Overview of Carbonyl Compounds.

   a) Aldehydes and ketones – RCOH and R₂CO. No leaving group attached to carbonyl C. Oxidation state +2.
   b) Carboxylic acids and their derivatives: esters, amides, acyl chlorides, acyl anhydrides (RCO-O-COR). One leaving group attached to carbonyl C. Oxidation state +3. Nitriles are honorary members of the carboxylic acid family, and have much the same reactivity.
   c) Carbonates (RO-CO-OR) and their derivatives: urethanes (carbamates, \( \text{H}_2\text{NCOOR} \)), ureas (\( \text{H}_2\text{NCONH}_2 \)). Two leaving groups attached to carbonyl C. Oxidation state +4.
   d) CO₂.

2. Reactivity of carbonyl compounds.
   a) Basic at O. O reacts with H⁺ or other Lewis acids such as BF₃, etc. Not much else.
   b) Electrophilic at carbonyl C. Under basic conditions, reacts as is. Under acidic conditions, O is protonated to give a compound even more electrophilic at C.
   c) Acidic at \( \alpha \)-C (e.g. CHR₂COR). Acidic because of electrophilic nature of carbonyl C. Under basic conditions, bases deprotonate immediately to give enolate. Under acidic conditions, protonated on O first, then weak base deprotonates at C to give enol. Both enolate and enol are nucleophilic at C (and O).

Nucleophilic Addition to Aldehydes and Ketones.

The best way to think of an aldehyde or ketone (or just about any carbonyl compound) is with a slight positive charge on carbon, and a slight negative charge on oxygen (see Figs 16.4 and 16.6):

![Diagram of nucleophilic addition to aldehydes and ketones]

Just about all of the chemistry of carbonyl compounds is explained by the oxygen being slightly nucleophilic (thus easily protonated) and the carbon being strongly electrophilic. Remember this!

1. Nomenclature.
   a) Aldehydes: common names are normally used for aldehydes containing 4 carbons or fewer then systematic naming takes over.
ii) Common names - formaldehyde, acetaldehyde, propionaldehyde, acrolein (H₂C=CHCHO), benzaldehyde.
i) Systematic – Alkanal- replace the terminal e of the corresponding alkane with al; methanal, ethanol, propanal, 2-propenal,
For aldehydes in which the CHO group is attached to a ring, the suffix carbaldehyde is used; benzenecarbaldehyde

b) Ketones.
i) Systematic. Alkanone - Propanone, 2-butanone, 5-hexen-3-one, 1-phenyl-1-ethanone. 3-Oxobutanoic acid.
ii) Common name- Acetone, acetophenone, benzophenone.

Preparation:
Aldehydes:
1) Oxidation of a primary alcohol with PCC (pyridinium chlorochromate) in CH₂Cl₂ at room temp.

\[
\text{citronellol} \quad \text{CH₂OH} \quad \xrightarrow{\text{PCC}} \quad \text{citronellal} \quad \text{CHO}
\]

\[
\text{[ } \text{CrO₃Cl} \text{]} = \text{PCC}
\]

2) Ozonolysis of an alkene with at least one vinylic hydrogen

\[
\text{O₃, -30 °C} \quad \text{Me₂S, 0 °C}
\]

REVIEW these reactions!
3) Reduction of an Acyl Halide.
Acyl halides can be reduced with a special reagent - lithium tri(t-butoxy) aluminum hydride, LiAl(O-t-Bu)₃H :

Alternately, aldehydes can be prepared from esters with DIBAH (diisobutylaluminum hydride). Typically, it is easier to reduce all the way to a primary alcohol (you need 2 equivalents of DIBAH for this), then re-oxidize:
Ketones
1) Oxidation of secondary alcohols – usually by the Swern oxidation (Me$_2$SO, ClCOCOCl, Et$_3$N), or with PCC
2) Ozonolysis of an alkene (if one of the unsaturated carbon atoms is disubstituted)

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{H} \\
\text{H}_3\text{C} & \quad \text{CH}_3
\end{align*}
\]

1. $\text{O}_3$
2. $\text{Me}_2\text{S}$

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

3) Friedel-Crafts Acylation.

