

## Unit 4. Oxidation–Reduction reactions

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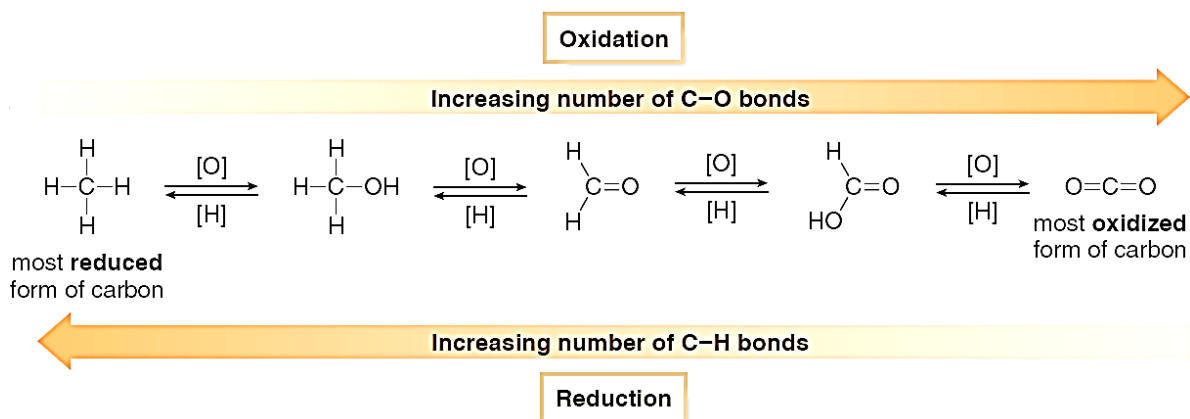
### Learning outcome

- identify the species that have undergone oxidation and those that have undergone reduction.
- know the oxidation states of different compounds
- Study chemistry of different oxidizing reagents
- choose appropriate reagent for selective oxidation.
- understand the chemistry of different reducing reagents.
- select appropriate reagent for selective reduction.

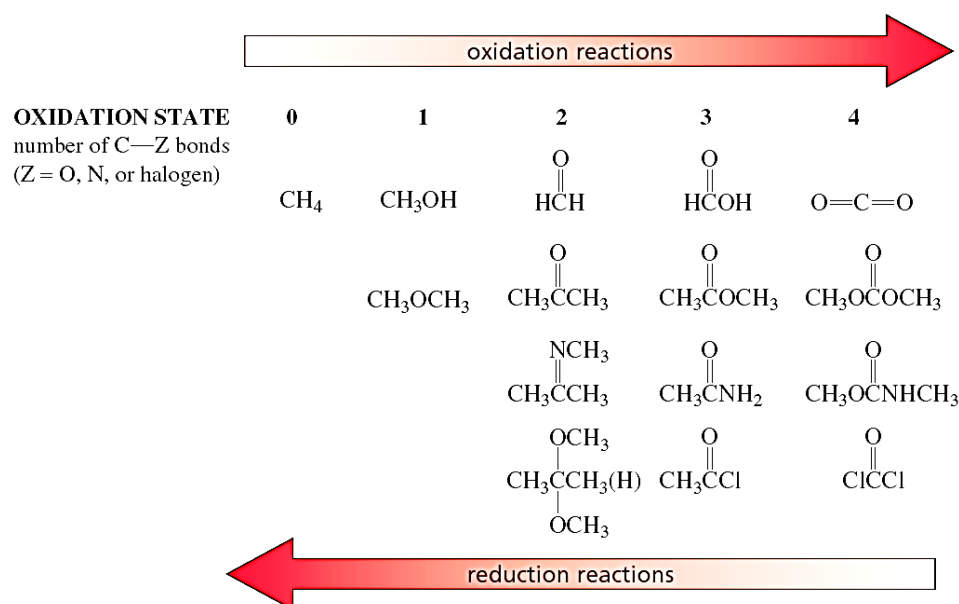
## Oxidation–Reduction reactions

The reaction involving the transfer of electrons from one molecule to another are called **oxidation-reduction reactions** or **redox reactions**. These reactions are used in the synthesis of a large variety of compounds and are known in biological systems as well. In an oxidation-reduction reaction, one compound is oxidized by losing electrons while the other compound is reduced by gaining electrons. Oxidation and reduction both undergo simultaneously in a reaction; a compound cannot gain electrons (be reduced) unless another compound in the reaction simultaneously loses electrons (is oxidized). The compound that is oxidized is called the **reducing agent** because it transfers electrons to the other compound to reduce it. Similarly, the compound that is reduced is called the **oxidizing agent** because it gains the electrons given up by the other compound when it is oxidized.

However, most organic compounds are uncharged, and gain or loss of electrons is not obvious. In an organic reaction, the oxidation and reduction of a compound is determined by the replacement of hydrogen atom with an electronegative atom (O, N, halogen) or vice versa. Thus, a compound is reduced, if the reaction increases the number of C–H bonds or decreases the number of C–O, C–N or C–X (a halogen) bonds. A compound is oxidized if the reaction decreases the C–H bonds or increases the number of C–O, C–N or C–X (a halogen) bonds. For example:



The total number of C–O, C–N or C–X (a halogen) bonds of a carbon is called the **oxidation state** of that carbon.



In the organic reactions, several oxidizing and reducing agents are used for the transformation of one functional group to another functional group. Some oxidizing and reducing agents are very selective to oxidize or reduce one functional group and not the other. Such type of oxidizing and reducing agents are very helpful in getting desirable results if the reactants contain more than one functional group.

## 4.1. Oxidation Reactions

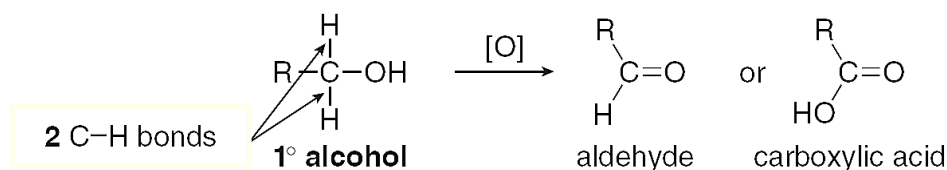
As described earlier, the oxidation at carbon decreases the number of C—H bond or increases the number of C—O, C—N or C—X bonds. The oxidation is carried out with oxidizing agents which are grouped into two categories:

- a) **Reagents that contain oxygen-oxygen bonds** – These reagents include  $\text{O}_2$  (oxygen),  $\text{O}_3$  (ozone),  $\text{H}_2\text{O}_2$  (hydrogen peroxide),  $(\text{CH}_3)_3\text{COOH}$  (*tert*-butyl hydroperoxide), and peracids. They all contain a weak O—O bond which is cleaved during oxidation.
- b) **Reagents that contain metal-oxygen bonds** – These reagents mostly contain either chromium in +6 oxidation state (six Cr—O bonds) or manganese in +7 oxidation state (seven Mn—O bonds). For example,  $\text{CrO}_3$  (chromium oxide),  $\text{K}_2\text{Cr}_2\text{O}_7$  (potassium dichromate),  $\text{Na}_2\text{Cr}_2\text{O}_7$  (sodium dichromate),  $\text{KMnO}_4$  (potassium permanganate). These reagents are used in presence of strong aqueous acids like  $\text{H}_2\text{SO}_4$ . Other oxidizing agents are  $\text{OsO}_4$  (osmium tetroxide) and  $\text{Ag}_2\text{O}$  (Silver oxide). Pyridinium chlorochromate (PCC) is soluble in halogenated organic solvents and can be used without strong acid present. This is a mild oxidizing agent, and thus is more selective oxidant.

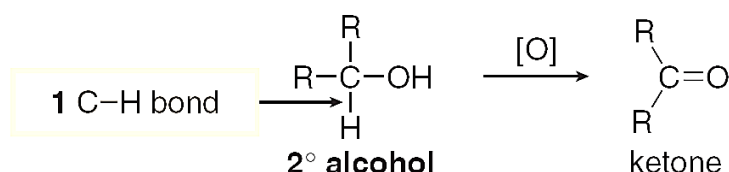
### 4.1.1. Oxidation of Alcohols

Oxidation of an alcohol results in the formation of an aldehyde, a ketone, or a carboxylic acid depending on the alcohol and on the oxidizing agent.

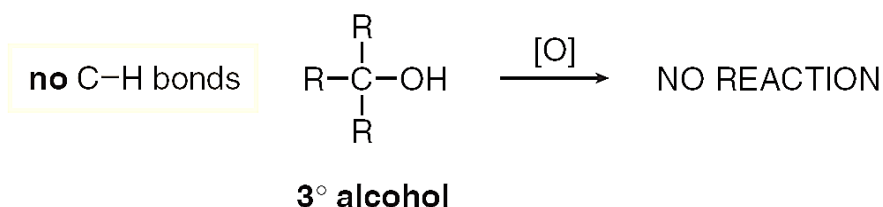
- Depending on the oxidizing agent used in the reaction, primary alcohols are oxidized to aldehydes or carboxylic acids by replacing either one or two C–H bonds by C–O bonds.



- Secondary alcohols on oxidation yield ketones by replacing one C–H bond by C–O bond.



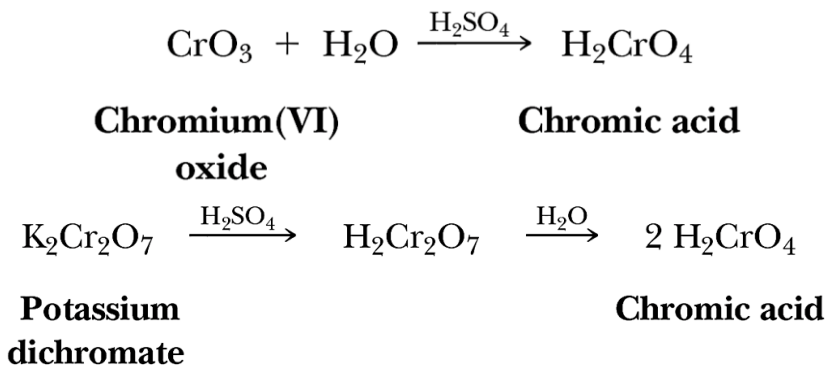
- Tertiary alcohols contain no H atoms on the carbon with the OH group, so they don't react with most of the oxidizing agents.



Different oxidizing agents are used to oxidize alcohols based on the product desired. The oxidation of primary alcohols with strong oxidizing agents results in the formation of aldehydes which is further oxidized to carboxylic acids while mild oxidizing agents produce aldehydes.

#### Oxidation by strong oxidizing agents:

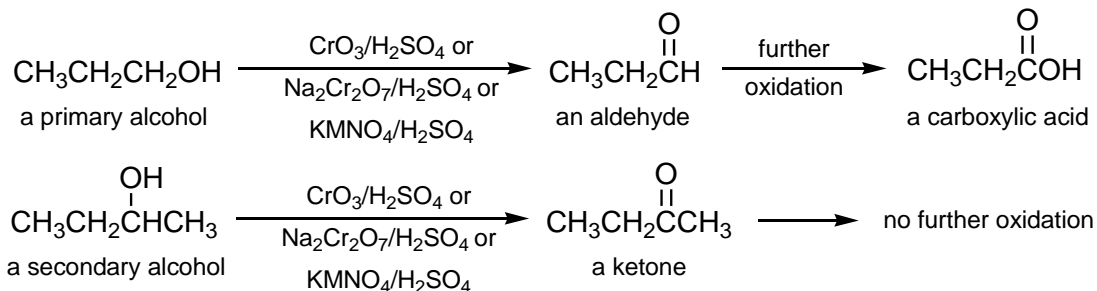
Chromic acid ( $\text{H}_2\text{CrO}_4$ ) is generally used to oxidize primary alcohols to carboxylic acids, and secondary alcohols to ketones. Chromic acid is prepared by dissolving either chromium trioxide ( $\text{CrO}_3$ ) or sodium (or potassium) dichromate in aqueous  $\text{H}_2\text{SO}_4$ .



