3- STEPS IN PLANNING A SYNTHESIS

- Construction of the carbon skeleton
- Functional group interconversions
- Control of relative stereochemistry
- Control of enantioselectivity
Table 1.3 Summary of Important Disconnections\textsuperscript{3c}

<table>
<thead>
<tr>
<th>TM</th>
<th>Synthons</th>
<th>SE (substrates)</th>
<th>Reaction type</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{Me} \cdot \text{OH} )</td>
<td>( \text{Me}^- + \text{OH}^+ )</td>
<td>( \text{Me}_2\text{MgX} + \text{HCHO} )</td>
<td>1,2-addition</td>
</tr>
<tr>
<td>( \text{Me} \cdot \text{OH} )</td>
<td>( \text{Me}^- + \text{OH}^+ )</td>
<td>( \text{Me}_2\text{MgX} + \text{O} )</td>
<td>1,3-addition</td>
</tr>
<tr>
<td>( \text{Me} \cdot \text{CN} )</td>
<td>( \text{Me}^+ - \text{CN}^- )</td>
<td>( \text{Me}_2\text{Br} + \text{NaCN} )</td>
<td>( S_{\text{N}}2 )</td>
</tr>
<tr>
<td>( \text{Me} \cdot \text{O} )</td>
<td>( \text{Me}^+ - \text{O} )</td>
<td>( \text{Me}_2\text{H}_2 + \text{HCHO} )</td>
<td>aldol condensation</td>
</tr>
<tr>
<td>( \text{Me} \cdot \text{CO}_2\text{R} )</td>
<td>( \text{Me}^- + \text{CO}_2\text{R}^+ )</td>
<td>( \text{Me}_2\text{CO}_2\text{R} + \text{HCHO} )</td>
<td>1,2-addition (Claisen condensation)</td>
</tr>
<tr>
<td>( \text{Me} \cdot \text{CO}_2\text{R} )</td>
<td>( \text{Me}^- + \text{CO}_2\text{R}^+ )</td>
<td>( \text{Me}_2\text{CO}_2\text{R} + \text{HCHO} )</td>
<td>1,4-addition (Michael addition)</td>
</tr>
<tr>
<td>( \text{Me} \cdot \text{CO}_2\text{R} )</td>
<td>( \text{Me}^- + \text{CO}_2\text{R}^+ )</td>
<td>( \text{Me}_2\text{CO}_2\text{R} + \text{HCHO} )</td>
<td>Wittig reaction</td>
</tr>
<tr>
<td>( \text{Me} \cdot \text{CO}_2\text{Me} )</td>
<td>( \text{Me}^- + \text{CO}_2\text{Me}^+ )</td>
<td>( \text{Me}_2\text{CO}_2\text{Me} + \text{HCHO} )</td>
<td>Diels-Alder cycloaddition</td>
</tr>
</tbody>
</table>
Table 1.4  Selected Functional Group Interconversions

a. Alkyl Chlorides

\[
\begin{align*}
R\text{--Cl} & \iff ROH \\
& \begin{cases}
\text{SOCl}_2 + \text{ZnCl}_2 \\
\text{PCl}_3 \text{ or } \text{PCl}_5 \\
[\text{Ph}_3\text{P + Cl}_2] & \rightarrow [\text{Ph}_3\text{P}^{+}\text{--Cl}] \text{ Cl}^- \\
[\text{Ph}_3\text{P + CCl}_4] & \rightarrow [\text{Ph}_3\text{P}^{+}\text{--CCl}_3] \text{ Cl}^-^a
\end{cases}
\end{align*}
\]

\(^a\) No HCl is formed; high yields of 1\(^o\) and 2\(^o\) alkyl chlorides; \textit{Angew. Chem., Int. Ed.} \textbf{1975}, \textit{14}, 801.

