References:

Synthesis
(from the Greek word synthesis \([ \textit{Suntithenai} ] = [\textit{Sun}(together) + \textit{tithenai}(to put)] = \)
the process of putting together)

Synthetic chemistry
is the science of constructing molecules from atoms and/or (usually) simpler molecules.

→ synthetic organic chemistry
→ synthetic inorganic chemistry
total synthesis is the chemical synthesis of a molecule, usually a natural product, from relatively simple starting materials.
ORGANIC SYNTHESIS

Target Oriented (Total Synthesis)
- Natural Products
- Designed Molecules

Methods Oriented
- Reagents
- Catalysts
- Synthetic Strategies
- Synthetic Tactics

Materials Science
- Interesting Molecules

Biologically Interesting Molecules

Theoretically Interesting Molecules

Medically Interesting Molecules
Organic synthesis

1. Design of a synthesis
2. Constraction reactions
3. Functional group interconversions
4. Stereochemistry
1. Design of synthesis
   
a. Initial consideration in synthesis design
   
   • Carbon skeleton
   
   • Functional group (Synthon)
   
b. The retro-synthetic approach (Disconnection)
   
c. Starting materials
d. **Yield and reaction specificity**

Overall yield is the mathematical product of the yields of all the individual steps

\[
\text{Overall yield} = 100 \times (1 \times 0.87 \times 0.67 \times 0.55) = 32\%
\]

1. minimum number of steps
2. a good precedent of high yields
3. competing reactions are minimal
2. **Construction reactions**

- **Half-reactions and recognition patterns**
- **Annelation reactions**
- **Fragmentation reactions**
1  Nucleophilic Half-Reactions

Organometallic

Aldol or Claisen
(enolate reactions)

Friedel- Crafts

2  Electrophilic Half-Reactions

Alkylation

Carbonyl addition

Conjugated addition
1  **Nucleophilic Half-Reactions**  
(Products)

**Organometallic**

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

**Aldol or Claisen**  
(enolate reactions)

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

**Friedel-Crafts**

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

2  **Electrophilic Half-Reactions**  
(Products)

**Alkylation**

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

**Carbonyl addition**

\[
\begin{align*}
\text{C} & \quad \text{R} \\
\text{OH} & \quad \\
\text{C} & \quad \text{R}
\end{align*}
\]

**Conjugated addition**

\[
\begin{align*}
\text{O} & \quad \text{H} & \quad \text{C} & \quad \text{C} & \quad \text{R} \\
\text{C} & \quad \text{C} & \quad \text{C}
\end{align*}
\]
1  Nucleophilic Half-Reactions

(Products)

Organometallic

\[ \text{C} - \text{R} \quad \Rightarrow \quad \text{C} - \text{MgX(Li)} + \left[ \text{R}^+ \right] \]

Aldol or Claisen
(enolate reactions)

\[ \text{C} - \text{C} - \text{R} \quad \Rightarrow \quad \text{C} - \text{CH} + \left[ \text{R}^+ \right] \]

Friedel- Crafts

\[ \text{R} \quad \Rightarrow \quad + \left[ \text{R}^+ \right] \]

2  Electrophilic Half-Reactions

(Products)

Alkylation

\[ \text{C} - \text{R} \quad \Rightarrow \quad \text{C} - \text{X} + \left[ \text{R}^- \right] \]

Carbonyl addition

\[ \text{OH} \quad \Rightarrow \quad \text{O} + \left[ \text{R}^- \right] \]

Conjugated addition

\[ \text{C} - \text{C} - \text{C} - \text{R} \quad \Rightarrow \quad \text{C} - \text{C} = \text{C} + \left[ \text{R}^- \right] \]
Construction chart of the Major half-reactions.