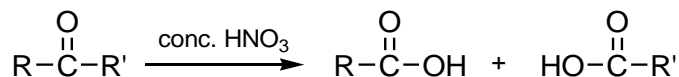
A solution of chromic acid in aqueous sulfuric acid is known as the **Jones reagent**. Because most of the organic compounds are insoluble (or slightly soluble) in

water, they are first dissolved in acetone and then Jones reagent is added to complete the oxidation. Acidified  $\text{KMnO}_4$  is also used to oxidize alcohols.

Primary alcohols are initially oxidized to aldehydes by these reagents. The reaction, however, does not stop at the aldehyde. Instead, the aldehyde is further oxidized to a carboxylic acid. Secondary alcohols are oxidized to ketones which do not oxidize further because ketones don't have any C-H bond to be converted to C-O bond.



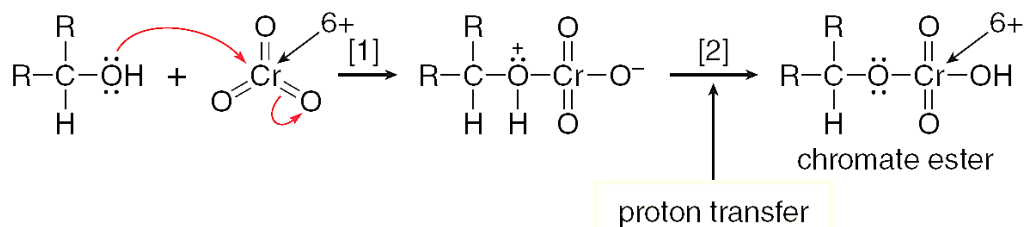
However, ketones are cleaved at carbonyl carbon on either side to give carboxylic acid in presence of strong oxidizing agents such as conc.  $\text{HNO}_3$ .



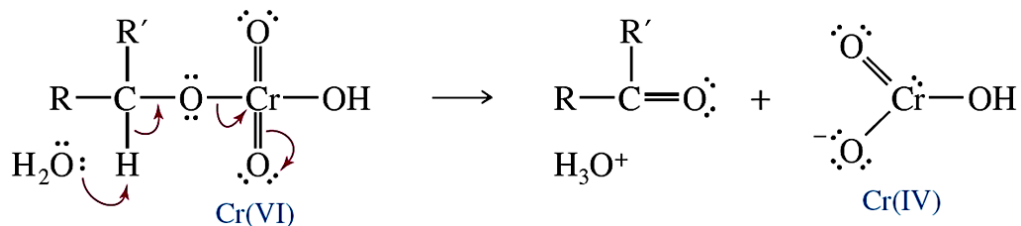
### Mechanism:

#### *Oxidation of secondary alcohol:*

**Step 1 and 2: Formation of chromate ester.** Nucleophilic attack of the alcohol on the electrophilic metal followed by proton transfer forms a chromate ester. No oxidation takes place in these steps.



**Step 3: Elimination of the chromate ester and oxidation of the carbinol carbon (formation of ketone).** A base ( $\text{H}_2\text{O}$  or alkoxide of the starting alcohol) removes a proton, with the electron pair in the C-H bond forming the new  $\pi$  bond of the C=O. Oxidation at carbon occurs in this step because the number of C-H bonds decreases and the number of C-O bonds increases.

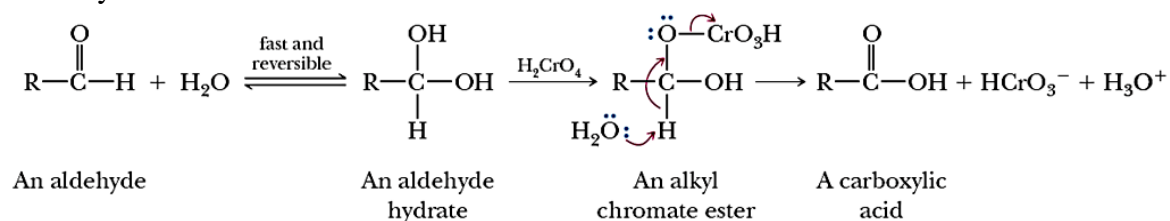


#### *Oxidation of primary alcohol:*

Oxidation of primary alcohol undergoes in two parts – oxidation to aldehyde and then further oxidation of aldehydes to carboxylic acid.

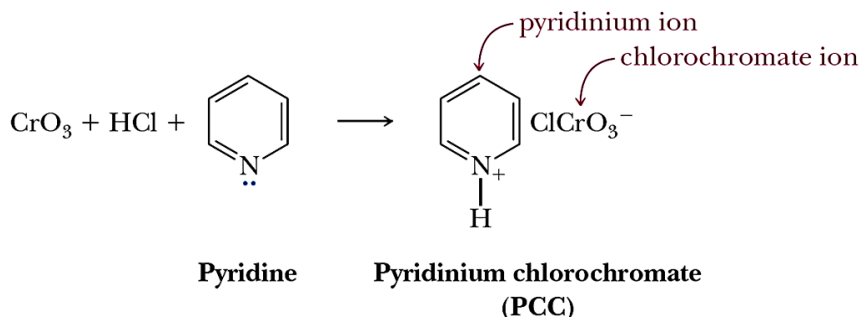
**Part 1: Oxidation to aldehydes.** The mechanism of oxidation of primary alcohol to aldehyde is same as described in the oxidation of secondary alcohol to ketone.

**Part 2: Oxidation of aldehydes to carboxylic acid.** Aldehyde itself is not oxidized by chromic acid, because chromic acid can only react with an  $-OH$ , not with carbonyl. Therefore, aldehyde is first converted to its hydrate by the addition of a molecule of water to the aldehyde carbonyl group. Then, an  $-OH$  of the aldehyde hydrate reacts with chromic acid to complete the oxidation of the aldehydes to carboxylic acids.



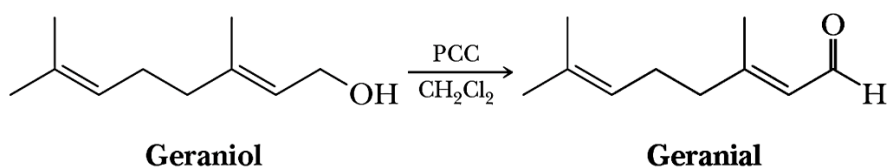
### Mild oxidizing agents:

**Pyridinium chlorochromate (PCC):** The oxidation of a primary alcohol can be easily stopped at the aldehyde if pyridinium chlorochromate (PCC) or pyridinium dichromate (PDC)  $(\text{C}_6\text{H}_5\text{NH})_2^{2+}\text{Cr}_2\text{O}_7^{2-}$  are used as the oxidizing agents. PCC, also known as **Corey's reagent**, is a complex of chromium trioxide with pyridine and HCl, and oxidizes most primary alcohols to aldehydes in excellent yields.



Unlike most other oxidants, PCC and PDC are soluble in nonpolar solvents such as dichloromethane ( $\text{CH}_2\text{Cl}_2$ ), which is an excellent solvent for most organic compounds. Moreover, as the reaction undergoes in absence of water, the product aldehyde is not converted to aldehyde hydrate; therefore, further oxidation of aldehyde to carboxylic acid is stopped.

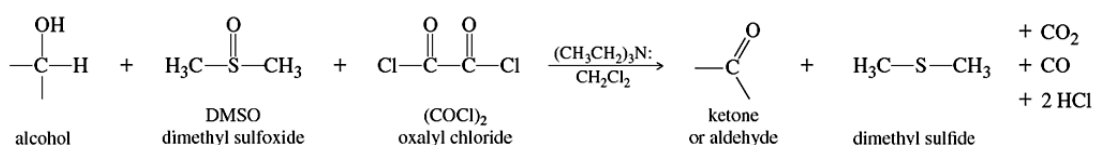
PCC and PDC are not only selective for the oxidation of primary alcohols to aldehydes but also do not affect carbon-carbon double bonds or other easily oxidized functional groups. For example,



Secondary alcohols are also oxidized by PCC or PDC to ketone.

### Swern Oxidation:

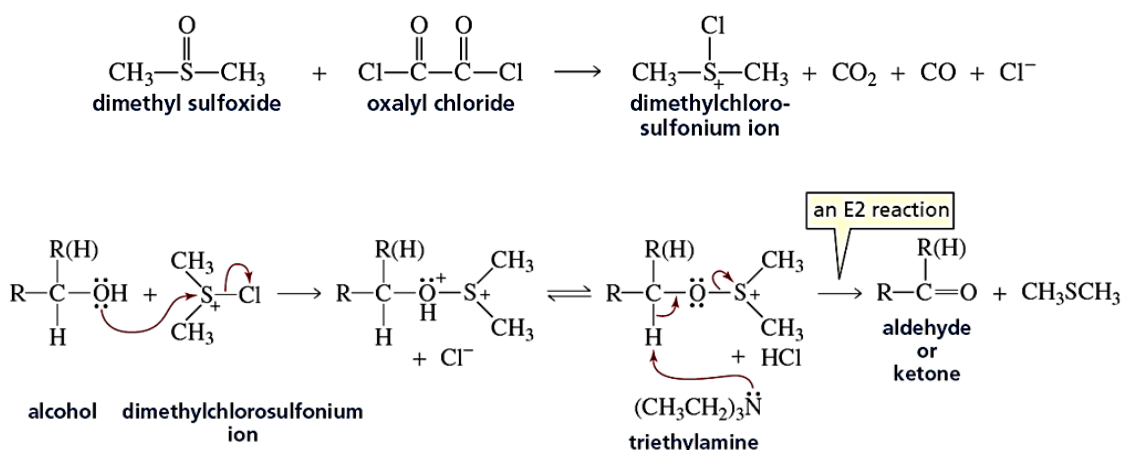
Because of the toxicity of chromium-based reagents discussed above, other methods like **Swern oxidation** is widely in practice for the oxidation of alcohols, which uses dimethyl sulfoxide (DMSO) as the oxidizing agent to convert primary alcohols to aldehydes and secondary alcohols to ketones. DMSO and oxalyl chloride are added to the alcohol at low temperature, followed by a hindered base such as triethylamine. The actual reactive species  $(\text{CH}_3)_2\text{S}^+\text{Cl}$  (dimethylchlorosulfonium ion), formed in the solution from the reaction of dimethyl sulfoxide and oxalyl chloride, is the oxidizing agent in the Swern oxidation.



Since the reaction is *not* carried out in an aqueous solution, the oxidation of a primary alcohol (like PCC oxidation) stops at the aldehyde. Secondary alcohols are oxidized to ketones. The by-products of this reaction are all volatile and are easily separated from the organic products.

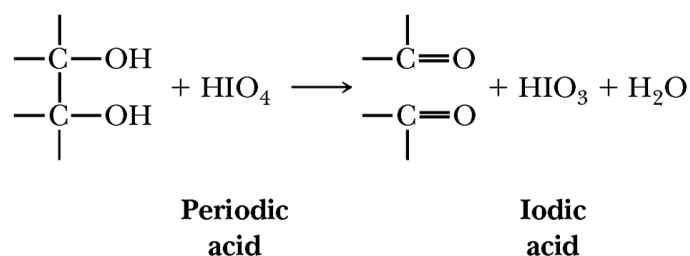
### Mechanism:

Like chromic acid oxidation, the Swern oxidation uses an E2 reaction to form the aldehyde or ketone.



### Oxidation of Glycols (vicinal diols):

Glycols, on oxidation with periodic acid,  $\text{HIO}_4$  or lead tetraacetate,  $\text{Pb}(\text{OCOCH}_3)_4$  result in the formation of acid and/or ketone depending upon the substitution. In the process, periodic acid is reduced to iodic acid.

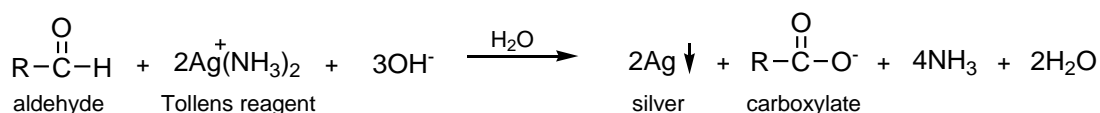


In case of small-ring cyclic glycols, *cis*-isomer oxidizes faster than the *trans*-isomer; for example, *cis*-cyclohexan-1, 2-diol is oxidized to dialdehyde while *trans*-isomer remains unchanged.