b. Alkyl Bromides

\[
\begin{align*}
R\text{--Br} & \iff \\
& \begin{cases}
\text{PBr}_3 \\
\text{ROH} & \rightarrow [\text{Ph}_3\text{P}^{+}\text{--Br}] \text{ Br}^- \\
[\text{Ph}_3\text{P + Br}_2] & \rightarrow [\text{Ph}_3\text{P}^{+}\text{--CBr}_3] \text{ Br}^- \\
\text{RCOOH} & \rightarrow \text{HgO + Br}_2^b \\
\end{cases}
\end{align*}
\]

\[
\begin{align*}
\text{RCH}_2\text{CH}_2\text{--Br} & \iff \\
& \begin{cases}
\text{RCH==CH}_2 & \rightarrow \text{HBr + free-radical initiator} \\
\text{RCH==CH}_2 & \rightarrow \text{a. BH}_3\cdot\text{THF; b. Br}_2 + \text{NaOCH}_3
\end{cases}
\end{align*}
\]

c. Allylic and Propargylic Bromides

Allylic bromination \(\rightarrow\) alkene \(\rightarrow\) NBS + free-radical initiator

\[
\begin{align*}
RCH\equiv CHCH_2Br \rightarrow & \begin{cases}
RCH\equiv CHCH_2OH \rightarrow \text{NaBr, BF}_3\cdot\text{OE}t_2^c \\
RCH\equiv CHCH_2OH \rightarrow \text{NBS, Me}_2\text{S}^d
\end{cases} \\
RC\equiv CCH_2Br \rightarrow & \text{RC\equiv CCH}_2OH \rightarrow \text{CBr}_4, \text{Ph}_3\text{P}
\end{align*}
\]


d. Alkyl Iodides

\[
\begin{align*}
\text{ROH} \rightarrow & \text{[(PhO)}_3\text{P + CH}_3\text{I]} \rightarrow \text{[(PhO)}_3\text{P\text{--CH}_3]}^e \\
\text{R--I} \rightarrow & \text{RBr} \rightarrow \text{Nal in acetone, heat}^f \\
& \text{ROT}s \rightarrow \text{Nal}
\end{align*}
\]


e. Nitriles

\[
\begin{align*}
\text{RCH}_2\text{--CN} \rightarrow & \begin{cases}
\text{RCH}_2\text{--X} \rightarrow \text{NaC\equiv N in DMSO} \\
\text{RCH}_2\text{CONH}_2 \rightarrow \text{oxalyl chloride + DMF + CH}_3\text{C\equiv N} \\
& \text{(Vilsmeier reagent)}
\end{cases} \\
\text{R--CN} \rightarrow & \begin{cases}
\text{RCONH}_2 \rightarrow \text{(CF}_3\text{SO)}_2\text{O}^g \text{ or (CHO)}_n \text{+ HCOOH}^h \\
\text{RCH\equiv NOH} \rightarrow \text{TBSCl, imidazole}^i 
\end{cases} \\
\text{R--CN} \rightarrow & \text{R'}_2\text{C=O} \rightarrow \text{TsCH}_2\text{NC, t-BuOK}^j
\end{align*}
\]

f. 1° and 2° Alcohols

\[
\begin{align*}
RCH_2COOH & \quad \text{------ a. LiAlH}_4; \text{ b. H}_3\text{O}^+ \text{ or} \\
RCH_2CH_2OH & \Rightarrow & \text{BH}_3, \text{ THF} \\
RCH_2COOR' & \quad \text{------ a. LiAlH}_4; \text{ b. H}_3\text{O}^+ \\
RCH_2CHO & \quad \text{------ NaBH}_4, \text{ EtOH} \\
RCH=CH_2 & \quad \text{------ a. BH}_3, \text{ THF}; \text{ b. NaOH, H}_2\text{O}_2
\end{align*}
\]

\[
\begin{align*}
\text{R} & \quad \text{CH–OH} & \Rightarrow & \text{R} & \quad \text{C}=\text{O} & \quad \text{------ NaBH}_4, \text{ EtOH or} \\
\text{R} & \quad \text{R'} & \quad \text{CH–OH} & \Rightarrow & \text{RCH=CH}_2 & \quad \text{------ 1. Hg(OAc)}_2, \text{ H}_2\text{O}; \\
\text{H}_3\text{C} & \quad \text{H}_3\text{O}^+ & \quad \text{2. NaBH}_4, \text{ NaOH}
\end{align*}
\]

