTURE

SYNTHESIS

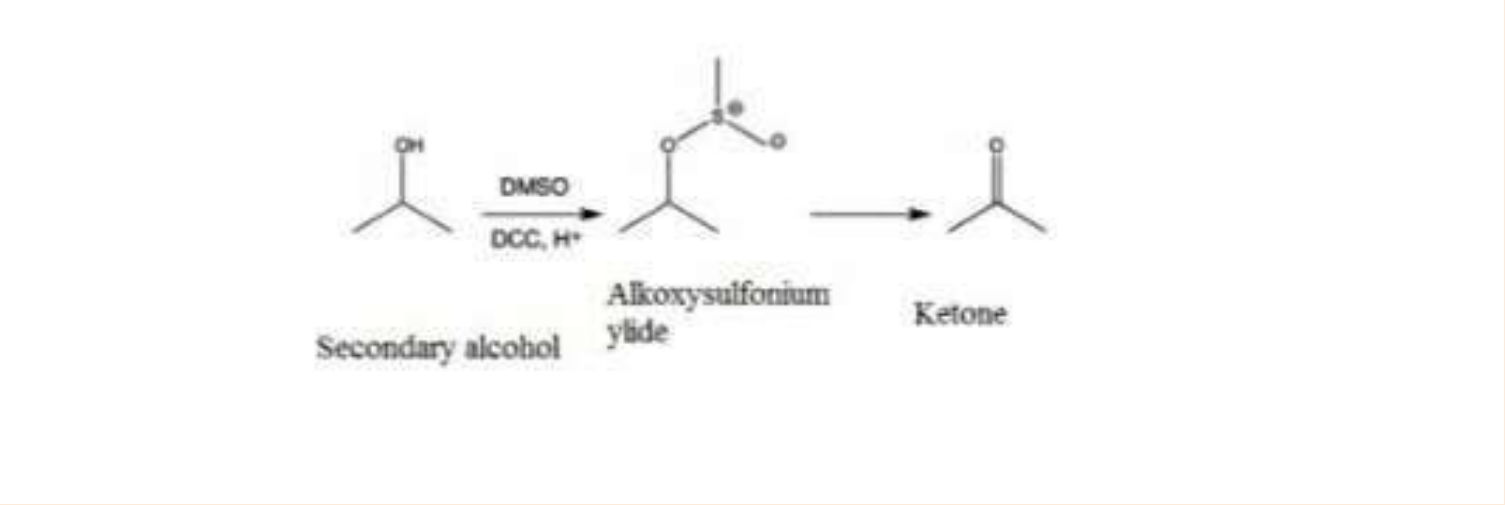
- It can also be prepared by oxidation of dicyclohexylurea with p-toluene sulfonyl chloride in hot pyridine or by heating dicyclohexylthiourea with yellow mercuric oxide

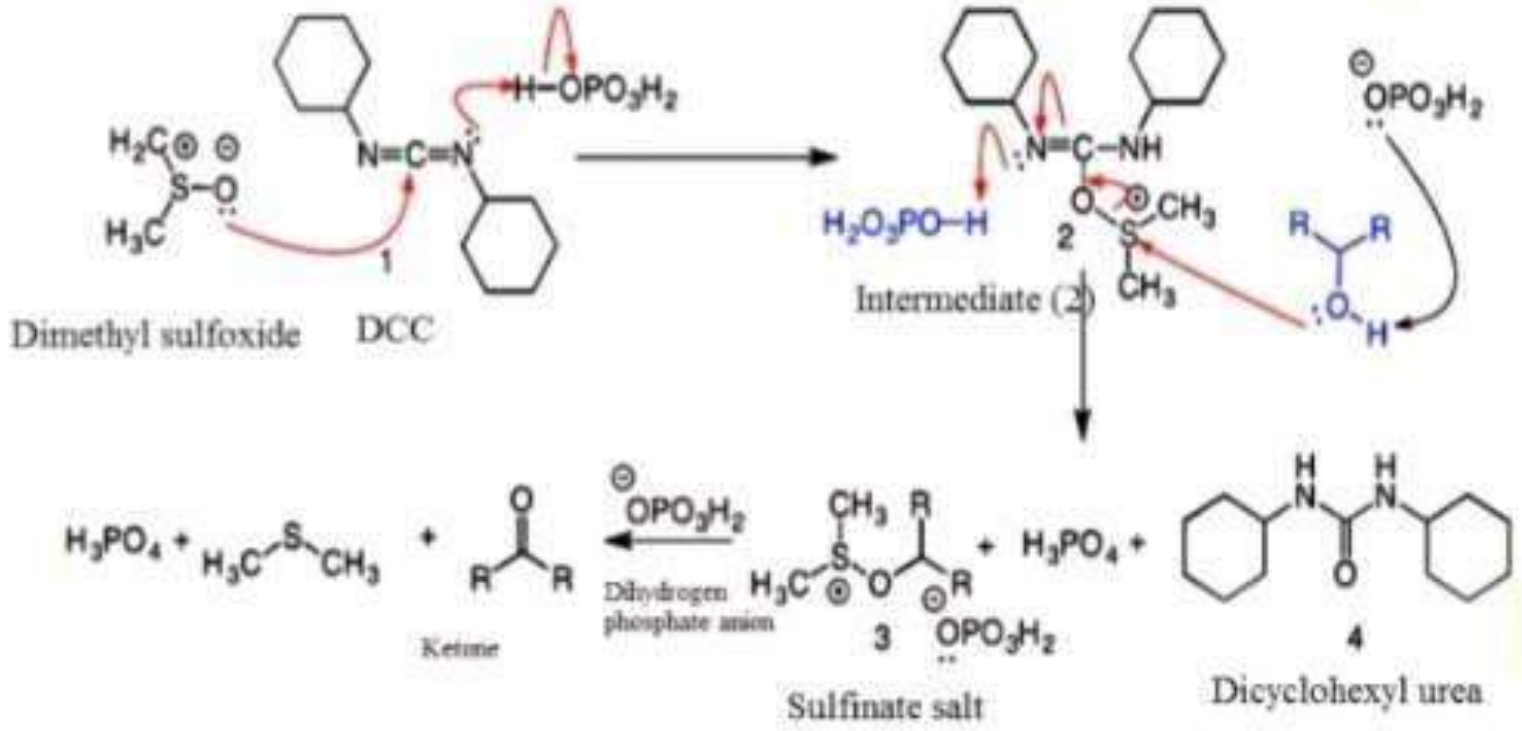


APPLICATION

1. MOFFATT OXIDATION

- Moffatt oxidation is the oxidation of primary and secondary alcohol in presence of dimethyl sulfoxide (DMSO) and dicychexylcarbodimide (DCC) To form a alkoxysulfonium ylide intermediate, which re



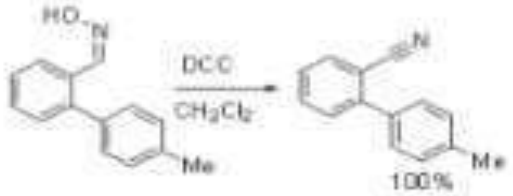

Dimethyl sulfoxide
DCC
1
Intermediate (2)
2
Ketone
Dihydrogen phosphate anion
Sulfinate salt
3
4
Dicyclohexyl urea

MECHANISM

- Dicyclohexyl carbodiimide (1) is attacked by dimethyl sulfoxide to from an intermediate (2)
- It is then promotated by the addition of the alcohol oxygen on the sulfur atom
- Then a stable dicyclohexyl urea (4) is formed along with sulfenate salt (3)
- It then react with a dihydeogen phosphateanion to from ketone

2) SYNTHESIS OF NITRILE

- The oximes undergo dehydration in the presence of DCC to nitriles.

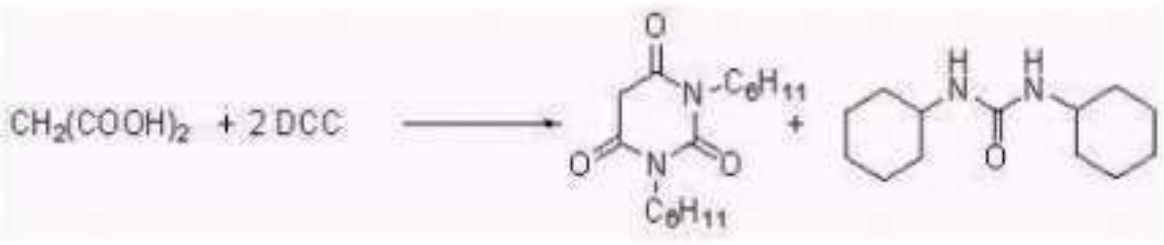


4'-methyl,1,1'-biphenyl,2-methylidene hydroxylamine

4-methyl, 1,1'-biphenyl 2-carbo nitrile

3) SYNTHESIS OF BARBITURIC ACID

- Barbituric acid and its derivatives can be prepared by the reaction of malonic acid with DCC.



BAKER'S YEAST PRODUCTION

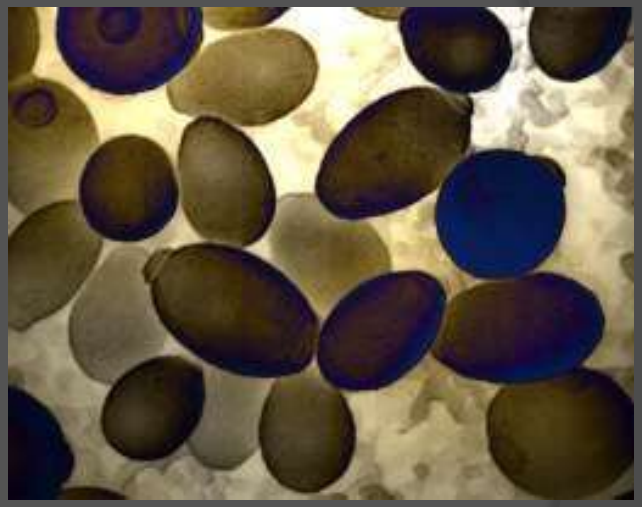
Contents

Overview

- One of the largest profit grossing industry
- Since demand is directly associated with bread demand & there is an ever increasing demand for bread.
- An annual increase in demand by 1-5% in developing countries and 10-15% in developed countries.

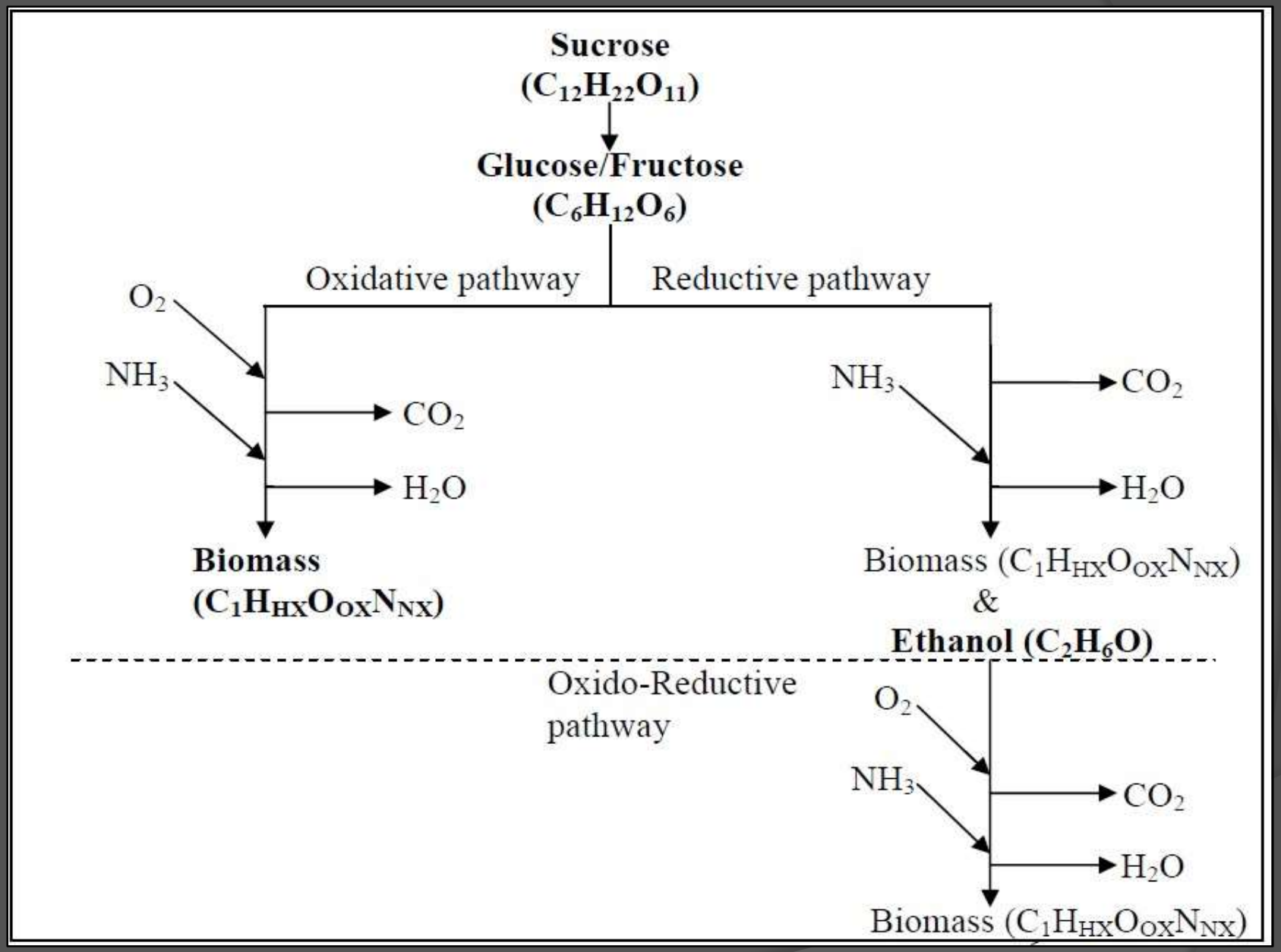
Introduction

- *Marketed in the form of cake, powder or cream*
- *By-products are not required so --- directed towards max. biomass production*
- *Saccharomyces cerevisiae*
  - *Most commonly used organism*
  - *Unicellular*
  - *Rich in protein & vitamin B*
  - *Budding*
  - *Enzymes*
    - *Maltase; converts maltose to glucose*
    - *Invertase; sucrose to glucose & fructose*
    - *Zymase complex; sugars to CO_2 & ethanol*



