Ketones and Aldehydes

The carbonyl group is of central importance in organic chemistry because of its ubiquity.

Without studying the carbonyl group in depth we have **already** encountered numerous examples of this functional group (ketones, aldehydes, carboxylic acids, acid chlorides, etc).

The simplest carbonyl compounds are *aldehydes* and *ketones*.
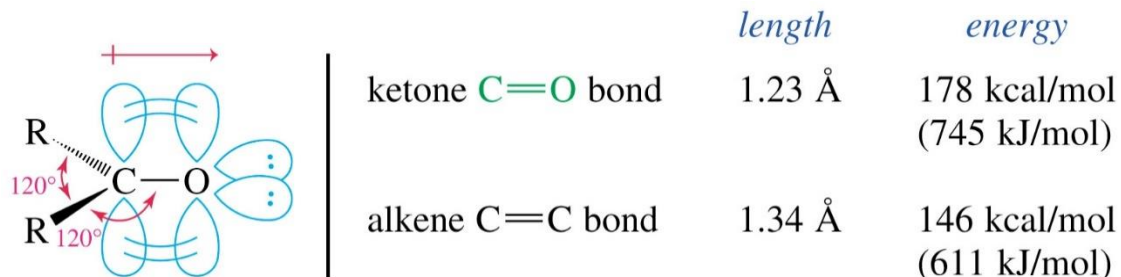
A *ketone* has two alkyl (or aryl) groups bonded to the carbonyl carbon.

An *aldehyde* has one alkyl (or aryl) group and one hydrogen bonded to the carbonyl carbon.

Structure of the carbonyl group

The carbonyl carbon is sp^2 hybridized, and has a partially filled unhybridized p orbital perpendicular to the σ framework.

	length	energy
ketone C=O bond	1.23 Å	178 kcal/mol (745 kJ/mol)
alkene C=C bond	1.34 Å	146 kcal/mol (611 kJ/mol)

The oxygen is also sp^2 hybridized, with the 2 lone pairs occupying sp^2 orbitals. This leaves one electron in a p orbital.

These p orbitals form the carbon oxygen π bond.
The C=O double bond is like a C=C double bond except the carbonyl double bond is <u>shorter</u> and <u>stronger</u>.

The carbonyl group has a large dipole moment due to the *polarity* of the double bond.

Oxygen is more electronegative than carbon, and so the bond is polarized toward the oxygen.

The attraction of the weakly held π electrons toward oxygen can be represented by the two following resonance structures.

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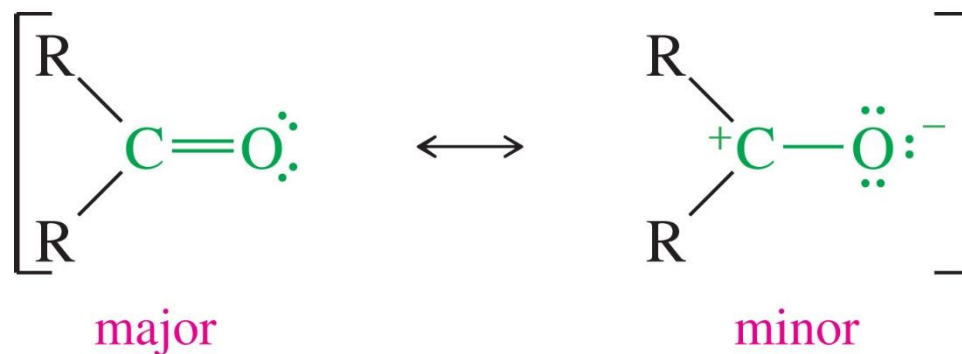
The first resonance structure is the major contributor, but the other contributes in a small amount, which helps explain the dipole moment.
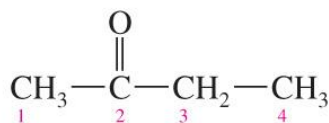
It is this polarization that creates the reactivity of the carbonyl groups (carbon is electrophilic/LA, and the oxygen is nucleophilic/LB).

Nomenclature

IUPAC nomenclature requires **ketones** to be named by replacing the *-e* ending of the alkyl name with *-one*.
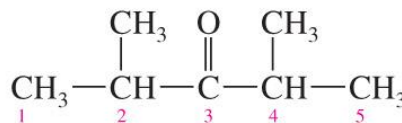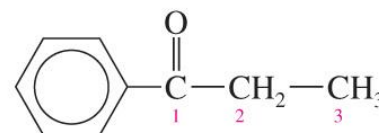
Alkane → alkanone

E.g.

old IUPAC names in blue:
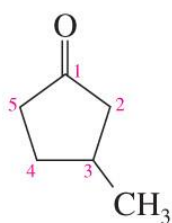new IUPAC names in green:
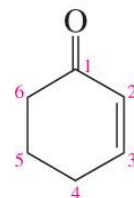
2-butanone
butan-2-one

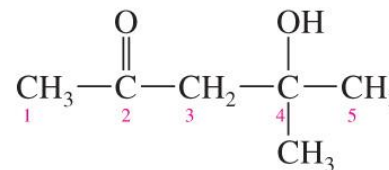2,4-dimethyl-3-pentanone
2,4-dimethylpentan-3-one

1-phenyl-1-propanone
1-phenylpropan-1-one

3-methylcyclopentanone

2-cyclohexenone
cyclohex-2-en-1-one

4-hydroxy-4-methyl-2-pentanone
4-hydroxy-4-methylpentan-2-one

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Systematic names for **aldehydes** are obtained by replacing -*e* with -*al*.

An aldehyde <u>has to be</u> at the end of a chain, and therefore it is carbon number 1.

$$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-H$$

ethanal

$$H_3C-CH_2-CH=CH-CHO$$
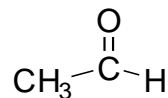
pent-2-enal

If the aldehyde is attached to a large unit, the suffix -*carbaldehyde* is used.

CHO

cyclohexanecarbaldehyde

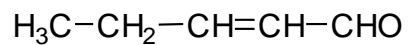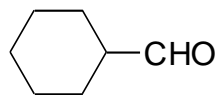A ketone or aldehyde group can also be named as a substituent on a molecule with another functional group as its root.

The ketone carbonyl is given the prefix *oxo-*, and the aldehyde group is named as a *formyl-* group. (This is especially common for carboxylic acids).

CH₃CH₂-C(=O)-CH₂-CHO
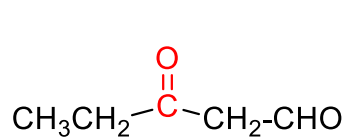
3-oxopentanal
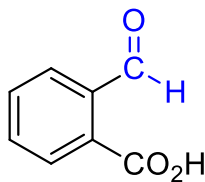
2-formylbenzoic acid

H₃C-C(=O)-CH₂-CO₂H
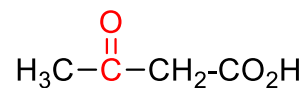
3-oxobutanoic acid

Common Names

The wide spread use of carbonyl compounds means many *common names* are entrenched in their everyday use.

E.g.

H₃C-C(=O)-CH₃
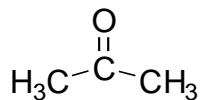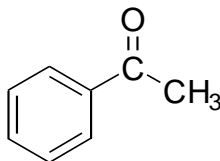
acetone

acetophenone
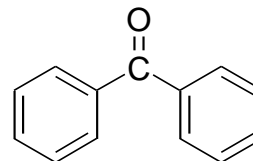
benzophenone

Syntheses of the Aldehydes and Ketones (*Recap?*)

From Alcohols (Ch 11)

Secondary alcohols are readily oxidized to ketones by Chromic acid (or $KMnO_4$).

borneol → camphor (with $Na_2Cr_2O_7$, H_2SO_4)
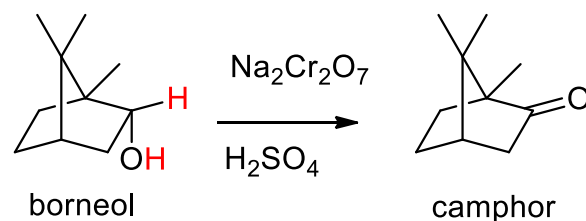
Complicated ketones can be made by the oxidation of alcohols, which in turn can be made from reaction of a Grignard and an aldehyde.
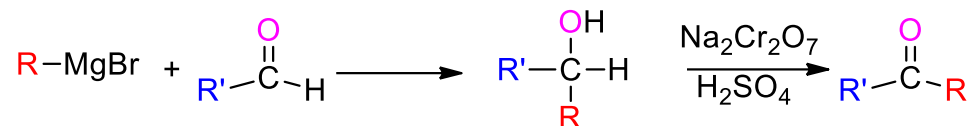
Aldehydes are made from the oxidation of primary alcohols. This oxidation needs to be done carefully to avoid over-oxidation to carboxylic acids.
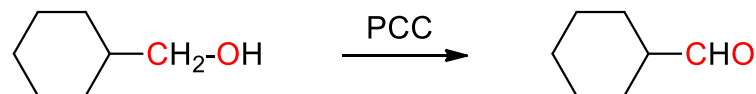
This is achieved by the use of PCC.

Ozonolysis (Ch 8)

Alkenes can be cleaved by ozone (followed by a mild reduction) to generate aldehydes and/or ketones.

(1) O_3

(2) CH_3SCH_3
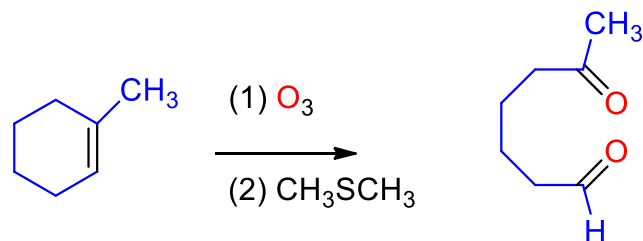
Phenyl Ketones and Aldehydes (Ch 17)

Friedel-Crafts acylation is an excellent method for the preparation of aryl ketones.

$AlCl_3$

para-nitrobenzophenone
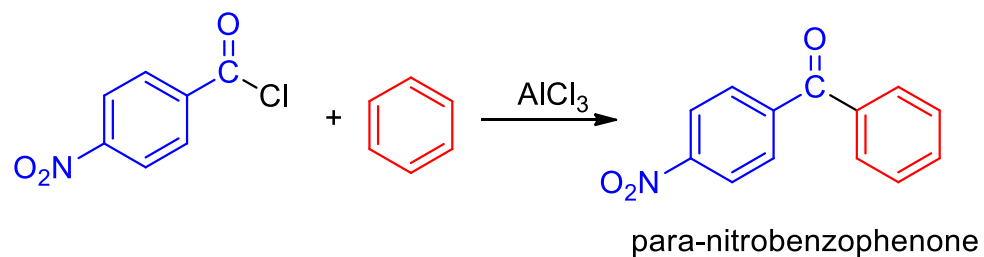
The Gattermann-Koch reaction produces benzaldehyde systems.

CO, HCl

CuCl, $AlCl_3$
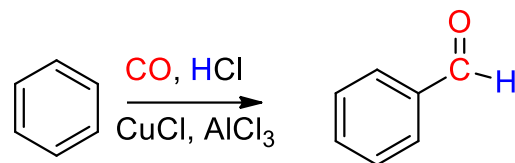
Hydration of Alkynes (Ch 9)

Hydration of alkynes can either be achieved with **Markovnikov** (acid and mercury (II) catalyzed reaction) or **anti-Markovnikov** (hydroboration-oxidation) regiochemistry.
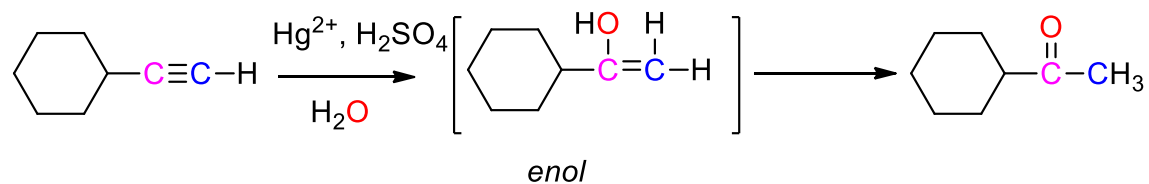
enol

In both cases the *enols* produced rearrange to their more stable *keto* forms (in the hydroboration case the keto form is an aldehyde).

enol
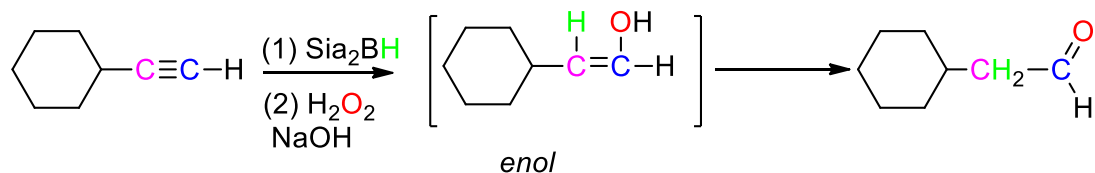
Other Syntheses of Aldehydes and Ketones

Use of 1,3-Dithiane

Dithiane has relatively acidic hydrogens located between the two sulfur atoms, and these can be removed by a strong base.