g. 1°, 2° and 3° Amines

\[
\begin{align*}
\text{RCH}_2\text{NH}_2 & \Rightarrow \quad \text{------ a. LiAlH}_4, \text{ Et}_2\text{O}; \text{ b. H}_3\text{O}^+ \\
\text{RCH}_2\text{NH}_2 & \Rightarrow \quad \text{------ a. LiAlH}_4, \text{ Et}_2\text{O}; \text{ b. H}_3\text{O}^+ \\
\text{RCH}_2\text{NH}_2 & \Rightarrow \quad \text{------ NH}_3, \text{ NaBH}_3\text{CN, EtOH} \\
\text{RCH}_2\text{NH}_2 & \Rightarrow \quad \text{(reductive amination)} \\
\text{RCH}_2\text{OH} & \Rightarrow \quad \text{------ 1. MsCl; 2. NaN}_3; \text{ 3. Ph}_3\text{P, H}_2\text{O}^\uparrow \\
\text{RCH}_2\text{N}_3 & \Rightarrow \quad \text{H}_2\text{N}–\text{NMe}_2, \text{ FeCl}_3\cdot6\text{H}_2\text{O}^\uparrow \\
\text{RCH}_2\text{NHR'} & \Rightarrow \quad \text{------ a. LiAlH}_4, \text{ Et}_2\text{O}; \text{ b. H}_3\text{O}^+ \\
\text{RCH}_2\text{NHR'} & \Rightarrow \quad \text{------ R'}\text{NH}_2, \text{ NaBH}_3\text{CN, EtOH} \\
\text{RCH}_2\text{NHR'} & \Rightarrow \quad \text{(reductive amination)} \\
\text{RCH}_2\text{NR}_2 & \Rightarrow \quad \text{------ a. LiAlH}_4, \text{ Et}_2\text{O}; \text{ b. H}_3\text{O}^+ \\
\text{RCH}_2\text{NR}_2 & \Rightarrow \quad \text{------ R'}\text{NH}, \text{ NaBH}_3\text{CN, EtOH} \\
\text{RCH}_2\text{NR}_2 & \Rightarrow \quad \text{(reductive amination)}
\end{align*}
\]

h. Aldehydes and Ketones

\[
\begin{align*}
\text{RCH}_2\text{CHO} \rightarrow & \quad \begin{cases} 
\text{RCH}_2\text{MgX} \quad \text{a. Me}_2\text{NCHO (DMF); b. H}_3\text{O}^+ \\
\text{RCH}_2\text{CH}_2\text{OH} \quad \text{PCC, Swern}\,{}^m \\
\quad \quad \quad \text{or Dess-Martin oxidation}\,{}^n \\
\text{RC}=\text{CH} \quad \text{a. Si}2\text{BH; b. NaOH, H}_2\text{O}_2 \\
\text{RCH}_2\text{CH}=\text{CH}_2 \quad \text{a. O}_3, -78 \,{}^\circ\text{C}; \text{b. Me}_2\text{S} \\
\text{RCH}_2\text{COCl} \quad \text{H}_2, \text{Pt}\text{BaSO}_4\,{}^o \text{or LiAlH(Ot-Bu)}_3\,{}^p \\
\text{RCH}_2\text{COOH} \quad \text{thexylchloroborane} \\
\text{RCH}_2\text{COOR}' \quad \text{a. i-Bu}_2\text{AlH, -78 °C; b. H}_3\text{O}^+ \\
\text{RCH}_2\text{CN} \quad \text{a. i-Bu}_2\text{AlH, -78 °C; b. H}_3\text{O}^+ \\
\end{cases}
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3\text{C}=\text{O} \rightarrow & \quad \begin{cases} 
\text{RCOCl} \quad \text{a. }\text{(CH}_3)_2\text{CuLi, -78 °C; b. H}_3\text{O}^+ \\
\text{RCOOH} \quad \text{a. MeLi (2 eq); b. H}_3\text{O}^+ \\
\text{RC}=\text{CH} \quad \text{HgSO}_4, \text{H}_3\text{O}^+ \\
\end{cases}
\end{align*}
\]