Introduction (Cont,)

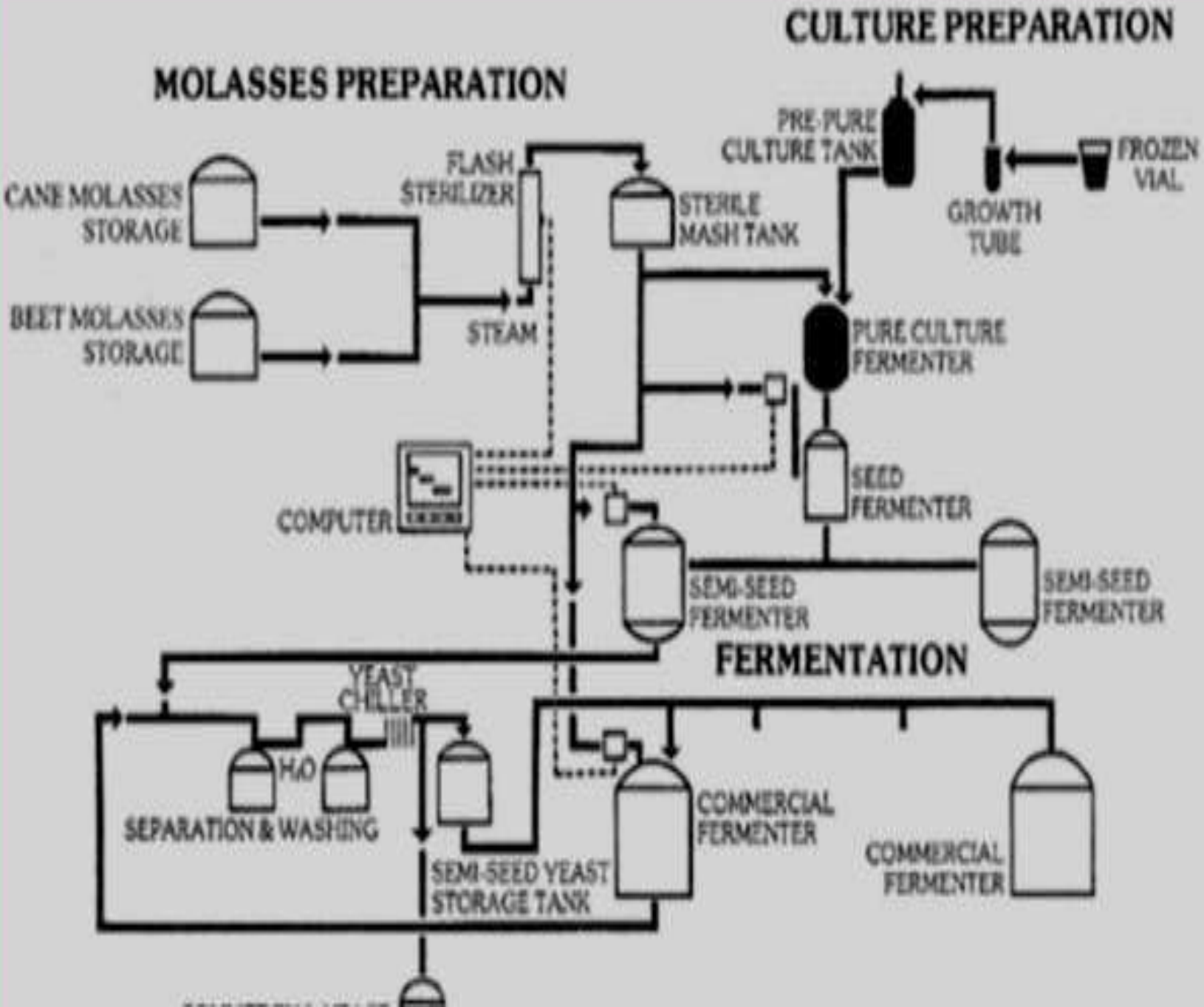
- Process Biochemistry
- Grow either in the absence or presence of O2
- Grows efficiently… O2 present
- Grows inefficiently… O2 not present
  - Produces ethanol in large quantity
- Fed-batch is best method
  - Incremntal feeding & high aeration



Simplified pathway of yeast prduction

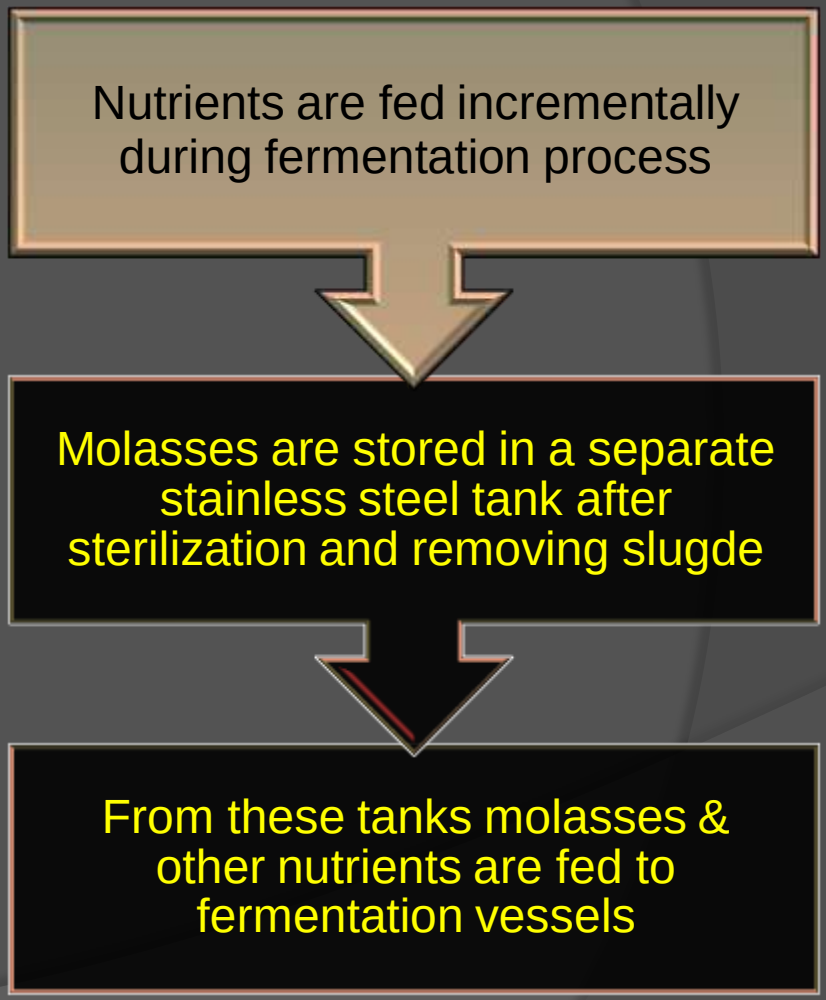
Production

- Overview
- Introduction
- Production
  - Upstream
    - Media and other raw material preparation
    - Production of Seed Culture
    - Fermentation (large scale production)
  - Downstream
    - Harvesting, filtration and packeging


CULTURE PREPARATION
MOLASSES PREPARATION
PRE-PURE CULTURE TANK
FROZEN VIAL
GROWTH TUBE
FLASH STERILIZER
STERILE MASH TANK
CANE MOLASSES STORAGE
BEET MOLASSES STORAGE
STEAM
PURE CULTURE FERMENTER
COMPUTER
SEED FERMENTER
SEMI-SEED FERMENTER
SEMI-SEED FERMENTER
FERMENTATION
YEAST CHILLER
H2O
SEPARATION & WASHING
SEMI-SEED YEAST STORAGE TANK
COMMERCIAL FERMENTER
COMMERCIAL FERMENTER

Media & other raw material preparation

- Pure Culture
  - *S. cerevisiae*
- Media
  - Sugars(Molasses)
  - Nitrogen, (Urea, NH_3 salts or NH_3)
  - Phosphorus (Phosphoric acid)
  - Trace elements (magnesium, iron, calcium, zinc) are provided by their sulfates e.g. magnesium sulfate is used for magnesium source.



Production of Seed Culture

Pure culture of S.cerevisiae is inoculated in vessels containing media and incubated for 2-4 days.

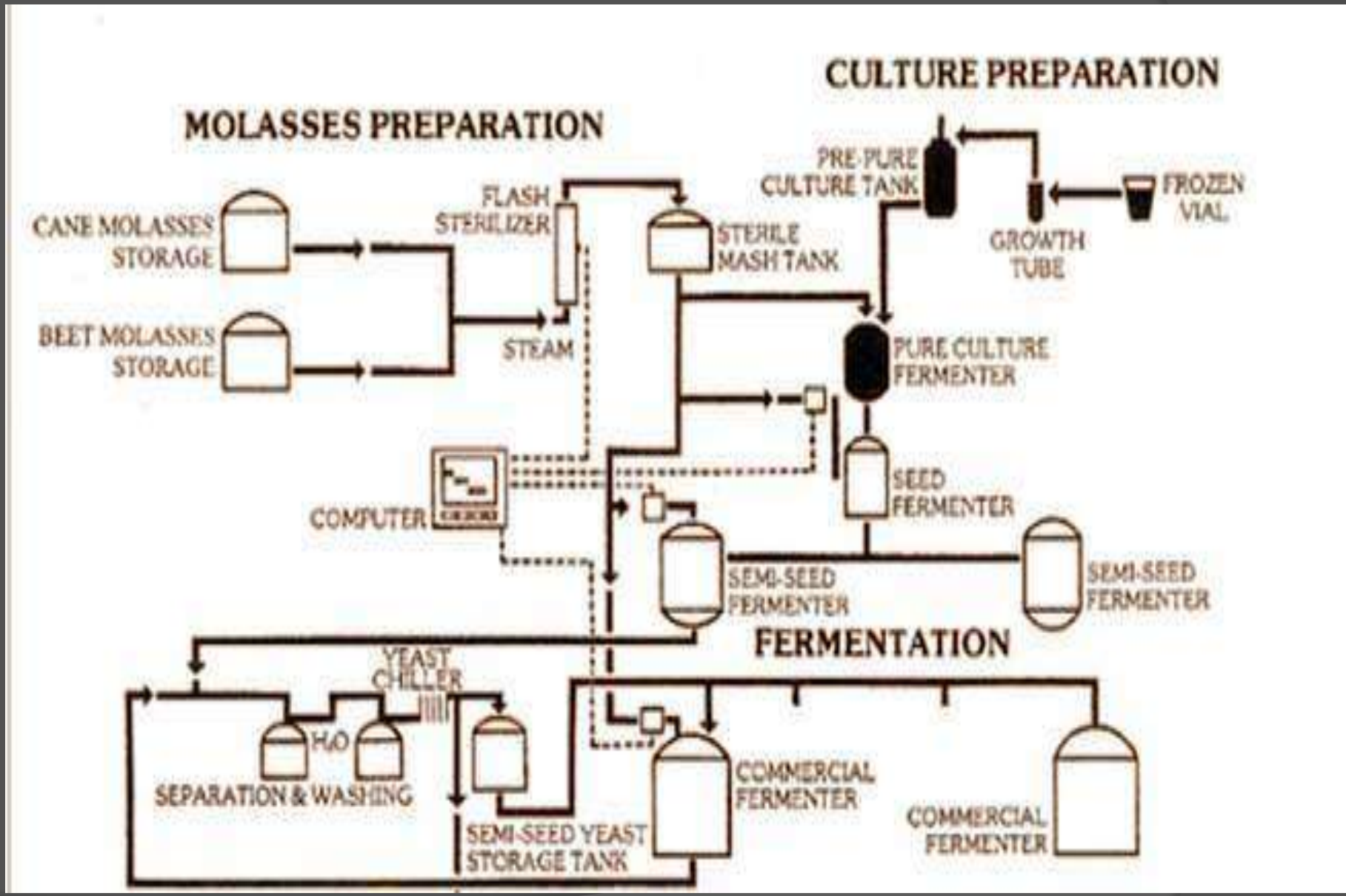
After incubation period contents of this flask are transferred to a larger vessel in the next step and allowed to grow for 16 to 24 hrs.