#### 4.1.2. Oxidation of Aldehydes

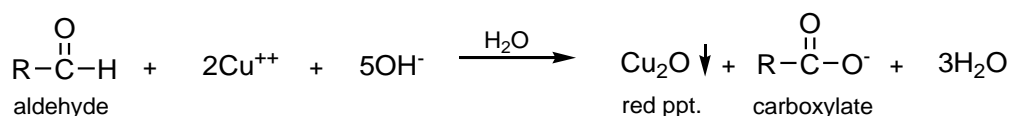
Aldehydes are oxidized much more readily; therefore, in addition to chromic acid (a strong oxidizing agent), potassium permanganate, and potassium dichromate oxidation, as discussed above, aldehydes undergo oxidation even with mild oxidizing reagents, e.g. Tollens reagent, Fehling's solution, and Benedict's reagent. Ketones do not get oxidized by these reagents; hence these reagents are used to distinguish aldehydes and ketones.

**Tollens reagent:** Tollens reagent is an ammoniacal silver nitrate solution. Tollens reagent on heating with aldehydes forms a black suspension with shiny silver mirror deposited on the side of the test tube; silver ion ( $\text{Ag}^+$  in silver nitrate) oxidizes aldehydes to carboxylic acids and itself gets reduced to metallic silver. Hence the reaction is called silver mirror test.



Simple hydrocarbons, ethers, ketones and even alcohols do not react with the Tollens reagent. The reaction is used industrially to produce shiny silver mirror on glass surfaces, such as the inside of Thermos flasks.

**Fehling's solution:** The Fehling's solution is a mixture of two solutions – *Fehling's solution A* (alkaline  $\text{CuSO}_4$ ) and *Fehling's solution B* (sodium potassium tartarate in sodium hydroxide). The two solutions are mixed in equal amounts which results in the formation of deep blue coloured copper tartarate complex furnishing cupric ( $\text{Cu}^{++}$ ) ions. The cupric ion on heating with aldehydes is reduced to cuprous oxide giving a red precipitate, and the aldehydes are oxidized to carboxylic acids.

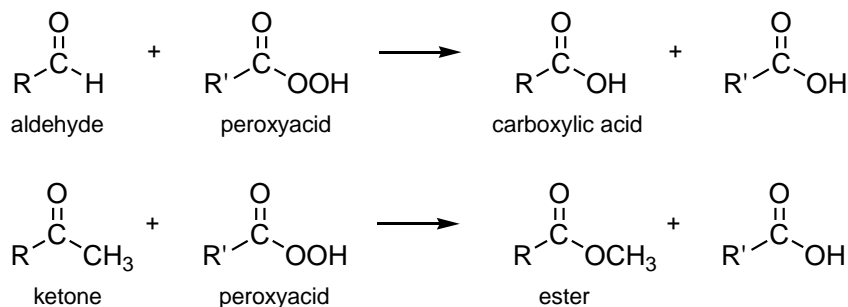


**Benedict solution:** An alkaline solution of copper sulfate, sodium acetate, and sodium carbonate is called Benedict solution. The reaction of aldehydes with Benedict solution is same as with Fehling's solution. Like Fehling's solution, it furnishes cupric ion which oxidizes aldehydes to carboxylic acid and itself get reduced to form red precipitate of cuprous oxide.

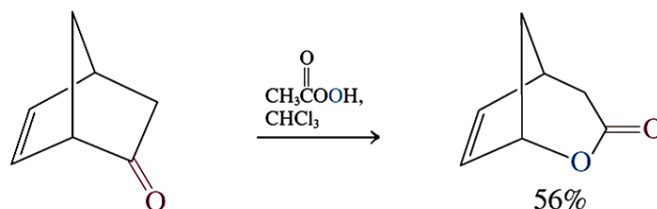


**Baeyer-Villiger oxidation:**

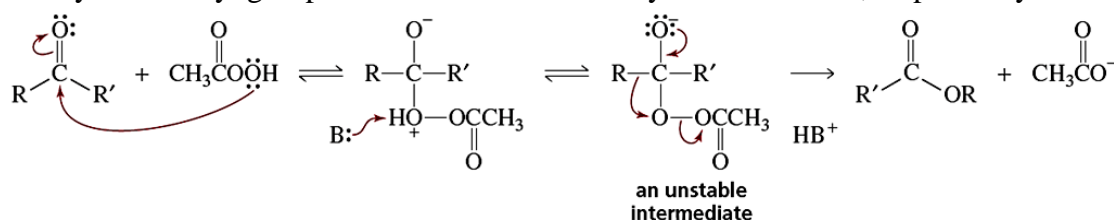
Ketones do not react with most of the reagents used to oxidize aldehydes. However, both aldehydes *and* ketones can be oxidized by a peroxyacid. Aldehydes are oxidized to carboxylic acids and ketones are oxidized to esters. An oxygen atom is inserted between the carbonyl carbon and the H of an aldehydes or the R of a ketone.



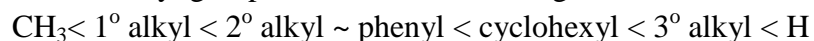
A cyclic ketone undergoes Baeyer-Villiger rearrangement to form a cyclic ester called lactone.

**Mechanism:**

The nucleophilic addition of peroxyacid to carbonyl carbon results in the formation of unstable tetrahedral intermediate with a very weak O–O bond. This step is analogous to the formation of hemiacetal. The weak O–O bond breaks with the 1, 2-shift of H of aldehydes or alkyl group of ketone to form carboxylic acid or ester, respectively.

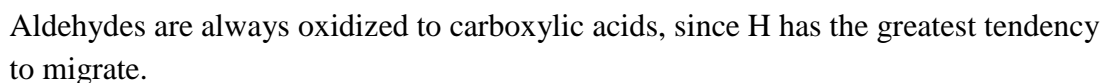


When the two alkyl groups attached to the carbonyl group of the ketone are different, the migration of the alkyl group occurs in the following order:



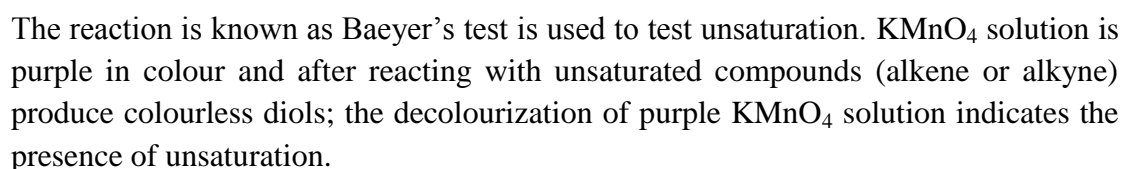
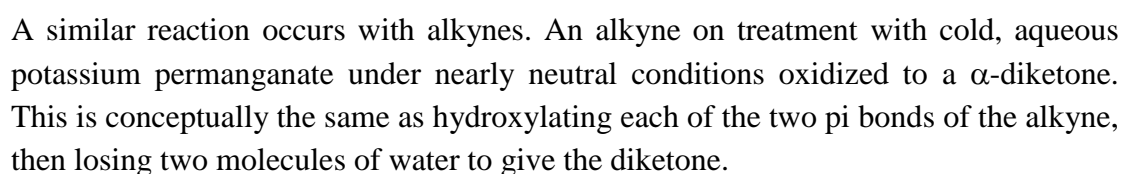
For example:

Baeyer-Villiger oxidation of cyclohexyl methyl ketone results in the formation of cyclohexyl acetate, not methyl cyclohexanecarboxylate because cyclohexyl group is more likely to migrate than a methyl group.

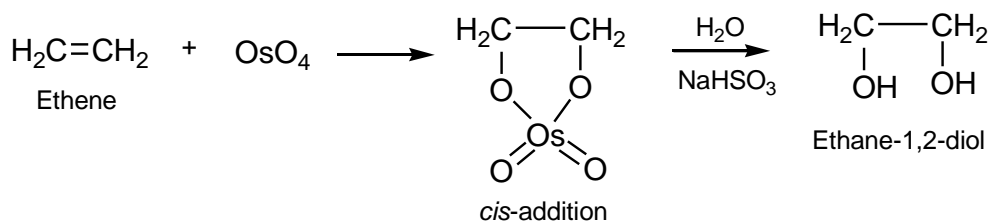


Compounds having multiple bonds like alkenes and alkynes are oxidized to produce different compounds depending on the type of oxidizing reagent as well as on the reaction conditions.

The aqueous alkaline solution of potassium permanganate oxidizes alkenes and results to the formation of *cis*-diols; hydroxylation occurs at the double bond position. The permanganate adds to the alkene double bond to form a cyclic ester which is hydrolyzed by the base to form diol.

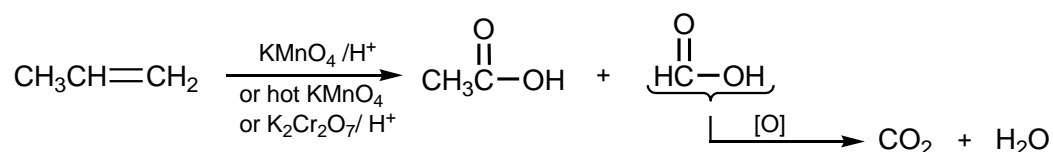


Reaction of alkene with osmium tetroxide is same as with potassium permanganate; alkene reacts with  $\text{OsO}_4$  to form an osmate ester which on hydrolysis produces *cis*-diols.

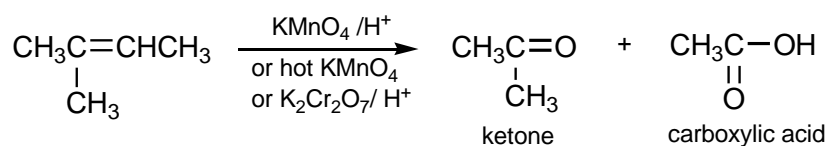


### Oxidative cleavage with acidified or hot $\text{KMnO}_4$ or acidified $\text{K}_2\text{Cr}_2\text{O}_7$ :

A cold aqueous  $\text{KMnO}_4$  solution oxidizes an alkene to a *cis*-diol. However, acidified or hot  $\text{KMnO}_4$  solution is much stronger oxidizing agent and oxidizes diol further to give carboxylic acid or ketones through the cleavage of C–C double bond. The terminal  $=\text{CH}_2$  group is oxidized completely to produce  $\text{CO}_2$  and  $\text{H}_2\text{O}$ . Acidified  $\text{K}_2\text{Cr}_2\text{O}_7$  or  $\text{Na}_2\text{Cr}_2\text{O}_7$  also give the same reaction.



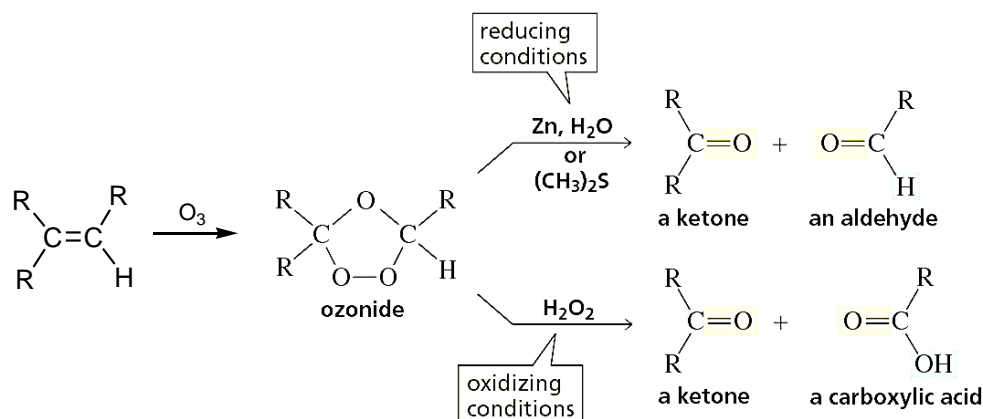
Olefinic carbon with no hydrogen attached to it gets oxidized only upto ketones, which are very difficult to oxidize further to carboxylic acids.



