Reactions of Ketones and Aldehydes

Nucleophilic Addition

The most characteristic reaction of aldehydes and ketones is *nucleophilic addition* to the carbon-oxygen double bond.

\[
\text{Aldehyde/Keotne} \quad \xrightarrow{\text{Nu, H}} \quad \text{Nu, H are added}
\]
The nucleophile can be neutral or negatively charged.

Neutral (H-Nu:)

Water
\[
\begin{align*}
H & \quad \text{O} \\
& \quad \text{H}
\end{align*}
\]

Alcohol
\[
\begin{align*}
R & \quad \text{O} \\
& \quad \text{H}
\end{align*}
\]

Amines
\[
\begin{align*}
R_1 & \quad \text{N} \\
& \quad \text{H} \\
\end{align*}
\]

Negatively charged (Nu:\-)

Hydroxide
\[
\begin{align*}
\text{H} & \quad \text{O}\- \\
&
\end{align*}
\]

Hydride
\[
\begin{align*}
\text{H} & \\
& \quad \Theta
\end{align*}
\]

Carbanion
\[
\begin{align*}
\text{R} & \quad \Theta \\
&
\end{align*}
\]

Alkoxide
\[
\begin{align*}
\text{R} & \quad \text{O}\- \\
&
\end{align*}
\]

Acetylide
\[
\begin{align*}
\text{R} & \quad \text{H} \\
& \quad \Theta
\end{align*}
\]

Ylide
\[
\begin{align*}
\text{Ph} & \quad \text{H} \\
& \quad \Theta \\
\text{Ph} & \quad \Theta \\
& \quad \text{Ph}
\end{align*}
\]
Reaction of Organometallic Reagents with Aldehydes and Ketones

Treatment of an aldehyde or ketone with a Grignard reagent, organolithium and sodium (lithium) acetylide followed by an acid treatment gives an alcohol.

Grignard reagent (\( :R^\ominus \text{Mg}^2\oplus :X^\ominus \) )

Organolithium (\( :R^\ominus \text{Li}^\oplus \) )

Sodium acetylide (\( R\overset{\equiv}{\cdots}^\ominus \text{Na}^\oplus \) )
General reaction

Aldehyde/Ketone + $\text{R}^-$ Mg$^{2+}$ $\text{X}^-$ or $\text{R}^-$ Li$^+$

Alkoxide

Alcohol ($1^0, 2^0$ or $3^0$)

Aldehyde/Ketone + $\text{R}^-\text{Na}^+$

Alkoxide

Alcohol ($1^0, 2^0$ or $3^0$)
I. Addition of the organometalics to formaldehyde (CH$_2$=O) forms a 1° alcohol.

II. Addition of the organometalics to all other aldehydes forms a 2° alcohol.

III. Addition of the organometalics to ketones forms a 3° alcohol.
Preparation of Organometallics

Grignard reagent ( \( :R^- \text{Mg}^2^+ :X^- \) )

\[
\text{R} \equiv \text{X} + \text{Mg} \xrightarrow{\text{Et}_2\text{O}} :R^- \text{Mg}^2^+ :X^- \\
\text{Alkyl halide}
\]

Organolithium ( \( :R^- \text{Li}^+ \) )

\[
\text{R} \equiv \text{X} + 2\text{Li} \xrightarrow{\text{THF}} :R^- \text{Li}^+ + \text{LiX} \\
\text{Alkyl halide}
\]

Sodium acetylide ( \( \text{R} \equiv \equiv :^\ominus \text{Na}^+ \) )

\[
\text{R} \equiv \equiv \equiv \text{H} + \text{NaNH}_2 \xrightarrow{\text{NH}_3} \text{R} \equiv \equiv :^\ominus \text{Na}^+ \\
\text{Acidic hydrogen}
\]
Organometallic Reagents

Organometallic reagents contain a carbon atom bonded to a metal.

Because metals are more electropositive (less electronegative) than carbon, they donate electron density towards carbon, so that carbon bears a partial negative charge.
The more polar the carbon–metal bond, the more reactive the organometallic reagent. Electronegativity values for carbon and the common metals in R – M reagents are C (2.5), Na (0.93), Li (1.0), Mg (1.3), and Cu (1.8).

Because Na, Li and Mg are very electropositive metals, organomagnesium reagents (RMgX), organolithium (RLi) and acetylide R-C≡CNa) contain very polar carbon–metal bonds and are therefore very reactive reagents.
Organocopper reagents (R$_2$CuLi), also called organocuprates, have a less polar carbon–metal bond and are therefore less reactive.