Contents from this large vessel are transferred to an intermediate fermentor

Then from intermediate to a stock fermentor. Yeast separated through centrifugation

Next is Pitch fermentation, to prepare a pitch, fed-batch is followed

After this yeast is separated and stored for several days before using in final trade fermentation

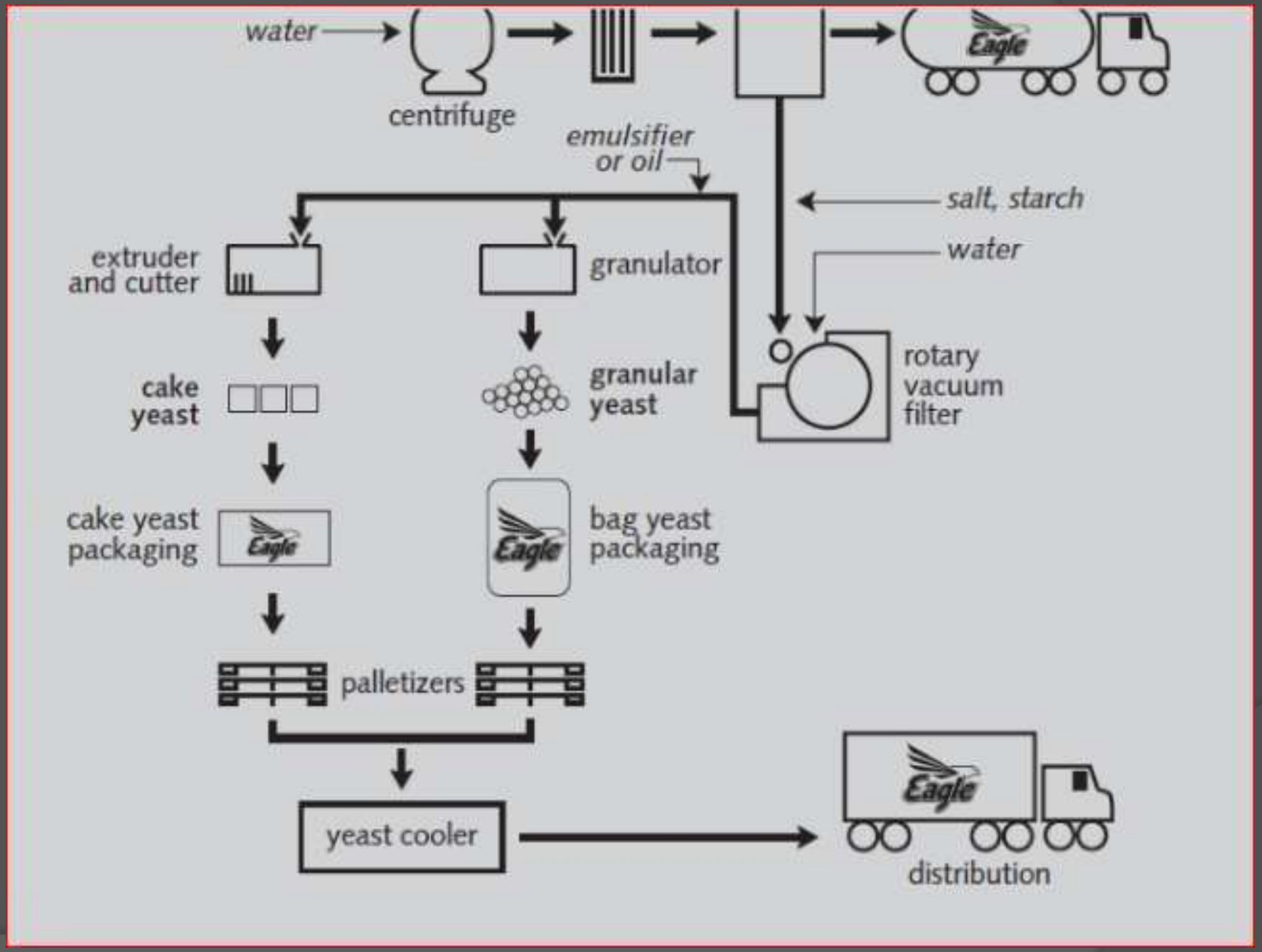

CULTURE PREPARATION
MOLASSES PREPARATION
PRE-PURE CULTURE TANK
FROZEN VIAL
GROWTH TUBE
FLASH STERILIZER
STERILE MASH TANK
CANE MOLASSES STORAGE
BEET MOLASSES STORAGE
STEAM
PURE CULTURE FERMENTER
COMPUTER
SEED FERMENTER
SEMI-SEED FERMENTER
SEMI-SEED FERMENTER
FERMENTATION
YEAST CHILLER
H2O
SEPARATION & WASHING
SEMI-SEED YEAST STORAGE TANK
COMMERCIAL FERMENTER
COMMERCIAL FERMENTER

Fermentation

- After seed production final trade production is carried out
- Duration of final trade fermentation is about 19 to 22 hrs,
- During final trade production yeast cells increase in number 5 to 8 fold
- During fermentation pH, regulation of nutrients, airflow are monitored carefully.
- Temperature is kept at 85°F and pH at 4.5-5.5

Downstream Processing

- After completion of the process yeast is separated with centrifugation and washed with water and re-centrifuged to yield cream yeast.
- Yeast cream is stored in a separate, refrigerated stainless steel tank.
- Cream is then pumped to rotary vacuum filter or plate frame filter press and dewatered-Solid content 30-32%
- After this two types of baker's yeast is obtained


water
centrifuge
emulsifier
or oil
salt, starch
water
extruder
and cutter
granulator
cake
yeast
granular
yeast
rotary
vacuum
filter
cake yeast
packaging
bag yeast
packaging
palletizers
yeast cooler
distribution

Types of Baker's Yeast

- Cream Yeast
  - Suspension of yeast cells
  - Cream yeast is not termed as baker's yeast but is a marketable product
  - Solid contents about 18-20
- Compressed Yeast
  - Solid contents range between 27-33%
  - Most of the moisture is removed & dried by passing through fluid-bed drier.
  - Emulsifiers and oils are added to texturize & aid in cutting process

- Compressed yeast can be granular or in the form of cake
  - Granular Yeast
    - Small granules
    - High %age of live cells
    - Can be added to driest doughs
    - Perishable
    - Small amount of ascorbic acid added as preservative

- Cake Yeast
  - Also known as active dry yeast
  - Long shelf life
  - Cells encapsulated in a thick jacket of dead cells
  - More sensitive
- Shelf life of compressed yeast is about 1-2 years.

Yeast Testing

- Strain purity and trueness to type is tested
- Strict adherence to GMP rules is required
- Complete microbiological testing
- Tested for gassing activity
- pH
- Gm/ltr of yeast

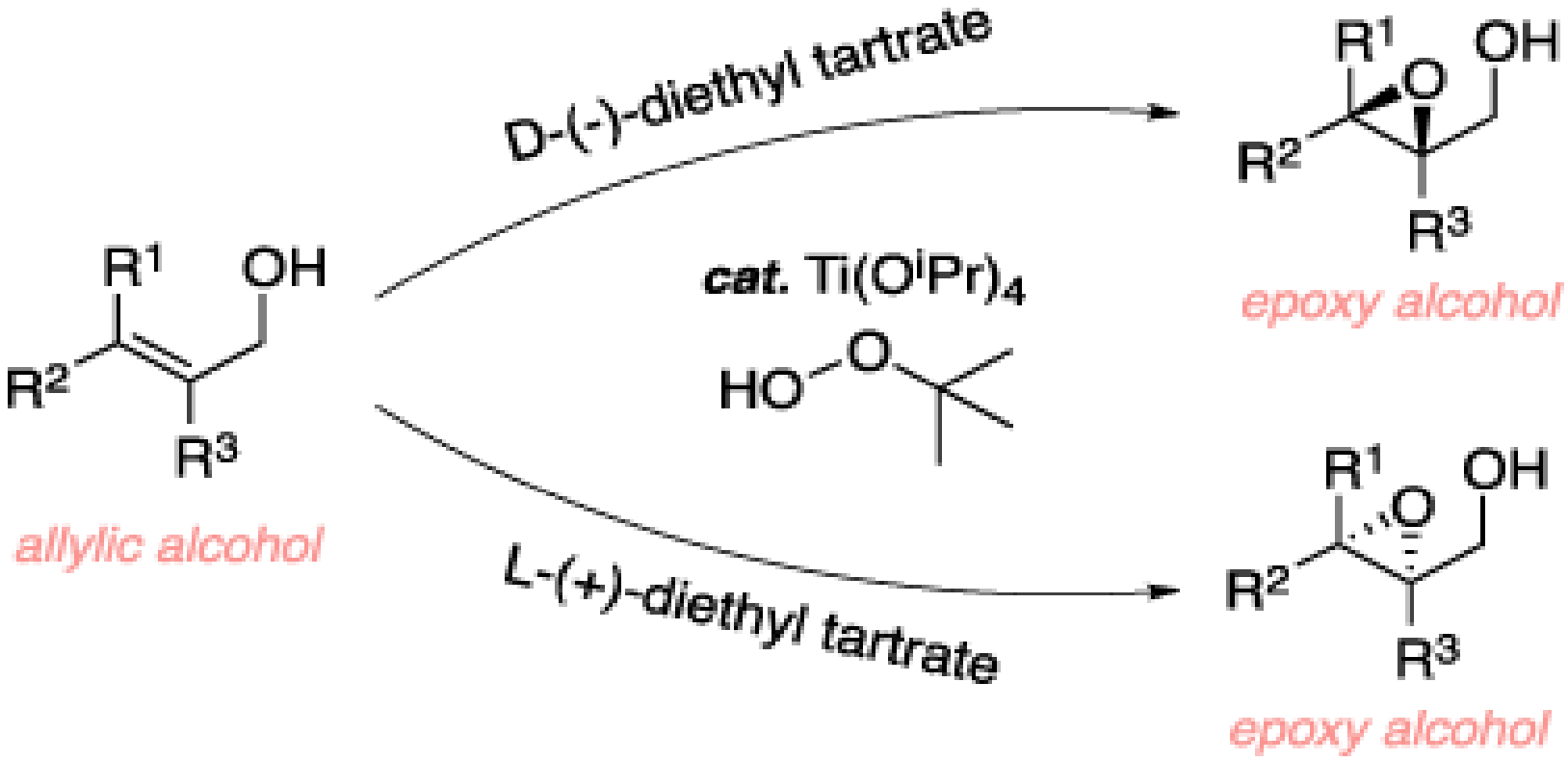
Application

- Production of CO_2
  - Cause expansion of dough
- Dough maturation
  - Result in light airy (leavening agent) physical structure
- Development of Flavour
  - Characteristic flavor bread