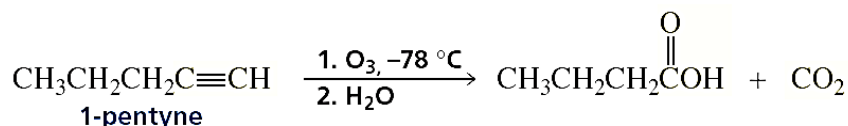
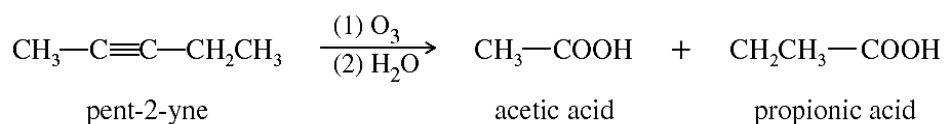
### With ozone:

Electrophilic addition of ozone to alkene produces a cyclic peroxide known as *ozonide*; the reaction results in the cleavage of C–C double bond. The ozonide being explosive is not isolated; rather further decomposition of ozonide is carried out by reduction (known as reductive ozonolysis) or by oxidation (called oxidative ozonolysis).

- The reductive ozonolysis with  $\text{Zn}/\text{H}_2\text{O}$  forms aldehydes and/or ketone; aldehyde is formed if the  $sp^2$  carbon of the alkene contains at least one hydrogen atom, and ketone is formed if the  $sp^2$  carbon of the alkene is bonded to two alkyl substituents.
- The oxidative ozonolysis with  $\text{H}_2\text{O}_2$  produces carboxylic acid and /or ketones. Carboxylic acids are formed instead of aldehydes because any aldehyde that is initially formed will be immediately oxidized to a carboxylic acid by hydrogen peroxide.



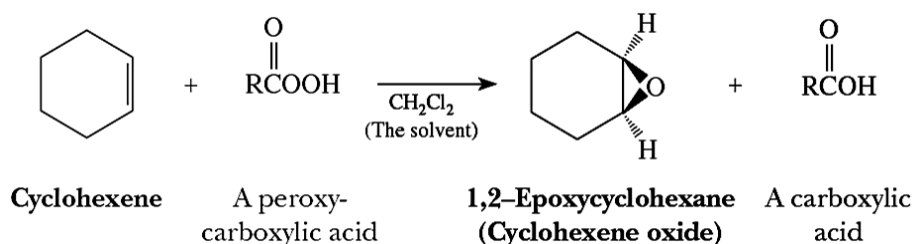
The reaction of **alkynes** with ozone followed by hydrolysis results in the cleavage of triple bond and forms two carboxylic acids. Unlike in alkenes, no oxidizing or reducing agents are required here to react with ozonide; only hydrolysis is required. The terminal alkyne group is oxidized to  $\text{CO}_2$ .



Ozonolysis is used to determine the position of double or triple bond in a compound.

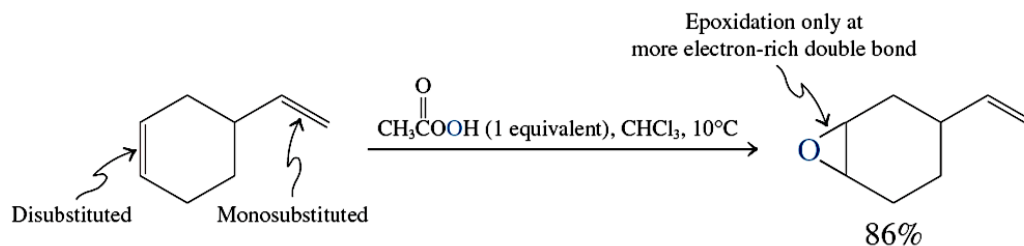
**With peroxyacids:**

The reaction of peroxyacids with alkene gives epoxide i.e. three-membered oxygen containing ring. The reaction is called epoxidation and follows the electrophilic addition mechanism. *meta*-Chloroperoxybenzoic acid (MCPBA), the magnesium salt of monoperoxyphthalic acid (MMPP), and peroxyacetic acid are commonly used peroxyacids.



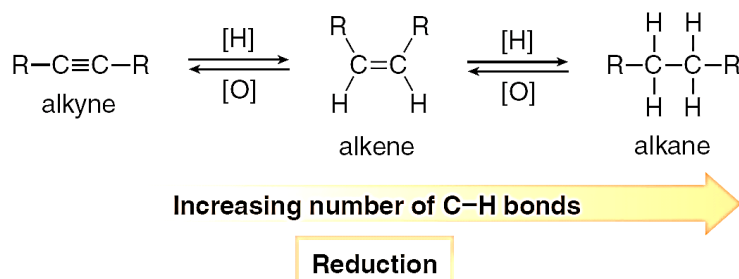
Epoxidation of alkenes with peroxy acids is a *syn* addition to the double bond. Substituents that are *cis* to each other in the alkene remain *cis* in the epoxide; substituents that are *trans* in the alkene remain *trans* in the epoxide.

The reactivity of alkenes toward peroxycarboxylic acids increases with alkyl substitution, allowing for selective oxidations. For example,

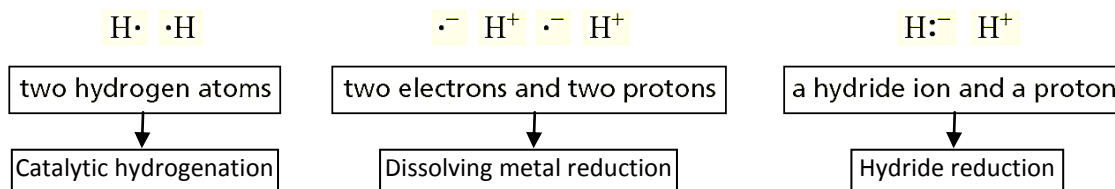


## 4.2. Reduction Reaction

In general, gain of one or more electrons by an atom is called reduction. However, in organic chemistry, reduction is defined as a gain of electron density by carbon, which is achieved either by bond formation between carbon and a less electronegative atom (usually hydrogen) or by bond-breaking between carbon and a more electronegative atom (usually O, N, or a halogen). In other words, in reduction reactions, number of C–H bonds increases and/or number of C–Z (where Z = O, N, or halogen) decreases.

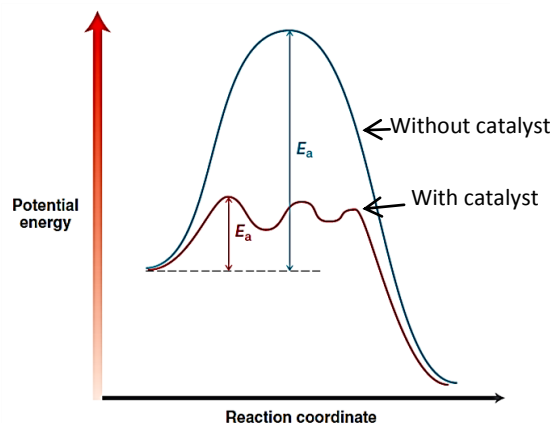


During reduction hydrogen is added in three different forms to the compound to be reduced corresponding three different mechanisms:



### 4.2.1. Catalytic Hydrogenation (Reduction by addition of two hydrogen atoms)

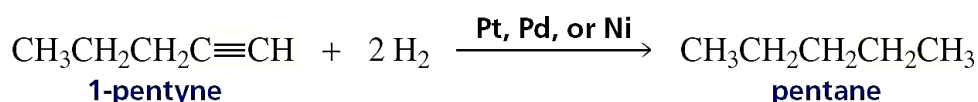
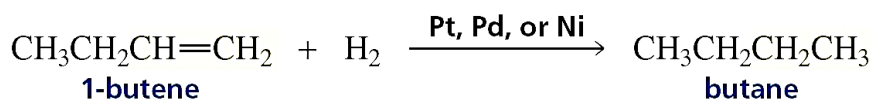
Catalytic hydrogenation is carried out by passing hydrogen, in the presence of catalyst to the unsaturated organic compounds to yield corresponding reduced products. The catalyst reduces the energy of activation of the reaction and hence allows the reaction to occur more rapidly. Without catalyst, the reaction pathway has a very high energy of activation and thus undergoes too slow to be of practical use. A number of metals are used as catalyst; the most widely used metals are palladium, nickel, platinum, and nickel. Platinum and palladium are used in finely divided state absorbed over charcoal (Pt/C or Pd/C) to



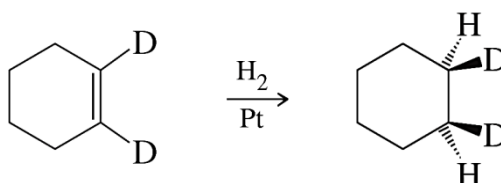
maximize surface area. Platinum is also used in the form of oxide ( $\text{PtO}_2$ ) and is then called as **Adam's catalyst**. Nickel is generally used at a higher temperature ( $\sim 300^\circ\text{C}$ ) and the reaction is called **Sabatier Senderens reaction**.

Different compounds are catalytically reduced by using selective catalyst, temperature, pressure, and solvent.

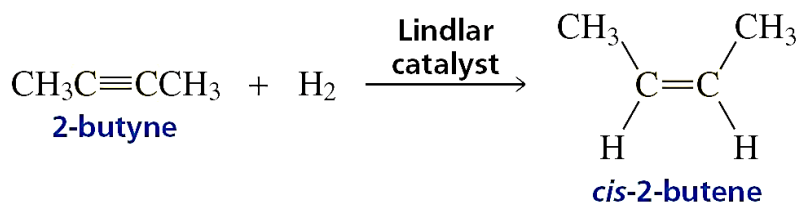
- **Alkene and alkyne** both are reduced to alkane by catalytic hydrogenation in presence of Pd, Pt, or Ni.



The hydrogenation generally occurs with *syn* stereochemistry; both hydrogens add to the double bond from the same face.



Partial hydrogenation of alkyne may be carried out by using specific catalysts/reagents, which results in the formation of alkenes with specific stereochemistry. For example, *cis*-alkene is formed if partially deactivated Lindlar's catalyst ( $\text{Pd}/\text{CaCO}_3$  in lead acetate poisoned with a small amount of quinoline) is used in the reaction. Quinoline partially deactivates ("poison") the catalyst making it a poor catalyst for alkene hydrogenation while retaining its ability to catalyze the addition of hydrogen to alkynes.

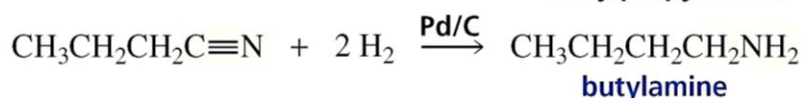
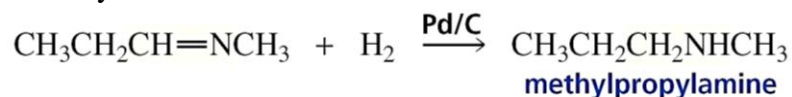


The hydrogenation of alkene or alkyne is exothermic reaction, and the energy released in the reaction is called heat of hydrogenation. More heat of hydrogenation of a compound means more easily it can be hydrogenated. The more alkyl substituents bonded to  $sp^2$  carbons of an alkene, the greater is its stability, and less is its heat of hydrogenation; means more substituted alkenes are less reactive for hydrogenation. The order of reactivity of substituted alkenes towards hydrogenation is:

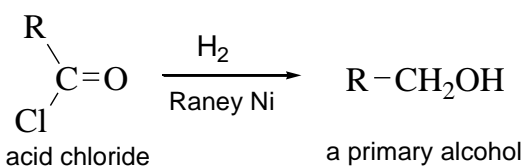
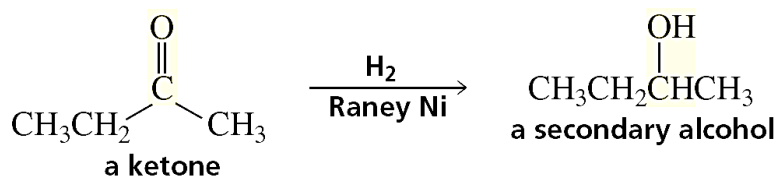
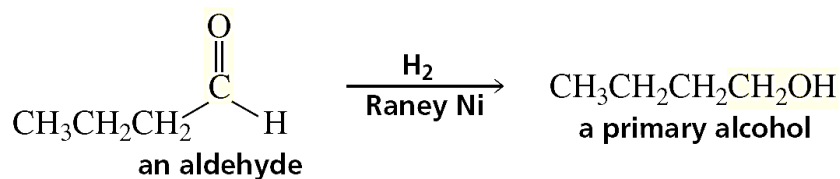
Ethene > mono-substituted alkene > *trans*-alkene (di-substituted) > *cis*-alkene (di-substituted) > tri-substituted alkene > tetra-substituted alkenes

The heat of hydrogenation of an alkyne is greater than twice the heat of hydrogenation of the derived alkene. Therefore, the first hydrogenation step of an alkyne is more exothermic than the second.