<table>
<thead>
<tr>
<th>A. Organometallics</th>
<th>b. Aldehydes, Ketones</th>
<th>c. Carboxylic Acid Derivatives</th>
<th>d. CO₂ Derivatives</th>
<th>e. Unsaturated Electrophiles</th>
</tr>
</thead>
<tbody>
<tr>
<td>C−M (Li, Na, K, MgX, Cu, Zn)</td>
<td>C=O</td>
<td>R−COCl</td>
<td>CO₂</td>
<td>−CH=CH=CH=CH− (CN)</td>
</tr>
<tr>
<td>C−CH₂−R</td>
<td></td>
<td>R−CO₂R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C−OH</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>C−C−R</td>
<td>Carboxylation</td>
<td></td>
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</tr>
<tr>
<td>or</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wittig reagent</td>
<td>Wittig</td>
<td>Aldol</td>
<td>Claisen</td>
<td>Michael</td>
</tr>
<tr>
<td>−CH=CH=P(C₆H₅)₃</td>
<td>−C≡C−</td>
<td>−C≡C−CH₂−R</td>
<td>−C≡C−</td>
<td>−C≡C−CO₂H</td>
</tr>
<tr>
<td>or</td>
<td>or</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Enolate ion (or enamine)</td>
<td>Aldol</td>
<td>Claisen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>C−C−CH₂−R</td>
<td></td>
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<tr>
<td>D. Acetylene anion</td>
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</tr>
<tr>
<td>−C≡C−</td>
<td>−C≡C−CH₂−R</td>
<td>−C≡C−</td>
<td>−C≡C−CO₂H</td>
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<td>or</td>
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</tr>
<tr>
<td>Cyanide</td>
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</tr>
<tr>
<td>E. Cyanide</td>
<td>−N≡C−</td>
<td>−N≡C−CH₂−R</td>
<td>−N≡C−</td>
<td>−N≡C−CO₂H</td>
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<tr>
<td>or</td>
<td></td>
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<tr>
<td>F. Aromatics</td>
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<tr>
<td>or</td>
<td>Friedel-Crafts</td>
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</tr>
<tr>
<td>−C=C−H</td>
<td>−C≡C−CH₂−R</td>
<td>−C−C−R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or</td>
<td></td>
<td>−C−C−R</td>
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</tr>
</tbody>
</table>

Reactions: Alkylations, Acylations, Conjugate Additions
<table>
<thead>
<tr>
<th>Electrophilic Half-reaction Starting Materials</th>
</tr>
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<tbody>
<tr>
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</tbody>
</table>
### Electrophilic Half-reaction Starting Materials

<table>
<thead>
<tr>
<th></th>
<th>a. Halides, Tosylates, Epoxides R—CH₂X</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Organometallics</td>
<td>![Chemical Structure]</td>
</tr>
<tr>
<td></td>
<td>C—M</td>
</tr>
<tr>
<td></td>
<td>(Li, Na, K, MgX, Cu, Zn)</td>
</tr>
<tr>
<td></td>
<td>![Chemical Structure]</td>
</tr>
<tr>
<td></td>
<td>C—CH₂—R</td>
</tr>
<tr>
<td></td>
<td>a. Halides, Tosylates, Epoxides $R-CH_2X$</td>
</tr>
<tr>
<td>----------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>A.</td>
<td>Organometallics $\text{C}\equiv\text{M}$ (Li, Na, K, MgX, Cu, Zn)</td>
</tr>
<tr>
<td>B.</td>
<td>Wittig reagent $\text{CH}≡\text{P(C}_6\text{H}_5)_3$</td>
</tr>
<tr>
<td>C.</td>
<td>Enolate ion (or enamine) $\text{O}$</td>
</tr>
</tbody>
</table>
Another method used to recognize potential construction patterns is to count the distance, in carbon atoms, from - one functional group to another or - from one functional group to the point of bond formation

**span** = A relation between the functional groups which are usually the key to bond-forming processes

<table>
<thead>
<tr>
<th>Span</th>
<th>Molecular Pattern</th>
<th>Reactions</th>
</tr>
</thead>
</table>
| 2    | \( \text{C} \equiv \text{C} \)  
\( \text{C} \equiv \text{C}^\dagger \)  
\( \text{C} \equiv \text{C} \)  | \( \text{Aa} \)  
\( \text{Ab}, \text{Ac}, \text{Ad}, \text{Ea}, \text{Fa} \)  
\( \text{Bb}, \text{Eb}, \text{Fc} \) |
| 3    | \( \text{C} \equiv \text{C} \equiv \text{C}^\dagger \)  
\( \text{C} \equiv \text{C} \equiv \text{C} \)  | \( \text{Ca}, \text{Da} \)  
\( \text{Cb}, \text{Cc}, \text{Cd}, \text{Db}, \text{Dc}, \text{Dd} \) |
| 4    | \( \text{C} \equiv \text{C} \equiv \text{C} \equiv \text{C}^\dagger \)  
\( \text{C} \equiv \text{C} \equiv \text{C} \equiv \text{C} \)  | \( \text{Ae} \)  
\( \text{Ee} \) |
| 5    | \( \text{C} \equiv \text{C} \equiv \text{C} \equiv \text{C} \equiv \text{C} \)  | \( \text{Ce} \) |