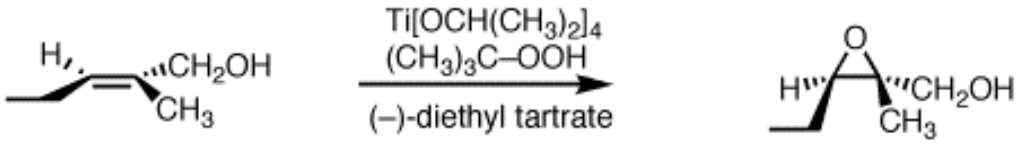
Sharpless epoxidation

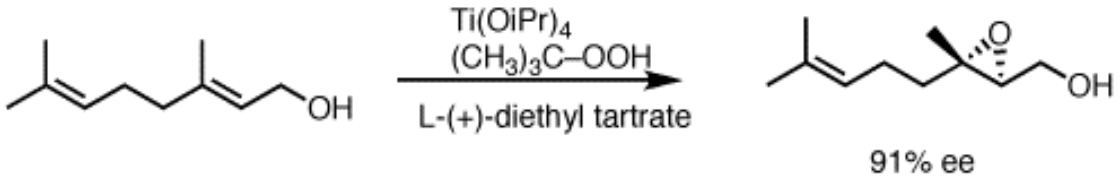
- **The Sharpless Epoxidation is an enantioselective epoxidation of allylic alcohols.**
- **The Sharpless epoxidation only works for alkenes adjacent to an alcohol (CH_2OH).**
- **The oxidant is t-butyl hydroperoxide, sometimes written $(CH_3)_3C–OOH$ or abbreviated TBHP.**
- **The catalyst is titanium tetraisopropoxide, written $Ti[O\textit{i}\text{-}Pr]_4$ or $Ti[OCH(CH_3)_2]_4$.**
- **The additive that imparts chirality is diethyl tartrate (DET).**
- **Choosing (+) or (–) diethyl tartrate [full names: L-(+)-diethyl tartrate and D(–)-diethyl tartrate – one can omit the L or D without penalty] allows one to choose the major enantiomer that is formed in this reaction**

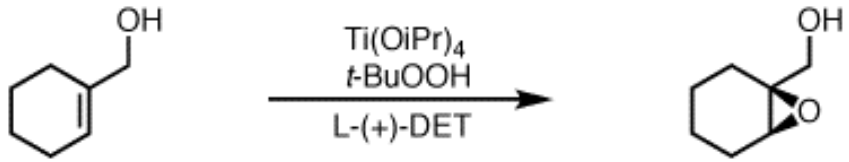
Sharpless epoxidation

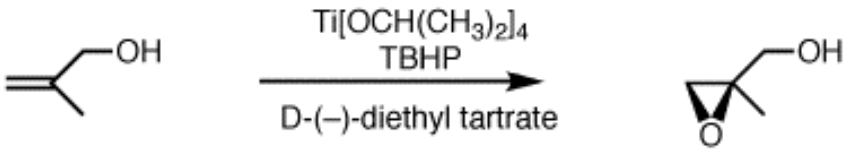


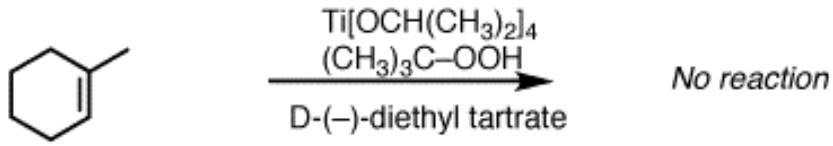
Sharpless epoxidation







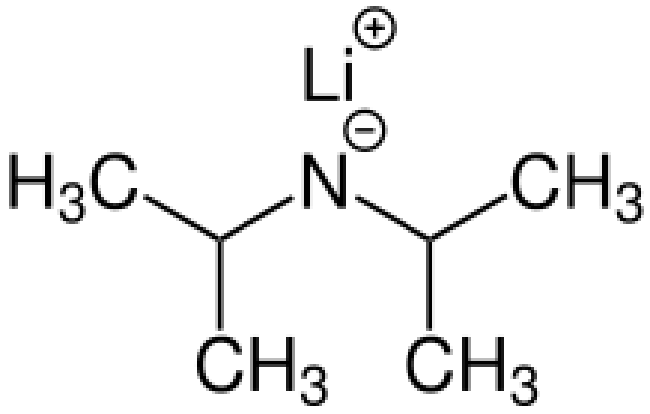




Lithium diisopropylamide

- **Lithium diisopropylamide** (commonly abbreviated **LDA**) is a chemical compound with the molecular formula $[(CH_3)_2CH]_2NLi$.
- It is used as a strong base and has been widely accepted due to its good solubility in non-polar organic solvents and non-nucleophilic nature.
- It is a colorless solid, but is usually generated and observed only in solution.

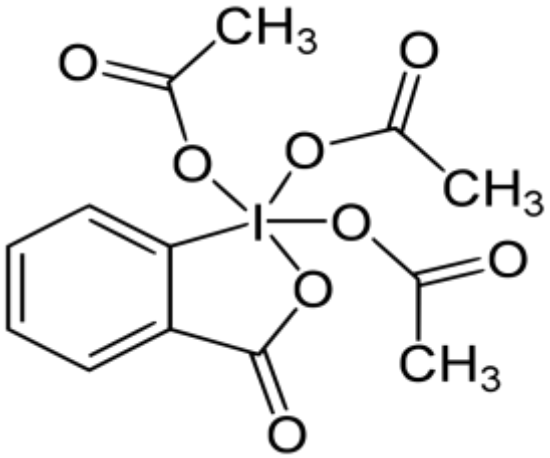
➢LDA is commonly formed by treating a cooled (0 to −78 °C) tetrahydrofuran (THF) solution of diisopropylamine with *n*-butyllithium.



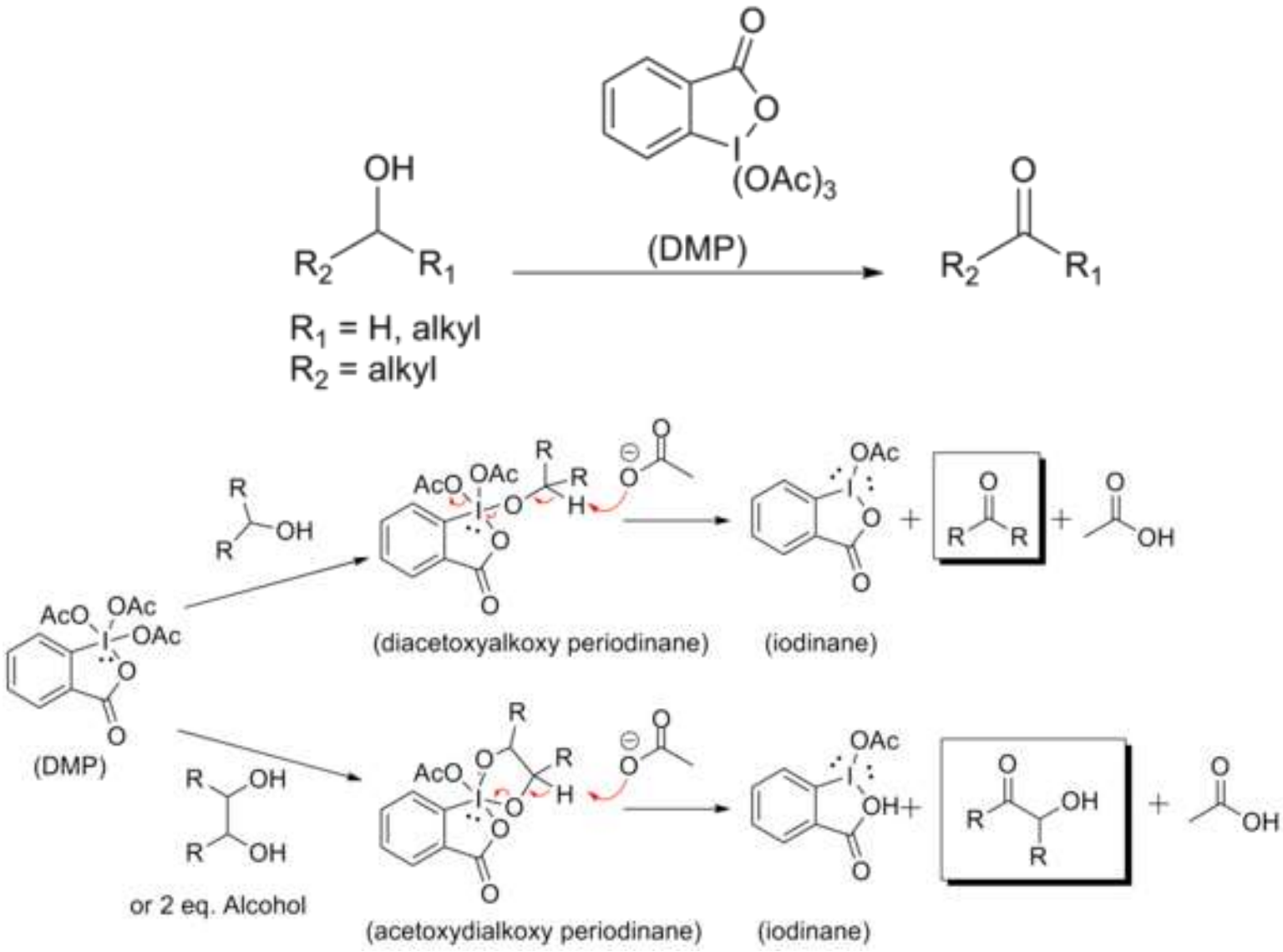
Dess–Martin periodinane

- **Dess–Martin periodinane** (**DMP**) is a chemical reagent used to oxidize primary alcohols to aldehydes and secondary alcohols to ketones.
- This periodinane has several advantages over chromium- and DMSO-based oxidants that include milder conditions (room temperature, neutral pH), shorter reaction times, higher yields, simplified workups, high chemoselectivity, tolerance of sensitive functional groups, and a long shelf life.
- However, use on an industrial scale is made difficult by its cost and its potentially explosive nature.

It is named after the American chemists Daniel Benjamin Dess and James Cullen Martin who developed the reagent in 1983



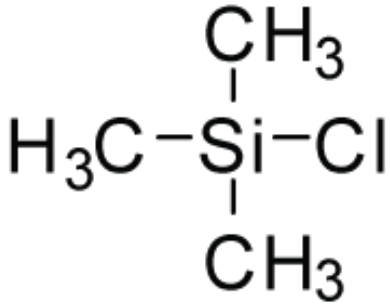
Dess–Martin periodinane



Trimethylsilyl chloride

- **Trimethylsilyl chloride**, also known as **chlorotrimethylsilane** is an organosilicon compound (silyl halide), with the formula $(CH_3)_3SiCl$, often abbreviated **Me_3SiCl** or **TMSCl**.
- It is a colourless volatile liquid that is stable in the absence of water. It is widely used in organic chemistry.

TMSCl is reactive toward nucleophiles, resulting in the replacement of the chloride. In a characteristic reaction of TMSCl, the nucleophile is water, resulting in hydrolysis to give the hexamethyldisiloxane:



$2\ Me_3SiCl + H_2O \rightarrow Me_3Si\text{-}O\text{-}SiMe_3 + 2\ HCl$

Trimethylsilyl chloride

- Trimethylsilyl chloride is used for a salt metathesis reaction between trimethylsilyl chloride and a salt of the (pseudo)halide (MX):

$$MX + Me_3Si\text{-}Cl \rightarrow MCl + Me_3Si\text{-}X$$

- TMSCl, lithium, and nitrogen molecule react to give tris(trimethylsilyl)amine, under catalysis by nichrome wire or chromium trichloride

$$3\ Me_3SiCl + 3\ Li + {}^1\!/_2\ N_2 \rightarrow (Me_3Si)_3N + 3\ LiCl$$

Organolithium Reagents

General Characteristics

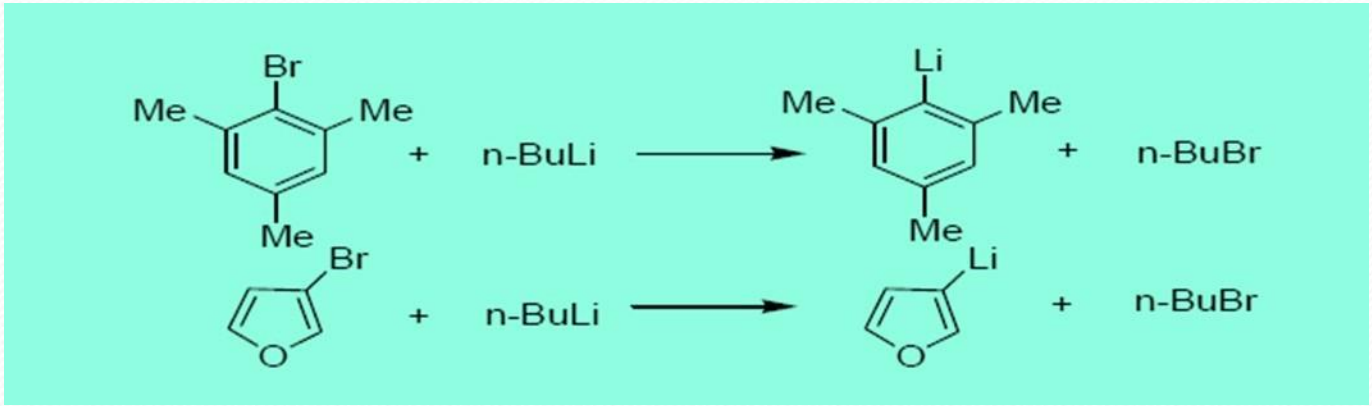
- The organo-lithium reagents, characterized by a C-Li bond, are important in organic synthesis as R-Mg-X.
- Lithium is less electronegative than carbon, and the C-Li bond is polarized as in organo-magnesium halide.
- The organo-lithium reagents are more reactive than organo-magnesium halides and are expected to behave both as a *nucleophile* and a *base*.