Regardless of the metal, organometallic reagents are useful synthetically because they react as if they were free carbanions; that is, carbon bears a negative charge, so the reagents react as bases and nucleophiles.

\[ R \text{--M} \text{ reacts like } R^- \text{--M}^+ \]

carbanion

a base and a nucleophile
Examples

1. CH₃CH₂Li, THF
2. H₃O⁺

1. H₃C≡C⁻Na⁺
2. H₃O⁺
I. What Grignard reagent and carbonyl compound can be used to prepare the antidepressant venlafaxine?

II. Synthesize isopropylcyclopentane from alcohols having ≤ 5 C’s.
III. Predict the principal organic product of each of the following reactions:

a) \[
\text{[Structural formula]}
\]
\[\text{Na}^+ : \text{C} \equiv \text{CH}\]
\[\text{H}_3\text{O}^+\]

b) \[
\text{[Structural formula]}
\]
\[\text{Mg, Et}_2\text{O}\]
\[\text{H}_3\text{O}^+\]

IV. Show the mechanism of the following transformation
V. Design a stepwise synthesis to convert cyclopentanone and 4-bromobutanal to the hydroxy aldehyde A.

\[
\text{cyclopentanone} + \text{Br} - \text{hydroxycyclopentyl} \rightarrow \text{A}
\]

VI. Show how 1-(1-hydroxycyclopentyl)ethanone can be synthesized from cyclopentanone by providing all the reagents and intermediates.

\[
\text{Cyclopentanone} \rightarrow \text{hydroxy aldehyde} \rightarrow \text{1-(1-Hydroxycyclopentyl)ethanone}
\]
**Nucleophilic Addition of Hydride Reagents: Alcohol Formation**

Treating an aldehyde or a ketone with NaBH₄ or LiAlH₄, followed by water or some other proton source, affords an alcohol.
Sodium borohydride (NaBH₄) and lithium aluminum hydride (LiAlH₄) contain a polar metal-hydrogen bond that serves as a source of the nucleophile hydride, H:-.

LiAlH₄ is a stronger reducing agent than NaBH₄, because the Al–H bond is more polar than the B–H bond, aluminum is more electropositive than boron.

NaBH₄ selectively reduces aldehydes and ketones in the presence of most other functional groups. Reductions with NaBH₄ are typically carried out in CH₃OH as solvent. LiAlH₄ reduces aldehydes and ketones and many other functional groups as well.
Sodium borohydride is usually preferred over lithium aluminium hydride for the reduction of aldehydes and ketones. Sodium borohydride can be used safely and effectively in water as well as alcohol solvents, whereas special precautions are required when using lithium aluminium hydride.

The key step in the reduction of a carbonyl compound by either lithium aluminium hydride or sodium borohydride is the transfer of a hydride ion from the metal to the carbonyl carbon.
Mechanism

\[ \text{H} \quad \text{O} \quad \text{H} \]

1. LiAlH_4, ether

\[ \text{H} \quad \text{O} \quad \text{H} \]

2. H_3O^+

\[ \text{H} \quad \text{H} \quad \text{H} \]
Catalytic hydrogenation also reduces aldehydes and ketones to alcohols, using $\text{H}_2$ and Pd-C (or another metal catalyst). $\text{H}_2$ adds to the C=O in much the same way that it adds to the C=C of an alkene.

When a compound contains both a carbonyl group and a carbon–carbon double bond, selective reduction of one functional group can be achieved by proper choice of reagent.
A C=O is readily reduced with NaBH₄ and LiAlH₄, but a C=C is inert.

A C=O is reduced faster than a C=O with H₂ (Pd-C).
Assignment 9

Draw the products formed when

\[
\begin{align*}
o & \\
\text{is treated with each reagent:} \\
\text{a) } & \text{LiAlH}_4, \text{ then H}_2\text{O;} \\
\text{b) } & \text{NaBH}_4 \text{ in CH}_3\text{OH;} \\
\text{c) } & \text{H}_2 (1 \text{ equiv}), \text{ Pd-C;} \\
\text{d) } & \text{H}_2 (\text{excess}), \text{ Pd-C;} \\
\text{e) } & \text{NaBH}_4 (\text{excess}) \text{ in CH}_3\text{OH}
\end{align*}
\]
Nucleophilic Addition of Water: Hydrate Formation

Treatment of aldehydes and ketones with $\text{H}_2\text{O}$ in the presence of an acid or base catalyst adds the elements of H and OH across the carbon-oxygen $\pi$ bond, forming a geminal (gem) diol or hydrate.