* For functional carbons.  
† Product with only one functional group in the span.
6-methyl-2-heptanone
Span

1

2

Target

6-methyl-2-heptanone

3

4
Span

1

2

3

4

Half-reactions

N

+ C

Mg(Cu)

Target

6-methyl-2-heptanone
## Electrophilic Half-reaction Starting Materials

<table>
<thead>
<tr>
<th></th>
<th>a. Halides, Tosylates, Epoxides $R-\text{CH}_2X$</th>
<th>b. Aldehydes, Ketones $\text{C}=\text{O}$</th>
<th>c. Carboxylic Acid Derivatives $\text{R-COCl}, \text{R-CO}_2\text{R}, \text{R-CN}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.</td>
<td>Organometallics $\overset{\text{C-M}}{\text{C}} \quad (\text{Li, Na, K, MgX, Cu, Zn})$</td>
<td>$\overset{\text{C}}{\text{C-CH}_2-R}$</td>
<td>$\overset{\text{O}}{\text{C-C-R}}$ or $\overset{\text{O}}{\text{C-CH}_2-\text{R}}$</td>
</tr>
<tr>
<td>B.</td>
<td>Wittig reagent $\overset{\text{CH=PC_6H_5}_3}{\text{C}}$</td>
<td>Wittig $\overset{\text{CH=C}}{\text{C}}$</td>
<td>$\overset{\text{O}}{\text{C-C=CH}_2-R}$</td>
</tr>
<tr>
<td>C.</td>
<td>Enolate ion (or enamine) $\overset{\text{O}}{\text{C-C:C:}}$</td>
<td>Aldol $\overset{\text{O}}{\text{C-C=CH}_2-R}$ or $\overset{\text{O}}{\text{C-C=C}}$</td>
<td>Claisen $\overset{\text{C}}{\text{C-CH-C-R}}$</td>
</tr>
</tbody>
</table>
### Electrophilic Half-reaction Starting Materials

<table>
<thead>
<tr>
<th></th>
<th>a. Halides, Tosylates, Epoxides</th>
<th>b. Aldehydes, Ketones</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$R-\text{CH}_2\text{X}$</td>
<td>$\text{C}=\text{O}$</td>
<td>$R-\text{COCl}$</td>
</tr>
<tr>
<td></td>
<td>(Li, Na, K, MgX, Cu, Zn)</td>
<td></td>
<td>$R-\text{CO}_2\text{R}$</td>
</tr>
<tr>
<td></td>
<td>A. Organometallics $\text{C}-\text{M}$</td>
<td>2</td>
<td>$R-\text{CN}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B. Wittig reagent $-\text{CH}=\text{P(C}_6\text{H}_5)_3$</td>
<td>Wittig $-\text{CH}≡\text{C}$</td>
<td>2</td>
</tr>
</tbody>
</table>
|   | C. Enolate ion (or enamine) $\text{C}=\text{C}:-$ | Aldol $\text{O} \quad \text{C}=\text{C}=:\text{OH}$ | Claisen $\text{C}≡\text{CH}≡\text{C}=\text{R}$ | 3
|   |                                 |                         |                               |
|   | 3                               | 3                      | 3                             |
## Electrophilic Half-reaction Starting Materials

|--------------------------------------|-------------------------------------|----------------------------------|----------------------------------|----------------------------------|
| A. Organometallics C—M (Li, Na, K, MgX, Cu, Zn) | C—CH₂—R | C—C—R | Carboxylation C—CO₂H | Cuprate additions
| B. Wittig reagent —CH═P(C₆H₅)₃ | Wittig —CH═C— | | | |
| C. Enolate ion (or enamine) | | | | |
| D. Acetylene anion —C≡C— | | | | |
| E. Cyanide N≡C— | | | | |
| F. Aromatics | | | | |

<table>
<thead>
<tr>
<th>Alkylations</th>
<th>Acylations</th>
<th>Conjugate Additions</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>
Construction chart of the Major half-reactions.