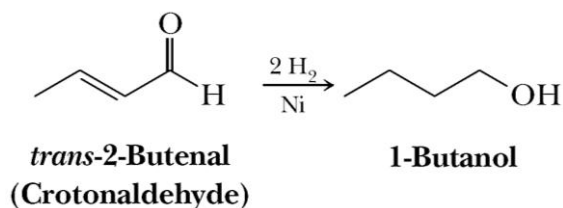
- Carbon-nitrogen double and triple bonds can be reduced by catalytic hydrogenation to yield amines:



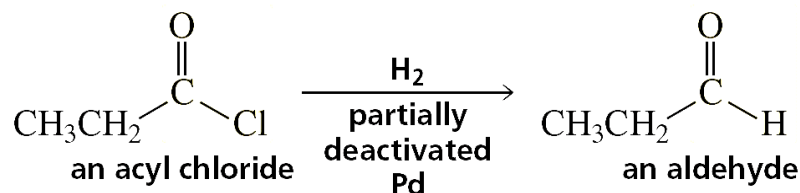
- Catalytic hydrogenation of carbonyl compounds is mostly carried out in presence of Raney nickel as a catalyst. Raney nickel is a finely divided hydrogen-bearing form of nickel made by treating a nickel–aluminum alloy with a strong sodium hydroxide solution. The aluminum in the alloy reacts to form hydrogen, leaving behind a finely divided nickel powder saturated with hydrogen. As it already has adsorbed hydrogen, so no external hydrogen is needed. Pt and Rh catalysts are also used for hydrogenation of aldehydes and ketones. Aldehydes and acid chlorides produce primary alcohols while ketones give secondary alcohols on hydrogenation.



Catalytic reduction of aldehydes and ketones is simple to carry out, yields are generally very high, and isolation of the final product is very easy. A disadvantage is that some other functional groups are also reduced under these conditions, for example, carbon-carbon double and triple bonds.



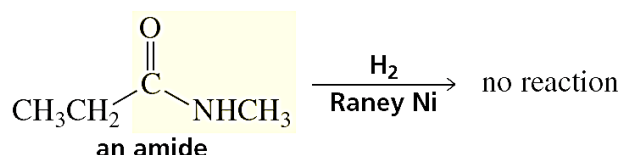
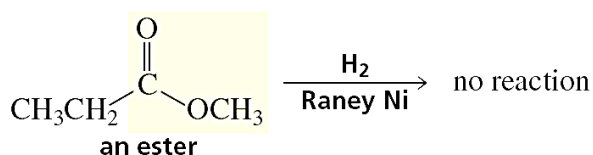
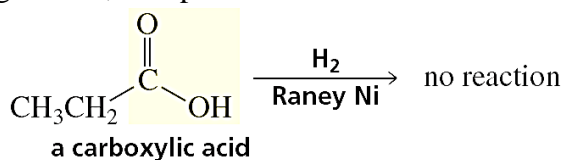
The reduction of acid chloride can be stopped at an aldehyde by using partially deactivated catalyst such as Pd catalyst supported over BaSO<sub>4</sub> and poisoned with little sulfur, which prevents further reduction of aldehyde to alcohol. The reaction is known as **Rosenmund reduction**.



- The order of reactivity of different functional groups towards catalytic hydrogenation is:

Acid chlorides > Alkyne > Aldehydes > Alkenes > Ketones > Nitriles > Imines

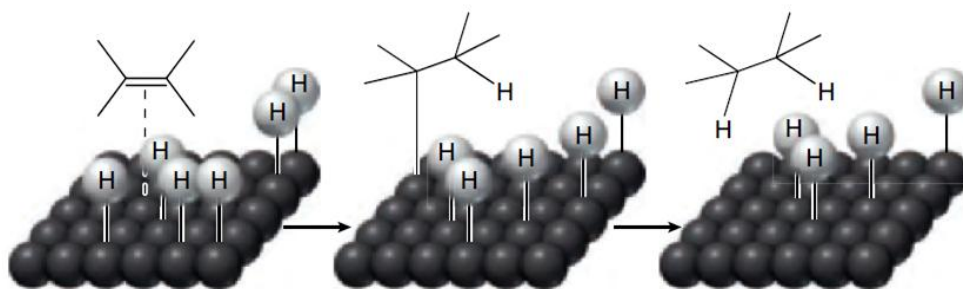
- Carboxylic acids, esters and amides are less reactive, and thus, cannot be reduced by catalytic hydrogenation, except under extreme conditions.



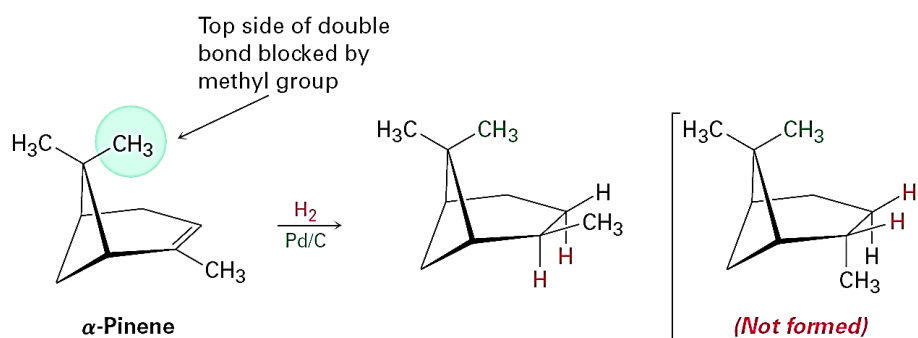
### Mechanism:

The process of hydrogenation is believed to begin with the interaction of hydrogen on the surface of metal catalyst, effectively breaking the H–H bonds and forming individual hydrogen atoms adsorbed to the surface of the metal. Then  $\pi$ -bond of the alkene coordinates with the metal surface, and that allows the reaction between the  $\pi$ -bond of alkene and two hydrogen atoms. As the alkane, so formed, no longer has any  $\pi$ -bond to complex with the metal, it is released from the catalyst surface. In this process two hydrogen atoms add to the same side of the alkene; that is called *syn* addition.



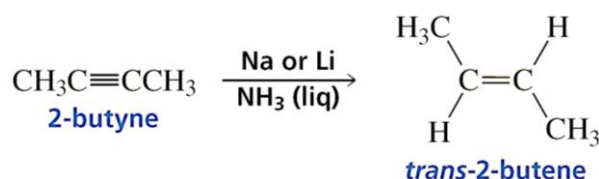


The reaction is extremely sensitive to the steric environment around the double bond. The less hindered side of the alkene makes complex with the metal. For example, in  $\alpha$ -pinene, the top side of the double bond is blocked by the methyl; therefore it complexes with the metal from downside and thus the hydrogenation also takes place exclusively from downside.



#### 4.2.2. Dissolving metal reduction (Reduction by addition of an electron, a proton, an electron and a proton)

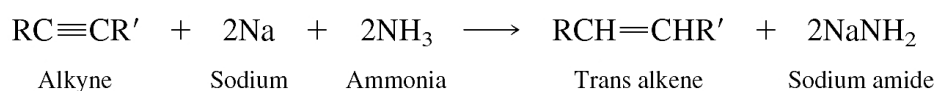
**Reduction of alkyne to *trans*-alkenes:** As described in previous section that alkynes are reduced to *cis*-alkenes by catalytic hydrogenation. Alkynes can be reduced to *trans*-alkenes also by using sodium or lithium metal in liquid ammonia. The reaction is called **dissolving metal reduction**.



Ammonia is a gas at room temperature (b.p.  $-33^\circ\text{C}$ ), so it is kept in the liquid state by using dry ice/acetone mixture, and the reaction is carried out at low temperature. When dissolved in liquid ammonia, sodium atom serves as a source of electrons and ammonia provides proton:

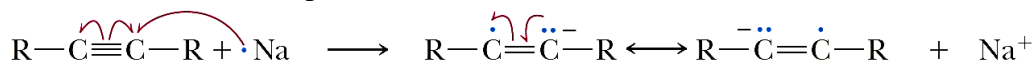


The overall reaction adds two electrons and two protons to the compound.



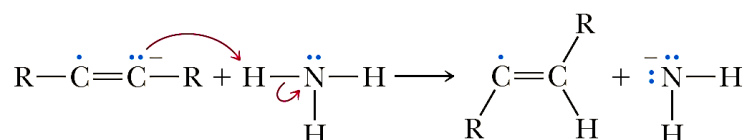
**Mechanism:**

**Step 1:** A single electron is transferred from the sodium atom to the alkyne, generating a radical anion intermediate. One carbon of alkyne carries negative charge while other contains an unpaired electron – thus called radical anion.



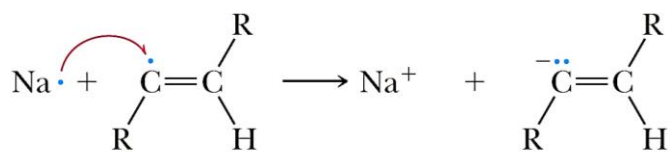
A resonance-stabilized alkenyl radical anion

**Step 2:** The anion radical is a strong base and removes  $\text{H}^+$  from ammonia to give an alkenyl radical.



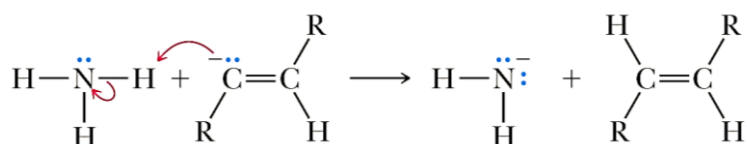
An alkenyl radical      Amide anion

**Step 3:** Another electron is transferred from the second sodium atom to the alkenyl radical, generating *trans*-alkenyl anion because *trans*-isomer is more stable than *cis*-isomer, and the stereochemistry of the final product is decided in this step.



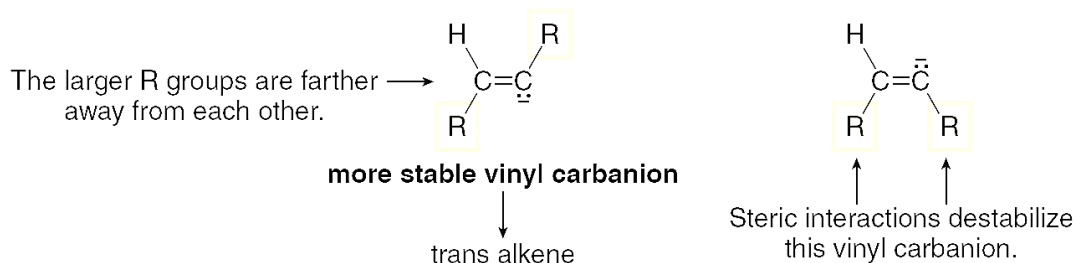
An alkenyl anion

**Step 4:** Alkenyl anion abstracts another proton from ammonia to give *trans*-alkene.

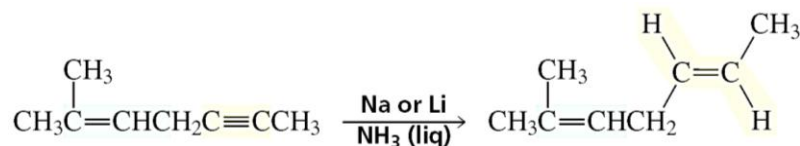


Amide anion      A *trans* alkene

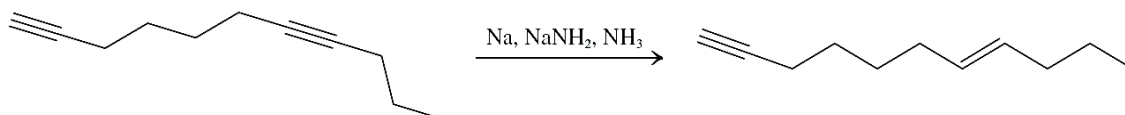
Dissolving metal reductions are stereoselective; they always form the more stable *trans* product preferentially, because *trans*-isomer is more stable than *cis*-isomer.