\[
\begin{align*}
\text{RCH}=\text{OH} \rightarrow & \quad \begin{cases} 
\text{RCH}=\text{OH} \quad \text{Jones, Swern,} \\
\quad \quad \text{or NaOCl, HOAc oxidation} \\
\end{cases}
\end{align*}
\]

\[
\begin{align*}
\text{RC}=\text{O} \rightarrow & \quad \begin{cases} 
\text{RCOCl} \quad \text{organometallic reagents}\,{}^q \\
\text{RC(O)N}^+\text{CH}_3 \quad \text{a. }\text{R'}\text{Li or R'MgX; b. H}_3\text{O}^+\,{}^r \\
\end{cases}
\end{align*}
\]

\[
\begin{align*}
\text{PhC}=\text{O} \rightarrow & \quad \text{benzene} \quad \text{RCOCl} + \text{AlCl}_3
\end{align*}
\]

\]

\]

\]
i. Carboxylic Acids

\[
\begin{align*}
\text{RCH}_2\text{CHO} & \quad \text{Jones reagent or NaClO}_2, \text{H}_2\text{O} \\
\text{RCH}_2\text{CH}_2\text{OH} & \quad \text{PDC, DMF or Na}_2\text{Cr}_2\text{O}_7, \text{H}_2\text{SO}_4 \\
\text{RCH}_2\text{CN} & \quad \text{H}_3\text{O}^+ \text{ or HO}^-, \text{heat} \\
\text{RCH}_2\text{COOR'} & \quad \text{a. LiOH, THF, H}_2\text{O; b. H}_3\text{O}^+ \\
\text{RCH}_2\text{COOt-Bu} & \quad \text{CF}_3\text{CO}_2\text{H, CH}_2\text{Cl}_2, 25 \, ^\circ\text{C} \\
\text{RCH}_2\text{Ph} & \quad \text{RuO}_4^s \\
\text{RCOOH} & \quad \text{RCH}=\text{CH}_2 \quad \text{NaIO}_4, \text{KMnO}_4, \text{t-BuOH, H}_2\text{O} \\
\text{RC(O)CH}_3 & \quad \text{LiOCl, chlorox}^t
\end{align*}
\]

j. Alkenes

\[
\begin{align*}
\text{Alkenes} & \quad \Rightarrow \\
R-\text{X; } R-\text{OTs} & \quad \text{t-BuOK or DBU (E2 elimination)} \\
R-\text{OH} & \quad \text{KHSO}_4 \text{ or TsOH or } \text{H}_3\text{PO}_4 \text{ (dehydration)} \\
\text{RC}≡\text{CR}' & \quad \left\{
\begin{array}{l}
\text{Lindlar catalyst + } \text{H}_2 \\
\text{Ni(OAc)}_2, \text{NaBH}_4, \text{H}_2\text{N(CH}_2\text{)}_2\text{NH}_2 \\
1. \text{Si}_2\text{BH}; \ 2. \text{AcOH}
\end{array}
\right\} \quad \text{cis alkenes} \\
\text{Li}^\circ, \text{liq. NH}_3, \text{t-BuOH} & \quad \rightarrow \text{trans alkenes} \\
\text{RCHO} \text{ or } \text{R}_2\text{CO} & \quad \text{Wittig reagent (ylide)}
\end{align*}
\]

k. Alkynes

\[
\begin{align*}
\text{RCH}≡\text{CH}_2 & \quad \text{1. Br}_2, \text{CCl}_4; \ 2. \text{NaNH}_2, \text{NH}_3 \text{ (liq.)} \\
\text{HC}≡\text{CH} & \quad \text{1. } n-\text{BuLi}; \ 2. \text{R}→\text{Br} \ (1^\circ \text{ alkyl only}) \\
\text{RC}≡\text{CH} & \quad \left\{
\begin{array}{l}
\text{R-C} \quad \text{1a. LDA; b. CIP(O)(OEt)}_2; \\
\text{CH}_3 & \quad 2a. \text{LDA; b. H}_2\text{O}^{\text{ii}}
\end{array}
\right\} \\
\text{RCHO} & \quad \left\{
\begin{array}{l}
\text{(MeO)}_2\text{P(O)CHN}_2, \text{t-BuOK}^{\text{v}} \\
1. \text{CBr}_4, \text{Ph}_3\text{P}, \text{Zn dust}; \ 2a. \text{n-BuLi; b. H}_2\text{O}^{\text{w}}
\end{array}
\right\}
\end{align*}
\]

\[
\begin{align*}
\text{RC}≡\text{CR'} & \quad \Rightarrow \\
\text{RC}≡\text{CH} & \quad \text{a. } n-\text{BuLi}; \ b. \text{R}'→\text{Br} \ (1^\circ \text{ alkyl only})
\end{align*}
\]