Below is the preparation of a ketone sequentially from a primary alcohol (through an intermediate aldehyde):

Some ketones can also be prepared from acyl halides and organo-copper reagents (called lithium dialkylcuprates), as shown below:

Further oxidation of aldehydes and ketones:
As you might imagine, most ketones are inert to all but the harshest oxidative conditions, and thus there is no synthetic utility in trying to oxidize them. However, aldehydes can generally be oxidized to carboxylic acids under relatively mild conditions:

Reactivity of Carbonyl compounds.
- aldehydes are much more reactive than ketones; they undergo nucleophilic addition:

\[\text{Nu} \quad \rightarrow \quad \text{O}^{-} \quad \rightarrow \quad \text{H}_2\text{O} \quad \rightarrow \quad \text{OH} \]

- carbonyl compound that contain leaving groups undergo nucleophilic substitution

\[\text{Nu} \quad \rightarrow \quad \text{O}^{-} \quad \rightarrow \quad \text{Z}^{-} \]

Reactivity increases as leaving group ability increases: $\text{NH}_2$<OH~OR<Cl
Nucleophilic addition to aldehydes and ketones.
a) Under basic conditions, nucleophiles (usually anionic, except for amines) add to neutral carbonyl compounds. After the addition, the former carbonyl O is protonated to give the product (see above)
i) Lone pair nucleophiles. HO⁻, RO⁻, RC=C⁻, C=N, H₃N, RNH₂.
ii) Sigma bond nucleophiles. NaBH₄ and LiAlH₄ (H⁻ sources), Grignard reagents such as EtMgBr or PhMgBr (R⁻ sources), organolithium reagents such as CH₃Li.
b) Under acidic conditions, nucleophiles (always neutral) add to protonated carbonyl compounds. H₂O, ROH, H₃N, RNH₂. After the addition, the nucleophilic atom is deprotonated to give the product.

Reversible nucleophilic addition to aldehydes and ketones.
Ketones and aldehydes in aqueous or alcoholic media frequently react reversibly with the medium to form hydrates or hemiacetals.
a) Carbonyl + H₂O + (acid or base) → ← hydrate. Slow in pure H₂O! Equilibrium favors hydrate only for carbonyl compounds with electron-withdrawing groups on α-C's, e.g. Cl₃CCHO (chloral). Thus, while acetophenone exists mostly as the ketone, trichloroacetaldehyde (chloral) exists almost entirely as the hydrate (if exposed to water):

b) Carbonyl + ROH + (acid or base) → ← hemiacetal. Slow in pure ROH! Equilibrium favors hemiacetal only for carbonyl compounds with electron-withdrawing groups on α-C's; take chloroacetaldehyde in methanol, for example:
Why do these hydrates and hemiacetals form better with electron-withdrawing substituents? Remember the polar nature of the carbonyl group? The mechanism for these additions is relatively straightforward:

![Mechanism Diagram]

This is the mechanism for the reaction in neutral media. As an exercise at home, figure out the mechanism in basic media (say, using MeOH/MeONa).

**Acetal and ketal formation.**

In acidic alcoholic media, an acetal is formed:

\[ RCHO \text{ or } R_2CO + R'OH + \text{cat. } H^+ \rightarrow \text{RCH(OR')}_2 \text{ or } R_2C(OR')_2 + H_2O. \]

The reaction involves nucleophilic addition followed by substitution and proceeds through **hemiacetal**. Equilibrium is pushed toward acetal by removal of \( H_2O \); and pushed toward carbonyl by addition of \( H_2O \)

![Acetal Formation Diagram]

The mechanism is quite straightforward:

![Mechanism Diagram]

Basically, this mechanism involves a series of protonation, nucleophile attack, and deprotonation steps. **Note that** acetal formation **CANNOT** occur under basic catalysis. Convince yourself that this is true...if you can’t, come see me.

Note also **that these steps are all in equilibrium** hence the reaction can be forced to the acetal by doing it under anhydrous conditions (or by distilling off
the water), or forced back to the ketone/aldehyde by the addition of excess water in the presence of acid (making it the perfect protecting group!):

Thus, the carbonyl group of an aldehyde or a ketone can be protected in the form of an acetal or ketal. Deprotection following reaction on other regions of the molecule then yields the carbonyl group again - this then is the first protection/deprotection protocol we have encountered.