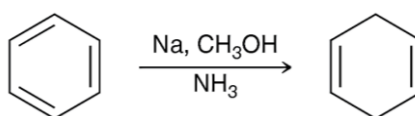
Sodium (or lithium) in liquid ammonia cannot reduce a carbon-carbon double bond, making it useful for reducing a triple bond in a compound that also contains a double bond.



Also it does not reduce terminal alkynes.



**Birch reduction:** Benzene and its derivatives can also be reduced to non-conjugated cyclohexa-1,4-dienes by treatment with sodium or lithium in a mixture of liquid ammonia and an alcohol.

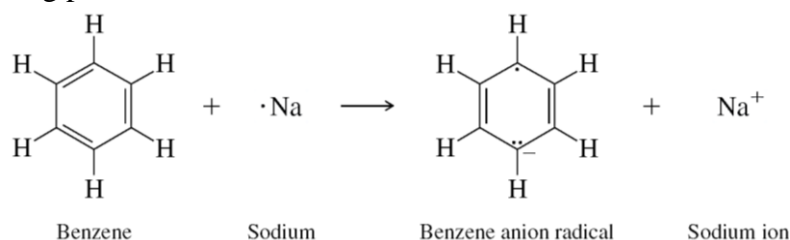


These metal-ammonia-alcohol reductions of aromatic rings are called **Birch reductions**. The Birch reduction not only provides a method to prepare dienes from arenes, which cannot be accomplished by catalytic hydrogenation, but also gives a non-conjugated diene system rather than the more stable conjugated one.

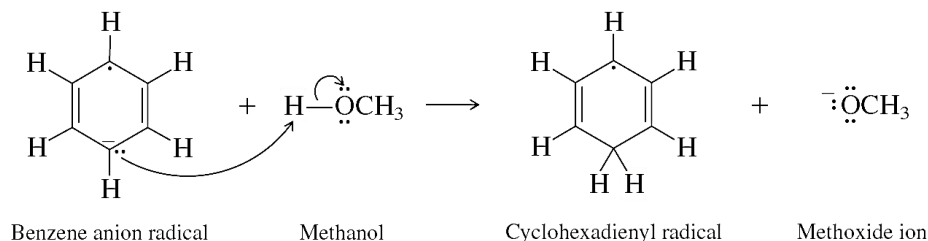
### Mechanism:

Mechanism of Birch reduction is analogous to the mechanism of dissolving metal reduction of alkyne. In this case the proton is provided by the alcohol instead of ammonia.

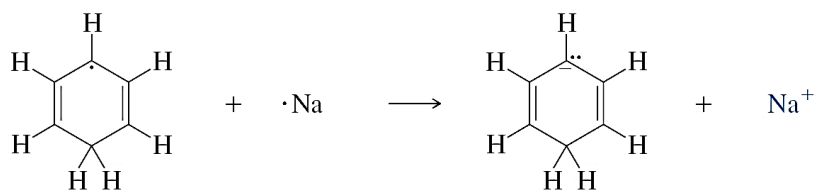
*Step 1:* Transfer of an electron from sodium (the reducing agent) to the  $\pi$ -system of the aromatic ring produces an anion radical.



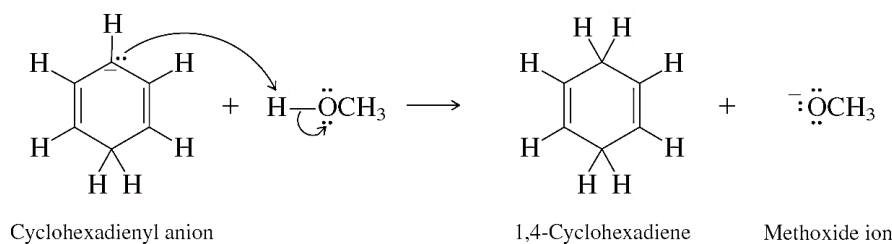
*Step 2:* Radical anion abstracts a proton from methanol to form cyclohexadienyl radical.



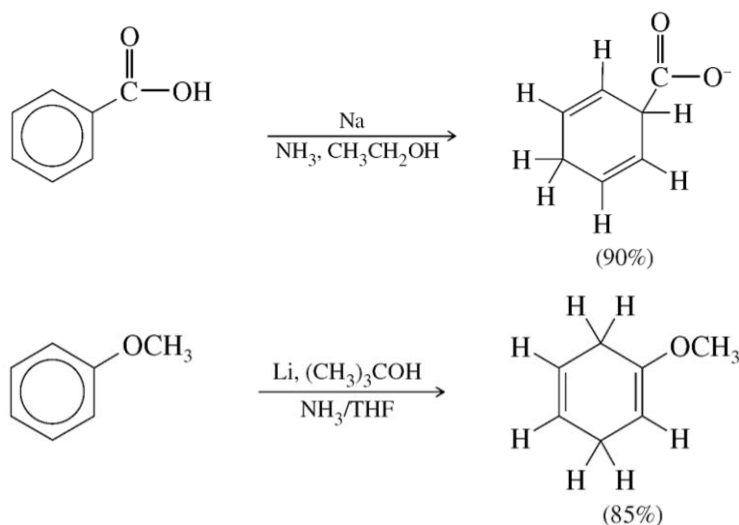
*Step 3:* Transfer of another electron from sodium to cyclohexadienyl radical converts it to cyclohexadienyl anion.



*Step 4:* Transfer of another proton from methanol produces the final product 1,4-cyclohexadiene.

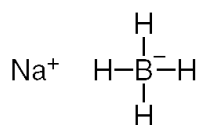


Electron-withdrawing substituents stabilize the carbanions, while electron-donating substituents destabilize them. Therefore, reduction takes place on carbon atoms bearing electron-withdrawing substituents (such as those containing carbonyl groups) and not on carbon atoms bearing electron-releasing substituents (such as alkyl or alkoxy groups).

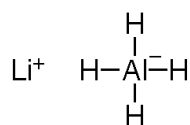


#### 4.2.3. Hydride Reduction (Reduction by addition of a hydride ion and a proton)

The third way of reducing a compound is the addition of hydride (H<sup>-</sup>) and a proton (H<sup>+</sup>). The most common hydride reducing agents contain hydrogen bonded to boron or aluminum, for example, **sodium borohydride (NaBH<sub>4</sub>)** and **lithium aluminum hydride (LiAlH<sub>4</sub>)**. These reagents provide hydride (H<sup>-</sup>) and thereby behave as a nucleophile. Thereafter, a proton is added from the solvent (H<sub>2</sub>O or an alcohol).

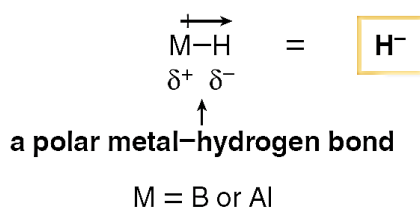


sodium borohydride



lithium aluminum hydride

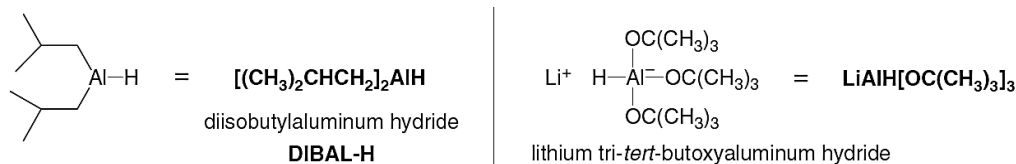
Metal hydride reagents act as a source of  $\text{H}^-$  because they contain polar metal–hydrogen bonds that place a partial negative charge on hydrogen.



Aluminum is less electronegative than boron, so more of the negative charge in the  $\text{AlH}_4^-$  is borne by the hydrogen atoms. Therefore, lithium aluminum hydride ( $\text{LiAlH}_4$ ) is more powerful reducing agent than sodium borohydride ( $\text{NaBH}_4$ ) and it is much more difficult to work with than sodium borohydride. Lithium aluminum hydride reacts violently with water, alcohols, and other protic solvents to liberate hydrogen gas and form metal hydroxides and alkoxides. Therefore, reductions of aldehydes and ketones using this reagent must be carried out in aprotic solvents, most commonly diethyl ether or tetrahydrofuran. Sodium borohydride is safer to use as it reacts very slowly with water or alcohol. Therefore, reductions using sodium borohydride are most commonly carried out in aqueous methanol, in pure methanol, or in ethanol. Both  $\text{LiAlH}_4$  and  $\text{NaBH}_4$  can be used to reduce reactive carbonyl compounds like aldehyde, ketones and acid halides, but less reactive carbonyl compounds like carboxylic acids, amides, esters can be reduced only by using  $\text{LiAlH}_4$ ; they cannot be reduced with milder reducing agents like  $\text{NaBH}_4$ . Therefore,  $\text{NaBH}_4$  being safer is generally used to reduce aldehydes, ketones, and acid halides, while  $\text{LiAlH}_4$  being more reactive is used to reduce carboxylic acids, esters, and amides.

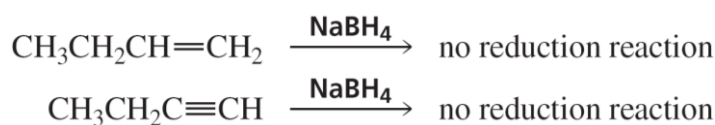
Two other milder reagents are used to reduce these compounds.

- **Diisobutylaluminum hydride** (abbreviated as DIBAL-H), is less reactive than  $\text{LiAlH}_4$  because of the two bulky isobutyl groups. Unlike  $\text{LiAlH}_4$ , which provides four H atom for reduction, DIBAL-H gives only one H atom for reduction.
- **Lithium tri-*tert*-butoxyaluminum hydride** is less nucleophilic than  $\text{LiAlH}_4$ . The three hydrogen atoms of  $\text{LiAlH}_4$  are replaced by  $-\text{OR}$  groups, which decreases its nucleophilic activity. Three electronegative oxygen atoms bonded to aluminum makes aluminum more electronegative and thus reduce electron density on hydride ion.



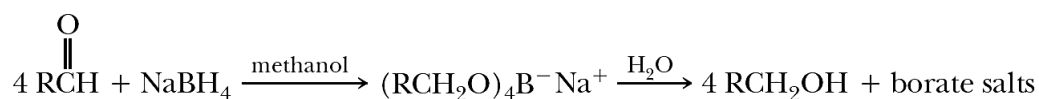
$\text{LiAlH}_4$  is a strong, non-selective reducing agent.  $\text{NaBH}_4$ , DIBAL-H and Lithium tri-*tert*-butoxyaluminum hydride are milder, more selective reducing agents.

Alkenes and alkynes are generally not affected by metal hydride reducing agents. These reagents function as hydride ion donors, that is, as nucleophiles, and alkenes and alkynes are not attacked by nucleophiles.