\text{ii} \text{ Org. Synth. 1986, 64, 44.} \quad \text{v} \text{ J. Org. Chem. 1979, 44, 4997.} \quad \text{w} \text{ Corey-Fuchs procedure;}
4. CHOICE OF SYNTHETIC METHOD

- Regiochemistry,
- Chemoselectivity
- Stereochemistry
- Efficiency
- High yields in each step
- Availability and costs of starting materials
- Most environmentally friendly route
- Simplicity of selected procedures
- Isolation and purification of reaction products
- Possibility of a convergent synthesis or a "one-pot process" (cascade or tandem reactions).
Linear and Convergent Synthesis

• In a *linear synthetic scheme*, the hypothetical TM is assembled in a stepwise manner.

![Diagram of linear synthetic scheme]

For the seven-step synthesis of the hypothetical TM

✓ If the yield of the intermediate at each step is 80%, the overall yield will be 21% \((0.87 \times 100)\)

✓ For a 70% yield at each step, the overall yield would be only 8%
In a **convergent synthesis** should be considered in which two or more fragments of the TM are prepared separately and then joined at the latest-possible stage of the synthesis.

For the synthesis of the above TM,

-checked- only three stages are involved in the convergent strategy shown below, with an overall yield of **51%** (0.8³ x 100).
An example of a triply convergent protocol is the synthesis of the prostaglandin PGE, derivative shown below, where the three fragments were prepared separately:

- The two side chains were then coupled sequentially with the cyclopentenone.
- Introduction of the first fragment involved conjugate addition of the nucleophilic vinylic organocopper reagent to the enone, followed by trapping of the resulting enolate with the electrophilic side chain.

Analysis

Three principal fragments for a convergent coupling

TBS = silyl protecting group
tert-butyldimethylsilyl
Synthesis

\[ \text{a. } [\text{Cu}] \rrbracket \text{OTBS} \]

\[ \text{b. } \text{I} \text{COOMe} \]

\[ \text{OTBS} \]
Convergent syntheses involve consecutive reactions, where the reagents or catalysts are added sequentially into "one pot":

Analysis

\[
\text{MeO}_2C-\text{H}-\text{OBn} \quad \rightarrow \quad \begin{array}{c}
\text{C}\text{N} \text{of}\text{A} \\
\text{OBn}
\end{array}
\]

Synthesis

\[
\text{LDA in THF, } -78^\circ \text{C} \quad \begin{array}{c}
a. \text{add A} \\
b. \text{add B} \\
c. \text{add C} \\
d. \text{workup}
\end{array} \quad \begin{array}{c}
\text{TM} \\
87\%
\end{array}
\]
5. DOMINO REACTIONS (CASCADE OR TANDEM REACTIONS)

**Domino-type reactions** involve careful design of a multistep reaction in a one-pot sequence in which the first step creates the functionality to trigger the second reaction and so on, making this approach economical and environmentally friendly.

A classical example of a tandem reaction is the **Robinson annulation** (a Michael reaction followed by aldol condensation and dehydration).
6. Computer-Assisted Retrosynthetic Analysis

Computer programs are available that suggest possible disconnections and retrosynthetic pathways.

Figure 1. The synthesis tree.

Figure 2. Bondsets, construction plans and weights for estrone (boldface = bonds constructed in numbered order).