Many nucleophilic additions to carbon-oxygen double bonds are reversible. The position of the equilibrium between hydrate and aldehyde/ketone depends on the structure of the carbonyl compound.
In most cases the equilibrium strongly favors the carbonyl compound.

Hydration of a carbonyl group gives a good yield of hydrate only with an unhindered aldehyde like formaldehyde, and with aldehydes containing nearby electron-withdrawing groups.
Whether addition of \( \text{H}_2\text{O} \) to a carbonyl group affords a good yield of the hydrate depends on the stabilities of the starting material and the product. With less stable carbonyl starting materials, equilibrium favors the hydrate product, whereas with more stable carbonyl starting materials, equilibrium favors the carbonyl starting material.
Electron-donating groups near the carbonyl carbon stabilize the carbonyl group, decreasing the amount of the hydrate at equilibrium.

Electron-withdrawing groups near the carbonyl carbon destabilize the carbonyl group, increasing the amount of hydrate at equilibrium.
Applications of hydrides

PRESERVING BIOLOGICAL SPECIMENS
A 37% solution of formaldehyde in water is known as formalin—commonly used to preserve biological specimens.
Forensic chemistry

Ninhydrin is probably the most widely used method for developing latent fingerprints on porous surfaces such as paper.

Ninhydrin can be applied to various surfaces to make fingerprints visible. The chemical reacts with amino acids and thus makes the residue from a finger detectable.
The nucleophilic addition of water to aldehydes and ketones is slow in pure water but is catalyzed by either a base or an acid.

**Base Catalyzed Hydration**

\[
\begin{align*}
\text{Base} & \quad \overset{\Theta}{\text{OH}} \quad \text{R}_1 \quad \text{R}_2 \\
\text{Alkoxide} & \quad \Theta:O: \quad \text{R}_1 \quad \text{R}_2 \\
\text{H}_2\text{O} & \quad \Theta:O: \quad \text{R}_1 \quad \text{R}_2 + \Theta:OH
\end{align*}
\]
Acid Catalyzed Hydration

\[
\text{Aldehyde/Ketone} \quad \xrightarrow{\text{H}^+} \quad \text{Oxonium ion} \quad \text{H}_2\text{O}^-
\]

\[
\begin{align*}
\text{R}_1 & \quad \text{O}^+ \quad \text{H}^- \\
\text{R}_2 & \quad \text{H}^- \\
\end{align*}
\]

\[
\begin{align*}
\text{R}_1 & \quad \text{O}^+ \quad \text{H}^- \\
\text{R}_2 & \quad \text{H}^- \\
\end{align*}
\]

\[
\begin{align*}
\text{R}_1 & \quad \text{O}^+ \quad \text{H}^- \\
\text{R}_2 & \quad \text{H}^- \\
\end{align*}
\]

\[
\begin{align*}
\text{R}_1 & \quad \text{O}^+ \quad \text{H}^- \\
\text{R}_2 & \quad \text{H}^- \\
\end{align*}
\]

\[
\begin{align*}
\text{R}_1 & \quad \text{O}^+ \quad \text{H}^- \\
\text{R}_2 & \quad \text{H}^- \\
\end{align*}
\]

\[
\begin{align*}
\text{R}_1 & \quad \text{O}^+ \quad \text{H}^- \\
\text{R}_2 & \quad \text{H}^- \\
\end{align*}
\]
Assignment 10

I. Which compound in each pair forms the higher percentage of gem-diol at equilibrium:

(a) CH₃CH₂CH₂CHO or CH₃CH₂COCH₃;

(b) CH₃CF₂CHO or CH₃CH₂CHO?

II. Rank in order of increasing favorability of hydration:

\[
\begin{align*}
\text{Cl} & \text{Cl} & \text{O} \\
\text{Cl} & \text{H} \\
\text{Cl} & \text{Cl} & \text{Cl} & \text{Cl} \\
\text{Cl} & \text{Cl} & \text{O} \\
\text{Cl} & \text{CH₃} \\
\text{Cl} & \text{Cl} & \text{Cl} & \text{Cl} \\
\text{Cl} & \text{Cl} & \text{Cl} & \text{Cl}
\end{align*}
\]
III. Draw a stepwise mechanism for the following reaction.