<table>
<thead>
<tr>
<th>Electrophilic Half-reaction Starting Materials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>a. Halides, Tosylates, Epoxides</strong>&lt;br&gt;( R\text{CH}_2X )</td>
</tr>
<tr>
<td><strong>b. Aldehydes, Ketones</strong>&lt;br&gt;( \text{C=O} )</td>
</tr>
<tr>
<td><strong>c. Carboxylic Acid Derivatives</strong>&lt;br&gt;( \text{R-COCl, R-CO}_2\text{R, R-CN}^- )</td>
</tr>
<tr>
<td><strong>d. CO(_2) Derivatives</strong>&lt;br&gt;( \text{CO}_2, \text{CICO}_2\text{R, CO(OR)}_2 )</td>
</tr>
<tr>
<td><strong>e. Unsaturated Electrophiles</strong>&lt;br&gt;(-\text{CH=C-C-} (\text{CN}))</td>
</tr>
</tbody>
</table>

| A. Organometallics <br>\(-\text{C-M} \)<br>(Li, Na, K, MgX, Cu, Zn) | **2**<br>\( \text{C=C} \) |
| B. Wittig reagent <br>\(-\text{CH=PC}_{6}\text{H}_5\text{CH} = \text{C} \) | **2**<br>\( \text{C=C} \) |
| C. Enolate ion <br>(or enamine) | **3**<br>\( \text{C=C=C=} \) |
| D. Acetylene anion <br>\(-\text{C}+=\text{C} \) | **3**<br>\( \text{C=C=C=} \) |
| E. Cyanide <br>\(-\text{N}=\text{C} \) | **2**<br>\( \text{NCCH}_2\text{R} \) |
| F. Aromatics | **3**<br>\( \text{NCCH}_2\text{R} \) |

<table>
<thead>
<tr>
<th>Alkylations</th>
<th>Acylations</th>
<th>Conjugate Additions</th>
</tr>
</thead>
</table>

24
**Nucleophilic Addition and Substitution Patterns**

<table>
<thead>
<tr>
<th>Nucleophiles</th>
<th>Electrophiles</th>
</tr>
</thead>
</table>
| H₂O | \[
\begin{align*}
\text{R} & \quad \text{C} - \text{OR}'' \\
\text{R}'(\text{H}) & \quad \text{or} \quad \text{R} & \quad \text{C} - \text{OR}'' \\
\text{R}'(\text{H})
\end{align*}
\] |
| R''OH | \[
\begin{align*}
\text{R} & \quad \text{C} - \text{OR}'' \quad \text{or} \quad \text{R} & \quad \text{C} - \text{OR}'' \\
\text{R}'(\text{H}) & \quad \text{or} \quad \text{R}'(\text{H})
\end{align*}
\] |
| N | \[
\begin{align*}
\text{R} & \quad \text{C} - \text{N} \\
\text{R}'(\text{H})
\end{align*}
\] | \[
\begin{align*}
\text{R} & \quad \text{C} - \text{N} \\
\text{R}'(\text{H})
\end{align*}
\] |
| H⁻ | \[
\begin{align*}
\text{R} & \quad \text{C} - \text{H} - \text{R}'(\text{H})
\end{align*}
\] | \[
\begin{align*}
\text{R} & \quad \text{CH}_2 - \text{OH} \\
\text{R} & \quad \text{H}
\end{align*}
\] |
| CN⁻ | \[
\begin{align*}
\text{R} & \quad \text{C} - \text{CN} \\
\text{R}'(\text{H})
\end{align*}
\] | Generally not useful | \[
\text{R} & \quad \text{CN}
\] |
| X⁻ | Generally not useful | \[
\begin{align*}
\text{R} & \quad \text{C} - \text{X} \\
\text{R} & \quad \text{X}
\end{align*}
\] |
| CMgX | \[
\begin{align*}
\text{R} & \quad \text{C} - \text{C} \\
\text{R}'(\text{H})
\end{align*}
\] | \[
\begin{align*}
\text{R} & \quad \text{C} - \text{C} \\
\text{R}'(\text{H})
\end{align*}
\] | Generally not useful | \[
\begin{align*}
\text{R} & \quad \text{C} - \text{C} \\
\text{R}'(\text{H})
\end{align*}
\] | \[
\begin{align*}
\text{R} & \quad \text{C} - \text{C} \\
\text{R}'(\text{H})
\end{align*}
\] | Generally not useful |
### Structural Patterns for Electrophilic Reactions