Preparations

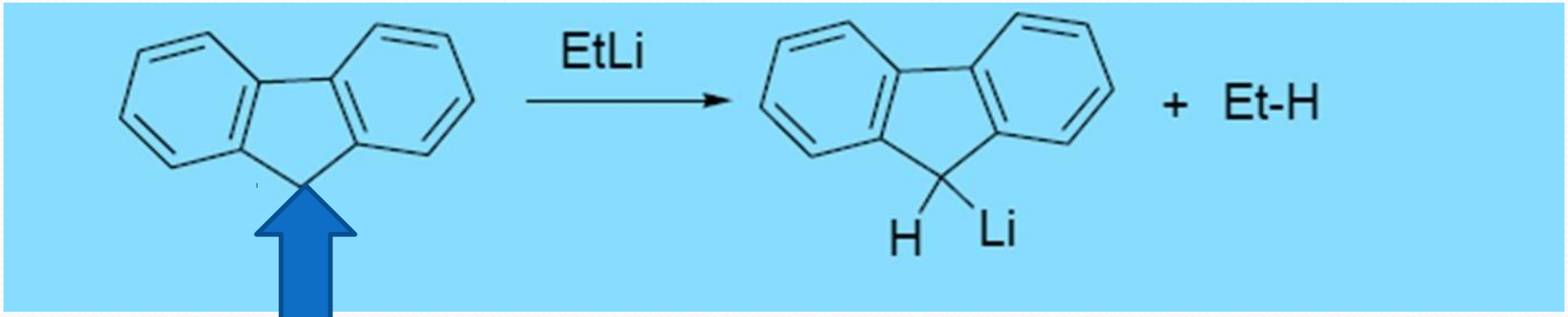
- The reaction of lithium metal at low temperature with an alkyl halide in a hydrocarbon solvent gives alkyl lithium.
- The reaction proceeds smoothly in the presence of above 0.02% of sodium and the reactivity of the alkyl halides is R-I >R-Br >R-Cl

Preparations conti.....

- Another route to the preparation of the organo-lithium compounds is the use of metal halogen exchange reactions.
- This method is useful for the preparation of organo-lithium reagents that cannot be obtained from alkyl halide and metal directly.
- In this method organic halide is treated with alkyl lithium.
- This process is best suited for the preparation of aryl lithium derivatives.

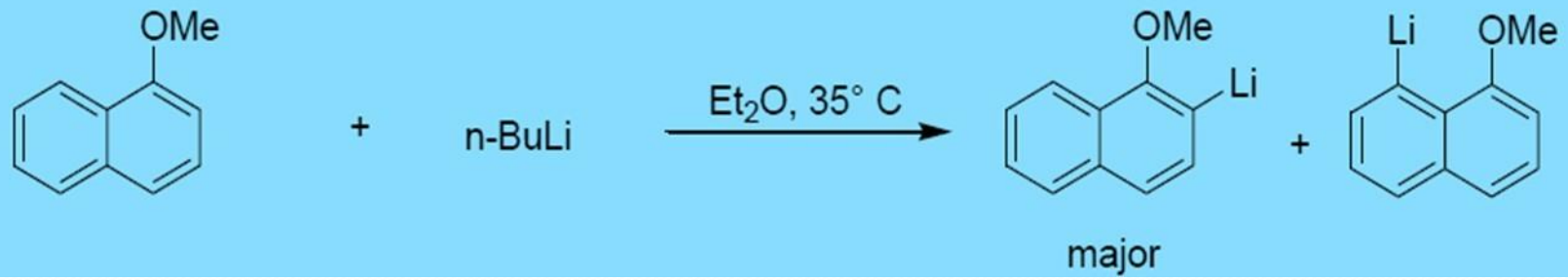


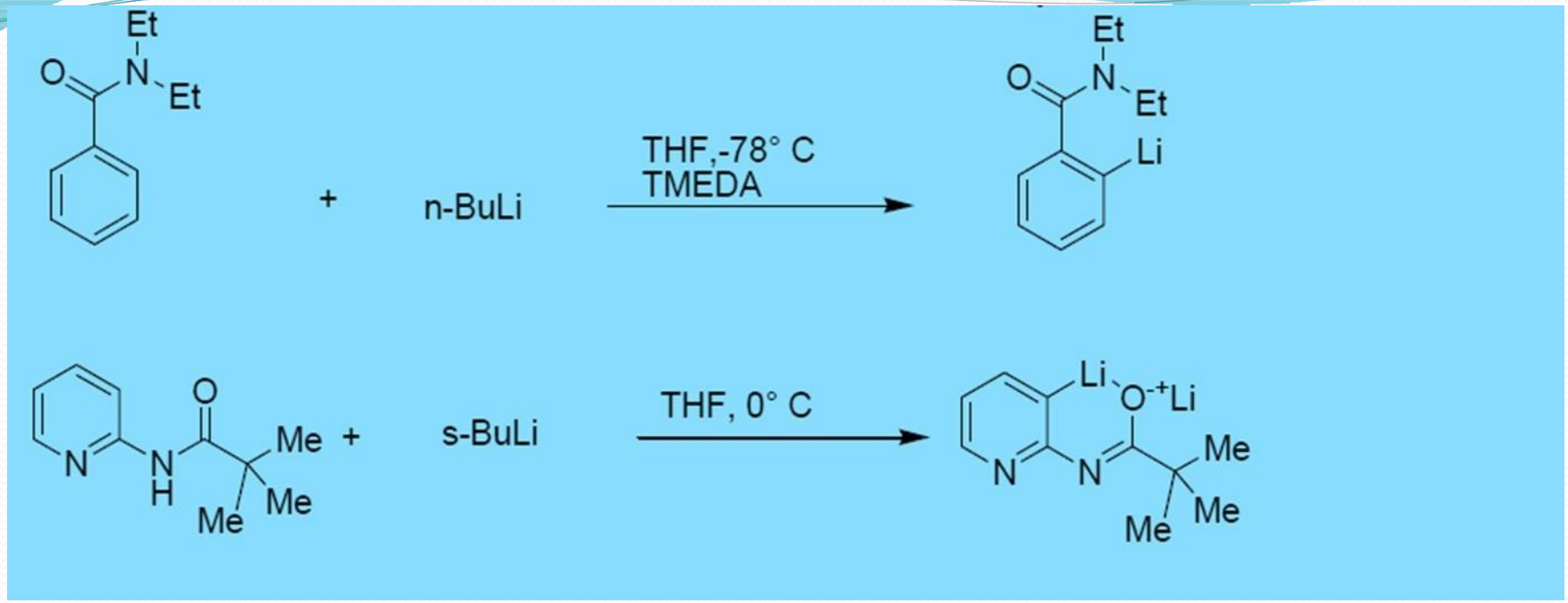
In addition, compounds containing acidic hydrogen can be easily converted into organo-lithium compound by treatment with a suitable organo-lithium compound.



Carbon have acidic hydrogen, as the conjugate base is stabilized by resonance

- The replacement of a hydrogen by a lithium (known as lithiation) can also be used to generate organo-lithium species.
- This reaction is essentially an acid base reaction.
- In the case, where there is activation by a coordinating group, the reaction occurs with considerable ease. This type of activation is particularly helpful in introducing an *ortho substituent to a preexisting coordinating group*.

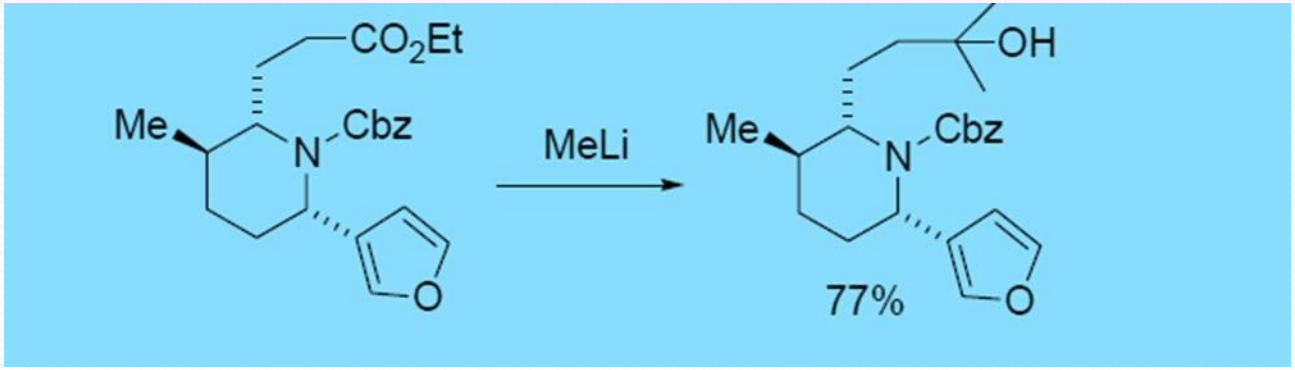




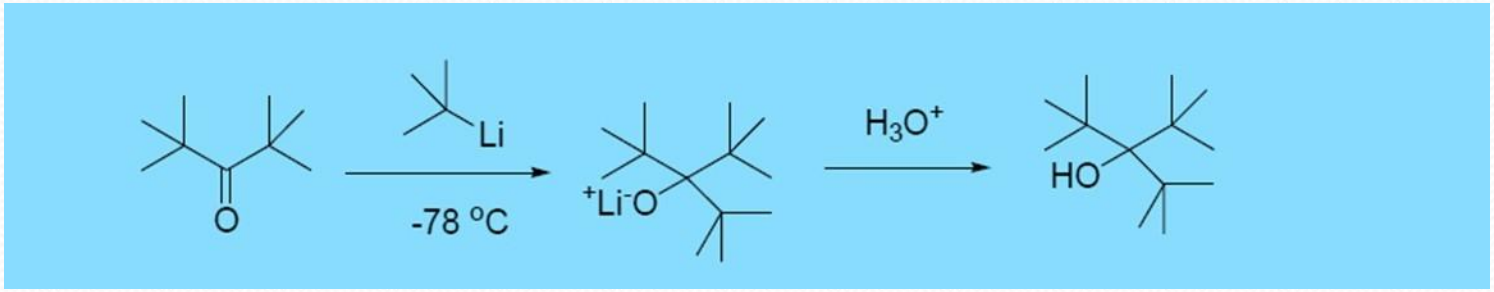
Note: The *ortho-directing groups are usually arranged in the following order in order of their reactivity: -SO2NR2 > -SO2Ar > -CONR2 > oxa-zolinyl > -CONHR > -CSNHR, -CH2NR2 > -OR > -NH-Ar > -SR > -CR2O-.*

Reactions of R-Li with Carbonyl Compounds

Organo-lithium reacts with aldehydes, ketones and esters to give alcohols as R-Mg-X.

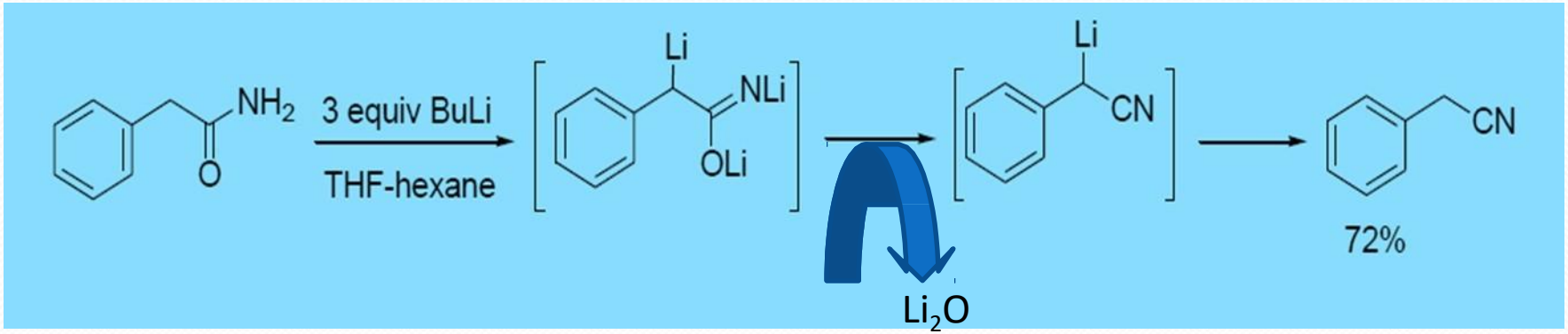


In comparison to R-Mg-X, R-Li are less susceptible to steric factors and react with hindered ketones to give tertiary alcohols.