IV. Cyclopropanone exists as the hydrate in water but 2-hydroxyethanal does not exist as its hemiacetal. Explain.
Electron-donating groups near the carbonyl carbon stabilize the carbonyl group, decreasing the amount of the hydrate at equilibrium.
Electron-withdrawing groups near the carbonyl carbon destabilize the carbonyl group, increasing the amount of hydrate at equilibrium.
Nucleophilic Addition of Alcohols: Acetal Formation

Aldehydes and ketones undergo a reversible reaction with alcohols in the presence of an acid catalyst to yield acetals, $R_2C(OR)_2$, compounds that have two ether-like OR groups bonded to the same carbon.

The initial nucleophilic addition step occurs by the usual mechanism and yields an intermediate hydroxy ether called a hemiacetal.
The hemiacetal then reacts further with a second equivalent of alcohol and gives the acetal plus water. Acetal formation is catalyzed by acids (not by a base). The most commonly used acid is the anhydrous acid \( p \)-toluenesulfonic acid (\( p \)-TsOH).

Example

\[
\begin{align*}
\text{H}_3\text{C} & \text{O} \\
\text{H} & \\
\text{H} \\
\text{H} & \\
\text{H} & \\
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\text{H} & \\ \\
2 \text{H}_3\text{C} & \text{OH} \\
\text{H}_3\text{CO} & \text{OCH}_3 \\
\text{H}_2\text{O} \\
\end{align*}
\]
When a diol such as ethylene glycol is used in place of two equivalents of ROH, a cyclic acetal is formed. Both oxygen atoms in the cyclic acetal come from the diol.

Like hydrate formation, the synthesis of acetals is reversible, and often the equilibrium favors reactants, not products. In acetal synthesis, however, water is formed as a by-product, so the equilibrium can be driven to the right by removing the water as it is formed by using drying agents or distilling the water.
Hemiacetals are generally unstable and are only minor components of an equilibrium mixture, except in one very important type of compound. When a hydroxyl group is part of the same molecule that contains the carbonyl group, and a five or six-membered ring can form, the compound exists almost entirely in the cyclic hemiacetal form.

\[
\begin{align*}
\text{Cyclic hemiacetals} \\
\end{align*}
\]
Five or six-membered cyclic hemiacetals are relatively strain free and thus form spontaneously from the corresponding hydroxy aldehydes in water.
As with hydrate formation, all the steps during acetal formation are reversible, and the reaction can be made to go either forward (from carbonyl compound to acetal) or backward (from acetal to carbonyl compound), depending on the reaction conditions.
Acetals as protecting groups

In an organic synthesis, it sometimes happens that one of the reactants contains a functional group that is incompatible with the reaction conditions. Consider, for example the following conversion:

The reaction involves extension of the chain by adding an ethyl group, which can be achieved by abstracting the terminal hydrogen of the alkyne with a strong base and reacting the resulting acetylide with ethyl chloride.
There is a complication, however. The carbonyl group in the starting alkyne will neither tolerate the strongly basic conditions required for anion formation nor survive in a solution containing carbanions. Acetylide ions add to carbonyl groups.

The strategy that is routinely followed is to protect the carbonyl group during the reactions with which it is incompatible and then to remove the protecting group in a subsequent step.

Acetals, especially those derived from ethylene glycol, are among the most useful groups for carbonyl protection, because they can be introduced and removed readily.
A key fact is that acetals resemble ethers in being inert to many of the reagents, such as hydride reducing agents and organometallic compounds, that react readily with carbonyl groups.

**Protection of the carbonyl group**

\[
\text{Ketone} + \text{H}_2\text{O} + \text{Hydroxide} \rightarrow \text{Acetal} + \text{Water}
\]

**Alkylation of alkyne**

\[
\text{Acetal} + \text{Hydride} \rightarrow \text{Alkylation Product} + \text{Water}
\]
**Removal of the protecting group by hydrolysis**

Although protecting and deprotecting the carbonyl group adds two steps to the synthetic procedure, both are essential to its success. The tactic of functional group protection is frequently encountered in preparative organic chemistry, and considerable attention has been paid to the design of effective protecting groups for a variety of functionalities.
Acetals as Prodrugs

Skin has several important functions, including preventing the absorption of foreign substances into the general circulation. This feature protects us from harmful substances, but it also prevents beneficial drugs from penetrating deep into the skin. This effect is most pronounced for drugs containing OH groups that can interact with binding sites on the skin’s surface. To circumvent this problem, two OH groups can be temporarily converted into an acetal. The acetal prodrug is capable of penetrating the skin more deeply, because it lacks the OH groups that bind to the skin. Once the prodrug reaches its target, the acetal moiety is slowly hydrolyzed, thereby releasing the active drug:

Treatment with fluocinonide is significantly more effective than direct treatment with the active drug, because the latter cannot reach all of the affected areas.
I. Each of these compounds is an acetal, that is a molecule made from an aldehyde or ketone and two alcohol groups. Which compounds were used to make these acetals?
II. Draw a step wise mechanism for the following transformation.