The anion is stabilized by the electron withdrawing effect of the highly polarizable sulfur atoms.
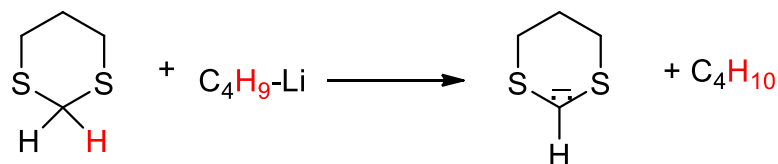
The dithiane anion can react as a nucleophile with primary alkyl halides, and this alkylation generates a thioacetal.
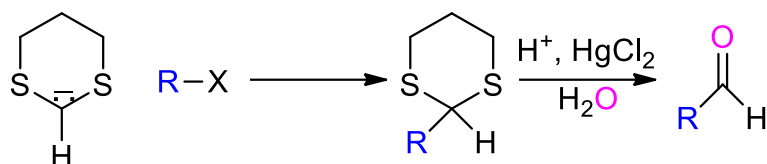
The hydrolysis of a thioacetal generates an aldehyde.

Alternatively, the thioacetal can be further deprotonated and reacted with another (different) alkyl halide to generate a new thioacetal with two alkyl substituents. On hydrolysis, this thioacetal produces a ketone.
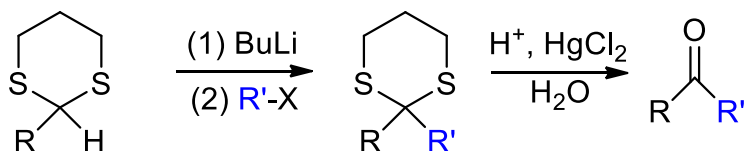
This is a good route for the construction of *unsymmetrical* ketones.

E.g.
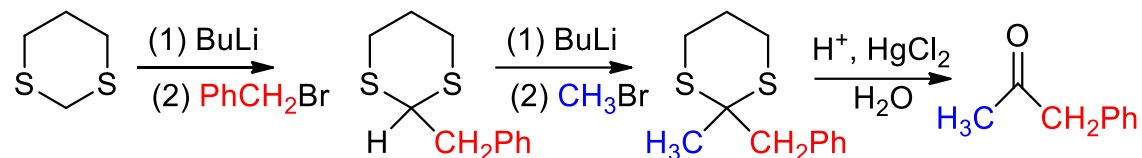
The dithiane can be thought of as a "masked" carbonyl group.

Ketones from Carboxylic Acids

Organolithium reagents are very reactive towards carbonyl compounds.

So much so, that they even attack the lithium salts of carboxylate anions.

These dianions can then be protonated, which generates hydrates, which then lose water and produce ketones.
E.g.
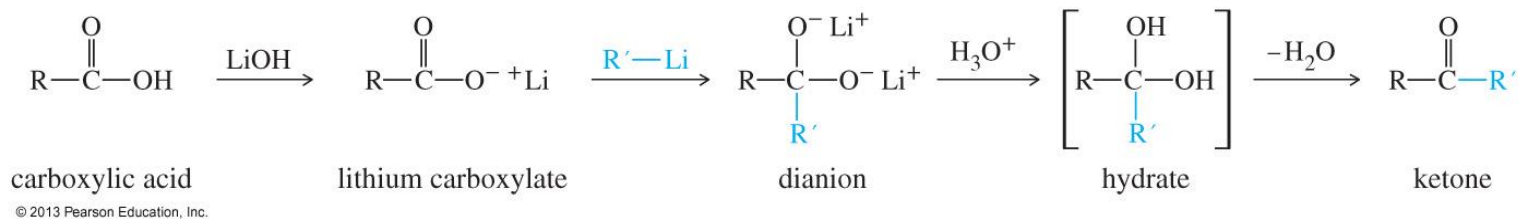
If the organolithium reagent is not expensive, then the carboxylic acid can be simply treated with two equivalents of the organolithium.

The first equivalent just deprotonates the carboxylic acid (*expensive base*).
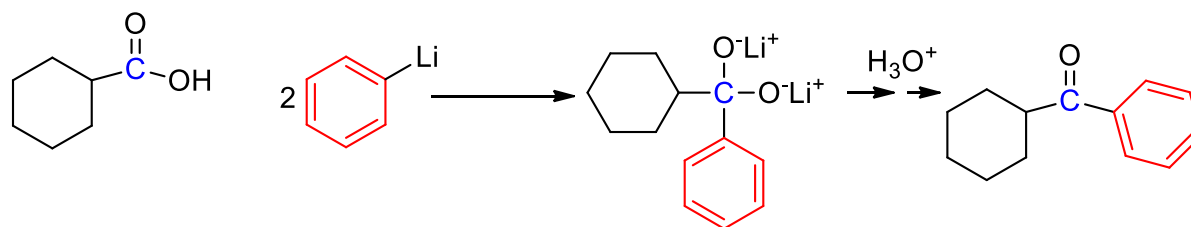
Ketones from Nitriles

Nitrile compounds contain the **cyano** group (carbon nitrogen triple bond).

Since N is more electronegative than C, the triple bond is polarized toward the nitrogen, (similar to the C=O bond).

Therefore nucleophiles can attack the electrophilic carbon of the nitrile group.

Grignard (or organolithium) reagents attack the nitrile to generate the magnesium (or lithium) salt of an imine.

nucleophilic attack   Mg salt of imine   imine   ketone
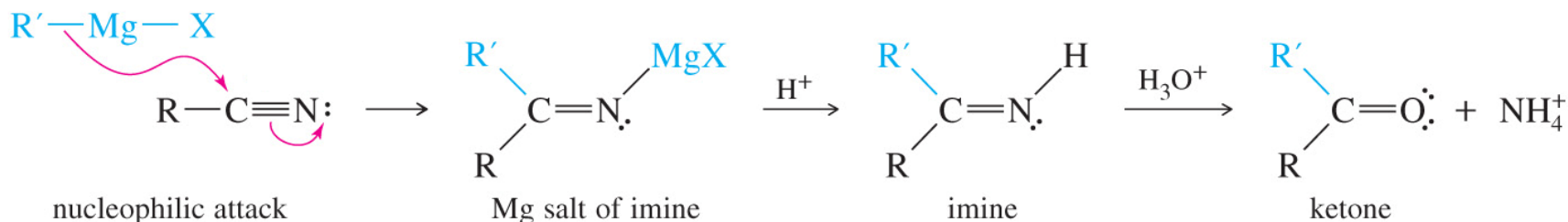
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Acid hydrolysis generates the *imine*, and under these acidic conditions, the *imine* is hydrolyzed to a *ketone*.

The mechanism of this hydrolysis is discussed in depth (for the reverse reaction) later.
E.g.
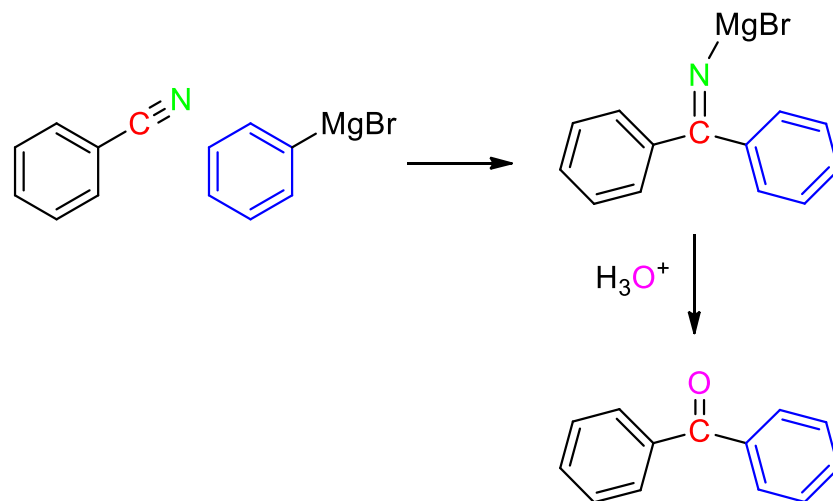
Aldehydes and Ketones from Acid Chlorides

Aldehydes
It is very difficult to reduce a carboxylic acid back to an aldehyde and to get the reduction to stop there.

Aldehydes themselves are very easily reduced (more reactive than acids), and so almost always, over-reduction occurs.
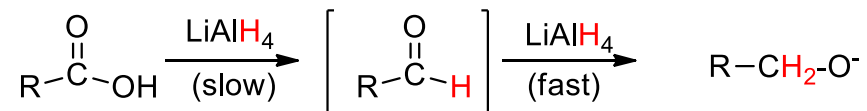
However, to circumvent this problem, carboxylic acids can be converted first into a functional group that is **easier** to reduce than an aldehyde group.

The group of choice is an **acid chloride**.

The reaction of carboxylic acids with thionyl chloride ($SOCl_2$) generates acid chlorides.

$$
\underset{\text{acid}}{R-\overset{\overset{\displaystyle O}{\|}}{C}-OH} \;+\; \underset{\text{thionyl chloride}}{Cl-\overset{\overset{\displaystyle O}{\|}}{S}-Cl} \;\longrightarrow\; \underset{\text{acid chloride}}{R-\overset{\overset{\displaystyle O}{\|}}{C}-Cl} \;+\; HCl\uparrow \;+\; SO_2\uparrow
$$

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Although **strong** reducing agents like $LiAlH_4$ still reduce acid chlorides all the way to primary alcohols, <u>milder</u> reducing agents like lithium aluminum tri(tbutoxy)hydride can **selectively** reduce acid chlorides to aldehydes.

$$
\underset{\text{acid chloride}}{R-\overset{\overset{\displaystyle O}{\|}}{C}-Cl} \quad\xrightarrow[\text{lithium tri-}tert\text{-butoxyaluminum hydride}]{Li^+\,{}^-AlH(O\text{-}t\text{-Bu})_3}\quad \underset{\text{aldehyde}}{R-\overset{\overset{\displaystyle O}{\|}}{C}-H}
$$

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Example

$$
\underset{\text{isovaleric acid}}{CH_3\overset{\overset{\displaystyle CH_3}{|}}{C}HCH_2-\overset{\overset{\displaystyle O}{\|}}{C}-OH} \quad\xrightarrow{SOCl_2}\quad \underset{\text{isovaleroyl chloride}}{CH_3\overset{\overset{\displaystyle CH_3}{|}}{C}HCH_2-\overset{\overset{\displaystyle O}{\|}}{C}-Cl} \quad\xrightarrow{Li^+\,{}^-AlH(O\text{-}t\text{-Bu})_3}\quad \underset{\text{isovaleraldehyde (65\%)}}{CH_3\overset{\overset{\displaystyle CH_3}{|}}{C}HCH_2-\overset{\overset{\displaystyle O}{\|}}{C}-H}
$$

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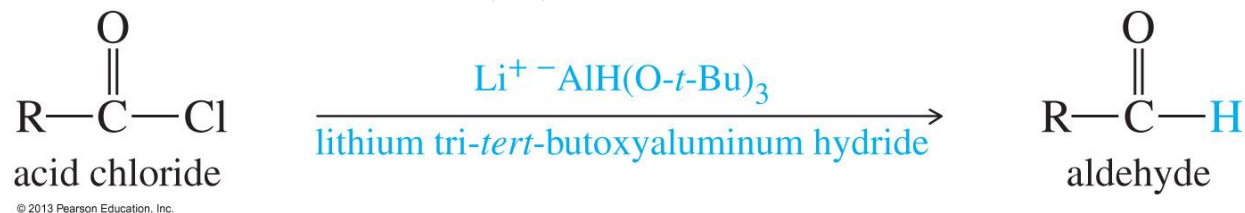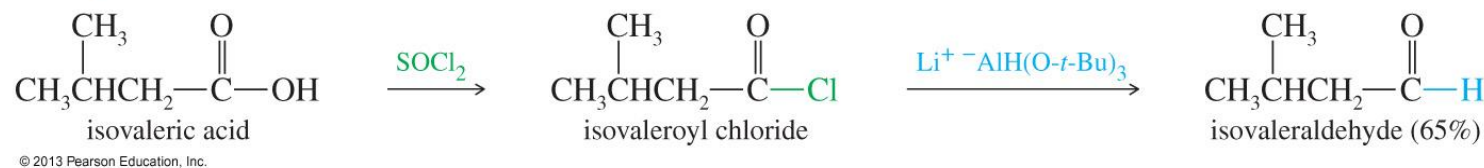
Ketones
Acid chlorides react with Grignard (and organolithium) reagents.
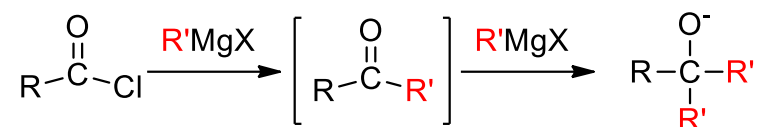
However the ketones produced also react with the nucleophilic species, and tertiary alcohols are produced.
To stop the reaction at the ketone stage, a *weaker* organometallic reagent is required - a lithium dialkylcuprate fits the bill.