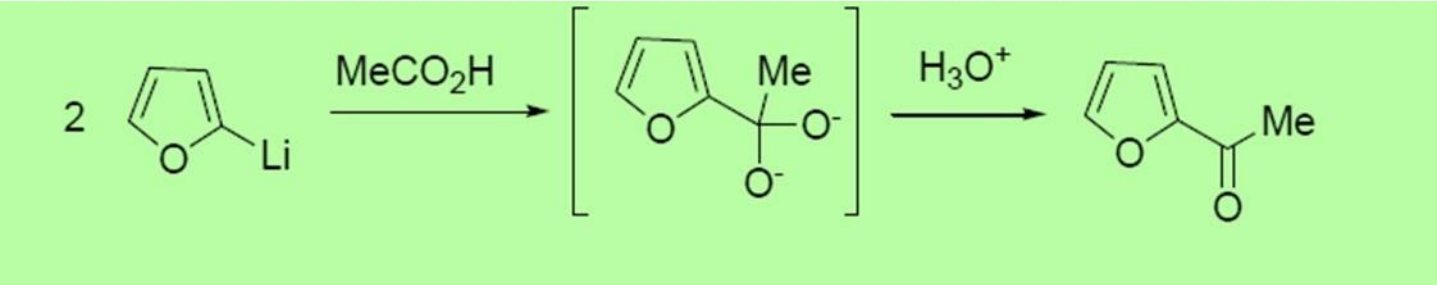
Reactions with primary amides

Primary amides undergo reaction with excess organo-lithium to give a nitrile. For an example, phenyl-acet-amide reacts with 3 equiv of butyl-lithium to give tri-lithiated species, which undergoes fragmentation to give intermediate that could be hydrolyzed to afford benzyl-nitrile



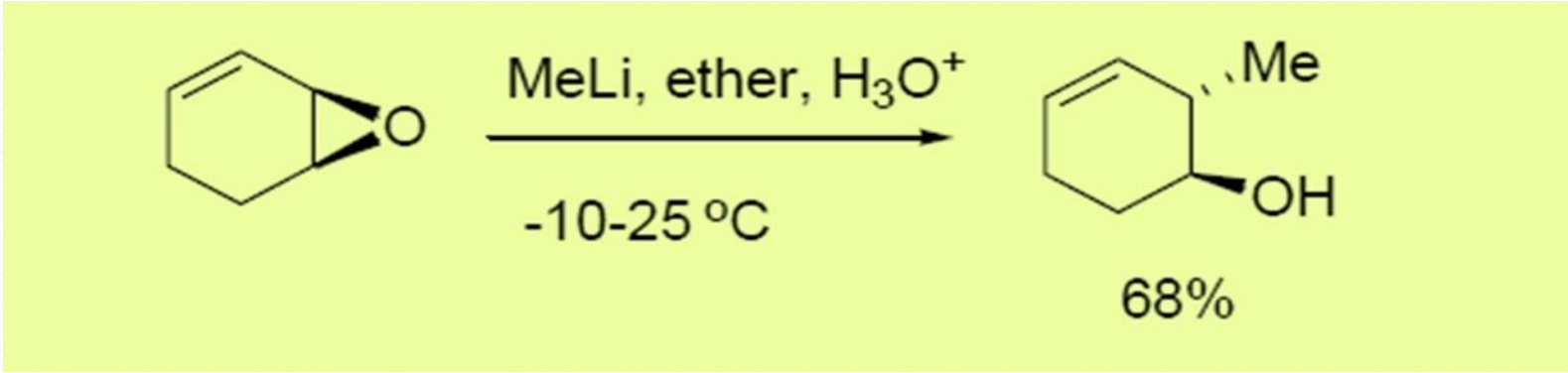
Reactions with Carboxylic acids

Reaction of carboxylic acid with organo-lithium reagent gives the expected carboxy-late salt, but a second equiv can add to the lithium carboxy-late to afford a ketone



Reactions with Epoxides

Epoxides react with organo-lithium reagents to give primary alcohols (as in the case of Grignard reagents) . In general, the organo-lithium attacks the epoxides at the less sterically hindered carbon, as with any nucleophile

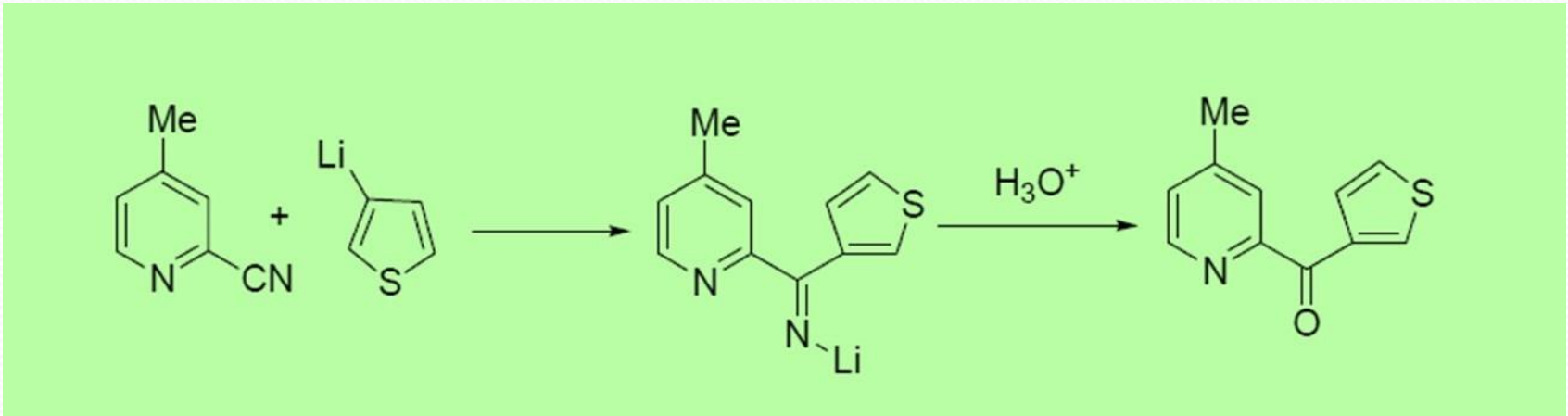


Reactions with Carbon Dioxide

- A major difference between the reactivity of R-Mg-X and organo-lithium reagent is observed in their reactivity towards CO2.
- The reaction of R-Mg-X with CO2 stops at the carboxylate stage, while in case of organolithium reagents, the carboxylate ion formed reacts with another equiv of organo-lithium to generate a ketone.

Reactions with Aryl Cyanides

As in the case of R-Mg-X, the reactions of organo-lithium reagents with aryl cyanides give imine salts, which undergo hydrolysis in the presence of water to give ketones



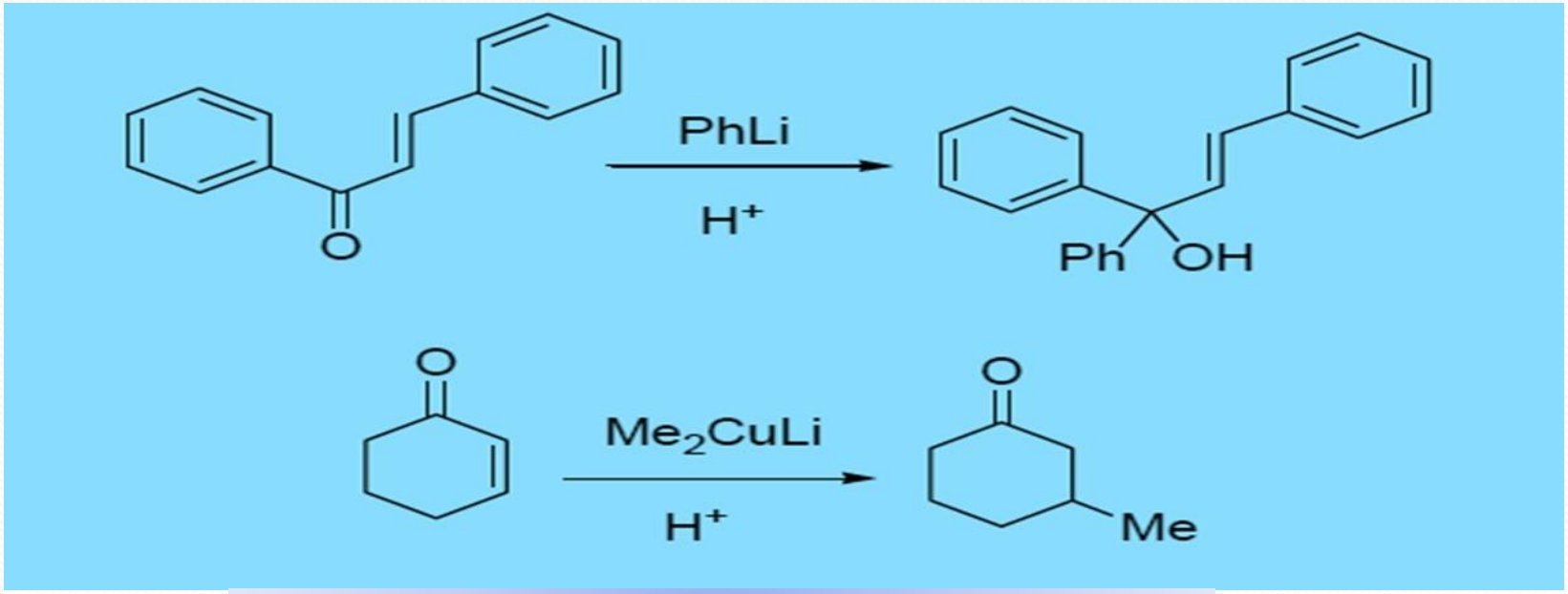
Reactions with α,β -Unsaturated Carbonyl Compounds

•In the case of Grignard reagents,α,β -unsaturated carbonyl compounds undergo reaction either at 1,2- or 1,4-addition depending on the structure of the carbonyl compound.

•The main reason is steric hinderance.

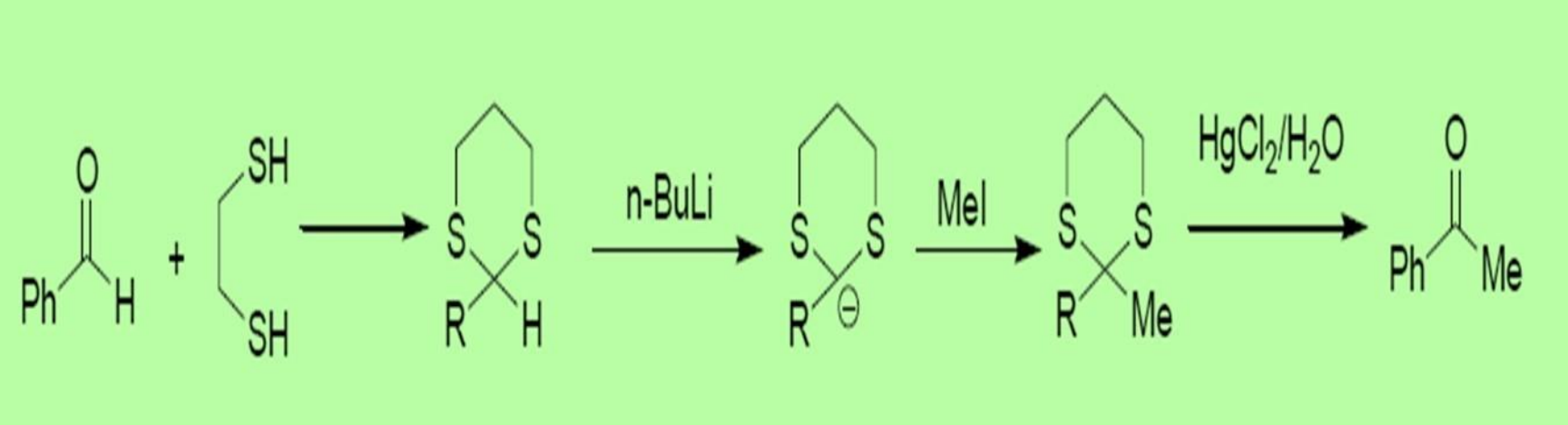
•The organo-lithium reagents undergo reaction exclusively to give 1,2-addition products.