| Alkenes and Alkynes | $Y_2$  
|---------------------|---------|----------------|----------------|
| $Y = X^*$, H       |          | $HY$  
| $Y = X$, OH, OX    |          | $-O-O-$       | $\cdot\cdot\cdot$ |
|                     |          |                |                |
| $C=\equiv C$        | 
|                     |          |                | $\cdot\cdot\cdot$ |
|                     |          |                | $\cdot\cdot\cdot$ |
| Nucleophiles        |          |                |                |
| Aromatics           | $X_2$   | $HNO_3$        | $H_2SO_4$      | $R-C-L$        | $R-X$ |
|                     | $X$     | $NO_2$         | $SO_3H$        | $R-C=O$        | $R$ |
|                     | $X$     | $NO_2$         | $SO_3H$        | $R$            | $R$ |
|                     | $X$     | $NO_2$         | $SO_3H$        | $R-C=O$        | $R$ |
| $Z = N, O, S$       |          |                |                |                |      |

* $X = Cl, Br, I*
2. Constraction reactions
   a. Half-reactions and recognition patterns
   b. Annelation reactions
   c. Fragmentation reactions

### The Main Annelation Reactions

\[ r = 3 \ (2 + 1) \]

\[
\begin{align*}
\text{Carbene} & \quad \Delta \text{ or } h\nu \\
\text{Base} & \quad N_2=\text{C-} \\
\end{align*}
\]

\[ r = 4 \ (2 + 2) \]

\[ h\nu \ (\text{ch. 27}) \]

\[ r = 6 \ (2 + 4) \]

\[ \Delta \]
(Continued)

II. Others

\[ r = 6 (2 + 4) \]

\[ r = 6 (3 + 3) \]

\[ r = m + 1 \]

\[ r = m \]
2. Construction reactions
   a. Half-reactions and recognition patterns
   b. Annelation reactions
   c. Fragmentation reactions

Reactions which make carbon-carbon bonds are construction reactions. Those that cleave carbon-carbon bonds are called fragmentation reactions:

Ozonolysis is an important fragmentation used as a source of carbonyl groups.
2. **Constraction reactions**
   a. Half-reactions and recognition patterns
   b. Annelation reactions
   c. Fragmentation reactions

Reactions which make carbon-carbon bonds are **construction reactions**. Those that cleave carbon-carbon bonds are called **fragmentation reactions**:

**Ozonolysis** is an important fragmentation used as a source of carbonyl groups.
The other important fragmentation is the decarboxylation of β-keto acids and β-diacids
The other important fragmentation is the decarboxylation of β-keto acids and β-diacids.

\[
\begin{align*}
\text{Keto acid} & \quad \rightarrow \quad \text{Keto acid} \quad \text{(CO}_2\text{R)} \quad \text{= CO}_2\text{R} + \text{Alkyne}
\end{align*}
\]
### 3. Functional group interconversions

- **a.** Altering functional groups
- **b.** Removing functional groups
- **c.** Selectivity
- **d.** Protecting groups

#### Hydroxy and carbonyl group interconversions

- **R – OH**
  - **\( \text{C}_7\text{H}_7\text{SO}_2\text{Cl/pyridine} \)**
  - **\( \text{R – OSO}_2\text{C}_7\text{H}_7 \)**

- **\( \text{HX; SOCl}_2; \text{PBr}_3 \)**
  - **\( \text{R – X} \)**

- **1) OAc^−**
- **2) OH^−**

- **\( \text{C} \equiv \text{O} \)**
  - **\( \text{LiAlH}_4 \text{ or NaBH}_4 \)**
  - **\( \text{NaOCl or CrO}_3 \)**
  - **\( \text{CH} \equiv \text{OH} \)**
3. Functional group interconversions
   a. Altering functional groups
   b. Removing functional groups
   c. Selectivity
   d. Protecting groups

Hydroxy and carbonyl group interconversions:

- \( R \rightarrow OH \) to \( R \rightarrow OSO_2C_7H_7 \)
- \( C=O \) to \( CH-OH \)
- \( R \rightarrow X \)
- Reagents: HX, SOCl₂, PBr₃, LiAlH₄, NaBH₄, NaOCl, CrO₃
3. Functional group interconversions
   a. Altering functional groups
   b. Removing functional groups
   c. Selectivity
   d. Protecting groups

Hydroxy and carbonyl group interconversions

\[ \text{R} \rightarrow \text{OH} \xrightarrow{\text{C}_7\text{H}_7\text{SO}_2\text{Cl/pyridine}} \text{R} \rightarrow \text{OSO}_2\text{C}_7\text{H}_7 \]

\[ \text{C} \equiv \text{O} \xrightarrow{\text{LiAlH}_4 \text{ or NaBH}_4} \text{CH} \rightarrow \text{OH} \]

\[ \text{R} \rightarrow \text{X} \xrightarrow{\text{HX, SOCl}_2, \text{PBr}_3} \]

1) OAc$^-$
2) OH$^-$
Some interaction versions of the carboxylic acid family and other terminal groups.

\[ \text{R--CH}_2\text{OH} \xrightarrow{\text{(Oxidation)}} \text{RCH=O} \]

\[ \text{R--CO}_2\text{H} \xrightarrow{\text{LiAlH}_4} \text{R--CN} \quad \xrightarrow{\text{H}_2\text{O}} \quad \text{R--CO}_2\text{H} \quad \xrightarrow{\text{SOCl}_2} \text{R--COCl} \]

\[ \text{R--CO}_2\text{H} \xrightarrow{\text{R'OH}} \text{R--CO}_2\text{R'} \quad \xrightarrow{\text{R'_2NH}} \text{R--CONR'_2} \quad \xrightarrow{\text{LiAlH}_4} \text{R--CH}_2\text{NR'_2} \]

\[ \text{R--CO}_2\text{H} \xrightarrow{\text{CrO}_3} \]
Some interaction versions of the carboxylic acid family and other terminal groups.

\[ R\text{-CH}_2\text{OH} \xrightarrow{(Oxidation)} R\text{CH}=\text{O} \]

\[ R\text{-CO}_2\text{H} \xrightarrow{\text{LiAlH}_4} \text{R'-OH} \xrightarrow{\text{H}_2\text{O}} R\text{-CO}_2\text{R'} \]

\[ R\text{-CO}_2\text{H} \xrightarrow{\text{SOCl}_2} R\text{-COCl} \]

\[ R\text{-CO}_2\text{H} \xrightarrow{\text{R'-OH}} R\text{-CO}_2\text{R'} \xrightarrow{\text{R'_2NH}} R\text{-CONR'_2} \]

\[ R\text{-CN} \xrightarrow{\text{LiAlH}_4} R\text{-CH}_2\text{NR'_2} \]
Some interaction versions of the carboxylic acid family and other terminal groups.

\[ \text{R–CH}_2\text{OH} \xrightarrow{\text{LiAlH}_4} \text{R–CO}_2\text{H} \xrightarrow{\text{CrO}_3} \text{R–CH}_2\text{OH} \]

\[ \text{R–CO}_2\text{H} \xrightarrow{\text{H}_2\text{O}} \text{R–CN} \xrightarrow{\text{LiAlH}_4} \text{R–CH}_2\text{NR}_2' \]

\[ \text{R–CO}_2\text{H} \xrightarrow{\text{SOCl}_2} \text{R–COCl} \xrightarrow{\text{R’OH}} \text{R–CO}_2\text{R’} \]

\[ \text{R–CO}_2\text{H} \xrightarrow{\text{R’}_2\text{NH}} \text{R–CONR}_2' \]

\[ \text{(Oxidation)} \]

\[ \text{(Reduction)} \]
Some interaction versions of the carboxylic acid family and other terminal groups.