III. Show step by step how you can achieve the following transformation:
IV. Design a stepwise synthesis to convert cyclopentanone and 4-bromobutanal to the hydroxy aldehyde A.

cyclopentanone  4-bromobutanal
Cyanohydrins are compounds containing a hydroxyl and a cyano group attached to the same carbon atom.
Cyanohydrin formation is reversible. Cyanohydrins can be reconverted to carbonyl compounds by treatment with base. This process is just the reverse of the addition of HCN: deprotonation followed by elimination of $-$CN.
Cyanohydrins and cassava

The reversibility of cyanohydrin formation is of more than theoretical interest. In parts of Africa the staple food is cassava. This food contains substantial quantities of the glucoside of acetone cyanohydrin, linamarin. The glucoside is not poisonous in itself, but enzymes in the human gut break it down and release HCN. Eventually 50 mg HCN per 100 g of cassava can be released and this is enough to kill a human being after a meal of unfermented cassava.

\[
\text{linamarin} \xrightarrow{\text{enzyme}} \text{acetone cyanohydrin} \xrightarrow{\text{enzyme}} \text{HCN} + \text{toxic by-product}
\]
If the cassava is crushed with water and allowed to stand (‘ferment’), enzymes in the cassava will do the same job and then the HCN can be washed out before the cassava is cooked and eaten.

The cassava is now safe to eat but it still contains some glucoside. Some diseases found in eastern Nigeria can be traced to long-term consumption of HCN. Similar glucosides are found in apple pips and the kernels inside the stones of fruit such as peaches and apricots. Some people like eating these, but it is unwise to eat too many at one sitting!
Assignment 12

Draw the products of each reaction.

a) \[
\text{PhCH}=\text{C}
\]

\[
\text{H} \rightarrow \text{NaCN}
\]

\[
\text{HCl}
\]
Aldehydes and ketones react with phosphorus ylides to yield alkenes. Wittig reaction is a synthetic method for converting aldehydes and ketones into alkenes.
Example

\[
\text{The reaction is regiospecific. It offers a great advantage over most other alkene syntheses in that } \textit{no ambiguity exists as to the location of the double bond in the product.}
\]
A ylide is a molecule which, when written in a Lewis structure showing all atoms with complete valence shells, has a positive and negative charges on adjacent atoms.
Preparation of Phosphonium Ylide

The bases used for this reactions are strong bases such as NaH and RLi. A ylide—is a neutral, dipolar compound with adjacent plus and minus charges.
The best way for making a terminal alkene

\[ \text{terminal alkene} \]

Other methods in general give poorer results

\[ \text{alcohol} \]
Planning a Wittig synthesis begins with recognizing in the desired alkene what can be the aldehyde or ketone component and what can be the halide component. Any or all of the R groups may be hydrogen, although yields are generally better when at least one group is hydrogen. The halide component must be a primary, secondary, or methyl halide.
Show two ways of synthesizing 2-methyl-1-phenylprop-1-ene using a Wittig reaction.

2-Methyl-1-phenylprop-1-ene
Nucleophilic Addition of Amines: Imine and Enamine

Primary amines, $RNH_2$, add to aldehydes and ketones to yield imines. Secondary amines, $RR'NH$, add similarly to yield enamines.
Examples

\[ \text{Enamine} \quad \xrightarrow{CH_3NH_2} \quad \text{Imine} \]
Nucleophilic attack on the ketone or aldehyde by the lone-pair electrons of an amine leads to a dipolar tetrahedral intermediate.
A proton is then transferred from nitrogen to oxygen, yielding a neutral carbinolamine.

A compound that has an sp$^3$ carbon bonded to an oxygen atom generally will be unstable if the sp$^3$ carbon is bonded to another electronegative element. The carbinolamine intermediate, therefore, is unstable because O and N are both electronegative atoms.
Acid catalyst protonates the hydroxyl oxygen.