•Exclusive formation of 1,4-addition product, however, can be achieved using lithium dialkyl-cuprates



Deprotonation

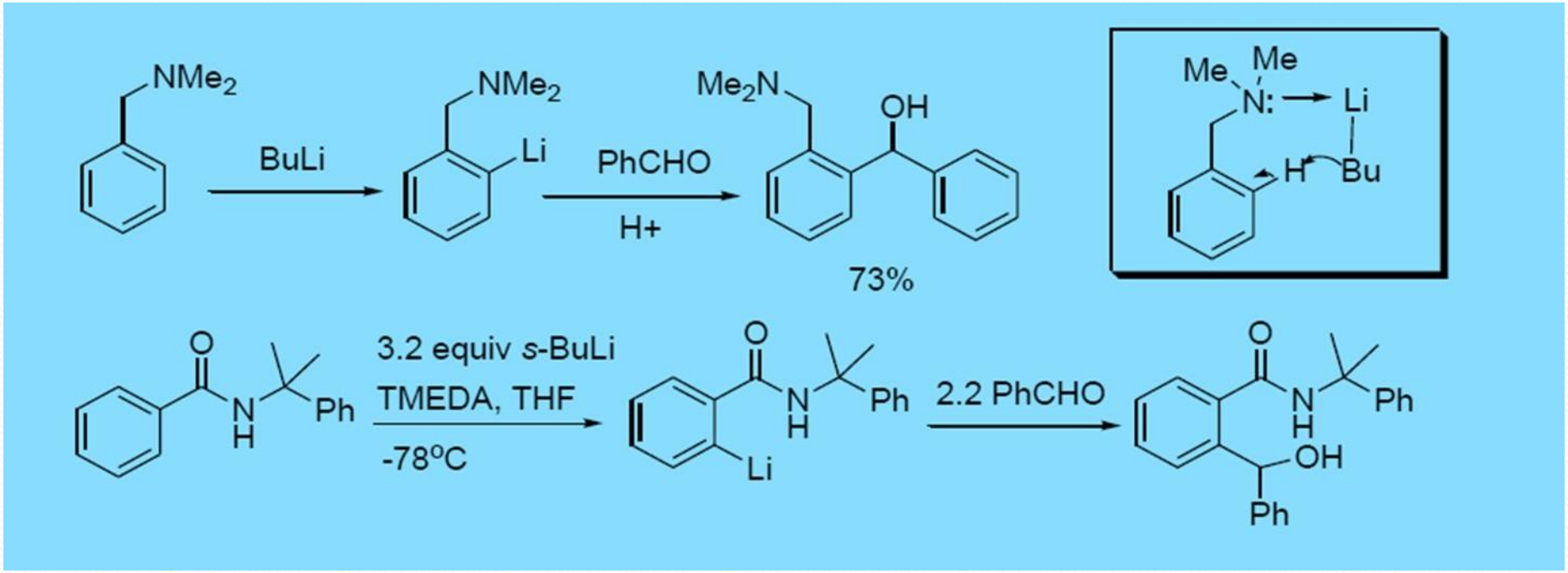
The basic nature of organo-lithiums can also be put to good use in achieving umpolang at the carbonyl centre of an aldehyde. In this protocol a C=O function is first protected by 1,3-dithiane and then the proton is removed by an organo-lithium



Ortholithiation

•The ortho-lithiation is useful reaction because the starting material does not need to have a halogen atom. For examples, in the case of benzyl-dimethyl-amine, the nitrogen atom directs attack of the butyl-lithium .

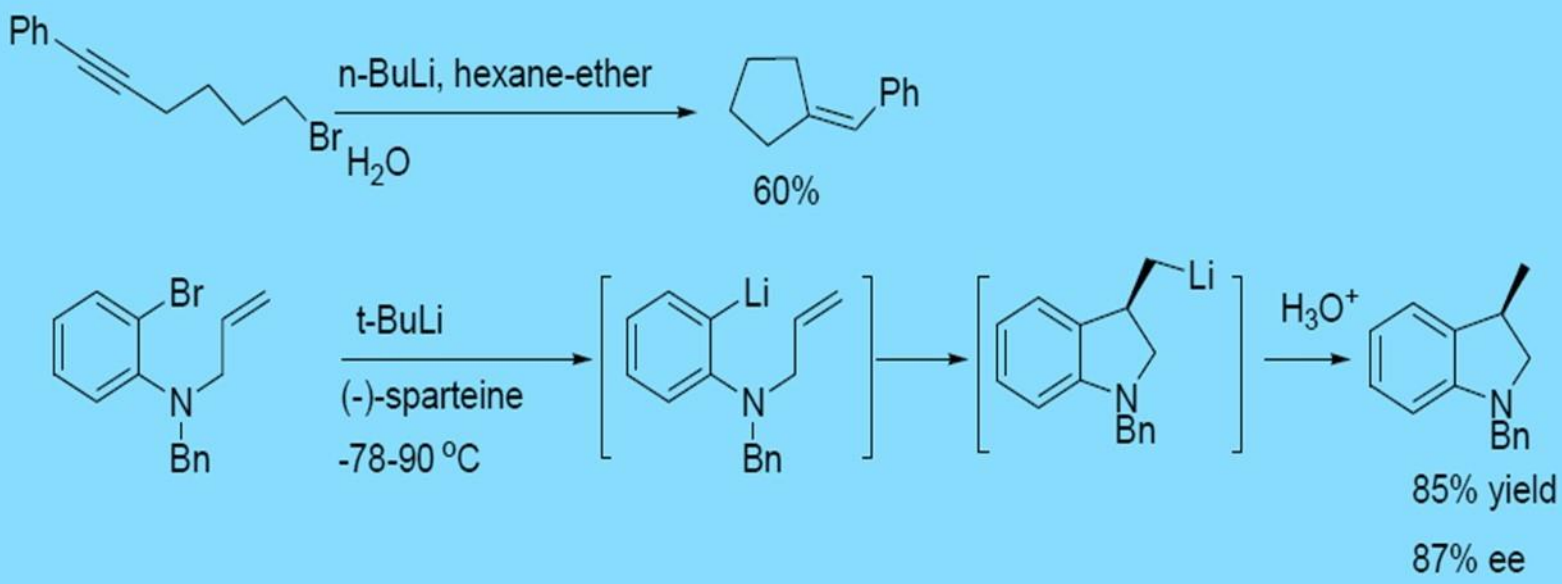
•Likewise, *N-cumylbenzamide with excess secondary butyllithium in the presence of TMEDA gives orotholithiated intermediate that could readily reacted with benzaldehyde with 80% yield*.



Reactions with Alkenes and Alkynes

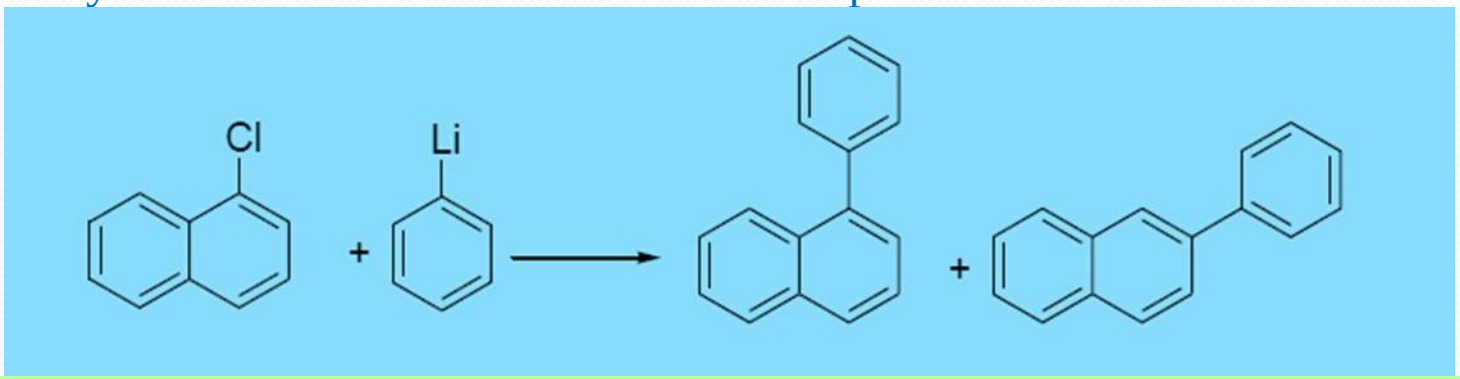
•The organo-lithium reagents undergo addition with alkenes or alkynes in an intra-molecular reaction. For examples, 1-(6-bromohex-1-ynyl)benzene in the presence of butyl-lithium gives alkyli-dene cyclo-pentane in 60% yield.

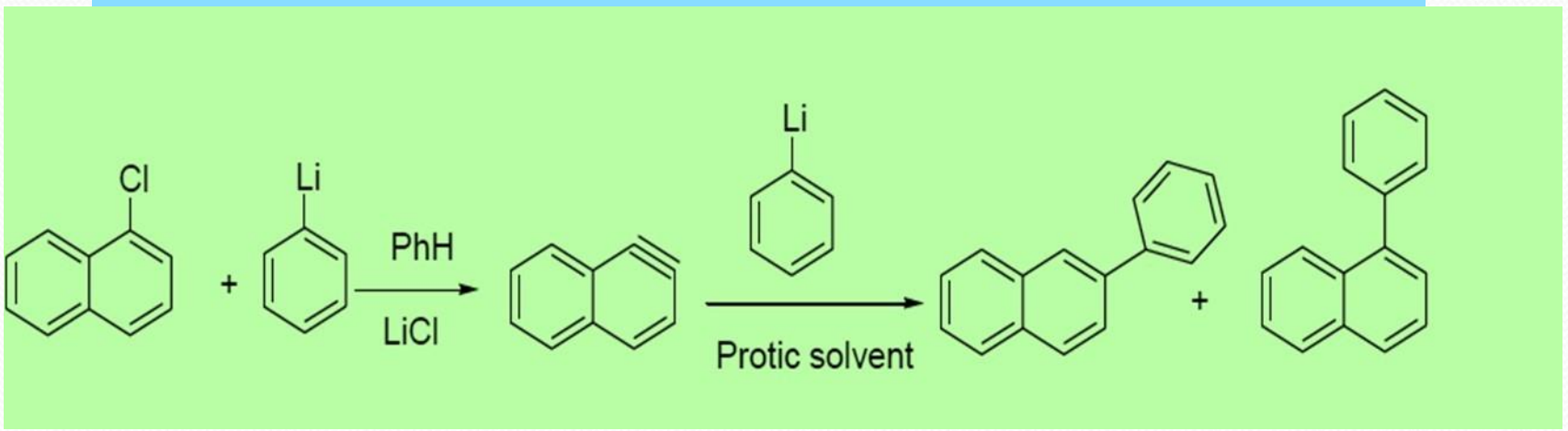
•The mechanism of the reaction is not well understood. While, N-allyl-N-benzyl-2- bromo-benza-mine reacts with tertiary butyl-lithium in the presence of (-)-sparteine to afford 1-benzyl-3-methylindoline in 87% ee



Nucleophilic Displacement

Reactions of alkyl and aryl halides can be reacted with alkyl and aryl lithium reagents to give hydrocarbons. The reaction of alkyl halides with alkyl lithium takes place by SN2 mechanism. While aryl halides react with aryl lithum via addition-elimination process





Electro-philic Displacement

•Reaction of an organic halide with an organo-metallic compound is known as metal-halogen exchange reaction is example for electro-philic displacement.