R—CH₂OH \xrightarrow{\text{(Oxidation)}} \rightarrow RCH=O

LiAlH₄ \xrightarrow{\text{CrO₃}} \rightarrow R—CO₂H

SOCl₂ \xrightarrow{\text{R'OH}} \rightarrow R—COCl

H₂O \xrightarrow{\text{R'OH}} \rightarrow R—CO₂R'

R₂NH \xrightarrow{\text{LiAlH₄}} \rightarrow R—CN

(\text{R' = H}) \xrightarrow{\text{LiAlH₄}} \rightarrow R—CH₂NR₂'}
3. Functional group interconversions
   a. Altering functional groups
   b. Removing functional groups
   c. Selectivity
   d. Protecting groups

Common methods for Removing functional groups.

\[
\begin{align*}
R-\text{CO}_2\text{H}(R') & \quad \xrightarrow{\text{(Reduction)}} \quad R\text{CH}_2-\text{OH} \\
R-\text{CHO} & \quad \xrightarrow{\text{Mg, Et}_2\text{O}} \quad R\text{CH}_2-X \\
R-\text{C} & \quad \xrightarrow{\text{H}_3\text{O}^+ / \Delta} \quad R-\text{C} - \text{CH} + \text{CO}_2 + R'\text{OH} \\
\end{align*}
\]
3. Functional group interconversions
   a. Altering functional groups
   b. Removing functional groups
   c. Selectivity
   d. Protecting groups

Common methods for Removing functional groups.

- Reducing carboxylic acids (R–CO₂H(R′)) to alcohols (RCH₂–OH) using methods like LiAlH₄.
- Converting aldehydes (R–CHO) to alcohols via reduction.
- Transforming esters (R–CO₂R′) to alcohols (RCH₂–OH) using methods like MgEt₂O or H₂O.
- Converting ketones (R–C=CO₂R′) to aldehydes (R–CHO) or to alcohols (RCH₂–OH) through reactions with H₂O or H₃O⁺/Δ.
3. Functional group interconversions
   a. Altering functional groups
   b. Removing functional groups
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   d. Protecting groups

Common methods for Removing functional groups.

\[
\begin{align*}
R-CO_2H(R') & \\
\text{or} & \\
R-CHO & \\
\xrightarrow{\text{(Reduction)}} RCH_2-OH & \\
\rightarrow RCH_2-OSO_2C_7H_7 & \\
& \xrightarrow{\text{LiAlH}_4} RCH_2-H \\
RCH_2-X & \\
& \xrightarrow{\text{Mg, Et}_2\text{O}} RCH_2-MgX \\
& \xrightarrow{\text{H}_2\text{O}} RCH_2-H \\
\rightarrow R-CH_2 & \\
& \xrightarrow{\text{H}_3\text{O}^+/\Delta} R-CH + CO_2 + R'OH
\end{align*}
\]
3. Functional group interconversions
   a. Altering functional groups
   b. Removing functional groups
   c. Selectivity
   d. Protecting groups

1. Hydride reductions:
   Sodium borohydride (NaBH₄) generally reduces only ketones, aldehydes, and acyl halides;
   lithium aluminum hydride (LiAlH₄) reduces those compounds as well as compounds of the carboxylic acid family.

2. Catalytic hydrogenation
3. Saturated carbons
4. Cyclic reactions
5. Carbonyl groups

\[
\begin{align*}
\text{R--COCl} & > \text{R--CHO} > \text{R--CO}-- \\
\text{C=C--CO}-- & > \text{R--CO₂R'} > \text{R--CN} \\
\text{C₆H₅--CO}-- & > \text{R--CONR₂'} > \text{R--CO₂} \\
\end{align*}
\]

6. Carbon-carbon double bonds
3. Functional group interconversions
   a. Altering functional groups
   b. Removing functional groups
   c. Selectivity
   d. Protecting groups

**Formation and Removal of Common Protecting Groups**

\[ \text{Carbonyl} + \text{HOCH}_2\text{CH}_2\text{OH} \xrightleftharpoons{\text{BF}_3 \text{ or } H^+} \xrightarrow{\text{H}_3\text{O}^+} \text{Ketal} \]
\[
\begin{align*}
&-\text{CO}_2\text{H} + \text{ROH} \xrightleftharpoons{\text{SOCl}_2/\text{NaOH}} \xrightleftharpoons{\text{H}_3\text{O}^+} -\text{CO}_2\text{R} \\
&\text{Carboxylic acid} \\
\end{align*}
\]

\[
\begin{align*}
&\text{NH}_2 \\
&\text{C} \quad + \quad (\text{CH}_3\text{CO})_2\text{O} \xrightarrow{\text{H}_3\text{O}^+} \quad \text{CH}_3\text{CONH} \\
&\text{Amine} \\
&\text{Amide}
\end{align*}
\]
4. **Stereochemistry**

A target molecule with $n$ chiral centers has $2^n$ possible stereoisomers. Many modern syntheses begin with one stereoisomer of a naturally occurring material such as a terpene, a carbohydrate, or an amino acid.