In general, simple alcohols like methanol and ethanol are not used in the formation of acetals (particularly from less-reactive ketones!) The main reason is entropy - you've got to get three molecules together to form one - that's not so good! Acetal formation is most convenient with diols, such as ethylene glycol. Entropy favors second reaction. It is very common to use a glycol - ethylene or propylene glycol – to form a cyclic acetal:

As you would expect for ethers, acetals are stable to base and most nucleophiles, such as Grignard reagents and alkylolithiums. They revert back to the carbonyl compound on exposure to aqueous acid.

iii) Acetal formation can be selective for aldehydes over ketal formation from ketones- ketones react more slowly due presumably to sterics

iv) Acetal formation does not work well for esters or acids!

Irreversible nucleophilic additions: organometallic reagents.

a) Grignard and organolithium reagents made from halides.

\[
\begin{align*}
R-X + 2 \text{Li} & \rightarrow R\text{Li} + \text{LiX} \\
R-X + \text{Mg} & \rightarrow R\text{-Mg-X} \\
2R\text{-Li} + \text{Cul} & \rightarrow R\text{-CuLi} + \text{Li}\text{I} \\
\text{lithium dialkylcuprates} & \\
\text{less reactive than organolithium or} & \\
\text{Grignard reagents} & \\
\text{only one R group is utilized in reaction} \\
\end{align*}
\]
- these reagents are strong bases as well as nucleophiles and readily abstract a proton from water to form hydrocarbons. Hence, they have to be used under anhydrous conditions.

(i) Reaction with aldehydes and ketones

Formaldehyde + RMgBr → 1° alcohol; Aldehyde + RMgBr → 2° alcohol; ketone + RMgBr → 3° alcohol. Work-up necessary. **Another way to make C–C bond!**

Aldehydes and ketones that also contain N-H or O-H bonds undergo an acid-base reaction with organometallic reagents. We can overcome this problem via a protection-deprotection strategy.

An O-H group is commonly protected as a silyl ether using TBDMS-Cl; the protecting group is TBDMS (tert-butyldimethylsilyl).

A 1° or 2° amine can be protected by reaction with phenacylsulfonyl chloride (PhCOCH$_2$SO$_2$Cl) to form a sulfonamide (PhCOCH$_2$SO$_2$NHR or (PhCOCH$_2$SO$_2$NR)$_2$). Deprotection can be achieved using Zn/CH$_3$COOH.

(ii) Reaction with carboxylic acid derivatives

- Grignard or organolithium reagents always form 3° alcohols when they react with esters and acid chlorides.

- to form a ketone from a carboxylic acid derivative, a less reactive organometallic reagent, i.e. an organocuprate is required. Acid chlorides react with organocuprates to give a ketone but esters do not react with organocuprates.
Related reactions of organometallic reagents with other compounds include:

(1) ring opening of epoxides to form alcohols:

\[
\begin{align*}
\text{O} & \quad \xrightarrow{1. \text{RLi, RMgX, or R}_2\text{CuLi}} \quad \text{OH} \\
\text{C} & \quad \text{Cl} & \quad 2. \text{H}_2\text{O} & \quad \text{OH} \\
\end{align*}
\]

(2) 1,2- and 1,4-additions to \(\alpha,\beta\)-unsaturated aldehydes and ketones

- \(\alpha,\beta\)-unsaturated compounds have two electrophilic sites as evident from the 3 possible resonance forms that can be drawn:

\[
\text{CH}_2=\text{CHCH} & \equiv \text{CH} \quad \equiv \text{CH} \equiv \text{CHCH}_2 \\
= \text{the nature of the organometallic reagent determines whether it will react with an } \alpha,\beta\text{-unsaturated aldehyde or ketone via } 1,2\text{- or } 1,4\text{-addition.}
\]

- RLi and RMgX reagents form 1,2 addition products; e.g.

\[
\begin{align*}
\text{H}_3\text{C} & \equiv \text{CH} \equiv \text{CH}_2 & \quad \xrightarrow{1. \text{PhLi}} & \quad \text{H}_3\text{C} \equiv \text{CH} \equiv \text{CH}_2 \\
& \quad \xrightarrow{2. \text{H}_2\text{O}} & \quad \text{H}_3\text{C} \equiv \text{CH} \equiv \text{CH}_2 \\
\end{align*}
\]

