18.1  \[ H \text{ adds to a } C=O \text{ is much more acidic than other } C-H \text{ bonds} \]
\[ pKa_{CH_3-CH} < pKa_{C=CH-CH} < 4.5-5.0 \]
\[ pKa_{C=C-CH} = 25 \]
\[ \text{but} \]
\[ pKa \text{ of } -C=CH^+ \text{ ranges from } 17-30 \]
\[ \alpha\text{-hydrogen} \rightarrow \text{H} \beta\text{-dcarbonyl compound} \]
\[ pKa \text{ of } -C=CH^+ \text{ ranges from } 6-13 \]
Reason: resonance stabilization of the carbocation

18.2  Keto-enol tautomerism

We've seen this before:
\[
R-C=CH + H_2O \xrightarrow{H^+ \text{ or } OH^-} \]}
\[ (R-C=CH) \rightarrow (R-C=CH_2) \rightarrow RCH=CH_3 \]

18.3 "Enolization" is rapid and reversible
So that enol is always present for any carbonyl compound with \( \alpha \text{-H} \)
18.4 Enols and enolates are electron-rich at carbon, and are good carbon nucleophiles.

18.5 Halogenation of the α-carbon using \( \text{X}_2 \) (di-halogen) is promoted by acid or base. This is a common motif in carboxyl α-substitution; it can be either acid- or base-catalyzed. However, base catalysis is more important (and common) because enolate ions are better nucleophiles than enols. (And also because, with the appropriate base, the population of enolate is large, while the population of enol is always small.)

18.6 The \( \text{H}_2\text{N-} \) reaction is just another acyl α-halogenation reaction, with a twist. Study the mechanism!

18.7 Tells how to use α-halo carboxyl compounds in synthesis, with \( \text{SN}_2 \) nucleophiles, and for \( \text{E}_2 \) reactions.
18.8 Lithium Diisopropyl Amide = LDA
most common base for generating enolate
ion.

Why? \(pK_a(\text{LDA}) = 35\)
\(pK_a\) of most aldehydes & ketones
(and esters and amides) is
(less) than 30.
(Not used with \(\beta\)-dicarbonyl compounds; too strong)

18.9 Enoles (enolate) can react as Sn2 nucleophiles
(seldom Sn1 — why?)

Product: \(\alpha\)-alkyl carboxyl compounds
of various sorts.

18.10 The Enamine Reaction
Enamines are "neutral enulates":

![Enamine structure]

Advantage: (1) react faster than enolate reactions;
typically only mono-alkyl product
see top of p. 868

Advantage: can be used to acylate; this
would not work with strong base enulates.
The Michael reaction

Conjugate addition (17.1b) of a β-dicarbonyl (enolate) to an α,β-unsaturated carbonyl compound.

Conjugate addition of any nucleophile is sometimes called "Michael addition."

The Söderquist reaction is the enamine version of the Michael reaction.

The Aldol addition reaction forms an "aldol" (aldehyde - alcohol) product.

Know the mechanism. The product is a β-hydroxy carbonyl compound...

... fact can eliminate to form an α,β-unsaturated carbonyl compound.

(worked because of the α-H acidity) - E1cb

The combination is "the aldol condensation" which converts an aldehyde or ketone to a "dimer" that is an α,β-unsaturated carbonyl:

\[
2 \text{R} - \text{C} - \text{CH}_3 \xrightarrow{\text{base}} \text{catalysis} \xrightarrow{\Delta} \text{R} - \text{C} - \text{CH} = \text{C} - \text{R} \text{second step}\]

one piece
\[ E_{1cb} = "E1 - conjugate base" \]

This is a common mechanism for elimination beta to a carbonyl group:

\[
\begin{align*}
\text{X} & \quad \text{box} & \quad \text{X} \\
\text{C} \quad \text{C} & \quad \text{C} \quad \text{C} & \quad \text{C} \quad \text{C} \quad \text{C} \\
\end{align*}
\]

Notice this: good leaving groups for E2 or S_N2 reactions must have pK_a lower than about 6 or 7.
But good leaving groups for E1_{CB} can have pK_a up to 25 or 30!!

\[
\begin{align*}
\text{S}_{\text{N}2} & \quad \text{S}_{\text{N}2} \\
\text{C} \quad \text{C} & \quad \text{C} \quad \text{C} \\
\end{align*}
\]

\( \alpha, \beta \)-unsaturated carbonyl compound

ex.

\[
\begin{align*}
\text{NBr} & \quad \text{NBr} \\
\text{C} \quad \text{C} & \quad \text{C} \quad \text{C} \\
\end{align*}
\]
15.14 The mixed Aldol reaction produces 4 possible products. Careful synthetic design can limit the number of possible products to one or two. Two possible ways are shown on p. 875.

15.15 The Claisen condensation

Differs from the Aldol in that an ester has a leaving group: an aldehyde or ketone does not. (p. 877, top)

Product:

2 esters $\rightarrow$ β-Ketoester ("dimer")

15.16 Mixed Claisen condensations have considerations similar to the mixed Aldol condensation. Use only one ester with α-H to limit the possible products.

KNOW THE MECHANISMS of the Aldol & Claisen condensation reactions!
18.17 Aldol + Claisen reactions can be used between two ends of the same molecule to form a ring. "Intramolecular"

Intramolecular Claisen = "Diels-Alder condensation"
Intramolecular Aldol = "Intramolecular Aldol"

These reactions favor the formation of 5 and 6-membered rings because they are reversible; 5 and 6-membered rings are more stable (less strained) as you calculated a month ago.

883 The Ruben Annulation combines a Michael addition with an intramolecular Aldol to form a ring from two molecules.

The product is always a cyclohexenone:

\[ \text{R} \]
Decarboxylation of β-ketoacids

\[ \text{Heat} \rightarrow \text{H} + \text{CO}_2 \]

This allows us to use 18.19 + 18.20

The Malonic ester synthesis allows synthesis of a carboxylic acid from a primary alkyl halide.

\[ R \text{CH}_2-\text{X} + \text{CH}_3\text{CO}_2\text{H} \rightarrow R\text{CH}_2\text{CH}_2\text{CO}_2\text{H} \]

\[ \text{Malonic ester} \xrightarrow{\text{H}^+\text{/H}_2\text{O/heat}} \]

\[ R\text{CH}_2\text{CH}_2\text{CO}_2\text{H} \to R\text{CH}_2\text{CO}_2\text{H} \]

The acetoacetic ester synthesis allows synthesis of a methyl ketone in the same way:

\[ R \text{-X} + \text{CH}_3\text{C}==\text{O} \xrightarrow{\text{Heat}} R\text{-CH}_3\text{C}==\text{O} \]
18.12 Designing synthesis

You need to go through the reaction in Ch. 18 (see the summary pp. 595-624) and carefully list what the reaction starts with and how the pieces end up put together.

All of Ch. 18 has been about putting small molecules together into bigger ones.

Note how (for example) the product of an Aldol + the product of a Claisen can get together in a Michael reaction, or the fact that the Claisen reaction of ethyl ethanoate forms an acetoacetic ester that can be used in the acetoacetin ester synthesis!

18.12 FYI