R_2CuLi + R′—C—Cl ⟶ R′—C—R + R—Cu + LiCl
a lithium dialkylcuprate   acid chloride   ketone
(Gilman reagent)
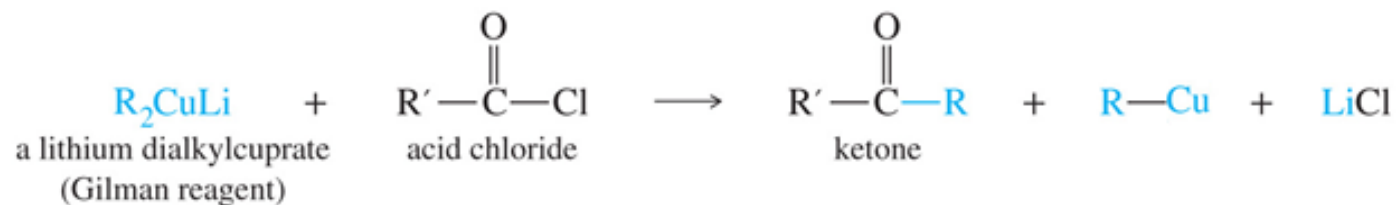
The lithium dialkyl cuprate is produced by the reaction of two equivalents of the organolithium reagent with copper (I) iodide.

$$2\ \textbf{R}\text{-Li} + \text{CuI} \rightarrow \textbf{R}_2\text{CuLi} + \text{LiI}$$
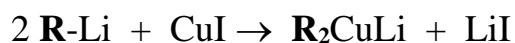
E.g.
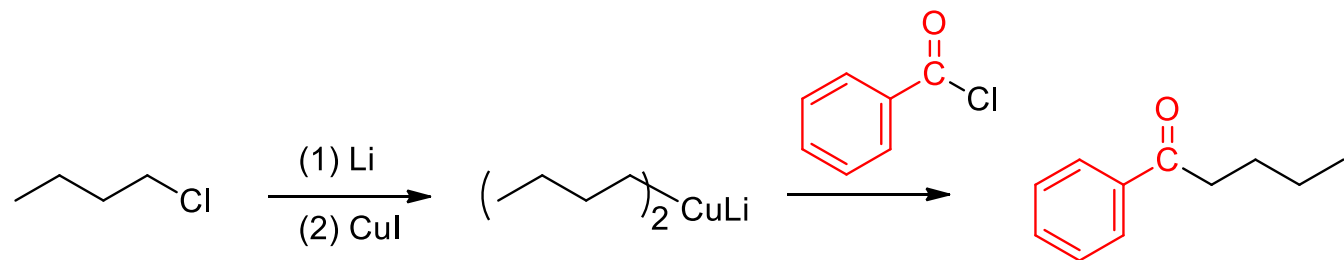
Reactions of Aldehydes and Ketones

The most common reaction of aldehydes and ketones is **nucleophilic addition**.

This is usually the addition of a *nucleophile* and a *proton* across the C=O double bond.

nucleophilic attack   alkoxide   product

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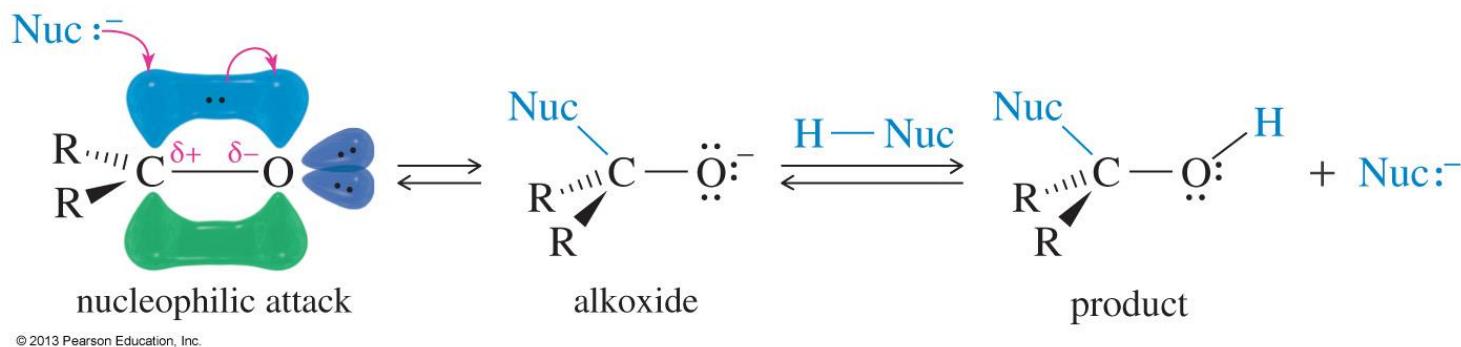
As the nucleophile attacks the carbonyl group, the carbon atom changes from sp^2 to sp^3.

The electrons of the π bond are pushed out onto the oxygen, generating an alkoxide anion.

Protonation of this anion gives the final product.

We have already encountered (at least) two examples of this:

Grignards and ketones → tertiary alcohols

ethylmagnesium bromide   acetone   alkoxide   2-methylbutan-2-ol

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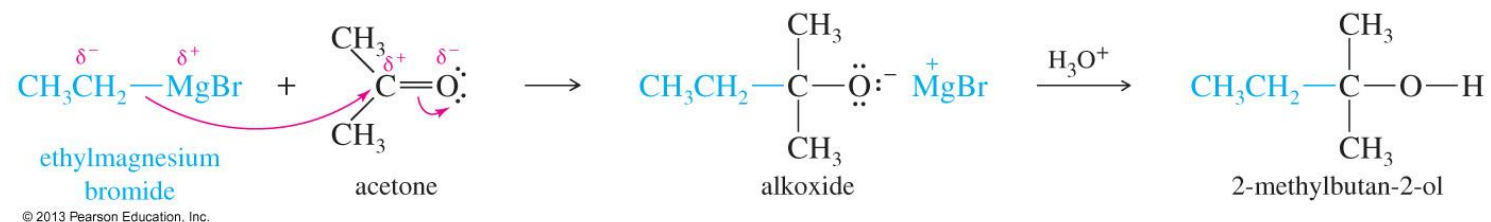
Hydride sources and ketones → secondary alcohols
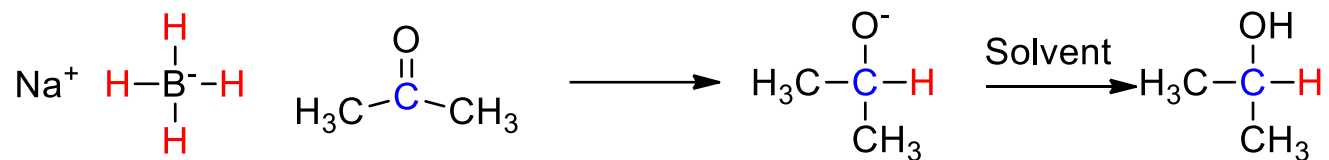
These reactions are both with **strong** nucleophiles.

Under acidic conditions, weaker nucleophiles such as water and alcohols can add.

The carbonyl group is a weak base, and in *acidic* solution it can become *protonated*.

activated carbonyl

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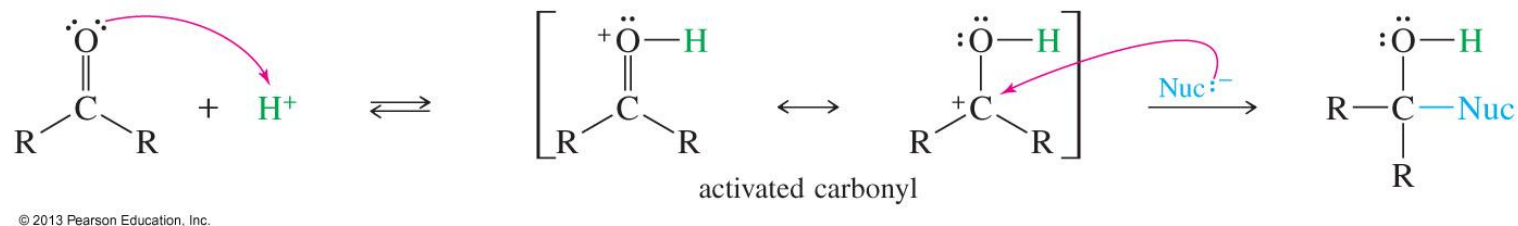
This makes the carbon very **electrophilic** (see resonance structures), and so it will react with **poor** nucleophiles.

E.g. the acid catalyzed nucleophilic addition of water to acetone to produce the acetone hydrate.

acetone   protonated, activated acetone

attack by water   loss of H+   acetone hydrate

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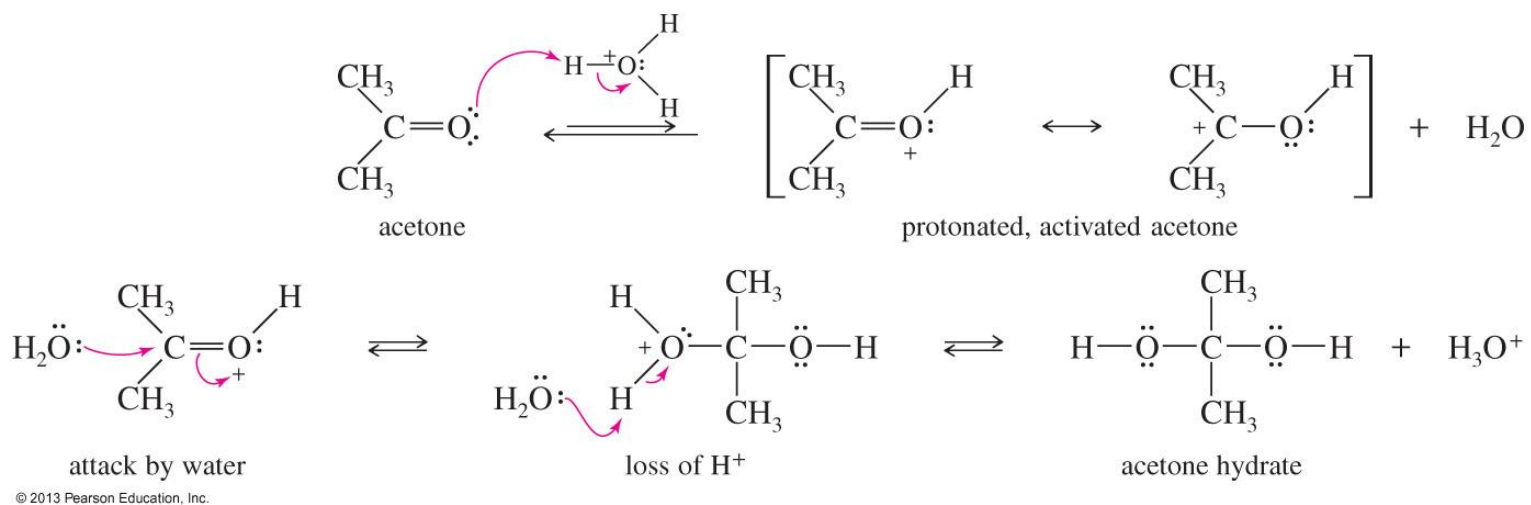
Summary

The **base** catalyzed addition reactions to carbonyl compounds result from initial attack of a strong nucleophile, whereas the **acid** catalyzed reactions begin with the protonation of the oxygen, followed by attack of the weaker nucleophile.