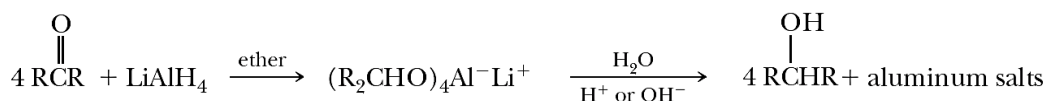
- Reduction of aldehydes, ketones and acid halides (or acyl halides) to alcohol - Aldehydes, ketones, and acid halides can be reduced either by  $\text{LiAlH}_4$  or  $\text{NaBH}_4$ . But sodium borohydride is generally used for this purpose because it is milder, selective and much safer than  $\text{LiAlH}_4$ .

Reductions using sodium borohydride are most commonly carried out in aqueous methanol, in pure methanol, or in ethanol. The initial product of reduction is a tetraalkyl borate, which, on warming with water, is converted to an alcohol and sodium borate salts. One mole of sodium borohydride reduces four moles of aldehyde or ketone.



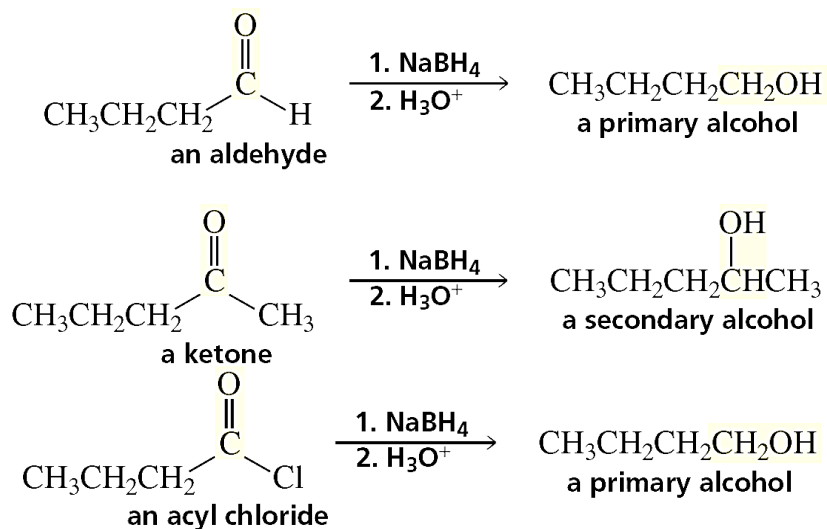
A tetraalkyl borate

In case of lithium aluminum hydride, the reaction is carried out in aprotic solvents, generally diethyl ether or tetrahydrofuran. One mole of lithium aluminum hydride reduces four moles of aldehyde or ketone. After reduction, a separate hydrolysis step is required to liberate the alcohol product. Because of the formation of gelatinous aluminum salts, aqueous acid or base work-up is usually used to dissolve these salts.

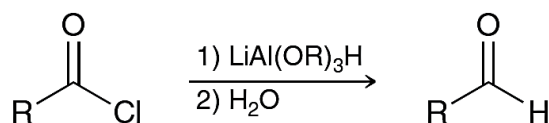


A tetraalkyl aluminate

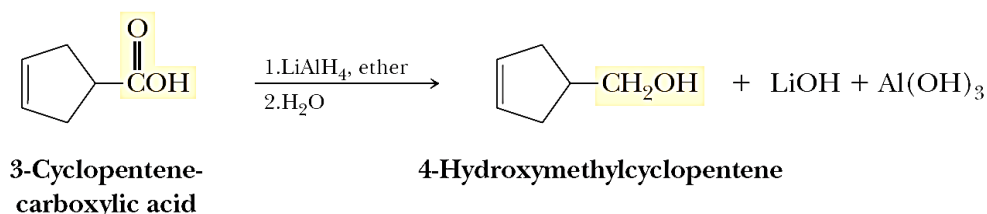
On reduction with  $\text{LiAlH}_4$  or  $\text{NaBH}_4$ , aldehydes and acid halides produce primary alcohol, while ketones give secondary alcohol.



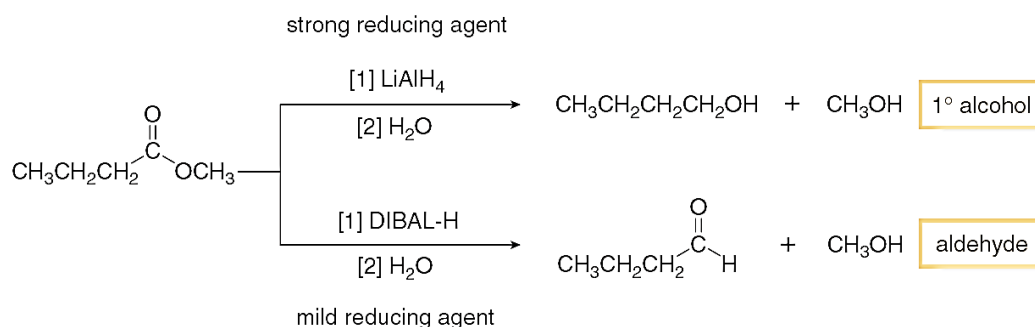
- Reduction of acid chloride to aldehyde – Strong reducing agents like  $\text{LiAlH}_4$  reduce acid chlorides all the way to primary alcohols. Lithium tri-*tert*-butoxyaluminum hydride is a milder reducing agent that reacts faster with acid chlorides than with aldehydes. Reduction of acid chlorides with lithium tri-*tert*-butoxyaluminum hydride gives good yields of aldehydes.



- Reduction of carboxylic acid to alcohol - Lithium aluminum hydride,  $\text{LiAlH}_4$  (LAH), reduces a carboxylic acid to a primary alcohol in excellent yield, although heating is required. LAH is usually dissolved in diethyl ether or tetrahydrofuran (THF). When carboxylic acids react with  $\text{LiAlH}_4$ , the initial product is a tetraalkoxy aluminate ion, which is then treated with water to give the primary alcohol and lithium and aluminum hydroxides. These hydroxides are insoluble in diethyl ether and THF and are removed by filtration. Evaporation of the solvent then yields the primary alcohol.



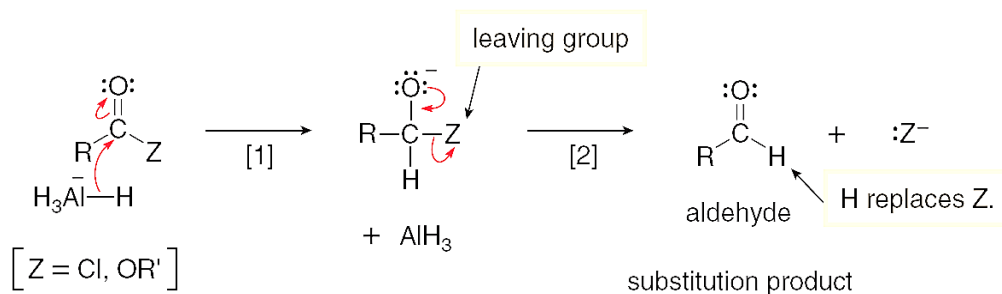
- Reduction of an ester to alcohol or aldehyde – Esters are more easily reduced than carboxylic acids. Depending on the reducing agent, esters give either primary alcohols or aldehyde. When treated with  $\text{LiAlH}_4$ , a strong reducing agent, acyl group of ester is cleaved to produce two alcohols, while diisobutylaluminum hydride,  $[(\text{CH}_3)_2\text{CHCH}_2]_2\text{AlH}$  abbreviated as DIBAL-H, a mild reducing agent reduces ester to aldehyde.



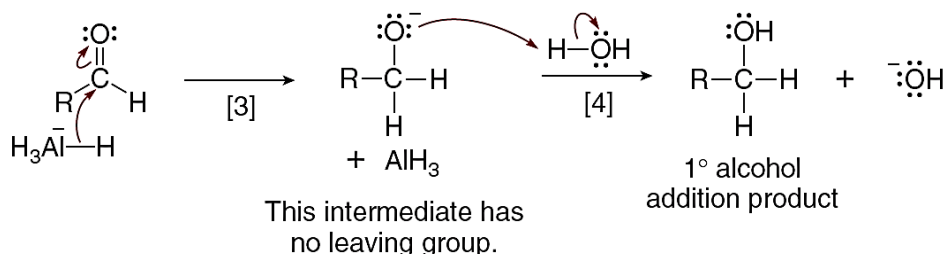
In the reaction,  $\text{CH}_3\text{O}^-$  comes off as a leaving group, which on protonation gives alcohol.

### Mechanism of reduction of acid chloride and ester by $\text{LiAlH}_4$ :

**Part 1:** Nucleophilic substitution forms an aldehyde.



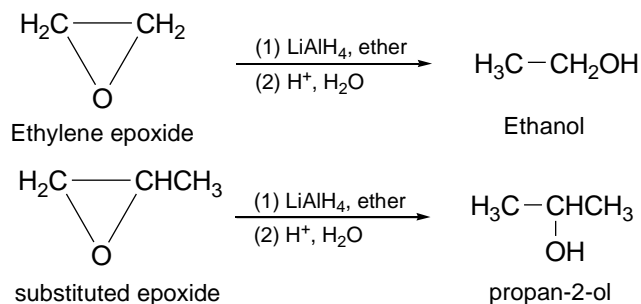
**Part 2:** Nucleophilic addition forms a primary alcohol.



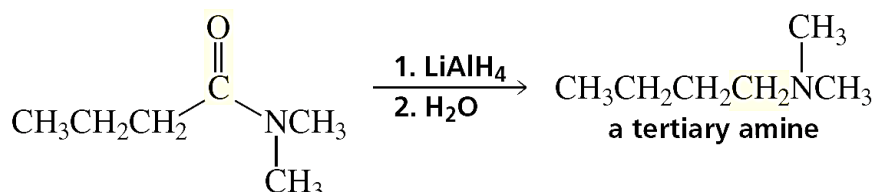
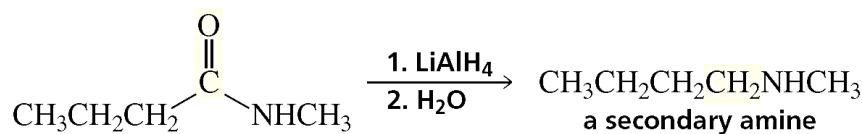
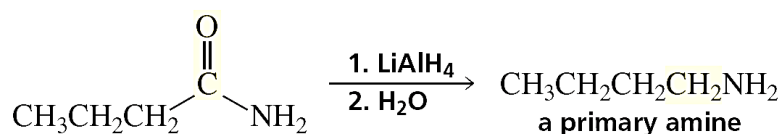
First part of the reaction ended with the formation of aldehyde. If the reaction is carried out by using  $\text{LiAlH}_4$ , a strong reducing agent, aldehyde is further reduced to form an alcohol. However, when DIBAL-H, a mild reducing agent, is used at a low temperature the reduction of the ester can be stopped after the addition of one equivalent of hydride ion. The reaction is carried out at  $-78^\circ\text{C}$  to avoid further reduction of aldehyde to alcohol. Hence the final products are an aldehyde and an alcohol (formed by protonation of  $\text{CH}_3\text{O}^-$ , a leaving group).

- Reduction of epoxide to an alcohol – On treatment with  $\text{LiAlH}_4$ , ethylene epoxide is reduced to primary alcohol while substituted epoxides are reduced to secondary alcohols because the hydride ion attacks preferentially at the less hindered carbon of epoxide, consistent with  $\text{S}_{\text{N}}2$  mechanism.



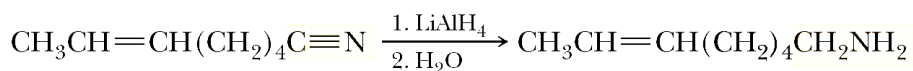


- Reduction of amides – Unlike the  $\text{LiAlH}_4$  reduction of other carboxylic acid derivatives, which results in the formation of primary alcohols, the  $\text{LiAlH}_4$  reduces amides to  $1^\circ$ ,  $2^\circ$  and  $3^\circ$  amines depending upon the degree of substitution of the amide. Both  $\text{C} \text{---} \text{O}$  bonds are reduced to  $\text{C} \text{---} \text{H}$  bonds. Because  $\text{---NH}_2$  (or  $\text{---NHR}$  or  $\text{---NR}_2$ ) are poor leaving group, it remain intact during the reaction and therefore the final product is amine.