The nitrogen lone-pair electrons expel water, giving an iminium ion.
Loss of $H^+$ from nitrogen then gives the neutral imine product.
Many different compounds of the form RNH₂ will react with aldehydes and ketones, including compounds in which R is not an alkyl group.

General reaction
Test for aldehydes and ketones

2,4-Dinitrophenylhydrazine (Brady’s reagent) can be used to detect the carbonyl functionality of a ketone or aldehyde functional group. A positive test is signaled by a yellow or red precipitate. If the carbonyl compound is aromatic, then the precipitate will be red; if aliphatic, then the precipitate will have a yellow color.
MECHANISM OF ENAMINE FORMATION

Reaction of an aldehyde or ketone with a secondary amine, $R_2NH$, rather than a primary amine yields an enamine. The process is identical to imine formation up to the iminium ion stage, but at this point there is no proton on nitrogen that can be lost to form a neutral imine product. Instead, a proton is lost from the neighboring carbon (the $\alpha$ carbon), yielding an enamine.
Loss of a proton from the $\alpha$ carbon atom yields the enamine product and regenerates the acid catalyst.

Imine and enamine formation are slow at both high pH and low pH but reach a maximum rate at a weakly acidic pH around 4 to 5. At low pH the amine will be protonated and will not attack the cabonyl while at high pH the acid concentration will be too low to protonate the carbinol amine.
Tertiary amines do not form stable addition products with aldehydes and ketones because, on forming the tetrahedral intermediate, the resulting formal positive charge cannot be neutralized by loss of a proton.
1. Predict the product of each of the following reactions:

   a) ![Reaction Diagram for Imine Formation with Water](image)

   b) ![Reaction Diagram for Imine Formation with Water](image)

   c) ![Reaction Diagram for Imine Formation with Water](image)

2. Imine formation is reversible. Show all the steps involved in the acid catalyzed reaction of an imine with water (hydrolysis) to yield an aldehyde or ketone plus primary amine.
3) Provide mechanism for the following transformation

![Chemical reaction diagram]
Additions of nucleophilies to $\alpha,\beta$-Unsaturated Aldehydes and Ketones

$\alpha,\beta$-Unsaturated carbonyl compounds are conjugated molecules containing a carbonyl group and a carbon–carbon double bond, separated by a single $\sigma$ bond.

Both functional groups of $\alpha,\beta$-unsaturated carbonyl compounds have $\pi$ bonds, but individually, they react with very different kinds of reagents. Carbon–carbon double bonds react with electrophiles and carbonyl groups react with nucleophiles. What happens, then, when these two functional groups having opposite reactivity are in close proximity?
Because the two $\pi$ bonds are conjugated, the electron density in an $\alpha,\beta$-unsaturated carbonyl compound is delocalized over four atoms. The three resonance structures show that the carbonyl carbon and the $\beta$ carbon bear a partial positive charge. This means that $\alpha,\beta$-unsaturated carbonyl compounds can react with nucleophiles at two different sites.
Addition of a nucleophile to the carbonyl carbon, called 1,2-addition or direct addition, adds the elements of H and Nu across the C=O, forming an allylic alcohol.

Addition of a nucleophile to the β carbon, called 1,4-addition or conjugate addition, forms a carbonyl compound.
Whether the product obtained from nucleophilic addition to an \( \alpha,\beta \)-unsaturated aldehyde or ketone is the direct addition product or the conjugate addition product depends on the nature of the nucleophile, the structure of the carbonyl compound and the conditions under which the reaction is carried out.

Nucleophiles that form unstable addition products - that is, nucleophiles that are weak bases, allowing direct addition to be reversible - form conjugate addition product because conjugate addition is not reversible.
Examples

Nucleophiles that form stable addition products—that is, nucleophiles that are strong bases, thereby making direct addition irreversible—can form either direct addition products or conjugate addition products.

Nucleophiles in this group include hydride ion and carbanions. The reaction that prevails is the one that is faster, so the product that is formed will depend on the reactivity of the carbonyl group.
Examples

Aldehyde

1. NaBH₄
2. EtOH

Product of direct addition

97%

Ketone

1. NaBH₄
2. EtOH

Product of direct addition

Product of conjugate addition

51% 49%
Compounds with reactive carbonyl groups form primarily direct addition products because for those compounds, direct addition is faster, whereas compounds with less reactive carbonyl groups form primarily conjugate addition products because for those compounds, conjugate addition is faster.