Relative Reactivity

Aldehydes are **more reactive** than ketones.

This (like all things in organic chemistry) stems from two factors: (1) electronics
                                                                      (2) sterics

Electronic Effect
Ketones have two alkyl substituents whereas aldehydes only have one.

Carbonyl compounds undergo reaction with nucleophiles because of the polarization of the C=O bond.
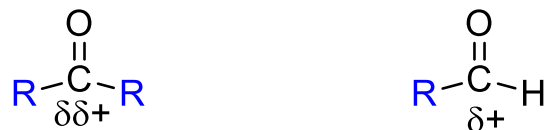
Alkyl groups are electron donating, and so ketones have their effective partial positive charge reduced **more** than aldehydes (two alkyl substituents vs. one alkyl substituent).

    (<u>Aldehydes</u> more reactive than ketones).

Steric Reason
The electrophilic carbon is the site that the nucleophile must approach for reaction to occur.

In ketones the two alkyl substituents create *more steric hindrance* than the single substituent that aldehydes have.

Therefore ketones offer more steric resistance to nucleophilic attack.

    (<u>Aldehydes</u> more reactive than ketones).

Therefore **both** factors make aldehydes more reactive than ketones.

Other Reactions of Carbonyl Compounds

Addition of Phosphorus Ylides (Wittig Reaction)
In 1954 Wittig discovered that the addition of a phosphorus stabilized anion to a carbonyl compound did not generate an alcohol, but an alkene! (= Nobel Prize in 1979).

The Wittig reaction

R'\
  C=O   +
R'/
ketone or aldehyde

R\   Ph
  :C̄—P⁺—Ph   ⟶ ⟶
H/   Ph
phosphorus ylide

R'\   R
   C=C   + $Ph_3P=O$
R'/   \H
alkene
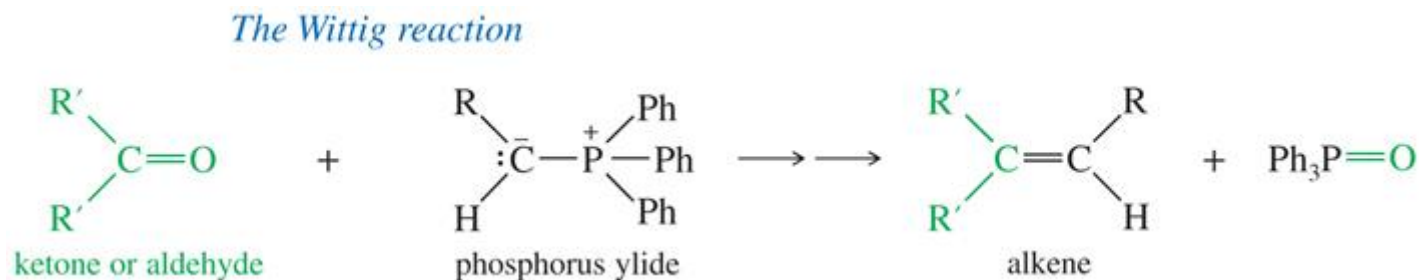
The phosphorus stabilized anion is called an YLIDE, which is a molecule that is overall neutral, but exists as a carbanion bound to a positively charged heteroatom.

Phosphorus ylides are produced from the reaction of triphenylphosphine and alkyl halides.

triphenylphosphine   alkyl halide

phosphonium salt
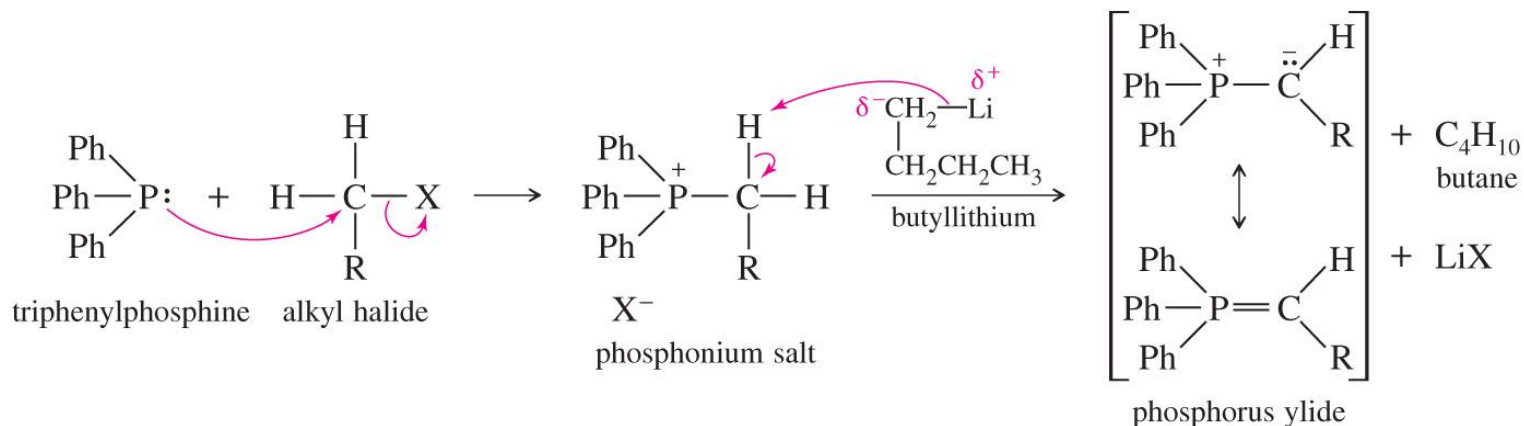
phosphorus ylide

This two step reaction starts with the nucleophilic attack of the Phosphorus on the (usually primary) alkyl halide. This generates an alkyl triphenylphosphonium salt.

Treatment of this salt with a strong base removes a proton from the carbon bound to the phosphorus, and generates the ylide.

The ylide is a *resonance form* of a C=P double bond.

The double bond resonance form requires 10 electrons around the P atom. This is achievable through use of its d electrons (3rd row element), but the π bond to carbon is weak, and this is only a **minor** contributor.

The <u>carbanionic</u> character of the ylide makes it a very powerful nucleophile, and so it reacts rapidly with a carbonyl group.

ylide   ketone or aldehyde   a betaine

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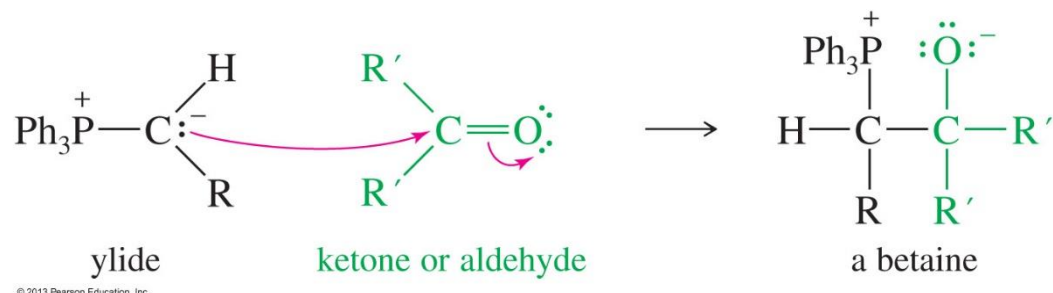
This produces an intermediate which has charge separation - a *betaine*.
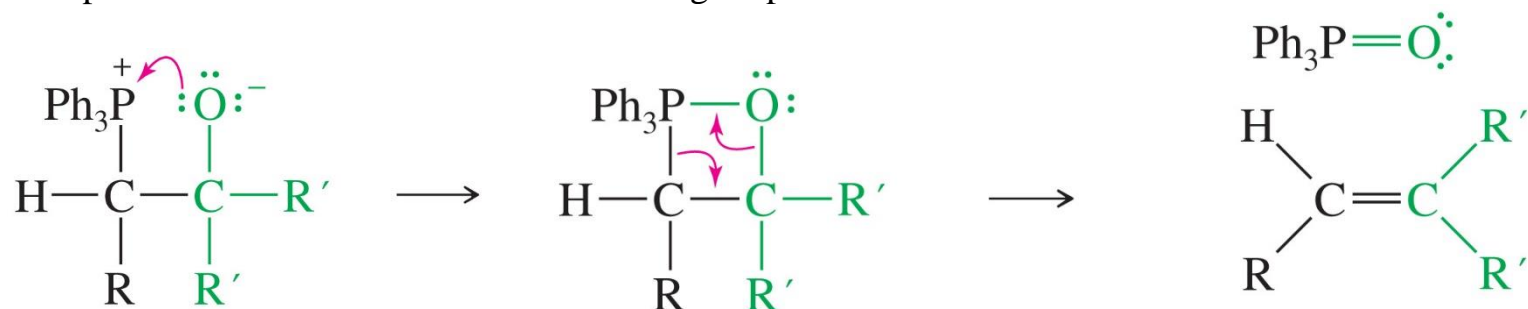
Betaines are unusual since they have a negatively charged oxygen and a positively charged phosphorus.

Phosphorus and oxygen always form strong bonds, and these groups therefore combine to generate a four membered ring - an *oxaphosphetane* ring.

This 4 membered ring quickly collapses to generate an alkene and (very stable) triphenyl phosphine oxide.

The elimination of $Ph_3P=O$ is the driving force of this reaction.

This is a good general route to make new C=C double bonds starting from carbonyl compounds.

Wittig Strategy

By dividing a target molecule at the double bond, you can decide which of the two components should best come from the carbonyl, and which from the ylide.

Analysis

$$\underset{H_3C}{\overset{H_3C}{\diagdown}}C{=}C\underset{H}{\overset{CH_2CH_3}{\diagup}} \quad \xrightarrow[\text{could come from}]{} \quad \begin{cases} \underset{H_3C}{\overset{H_3C}{\diagdown}}C{=}O \quad + \quad Ph_3\overset{+}{P}{-}\overset{-}{C}{:}\underset{H}{\overset{CH_2CH_3}{\diagup}} \\ \qquad\qquad\qquad\text{(preferred)} \\ \qquad\qquad\qquad\text{or} \\ \underset{H_3C}{\overset{H_3C}{\diagdown}}\overset{-}{C}{-}\overset{+}{P}Ph_3 \quad + \quad O{=}C\underset{H}{\overset{CH_2CH_3}{\diagup}} \end{cases}$$
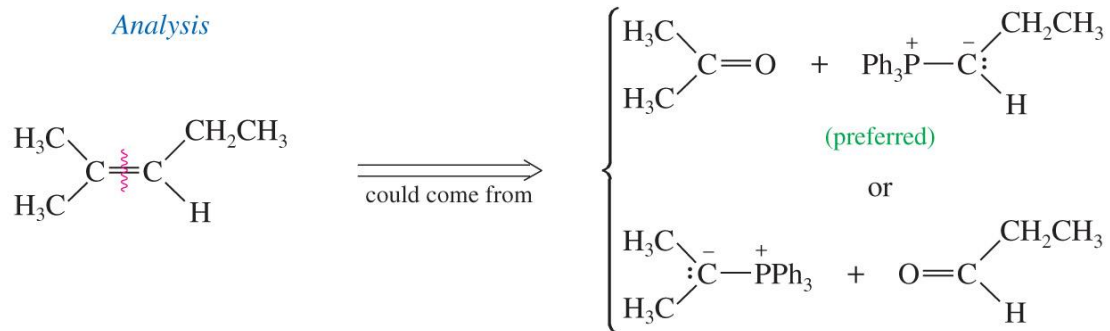
In general, the ylide should come from an *unhindered* alkyl halide since triphenyl phosphine is so bulky.