This is widely used method for the synthesis of amines as the yield is very good with no side products.

- Reduction of nitriles to primary amines – Nitriles are reduced to primary amines by using  $\text{LiAlH}_4$  as reducing agent.

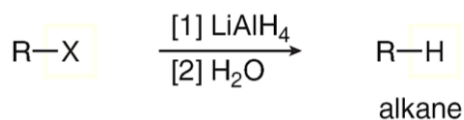


**6-Octenenitrile**

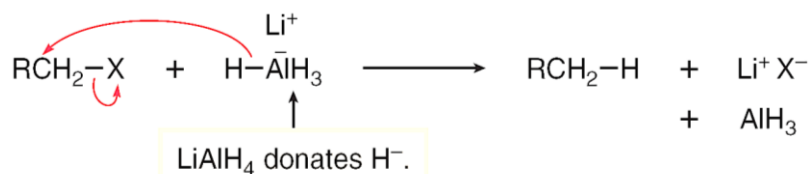
**6-Octen-1-amine**

This is an important method for the preparation of amines and is used for increasing the length of carbon chain during the synthesis of amine from haloalkanes; alkyl halides are converted to nitriles by the reaction with  $\text{KCN}$  (or  $\text{NaCN}$ ), thereafter nitriles are reduced by catalytic hydrogenation or by  $\text{LiAlH}_4$  to amines.

- Reduction of haloalkanes to alkanes – Haloalkanes are reduced, by using  $\text{LiAlH}_4$ , to alkanes with the loss of halide ion ( $\text{X}^-$ ) as a leaving group.

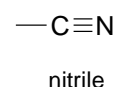
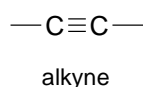
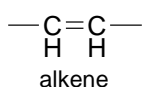
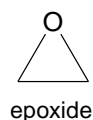
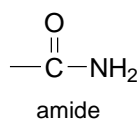
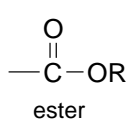
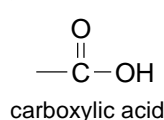


Because  $\text{H}^-$  is strong nucleophile, the reaction follows one-step  $\text{S}_{\text{N}}2$  mechanism.

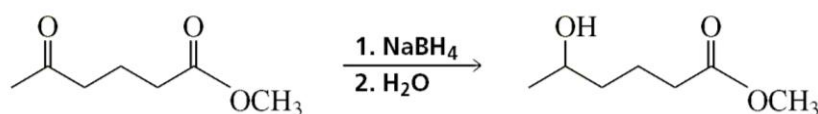


### Selective reductions

- ✓ Sodium borohydride cannot reduce following groups:



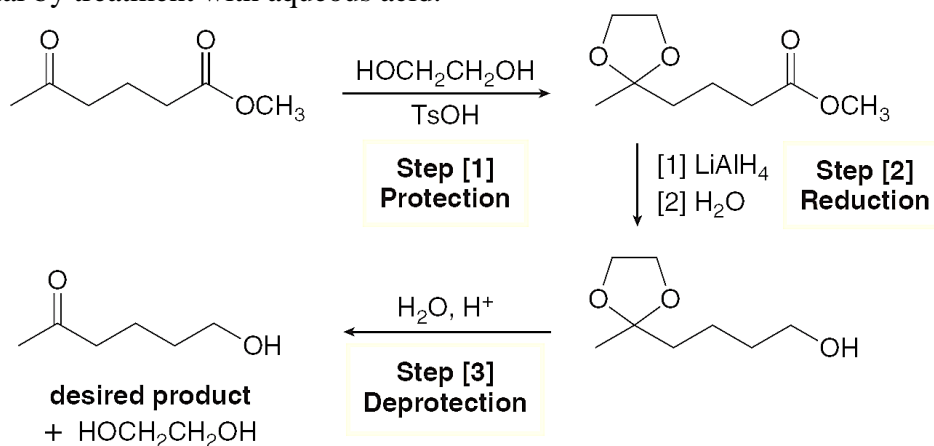
Therefore, it can be used to selectively reduce an aldehyde or a ketone group in a compound that also contains a less reactive group. Acid is not used in the second step of the following reaction, in order to avoid hydrolysis of the ester:



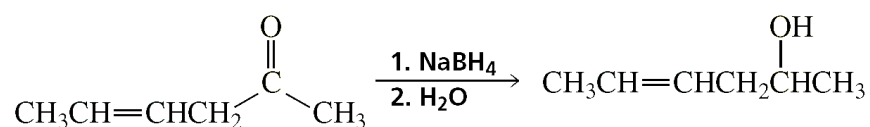
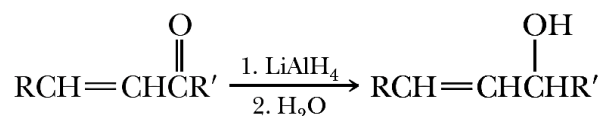
Note →  $\text{LiAlH}_4$  would reduce both keto and ester functions.

- ✓ The selective reduction of ester is not possible when the compound contains keto or aldehyde functions because aldehydes and ketones are more reactive so they will be reduced first.

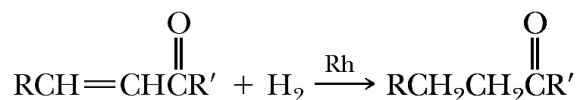
Acetals are unreactive to bases, hydride reducing agents, Grignard reagents, catalytic hydrogenation conditions, but they are cleaved by acids. Therefore, the selective reduction of ester group is accomplished by first protecting the keto group as an acetal, then reducing the ester with  $\text{LiAlH}_4$ , and then removing the acetal by treatment with aqueous acid.



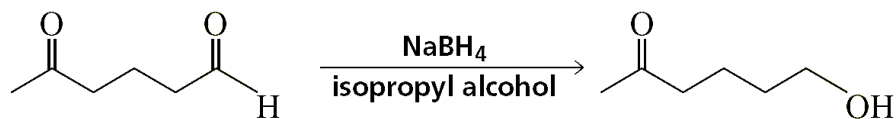
- ✓ The metal hydride reducing agents like  $\text{LiAlH}_4$  and  $\text{NaBH}_4$  being nucleophilic reagent cannot reduce alkenes and alkynes because they are not electrophiles. Therefore, selective reduction of a carbonyl group in presence of a carbon-carbon double or triple bonds can be carried out by using metal hydrides without affecting multiple bonds as long as they are not conjugated.



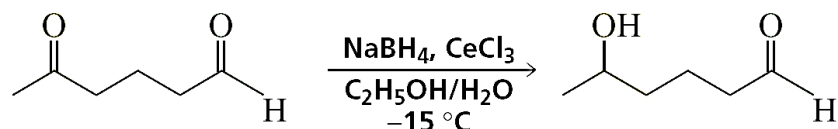
- ✓ Selective reduction of a carbon-carbon double in presence of carbonyl group can be achieved by using rhodium on powdered charcoal as a catalyst.



- ✓ A **chemoselective reaction** is a reaction in which a reagent reacts with one functional group in preference to another. For example,  $\text{NaBH}_4$  in isopropyl alcohol reduces aldehydes faster than it reduces ketones.



On the other hand, ketones are reduced faster than aldehyde with  $\text{NaBH}_4$  in aqueous ethanol at  $-15^\circ\text{C}$  in presence of cerium trichloride.



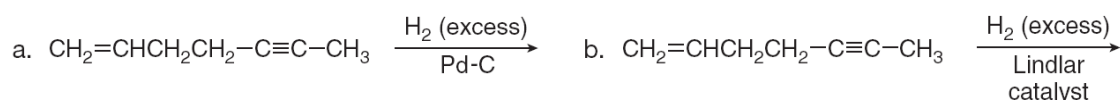
### 4.3. Summary

- Oxidation is coupled with reduction: A reducing agent is oxidized and an oxidizing agent is reduced.
- *Oxidation* results in an *increase* in the number of C-Z bonds (usually C-O bonds) or a *decrease* in the number of C-H bonds.
- *Reduction* results in a *decrease* in the number of C-Z bonds (usually C-O bonds) or an *increase* in the number of C-H bonds.
- The oxidation state of a carbon atom equals the total number of its C-O, C-N and C-X bonds.

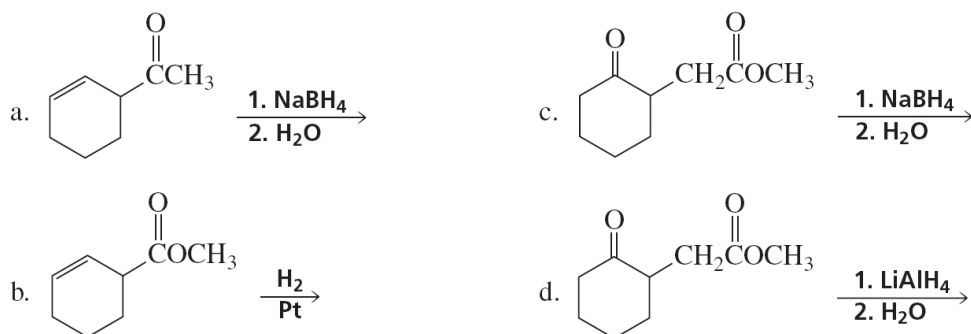
- An organic compound is reduced by the addition of by one of three mechanisms: Catalytic hydrogenations add two hydrogen atoms, dissolving metal reductions add two electrons and two protons, and metal hydride reductions involve the addition of a hydride ion followed by a proton.
- Multiple bonds can be reduced by catalytic hydrogenation.
- An alkyne is reduced by sodium and liquid ammonia to a trans alkene
- $\text{LiAlH}_4$  is stronger reducing agent than  $\text{NaBH}_4$ .
- $\text{NaBH}_4$  is used to reduce aldehydes, ketones, and acyl halides;  $\text{LiAlH}_4$  is used to reduce carboxylic acids, esters, and amides.
- Primary alcohols are oxidized to carboxylic acids by chromium-containing reagents and to aldehydes by PCC or a Swern oxidation.
- A peroxyacid oxidizes an aldehyde to a carboxylic acid, a ketone to an ester (in a Baeyer–Villiger oxidation), and an alkene to an epoxide.
- A regioselective reaction forms predominantly or exclusively one constitutional isomer
- A stereoselective reaction forms predominantly or exclusively one stereoisomer.
- An *enantioselective* reaction affords predominantly or exclusively one enantiomer.
- Alkenes are oxidized to 1,2-diols by potassium permanganate ( $\text{KMnO}_4$ ) in a cold basic solution or by osmium tetroxide ( $\text{OsO}_4$ ).

## 4.4. Exercise

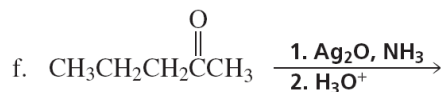
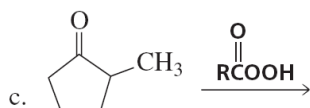
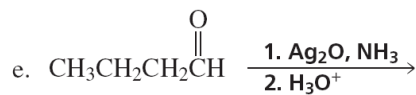
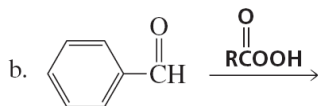
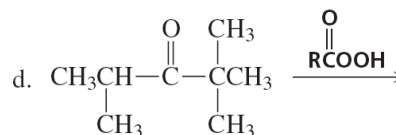
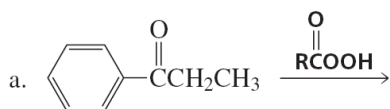
4.4.1. Draw the organic products formed in each hydrogenation.



4.4.2. Give the products of the following reactions.



4.4.3. Give the products of the following reactions:



4.4.4. What stereoisomers would be formed from the reaction of each of the following alkenes with  $\text{OsO}_4$  followed by  $\text{H}_2\text{O}_2$ ?

- (a) *trans*-2-butene
- (b) *cis*-2-butene
- (c) *cis*-2-pentene
- (d) *trans*-2-pentene