•This reaction is useful for the synthesis of vinyl- and phenyl lithium

Reactions with Aryl Cyanides

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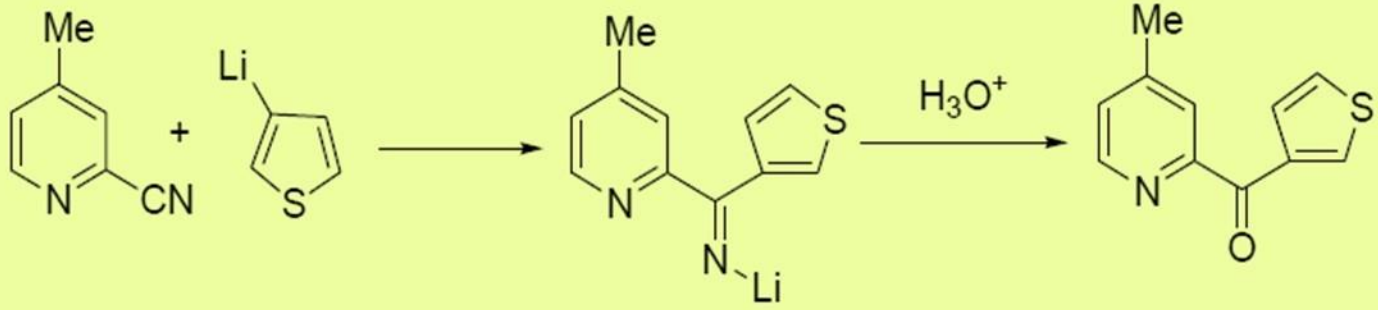

Lithium diisopropylamide

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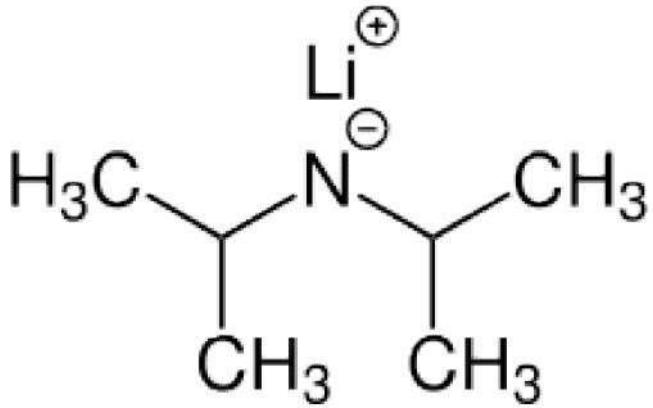
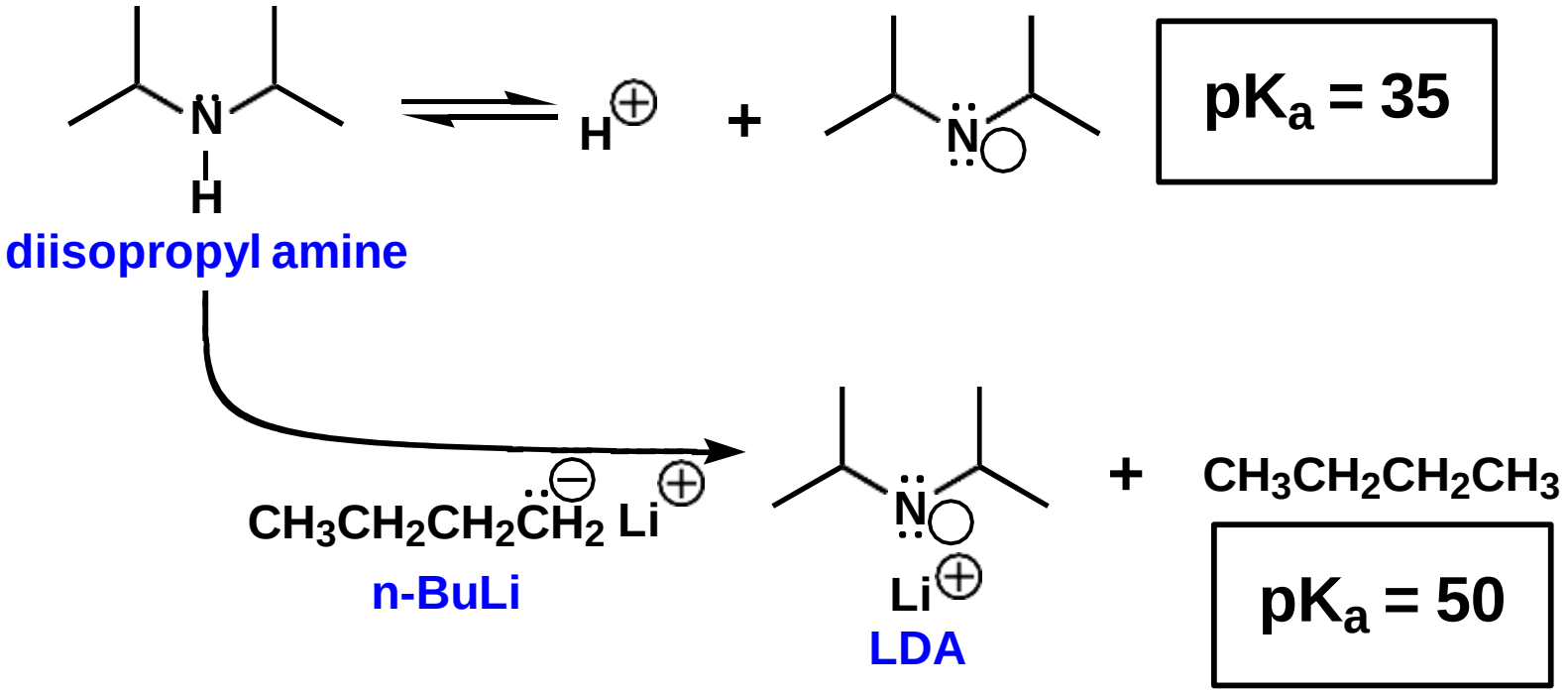
- It is a colorless solid, but is usually generated and observed only in solution.

➢LDA is commonly formed by treating a cooled (0 to −78 °C) tetrahydrofuran (THF) solution of diisopropylamine with *n*-butyllithium.



LDA is a Base Used to Form Enolate Anions

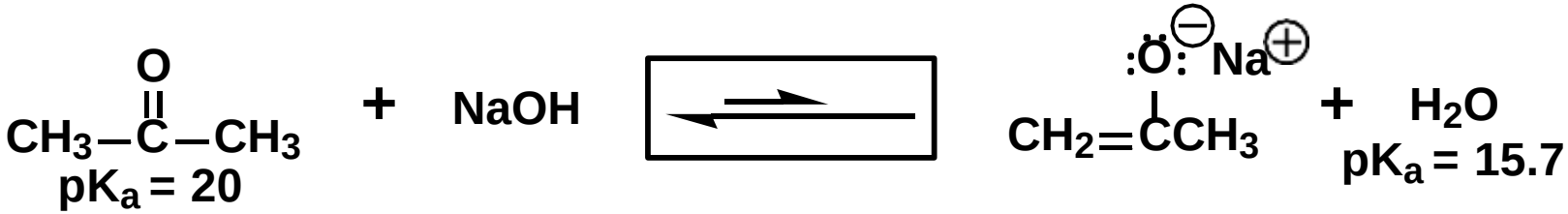
Strong organic bases such as **LDA** (**L**ithium **D**iisopropyl**A**mide) can be used to drive the ketone-enolate equilibrium completely to the enolate side. LDA is a strong base that is useful for this purpose. The steric bulk of its isopropyl groups makes LDA non-nucleophilic. Even so, it's a strong base. LDA is prepared by the deprotonation of diisopropyl amine using a very strong base such as n-butyl lithium as shown.



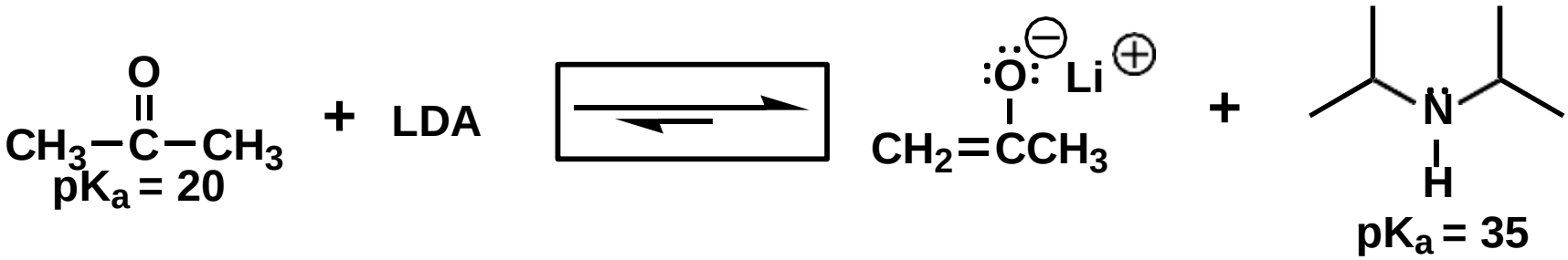
Enolate Equilibria are Acid-Base Reactions

To which side does the equilibrium lie?

$K_{eq} = 5 \times 10^{-5}$

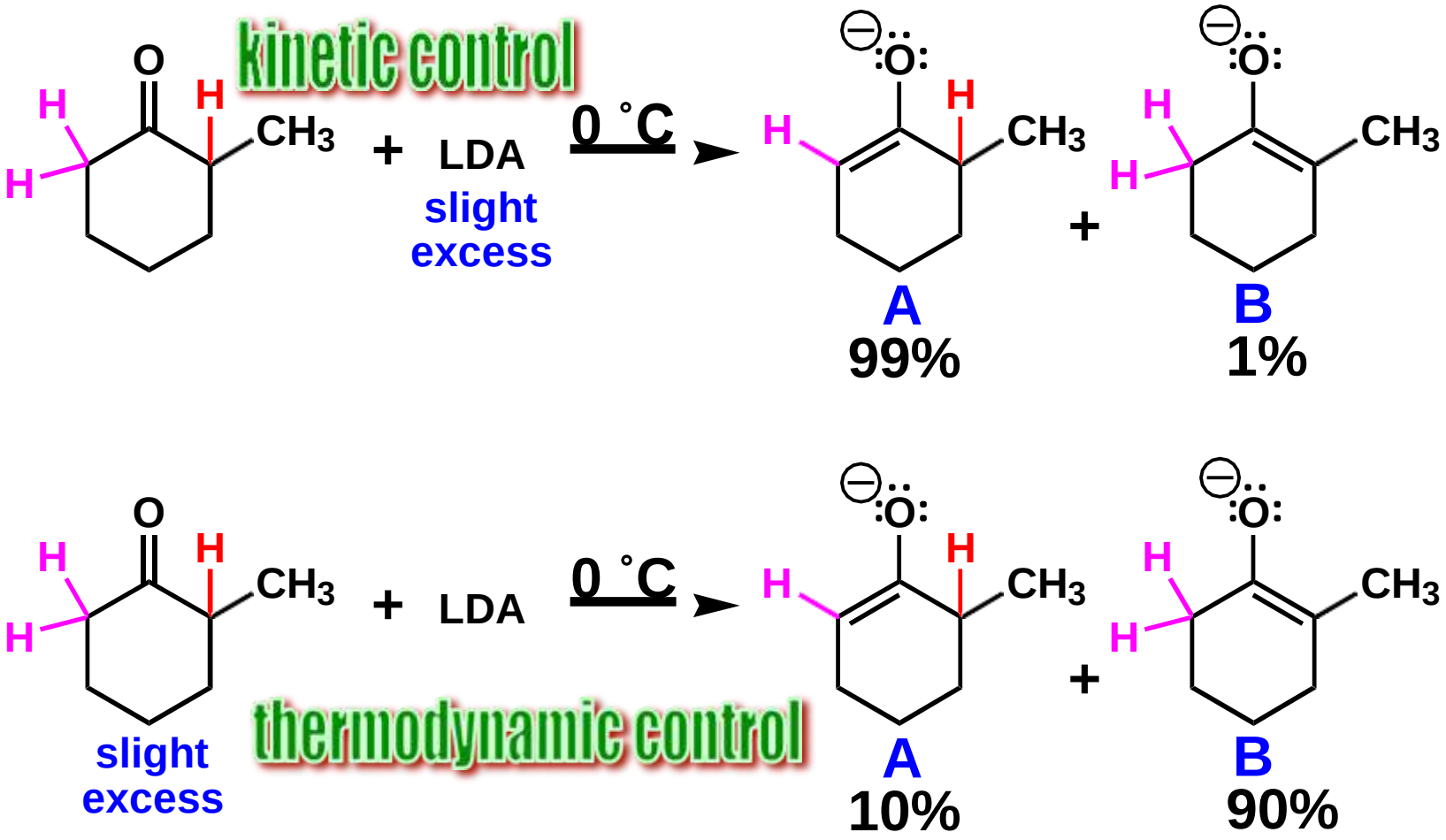


$K_{eq} = 1 \times 10^{15}$



Using a strong enough base, quantitative enolate formation is feasible.

Thermodynamic vs. Kinetic Control of Enolate Formation



The indicated difference in reaction conditions determines whether deprotonation is reversible or irreversible.

Which enolate is more stable? B

Which enolate is formed faster? A