(d) Hendrickson, J. B. Chemtech 1998, 28, 35.
# Computer-Assisted Organic Synthesis (CAOS)

## Programs/Concepts Discussed:

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>OCSS</td>
<td>7.</td>
</tr>
<tr>
<td>2.</td>
<td>LHASA</td>
<td>8.</td>
</tr>
<tr>
<td>3.</td>
<td>SYNCH EM</td>
<td>9.</td>
</tr>
<tr>
<td>4.</td>
<td>SYNGEN</td>
<td>10.</td>
</tr>
<tr>
<td>5.</td>
<td>WODCA</td>
<td>11.</td>
</tr>
<tr>
<td>6.</td>
<td>CHIRON</td>
<td>12.</td>
</tr>
<tr>
<td>13.</td>
<td>TRESOR</td>
<td></td>
</tr>
</tbody>
</table>
In 1969, the first major effort in developing a computer-based method for synthetic planning was reported by Corey and Wipke. The Program OCSS was the predecessor of the more well known LHASA program which is currently in its 18th version.

example:

Ring Perception Algorithm to Find all Cycles in a Chemical Graph.

1. algorithm arbitrarily chooses an atom as the origin and a path grows out along the molecular network, until the path doubles back on itself.
2. If the ring does not duplicate an already recorded one, it is placed in the ring list.
3. If when all paths from the origin have been traversed all atoms in the structure have not been converted, then the structure consists of more than one fragment.
4. A new origin is chosen in the next fragment, and the process is repeated.

consider the following ring system which contains 4 real rings

The number of chemical rings is then given by \( n_{\text{Real rings}} = nb-na-nf \), where \( nb \) = number of bonds, \( na \) = number of atoms, and \( nf \) = number of fragments in the structure.
ORGANIC SYNTHESIS

Concepts and Methods

With a Foreword by E. J. Corey

Third, Completely Revised and Enlarged Edition
Two molecular or ionic units ("synthons") are thus connected (Corey, 1967 A; Seebach, 1979).

Synthesis is accompanied by functional group inversions (FGI), which may make molecules larger (condensation), change heteroatoms (substitution, addition-elimination), or raise or lower the oxidation number of carbon atoms (redox).
The most common synthetic reactions are polar:

- A negatively polarized ("electronegative") carbon atom (electron donor, d) of one synthon is combined with a

- positively polarized ("electropositive") carbon atom (electron acceptor, a) of another synthon.
• **Donor synthons** are formal carbanions which **donate** an electron pair to an **acceptor synthon**.
• usually an electroneutral carbonyl group.

• It is the preparation of the **donor synthon**, which usually dictates the choice of reaction conditions such as:
  • reagent,
  • solvent,
  • anhydrous,
  • inert gas,
  • acidic, neutral, or basic conditions,
  • and temperature.
• The **donor** also determines the pathways, which reactions take as well as the yield and the structure of the final products.
- **Polar reactions** are fast and most suitable for adding small molecules with molecular weights up to about 200 to any substrate.

- **Polar addition reactions** often produce one or two chiral centers (*) and stereoselectivity is highly desirable, to avoid tedious separation of diastereomers and enantiomers.
Since the mid-1980s, synthetic procedures have been developed, which apply non-polar synthons, in particular the π-electrons of alkenes or aromatic compounds, as donors and organopalladium(II) halides, RPdX, as acceptors.

Pd-HX adducts are released as electroneutral leaving groups and, after removal of HX by a base, the Pd(0) complex is formed again and may activate a CX-bond in a catalytic cycle

(Beletskaya, 2000; Dedieu, 2000)
Radical reactions, however, are mostly restricted to intramolecular reactions.

Within a single molecule, a defined radical is formed at one center only, which then attacks neighboring alkene or alkyne groups.

Finally the unpaired electron must be removed within the same molecule by an intramolecular chain termination reaction.
The unsaturated groups accept a radical at one end and create a new radical at the other end, which then reacts with another double bond or forms a carbocycle.

The notation of radical synthons uses closed circles to represent radical precursors and open circles for radical acceptors.

(Ryu, 1996)
A fourth important type of reactions is preferred for the synthesis of carbo- and heterocycles.

It involves the covalent linking of two carbon-carbon double bonds by inter- or intramolecular rearrangements (electrocylic reactions, metathesis, Claisen rearrangement).

Six-π-electron systems are particularly useful for **one-step syntheses** of six-membered rings (Diels-Alder) or the replacement of C-O by C-C bonds (Claisen).
Polar reactions usually involve carbonyl compounds as electron acceptors and a functional carbanion bound to a metal (Li, Mg, Sn, Cu-Li) or electropositive nonmetal (B, Si, P).