In such sequences it is very important to utilize reactions of known **stereospecificity**.

The major reactions which offer stereochemical control:

1. Nucleophilic substitutions ($S_N2$) proceed with inversion of configuration. With that reaction stereoselectivity, a chiral center can be converted to one of the opposite configuration or a cis diastereomer can be converted to a trans diastereomer.

\[ \text{Cis} \xrightarrow{p-\text{TsCl/pyridine}} \text{TsOH} \xrightarrow{\text{K}^+\text{OAc}^-/\text{Acetone}} \text{AcOH} \xrightarrow{\text{1) KOH/H}_2\text{O, 2) H}_3\text{O}^+} \text{Trans} \]
4. Stereochemistry

A target molecule with \( n \) chiral centers has \( 2^n \) possible stereoisomers. Many modern syntheses begin with one stereoisomer of a naturally occurring material such as a terpene, a carbohydrate, or an amino acid.

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\[
\begin{align*}
\text{Cis (1R,3S)} & \quad \xrightarrow{p\text{-TsCl/pyridine}} \quad \text{(1R,3S)} \\
\text{AcO} & \quad \xrightarrow{1) \text{KOH/H}_2\text{O} \quad 2) \text{H}_3\text{O}^+} \quad \text{(1S,3S)} \\
\text{K}^+\text{OAc}^-/\text{Acetone} & \end{align*}
\]
2. Reductions of cyclohexanones usually yield the more stable equatorial isomer with sodium borohydride or lithium aluminum hydride. The less stable isomer is favored with hindered reagents, since the bulky reagent preferentially approaches from the less-hindered equatorial direction.

More stable equatorial alcohol

Less stable axial alcohol
2. Reductions of cyclohexanones usually yield the more stable equatorial isomer with sodium borohydride or lithium aluminum hydride. The less stable isomer is favored with hindered reagents, since the bulky reagent preferentially approaches from the less-hindered equatorial direction.

More stable equatorial alcohol

Less stable axial alcohol

Less stable Ax isomer
2. Reductions of cyclohexanones usually yield the more stable equatorial isomer with sodium borohydride or lithium aluminum hydride. The less stable isomer is favored with hindered reagents, since the bulky reagent preferentially approaches from the less-hindered equatorial direction.
Acid- or base-promoted enolization of compounds in which the chiral center is alpha to a carbonyl group can lead to the more stable isomer. Here again, mixtures may be obtained if the two isomers do not have a significant difference in free energy (Sec. 4-1B). The terpenoid compound isodihydrocarvone is converted to dihydrocarvone, a flavor in cloves, on heating with either acid or base. Note that the two compounds are diastereomers, not enantiomers; hence they have different values of free energy and their optical rotations are not equal and opposite.

\[
\begin{align*}
\text{Isodihydrocarvone} & \quad [\alpha]_D = -23.7^\circ C \\
\text{Dihydrocarvone} & \quad [\alpha]_D = -15.6^\circ C
\end{align*}
\]
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\end{align*}
\]
Ionic additions to carbon–carbon double bonds usually proceed stereospecifically by anti addition and regiospecifically following Markovnikov orientation (Sec. 15-2). Conformational factors must also be considered during reactions of cyclic alkenes. The “iodolactonization” reaction shown below is a rather interesting example of an intramolecular addition to a double bond within a six-membered ring.
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5 Catalytic hydrogenations are syn additions and are usually reliably stereospecific in proceeding from the less-hindered side of the molecule. When the double bond is in a ring, the addition is usually anti to the bulkiest substituent.

6 Cycloadditions like the Diels-Alder reaction are syn additions in which maximum overlap of the interacting pi bonds further directs the stereochemistry. The Diels-Alder reaction is a very powerful synthesis tool capable of controlling the generation of up to four chiral centers at one time.