For example, aldehydes have more reactive carbonyl groups than do ketones, so sodium borohydride forms primarily direct addition products with aldehydes. Compared with aldehydes, ketones form less of the direct addition product and more of the conjugate addition product.
Like hydride ions, Grignard reagents add irreversibly to carbonyl groups. Therefore, Grignard reagents react with $\alpha,\beta$-unsaturated aldehydes and unhindered $\alpha,\beta$-unsaturated ketones to form direct addition products.

If, however, the rate of direct addition is slowed down by steric hindrance, a Grignard reagent will form a conjugate addition product because conjugate addition then becomes the faster reaction.
Only conjugate addition occurs when lithium dialkylcuprates (R₂CuLi, Gilman reagents) react with α,β-unsaturated aldehydes and ketones. Therefore, Grignard reagents should be used when you want to add an alkyl group to the carbonyl carbon, whereas Gilman reagents should be used when you want to add an alkyl group to the β-carbon.
Examples

I. Give the major product of each of the following reactions

a) \[
\begin{align*}
\text{CH}_3\text{MgBr} & \quad \text{C} \equiv \text{N} \\
\text{H} & \quad \text{Cl}
\end{align*}
\]

b) \[
\begin{align*}
\text{NaBH}_4 & \\
\text{H}_3\text{O}^+ 
\end{align*}
\]

c) \[
\begin{align*}
\text{CH}_3\text{MgBr} & \\
\text{H}_3\text{O}^+ 
\end{align*}
\]

d) \[
\begin{align*}
(\text{CH}_3)_2\text{CuLi} & \\
\text{H}_3\text{O}^+ 
\end{align*}
\]
II. Propose the mechanism of the following transformation.

\[
\text{Acrolein} + \text{Hydrazine} \xrightarrow{\text{H}^+} \text{Dihydropyrazole}
\]
Reduction of a Carbonyl Group to a Methylene Group

I. Wolff-Kishner Reduction
II. Clemmensen Reduction
III. Desulfurization
I. Wolff-Kishner Reduction

General Reaction

\[ \text{Hydrazine} \rightarrow \text{Diethylamine} + \text{Water} \]

\[ \text{NaOH/KOH} \rightarrow \text{Diethylene glycol} \]

\[ \text{R}_1 \text{C} = \text{C} \text{R}_2 + \text{H}_2\text{N-NH}_2 \rightarrow \text{R}_1 \text{C} \equiv \text{NH} \text{R}_2 + \text{H}_2\text{O} \]
Heating an aldehyde or a ketone with hydrazine (H$_2$NNH$_2$) and sodium or potassium hydroxide in a high-boiling alcohol such as diethylene glycol (HOCH$_2$CH$_2$OCH$_2$CH$_2$OH) converts the carbonyl to a CH$_2$ group.

Example

Acetophenone $\xrightarrow{\text{H}_2\text{N}-\text{NH}_2, \text{KOH, Diethylene glycol, Heat}}$ Ethylbenzene
Mechanism of Wolff – Kishner Reduction

\[
\begin{align*}
\text{O} & \quad \text{H} \\
\text{H}_2\text{N} & \quad \text{NH}_2
\end{align*}
\]

\[R_1 \quad R_2\]
II. Clemmensen Reduction

General Reaction

\[ \text{O} \quad \xrightarrow{\text{Zn (Hg)}} \quad \text{H} \]

\[ \text{C} \quad \text{C} \quad \text{H} \]

\[ \text{R}_1 \quad \text{R}_2 \quad \text{R}_1 \quad \text{R}_2 \]

Conc HCl

The Clemmensen reduction uses an acidic solution of zinc dissolved in mercury as the reducing reagent.
This reaction is a good method for the reduction of acid-stable carbonyl compounds (Note that the reaction takes place in the presence of concentrated HCl).

**Examples**

- **Heptanal**
  - Reaction: \( \text{Heptanal} + \text{Zn (Hg)} \rightarrow \text{Heptane (72%)} \)
  - Conditions: \( \text{HCl, H}_2\text{O} \)

- **Cyclohexanone**
  - Reaction: \( \text{Cyclohexanone} + \text{Zn (Hg)} \rightarrow \text{Cyclohexane (75%)} \)
  - Conditions: \( \text{HCl, H}_2\text{O} \)
III. Desulfurization

When treated with Raney nickel, thioacetals undergo desulfurization, yielding an alkane:

\[
\text{Thioacetal} \quad \xrightarrow{\text{Raney Ni}} \quad \text{alkane} + \text{H}_2\text{O}
\]
Example

\[
\begin{align*}
\text{HS} & \quad \text{SH} \\
\text{BF}_3 & \quad \text{ether} \\
\text{H}_2 & \quad \text{Raney Ni}
\end{align*}
\]
Advantages