- organocuprate reagents form 1,4-addition products

\[
\begin{align*}
\text{H}_3\text{C} & \equiv \text{CH} \equiv \text{CH}_2 & \quad \xrightarrow{1. (\text{CH}_3)_2\text{CuLi}} & \quad \text{H}_3\text{C} \equiv \text{CH} \equiv \text{CH}_3 + \text{OH} \\
& \quad \xrightarrow{2. \text{H}_2\text{O}} & \quad \text{H}_3\text{C} \equiv \text{CH} \equiv \text{CH}_3 + \text{OH} \\
\text{H}_3\text{C} & \equiv \text{CH} \equiv \text{CH}_2 & \quad \xrightarrow{\text{H}_2\text{O}} & \quad \text{H}_3\text{C} \equiv \text{CH} \equiv \text{CH}_2 \\
& \quad \xrightarrow{\text{tautomerization} (\text{base-catalyzed})} & \quad \text{H}_3\text{C} \equiv \text{CH} \equiv \text{CH}_2 \\
\end{align*}
\]

b) Reduction of Aldehydes and Ketones with metal hydrides

Aldehyde + NaBH\(_4\) or LiAlH\(_4\) \(\rightarrow\) 1° alcohol; ketone + NaBH\(_4\) or LiAlH\(_4\) \(\rightarrow\) 2° alcohol. Workup necessary.

NaBH\(_4\) selectively reduces aldehydes and ketones in the presence of most other functional groups; LiAlH\(_4\) is less selective (also reduces esters, acid chlorides, etc).

\[
\begin{align*}
\text{O} & \quad \text{CH}_3 & \quad \text{CH}_2 \\
\text{H}_2\text{O} & \quad \text{H}_2\text{O} & \quad \text{OH} \\
\end{align*}
\]
(i) Catalytic Hydrogenation of aldehydes and ketones

\[
\text{NaBH}_4, \text{CH}_3\text{OH} \quad \text{H}_2(1 \text{ equiv}), \text{Pd/C} \quad \text{H}_2(\text{excess}), \text{Pd/C}
\]

A C=C bond is reduced faster than C=O bond with H\textsubscript{2} and Pd/C
A C=O bond is readily reduced with NaBH\textsubscript{4} and LiAlH\textsubscript{4} but a C=C bond is inert.

CBS Reagents for Enantioselective Carbonyl reductions
- formed by reaction of BH\textsubscript{3} and an oxazaborolidine

\[
\begin{align*}
\text{N-B-O} & \quad + \quad \text{BH}_3 \\
\text{active reductant} & \quad \text{(S)-CBS reagent}
\end{align*}
\]

(S)-oxazaborolidine
only catalytic amounts needed
- the (R)-CBS reagent is similar made from (R)-oxazaborolidine.
- CBS reagents are best when the ketone’s two substituents are sterically well differentiated, such as in ArCOR

\[
\begin{align*}
\text{(S)-CBS reagent} & \quad \text{H}_2\text{O} \\
\text{R isomer major product} & \quad \text{(topside attack)}
\end{align*}
\]

\[
\begin{align*}
\text{(R)-CBS reagent} & \quad \text{H}_2\text{O} \\
\text{S isomer major product} & \quad \text{(bottom side attack)}
\end{align*}
\]
(ii) Reduction of carboxylic acid derivatives
LiAlH₄ converts RCOCl and RCOOR' to 1˚ alcohols

\[
\begin{align*}
\text{RCOCl} & \xrightarrow{1. \text{ LiAlH}_4, 2H_2O} RCOH + ROH \text{ or LiCl} \\
Z &= \text{Cl or OR'} 
\end{align*}
\]

Milder reagents, such as DiBAL-H or LiAl(Ot-Bu)₃H, convert RCOCl and RCOOR' to RCHO at low temperatures

\[
\begin{align*}
\text{RCOCl} & \xrightarrow{1. \text{ DiBAL-H or LiAl(Ot-Bu)₃H, low T, 2H}_2O} RCHO \\
Z &= \text{Cl or OR'} 
\end{align*}
\]

LiAlH₄ converts RCOOH's to 1˚ alcohols; milder reagents such as Grignards etc. are not strong enough to even initiate the reaction

\[
\begin{align*}
\text{RCOOH} & \xrightarrow{1. \text{ LiAlH}_4, 2H_2O} RCOH \\
\end{align*}
\]

LiAlH₄ converts amidess to amines; below is an alternative mechanism (to the one in your textbook) for the reaction:

\[
\begin{align*}
\text{RCN} & \xrightarrow{\text{LiAlH}_4, 2H_2O} \text{RCONR}_2 \\
R &= \text{H or alkyl} \\
\end{align*}
\]