E.g.

Synthesis

$$\underset{H}{\overset{Br}{\diagdown}}\underset{H}{\overset{}{C}}\overset{CH_2CH_3}{\diagup} \quad \xrightarrow[\text{(2) BuLi}]{\text{(1) Ph}_3\text{P}} \quad Ph_3\overset{+}{P}{-}\overset{-}{C}{:}\underset{H}{\overset{CH_2CH_3}{\diagup}} \quad \xrightarrow[]{\underset{H_3C}{\overset{H_3C}{\diagdown}}C{=}O} \quad \underset{H_3C}{\overset{H_3C}{\diagdown}}C{=}C\underset{H}{\overset{CH_2CH_3}{\diagup}}$$
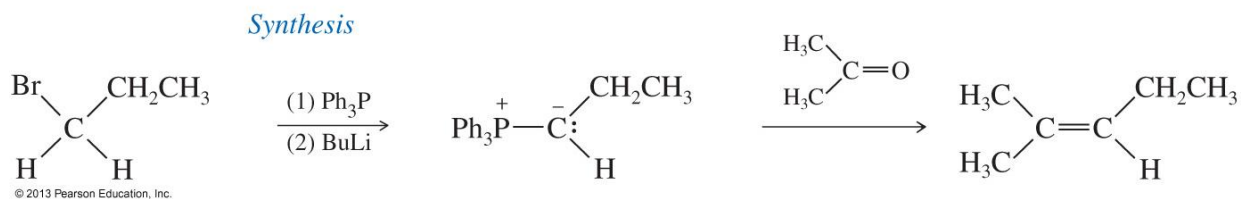
Nucleophilic Addition of Water (Hydration)

In aqueous solution, ketones (and aldehydes) are in equilibrium with their *hydrates* (gem diols).

$$K = \frac{[\text{hydrate}]}{[\text{ketone}][H_2O]}$$

keto form

hydrate
(a geminal diol)

Example

$$CH_3-C-CH_3 \;+\; H_2O \;\rightleftharpoons\; CH_3-C-CH_3 \qquad K = 0.002$$

acetone

acetone hydrate
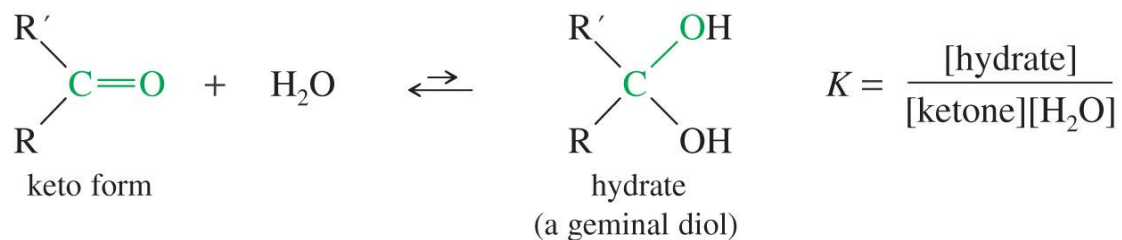
Most ketones have the equilibrium in favor of the *unhydrated* form.

Hydration proceeds through the two classic *nucleophilic addition* mechanisms with water (in acid) or hydroxide (in base) acting as the nucleophile.

(*Acidic Conditions* – Protonation followed by nuc attack)

(*Basic Conditions* – Nuc attack followed by protonation)

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Aldehydes are *more likely* to form hydrates since they have the larger partial positive charge on the carbonyl carbon (larger charge = less stable = more reactive).
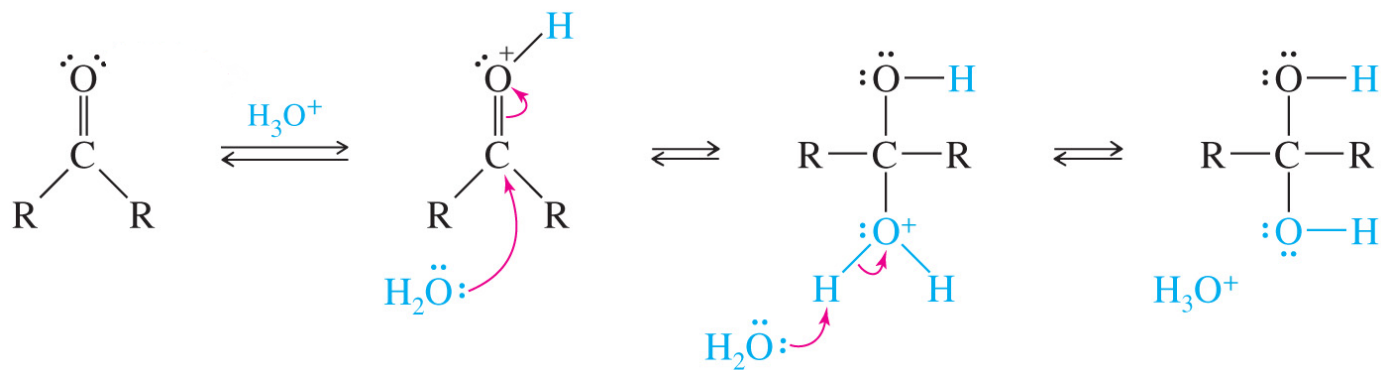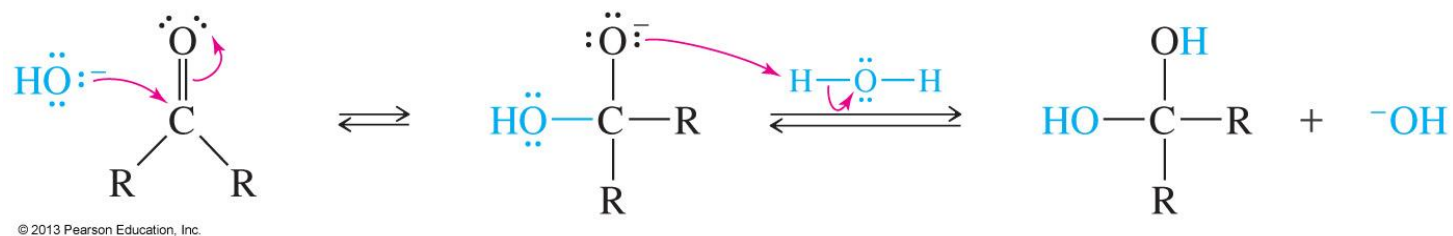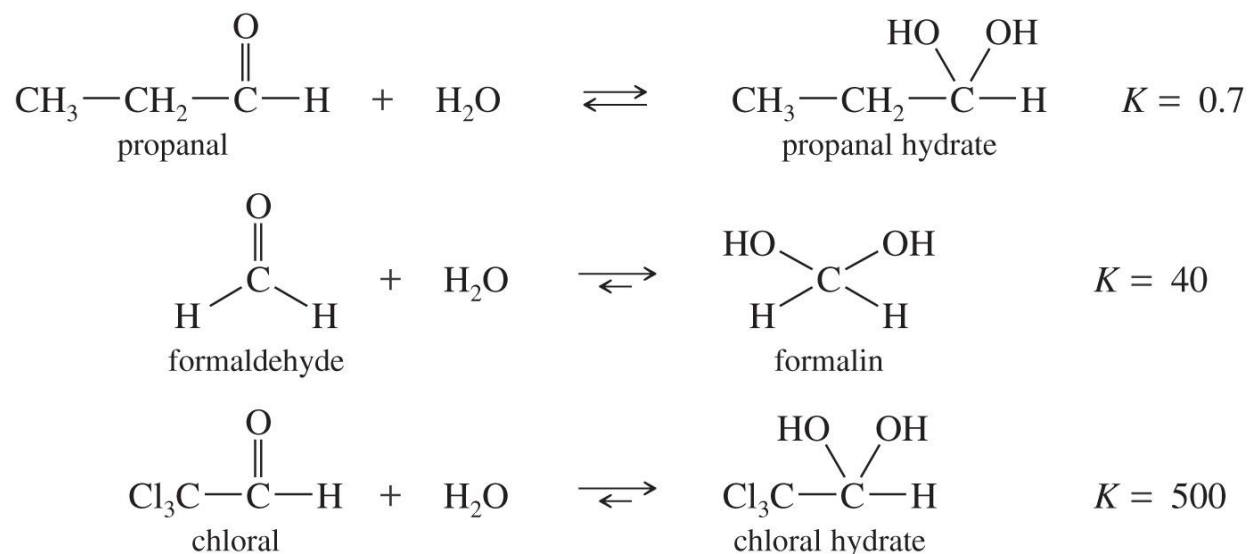
This is borne out by the following equilibrium constants.

$$CH_3-CH_2-\overset{\overset{\textstyle O}{\|}}{C}-H \;+\; H_2O \;\rightleftharpoons\; CH_3-CH_2-\overset{\overset{\textstyle HO\;\;OH}{\diagdown\diagup}}{C}-H \qquad K = 0.7$$

propanal $\qquad\qquad\qquad\qquad\qquad\qquad$ propanal hydrate

$$\underset{\underset{\textstyle H \qquad H}{}}{\overset{\overset{\textstyle O}{\|}}{C}} \;+\; H_2O \;\rightleftharpoons\; \underset{\underset{\textstyle H \qquad H}{}}{\overset{\overset{\textstyle HO\qquad OH}{}}{C}} \qquad K = 40$$

formaldehyde $\qquad\qquad\qquad\qquad$ formalin

$$Cl_3C-\overset{\overset{\textstyle O}{\|}}{C}-H \;+\; H_2O \;\rightleftharpoons\; Cl_3C-\overset{\overset{\textstyle HO\;\;OH}{\diagdown\diagup}}{C}-H \qquad K = 500$$

chloral $\qquad\qquad\qquad\qquad\qquad$ chloral hydrate

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Nucleophilic Addition of Hydrogen Cyanide (Cyanohydrins)
Hydrogen cyanide is a *toxic* volatile liquid (b.p.26°C).

$$H\text{-}CN + H_2O \rightarrow H_3O^+ + {}^-CN \qquad pK_a = 9.2$$
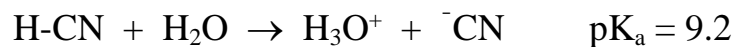
Cyanide is a strong base (HCN weak acid) and a good nucleophile.

Cyanide reacts rapidly with carbonyl compounds producing *cyanohydrins*, via the base catalyzed nucleophilic addition mechanism.

ketone or aldehyde   intermediate   cyanohydrin

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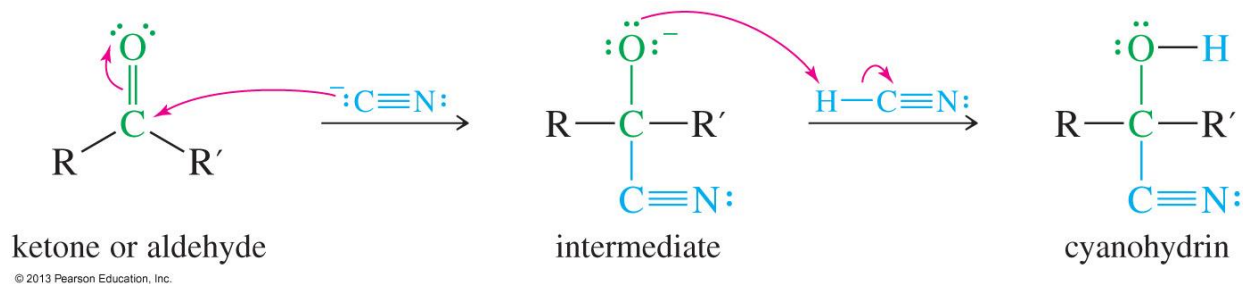
Like hydrate formation, cyanohydrin formation is an equilibrium governed reaction (i.e. reversible reaction), and accordingly aldehydes are more reactive than ketones.