• High yields
• Mild and nearly neutral Reaction conditions

Disadvantages

• Stinky!
• Raney Nickel is tricky to prepare
**Assignment 16**

a) \[
\text{\begin{align*}
\text{O} \\
\text{a)} \\
\text{1. } \text{NH}_2\text{NH}_2, \text{ H}^+ \\
\text{2. KOH/H}_2\text{O, Heat}
\end{align*}}
\]

b) \[
\text{\begin{align*}
\text{O} \\
\text{b)} \\
\text{1. } \text{HS} \text{ SH , H}^+ \\
\text{2. Raney Ni}
\end{align*}}
\]
Aldehydes are readily oxidized to carboxylic acids by common oxidizing agents such as Chromic acid, Silver oxide and Permanganate.

\[
\begin{align*}
\text{oxidizing agent} & \quad \rightarrow \\
\text{RCHO} & \quad \rightarrow \quad \text{RCOOH}
\end{align*}
\]

Notice that in these oxidations aldehydes lose the hydrogen that is attached to the carbonyl carbon atom.
Tollens silver mirror test

\[ \text{Ag}_2\text{O}, \text{NH}_4\text{OH} \to \text{R-CHO} \xrightarrow{+ \text{Ag}} \text{R-COOH} \]

Aldehydes are oxidized selectively in the presence of other functional groups using silver(I) oxide in aqueous ammonium hydroxide (\(\text{Ag}_2\text{O in NH}_4\text{OH}\)). This is called Tollens reagent and the test is called Tollens silver mirror test. Oxidation with Tollens reagent provides a distinct color change, because the \(\text{Ag}^+\) reagent is reduced to silver metal (\(\text{Ag}\)), which precipitates out of solution.
Baeyer-Villiger Oxidation

General Reaction

\[
\begin{align*}
R_1\text{R}_2\text{O} & \quad + \quad R\text{O}O\text{O}\text{H} \\
\text{Ketone} & \quad \text{Peroxy acids} & \quad \text{Ester} & \quad \text{Acids}
\end{align*}
\]

The Baeyer-Villiger oxidation involves the insertion of an oxygen atom (derived from a peroxo acid, like \textit{m}-chlorobenzoic acid (\textit{m}-CPBA)) between the carbonyl group of a ketone and one of the attached carbons to provide an ester.

\[
\text{Cl} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{H} \quad \text{m}-\text{chlorobenzoic acid (m-CPBA)}
\]
Mechanism of the Baeyer-Villiger Oxidation

\[
\begin{align*}
R_1 & \quad + \quad \text{HOOOCR} \\
\text{R}_2 & \quad \rightarrow \\
\text{Peroxymonoester}
\end{align*}
\]
The peroxymonoester undergoes rearrangement. Cleavage of the weak O-O bond of the peroxyster is assisted by migration of one of the substituents from the hemiacetal carbon to oxygen. The R group migrates with its pair of electrons in much the same way as alkyl groups migrate in carbocation rearrangements.
The group that migrates is the one that is better able to stabilize the emerging positive charge on the oxygen in the peroxo linkage.

Positive charge needs stabilization
The more electron-rich (most substituted) alkyl group migrates in preference.

Priority of migration: \textit{tert}-alkyl > \textit{sec}-alkyl > benzyl > phenyl > \textit{n}-alkyl > methyl

Examples

\begin{align*}
\text{Cyclohexyl methyl ketone} &\xrightarrow{\text{Ph COO HOH}} \text{Cyclohexyl acetate (67\%)}
\end{align*}
The reaction is stereospecific in the sense that the alkyl group migrates with retention of configuration.

\[ \text{cis-1-Acetyl-2-methylcyclopentane} \quad \xrightarrow{\text{PhO} \cdot \text{O} \cdot \text{OH}} \quad \text{cis-2-Methylcyclopentyl acetate (66\%)} \]

\[ \text{m-Chloroperbenzoic acid (m-CPBA)} \quad \xrightarrow{} \quad \text{Cyclic compound} \]
Assignment 17

Predict the product of each of the following reactions

a) 

b) 

c)
Compounds known as lactones, which are cyclic esters, are formed on Baeyer–Villiger oxidation of cyclic ketones. Suggest a mechanism for the Baeyer–Villiger oxidation shown.
Review of the reaction of aldehydes/ketones