Formation of Imines (Condensation Reactions)

Under appropriate conditions, primary amines (and ammonia) react with ketones or aldehydes to generate **imines**.

ketone or aldehyde   +   primary amine $\rightleftharpoons$ carbinolamine $\rightleftharpoons$ imine (Schiff base)   + H_2O
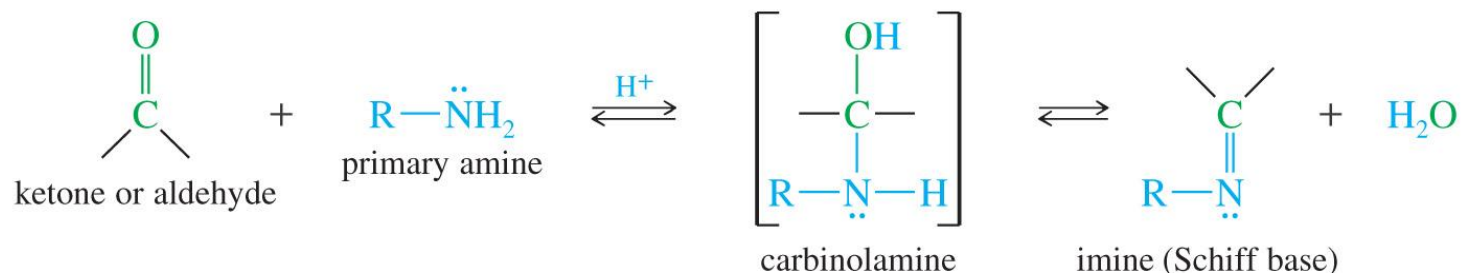
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An *imine* is a nitrogen analogue of a ketone (or aldehyde) with a C=N nitrogen double bond instead of a C=O.

Just as amines are nucleophilic and basic, so are imines.

(Sometimes *substituted* imines are referred to as *Schiff's bases*).

Imine formation is an example of a *condensation reaction* - where two molecules join together accompanied by the expulsion of a small molecule (usually water).

The mechanism of imine formation starts with the addition of the amine to the carbonyl group.
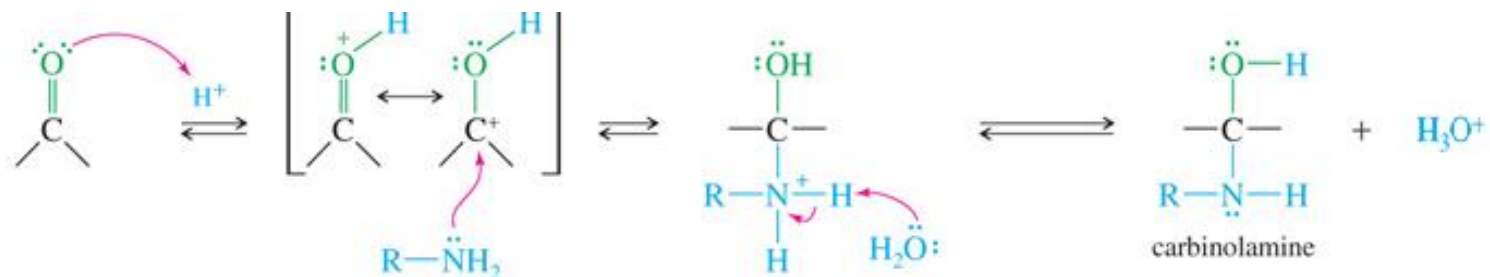
Protonation of the oxyanion and deprotonation of the nitrogen cation generates an unstable intermediate called a *carbinolamine*.
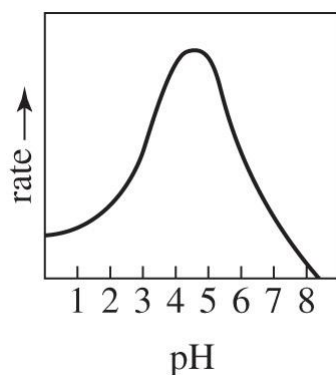

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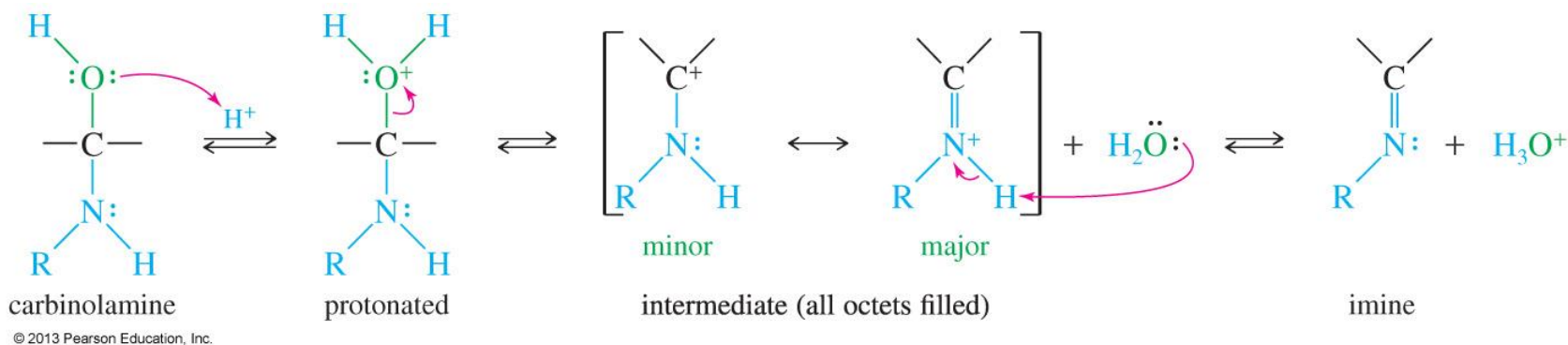
The carbinolamine has its oxygen protonated, and then water acts as the good leaving group.

This *acid catalyzed dehydration* creates the double bond, and the last step is the removal of the proton to produce the neutral amine product.

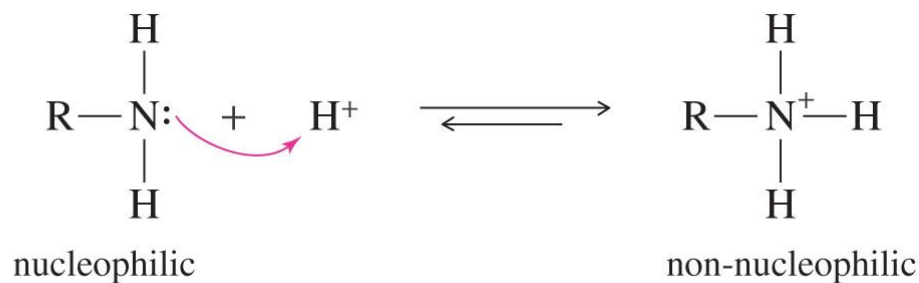The pH of the reaction mixture is **crucial** to successful formation of imines.

The pH must be **acidic** to promote the dehydration step, yet if the mixture is <u>too</u> <u>acidic</u>, then the reacting amine will be protonated, and therefore un-nucleophilic, and this would inhibit the first step.

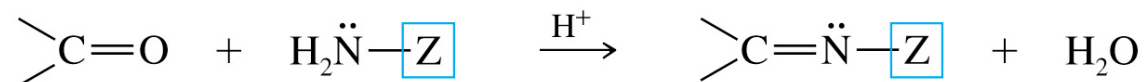The rate of reaction varies with the pH as follows:

The best pH for imine formation is around 4.5.

Condensations with Hydroxylamines and Hydrazines
Aldehydes and ketones also condense with other ammonia derivatives, such as *hydroxylamine* and *hydrazines*.

Generally these reactions are better than the analogous amine reactions (i.e. give superior yields).

$$\text{>C=O} \quad + \quad \text{H}_2\ddot{\text{N}}\!-\!\boxed{\text{Z}} \quad \xrightarrow{\text{H}^+} \quad \text{>C=}\ddot{\text{N}}\!-\!\boxed{\text{Z}} \quad + \quad \text{H}_2\text{O}$$

Z in Z—NH$_2$	*Reagent*	*Product*
—H	H$_2\ddot{\text{N}}$—$\boxed{\text{H}}$ ammonia	>C=$\ddot{\text{N}}$—$\boxed{\text{H}}$ an imine
—R	H$_2\ddot{\text{N}}$—$\boxed{\text{R}}$ primary amine	>C=$\ddot{\text{N}}$—$\boxed{\text{R}}$ an imine (Schiff base)
—OH	H$_2\ddot{\text{N}}$—$\boxed{\text{OH}}$ hydroxylamine	>C=$\ddot{\text{N}}$—$\boxed{\text{OH}}$ an oxime
—NH$_2$	H$_2\ddot{\text{N}}$—$\boxed{\text{NH}_2}$ hydrazine	>C=$\ddot{\text{N}}$—$\boxed{\text{NH}_2}$ a hydrazone
—NHPh	H$_2\ddot{\text{N}}$—$\boxed{\text{NHPh}}$ phenylhydrazine	>C=$\ddot{\text{N}}$—$\boxed{\text{NHPh}}$ a phenylhydrazone
$-\text{NH}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{NH}_2$	H$_2\ddot{\text{N}}$—$\boxed{\text{NH}-\overset{\overset{\text{O}}{\|}}{\text{C}}-\text{NH}_2}$ semicarbazide	>C=$\ddot{\text{N}}$—$\boxed{\text{NH}-\overset{\overset{\text{O}}{\|}}{\text{C}}-\text{NH}_2}$ a semicarbazone

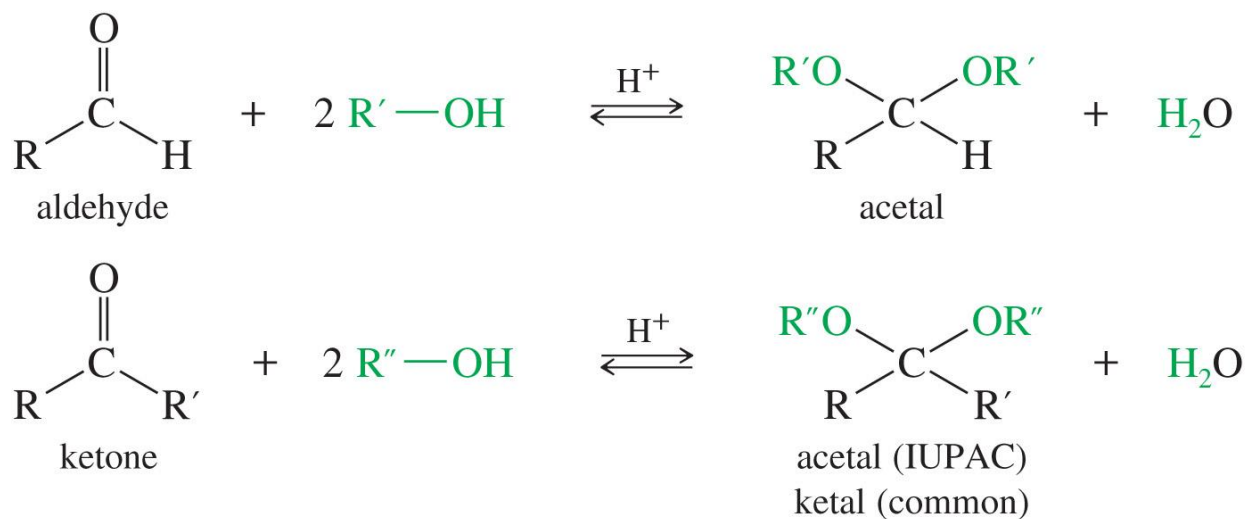*Oximes* are produced when *hydroxylamines* are reacted with aldehydes and ketones.

Hydrazones are produced through reaction of *hydrazines* with aldehydes and ketones.

Semicarbazones are formed from reaction with *semicarbazides*.
These derivatives are often used in practical organic chemistry for characterization and identification of the original carbonyl compounds (by melting point comparison, etc.).

Formation of Acetals (Addition of Alcohols)

In a similar fashion to the formation of hydrates with water, aldehydes and ketones form **acetals** through reaction with **alcohols**.

aldehyde   acetal

$$R-\underset{H}{\overset{O}{\parallel}}C \quad + \quad 2\,R'-OH \quad \underset{}{\overset{H^+}{\rightleftharpoons}} \quad \underset{R\quad H}{\overset{R'O\quad OR'}{C}} \quad + \quad H_2O$$

ketone   acetal (IUPAC)
                         ketal (common)

$$R-\underset{R'}{\overset{O}{\parallel}}C \quad + \quad 2\,R''-OH \quad \underset{}{\overset{H^+}{\rightleftharpoons}} \quad \underset{R\quad R'}{\overset{R''O\quad OR''}{C}} \quad + \quad H_2O$$
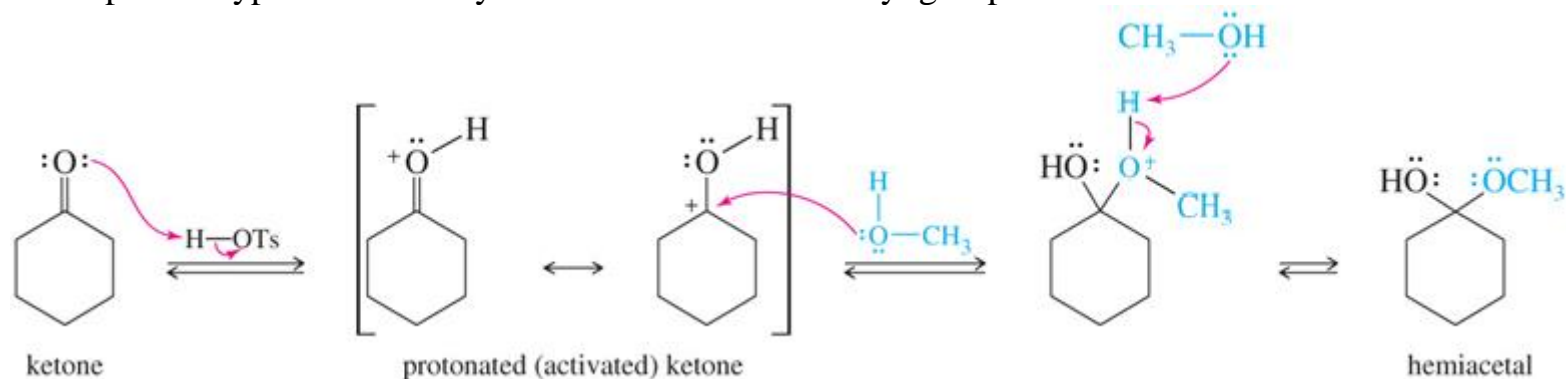
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In the formation of an *acetal*, two molecules of alcohol add to the carbonyl group, and one mole of water is eliminated.

Acetal formation *only* occurs with *acid* catalysis.

Mechanism of Acetal Formation
The first step is the typical acid catalyzed addition to the carbonyl group.

ketone   protonated (activated) ketone   hemiacetal

The *hemiacetal* reacts further to produce the more stable acetal:

The second half of the mechanism starts with protonation of the hydroxyl group, followed by its leaving.

hemiacetal   protonation, loss of water   resonance-stabilized carbocation

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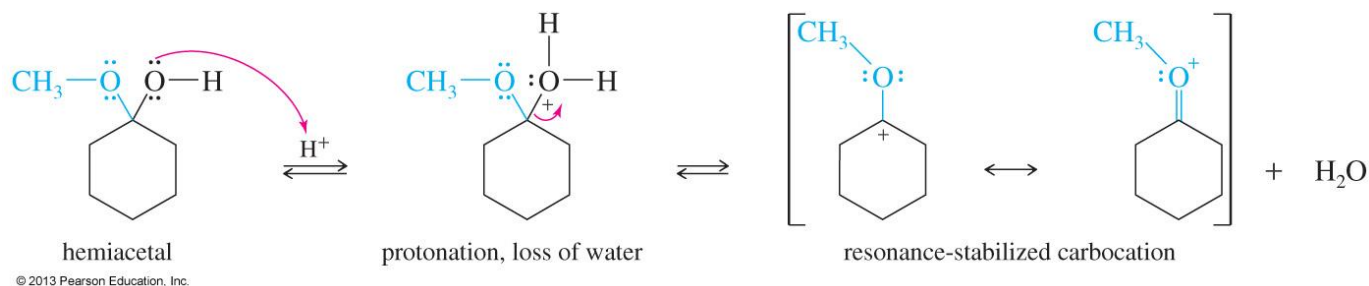
The carbocation thus generated is resonance stabilized, and attack of the alcohol, after proton loss, produces the final acetal.

attack by methanol   acetal

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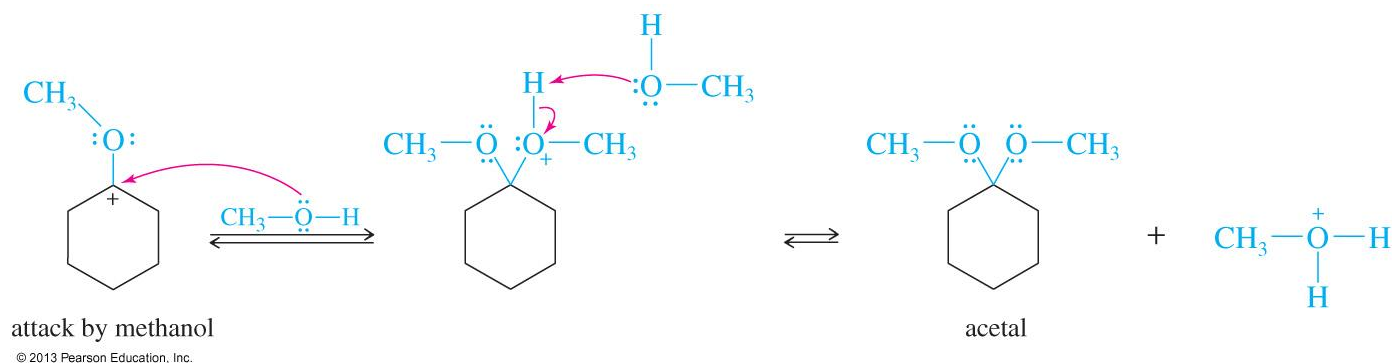
The second step (and therefore overall transformation) requires the *acidic* conditions to aid the replacement of the hydroxyl group (-OH is a bad leaving group, yet -OH$_2^+$ is a good leaving group).

Cyclic Acetals
More commonly, instead of two molecules of alcohols being used, a diol is used (entropically more favorable). This produces *cyclic acetals*.

E.g.
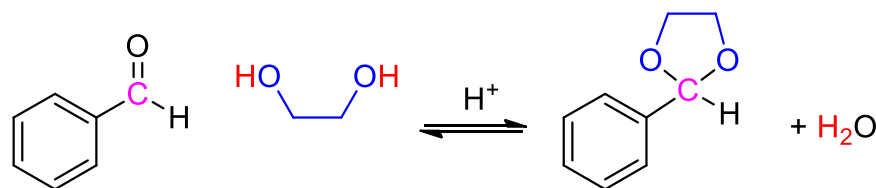
Ethane-1,2-diol (ethylene glycol) is usually the diol of choice, and the products are called ethylene acetals.

(Dithiane is a sulfur analogue of a cyclic acetal).

Acetals as Protecting Groups

Acetals will hydrolyze under acidic conditions, but are *stable* to strong bases and nucleophiles.

They are also easily formed from aldehydes and ketones, and also easily converted back to the parent carbonyl compounds.

These characteristics make acetals ideal **protecting groups** for aldehydes and ketones.

They can be used to 'protect' aldehydes and ketones from reacting with strong *bases* and *nucleophiles*.

Consider the strategy to prepare the following compound:
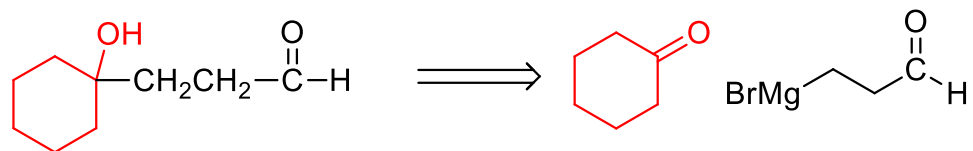
We might decide to use the Grignard reaction as shown above.

However, having a <u>Grignard</u> functionality and an <u>aldehyde</u> in the **same molecule** is bad news since they will react with one another.
The strategy is still okay, we just need to 'protect' the aldehyde as some unreactive group - an acetal.

The acetal group is unreactive towards Grignard reagents (strong nucleophiles), and therefore this would be a viable reagent.
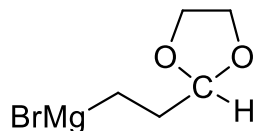
The "masked" aldehyde can be safely converted to the Grignard reagent, and then this can react with cyclohexanone.
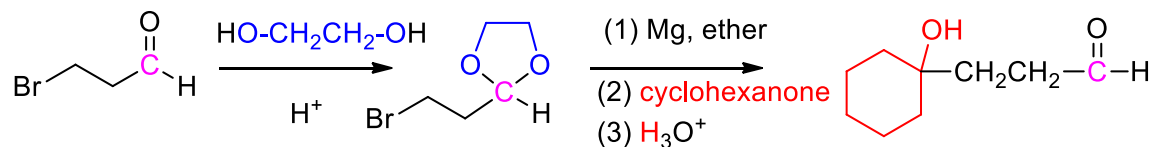
The acetal is easily removed with acidic hydrolysis (which is also required to remove the $MgBr^+$ from the oxyanion), giving the final product.

Selective Acetal Formation

We have previously seen that aldehydes are more reactive than ketones (**two reasons**), and therefore aldehydes will react to form acetals *preferentially* over ketones.

This means we can *selectively* protect aldehydes in the presence of ketones. (Remember to use only 1 equivalent!)
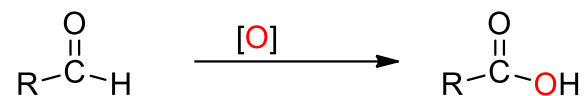
E.g.
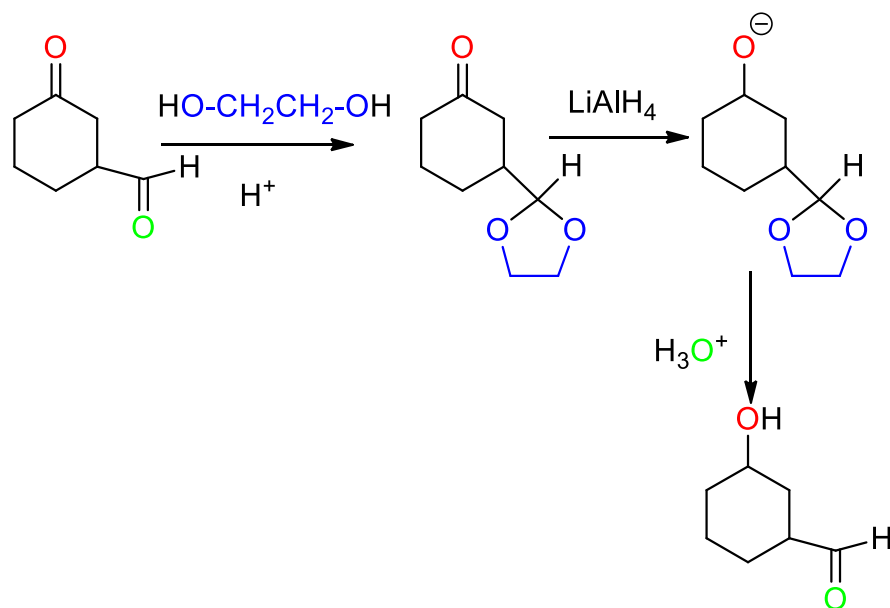
This is a useful way to perform reactions on ketone functionalities in molecules that contain *both* aldehyde and ketone groups.

(To selectively do reactions on the aldehyde, just do them!)

Oxidation of Aldehydes

Unlike ketones, aldehydes can be oxidized easily to carboxylic acids (Chromic acid, permanganate etc.).

$$R-\overset{\overset{\displaystyle O}{\|}}{C}-H \quad \xrightarrow{[O]} \quad R-\overset{\overset{\displaystyle O}{\|}}{C}-OH$$

Even weak oxidants like silver (I) oxide can perform this reaction, and this is a good, mild selective way to prepare carboxylic acids in the presence of other (oxidizable) functionalities.
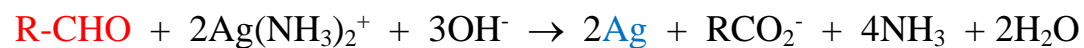E.g.
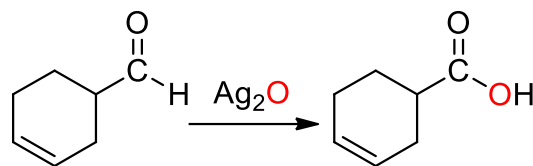
(E.g. could **not** use permanganate, for this transformation).

Silver Mirror Test (Tollens' Test)

This type of *oxidation* reaction is the basis of the most common chemical test for aldehydes - the Silver Mirror Test.

Tollens' reagent is added to an unknown compound, and if an aldehyde is present, it is oxidized.
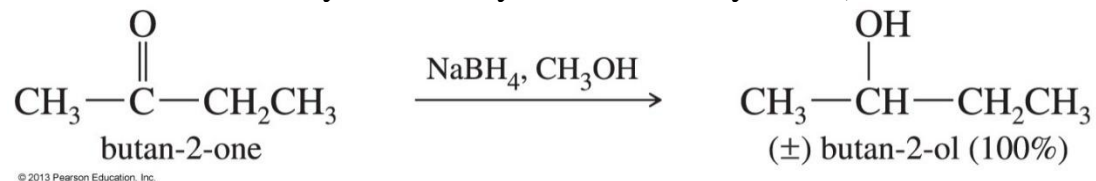
$$\text{R-CHO} + 2\text{Ag(NH}_3)_2{}^+ + 3\text{OH}^- \rightarrow 2\text{Ag} + \text{RCO}_2{}^- + 4\text{NH}_3 + 2\text{H}_2\text{O}$$

This process reduces the Ag^+ to Ag, and the Ag precipitates - it sticks to the flask wall, and forms a 'silver mirror'.

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Reduction of Ketone and Aldehydes

Aldehydes and ketones are most commonly reduced by sodium borohydride (Ch12, and earlier this chapter).

$NaBH_4$ reduces ketones to secondary alcohols, and aldehydes to primary alcohols.
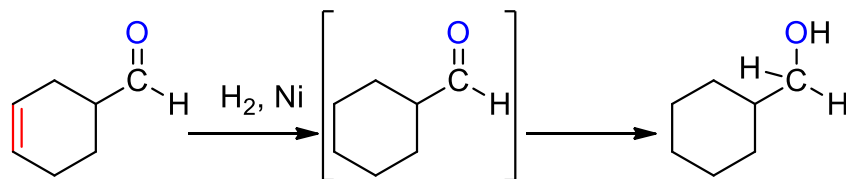
Other Reductions

Catalytic Hydrogenation
Just as C=C double bonds can be reduced by the addition of hydrogen across the double bond, so can C=O double bonds.

Carbonyl double bonds are reduced much more slowly than alkene double bonds.

Therefore, you cannot reduce a C=O in the presence of a C=C without reducing both (by this method).
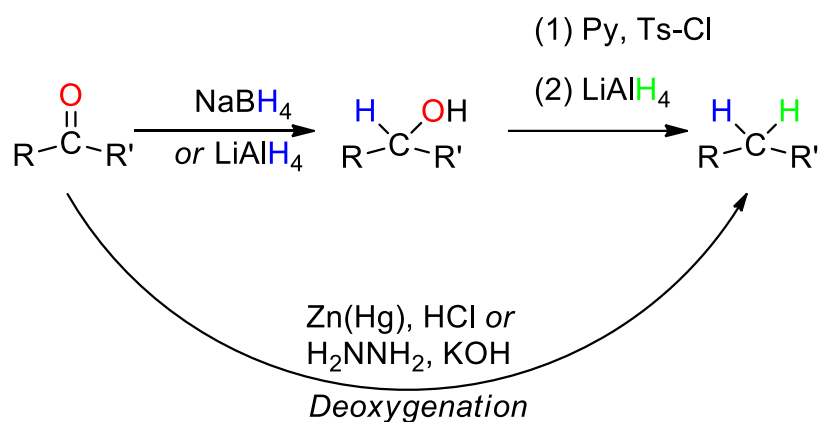
E.g.

The most common catalyst for these hydrogenations is Raney nickel, although Pt and Rh can also be used.

Deoxygenation of Ketones and Aldehydes

Deoxygenation involves the *removal of oxygen*, and its replacement with two hydrogen atoms.

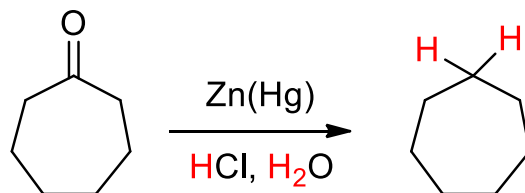This reduction takes the carbonyl (past the alcohol) to a methylene group.

Compare the following reduction processes:

Clemmensen Reduction (recap?)

This was used in the reduction of acyl benzenes into alkyl benzenes, but it also works for other aldehydes and ketones.
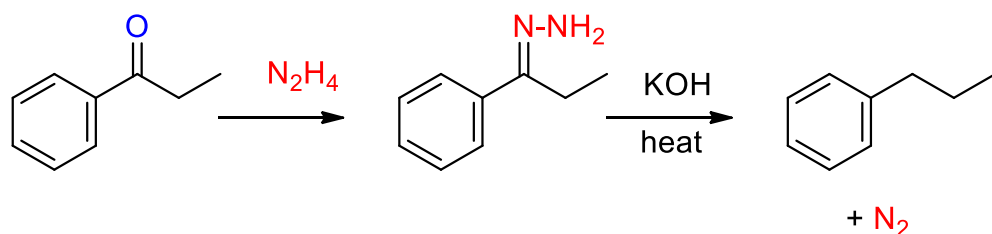
    E.g.

Wolff-Kishner

Sometimes the **acidic** conditions used in the Clemmensen reduction are unsuitable for a given molecule.

In these cases, **Wolff-Kishner** reduction is employed.
The ketone or aldehyde is converted to its hydrazone (by reaction with hydrazine) and is then treated with a strong base, which generates the reduced product.

E.g.

The mechanism of hydrazone formation is analogous to imine formation.

The strongly basic conditions then deprotonate the hydrazone, and the anion produced is resonance stabilized.
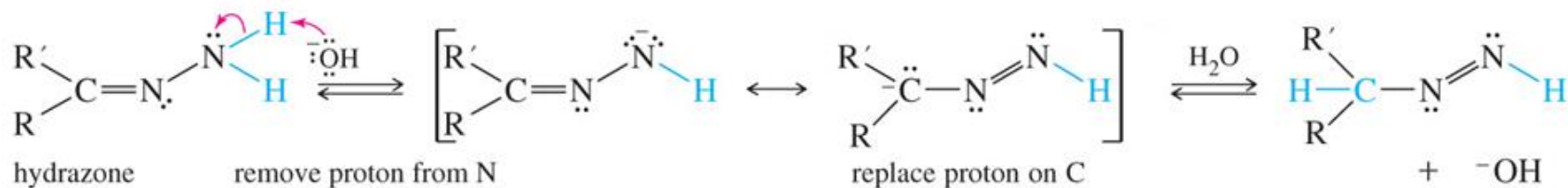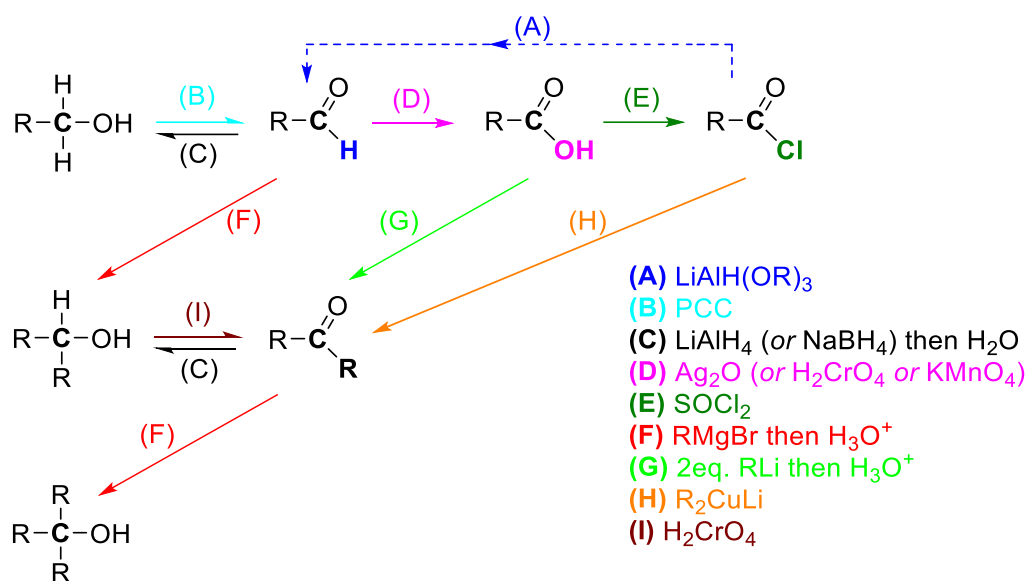
The carbanionic form picks up a proton, and another deprotonation of the nitrogen generates an intermediate which is set up to eliminate a molecule of nitrogen (N_2) and produce a carbanion.
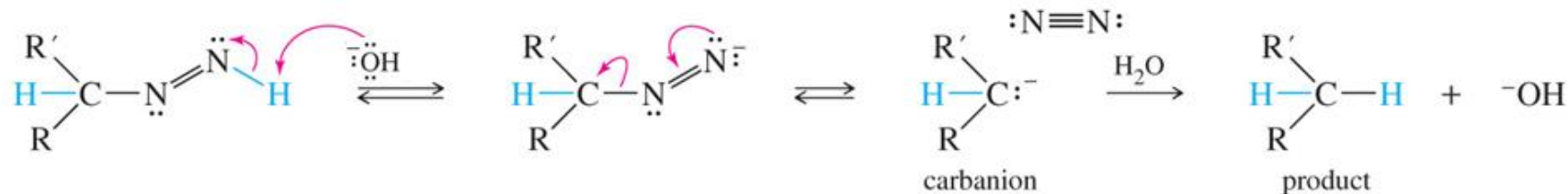
This carbanion is quickly protonated, giving the final reduced product.

ALDEHYDES & KETONES

Functional Group	Product	Reagent
Alkene	Aldehyde &/or Ketone	O_3, CH_3SCH_3
Aromatic	Aryl Aldehyde	CO, HCl, CuI, $AlCl_3$
	Aryl Ketone	RCOCl, $AlCl_3$
Terminal Alkyne	Aldehyde	R_2BH, H_2O_2, NaOH
(Term. and Int.) Alkyne	Ketone	$HgSO_4$, H_2SO_4, H_2O
1,3-Dithiane	Aldehyde	BuLi; RX then H_3O^+, $HgCl_2$
	Ketone	BuLi; RX; BuLi, R'X then H_3O^+, $HgCl_2$
Nitrile	Ketone	RMgBr then H_3O^+

(A) LiAlH(OR)$_3$
(B) PCC
(C) LiAlH$_4$ (*or* NaBH$_4$) then H$_2$O
(D) Ag$_2$O (*or* H$_2$CrO$_4$ *or* KMnO$_4$)
(E) SOCl$_2$
(F) RMgBr then H$_3$O$^+$
(G) 2eq. RLi then H$_3$O$^+$
(H) R$_2$CuLi
(I) H$_2$CrO$_4$

Nuc Addition		**ACIDIC** H$^+$ then Nuc$^-$ **BASIC** Nuc$^-$ then H$^+$	ALDEHYDES *more reactive* than KETONES. (CYCLIC ACETALS as *Protecting Groups*). **Deprotect** with **H$_3$O$^+$**
Condensation			
Wittig		Using PPh$_3$ / BuLi	
Reduction		**(A)** Zn(Hg), HCl, H$_2$O **(B)** H$_2$NNH$_2$, KOH **(C)** LiAlH$_4$ (*or* NaBH$_4$), then H$_2$O **(D)** Ts-Cl, Py, then LiAlH$_4$ (*or* NaBH$_4$)	

Aldehyde & Ketone AJR Summary