E-functions (E for Electrophile)

\[
\begin{align*}
\delta^+ & \quad \delta^- \\
H_3C-X & , \quad H_3C-OR \\
X = \text{Cl, Br, I} & , \quad R = \text{H, Ms, Ts, Tf} \\
\text{halogens} & , \quad \text{Alcohols and derivatives. This list is not exhaustive.} \\
\end{align*}
\]

\[
\begin{align*}
\delta^+ & \quad \delta^- \\
R_2C=O & , \quad R_2C=NR \\
\text{carbonyl compounds} & , \quad \text{imines}
\end{align*}
\]
N-functions (N for Nucleophile)

\[
\begin{align*}
\text{C–Li (Na, K)} & \quad \text{C–MgBr} \\
\text{C–Si (Sn)} &
\end{align*}
\]

main group organometallics

A-functions (for Alternate)

Triply Bonded Nitrogen as an A-function

\[
\begin{align*}
\text{C–A} & \quad \text{H–C≡N–H} \\
\text{Na} & \quad \text{C≡N}
\end{align*}
\]

\[\text{ArH} \rightarrow \text{ArC≡H}\]

\[\text{R′—Br} \rightarrow \text{R′–C≡N}\]
The reactive site of a polar synthon may either be on carbon atom C\(^1\).

which is part of the functional group (d\(^1\) or a\(^1\)), or on remote carbon atoms C\(^n\) (d\(^n\) or an; n\(\geq\)2).
Polar Synthons are accordingly numbered with respect to the relative positions of a functional group (FG) and the reactive carbon atom.

If the carbon atom C-1 of the functional group itself is reacting, one has a $d^1$- or $a^1$-synthon.

If the carbon atom C-2 next to the functional group (the a-carbon atom) is the reaction center, we call it a $d^2$ - or $a^2$-synthon.

If the $\beta$-carbon atom C-3 is the reactive one, we assign $d^3$ or $a^3$ to the corresponding synthon, etc.

Alkyl donor synthons without functional groups may also form covalent bonds with acceptor synthons.

In such cases we speak of $d^0$- or alkylating synthons.
Table 1.1: Examples of types of synthon.

<table>
<thead>
<tr>
<th>synthon type</th>
<th>example</th>
<th>reagent</th>
<th>functional group</th>
</tr>
</thead>
<tbody>
<tr>
<td>$d^0$</td>
<td>$\text{CH}_3\text{S}$</td>
<td>$\text{CH}_3\text{SH}$</td>
<td>$\text{C-S}$</td>
</tr>
<tr>
<td>$d^1$</td>
<td>$\text{C=\text{N}}$</td>
<td>$\text{KCN}$</td>
<td>$\text{C=\text{N}}$</td>
</tr>
<tr>
<td>$d^2$</td>
<td>$\text{CH}_2\text{-CHO}$</td>
<td>$\text{CH}_3\text{CHO}$</td>
<td>$\text{CHO}$</td>
</tr>
<tr>
<td>$d^3$</td>
<td>$\text{C=\text{C-}}\text{C-NH}_2$</td>
<td>$\text{LiC=\text{C-}}\text{C-NH}_2$</td>
<td>$\text{C-NH}_2$</td>
</tr>
<tr>
<td>alkyl d</td>
<td>$\text{CH}_3$</td>
<td>$\text{LiCH}_3$</td>
<td>$-$</td>
</tr>
<tr>
<td>synthon type</td>
<td>example</td>
<td>reagent</td>
<td>functional group</td>
</tr>
<tr>
<td>--------------</td>
<td>---------</td>
<td>---------</td>
<td>------------------</td>
</tr>
<tr>
<td>a&lt;sup&gt;0&lt;/sup&gt;</td>
<td>$\text{P(CH}_3\text{)}_3$</td>
<td>$(\text{H}_3\text{C})_2\text{P}^-\text{Cl}$</td>
<td>$\text{P(CH}_3\text{)}_2$</td>
</tr>
<tr>
<td>a&lt;sup&gt;1&lt;/sup&gt;</td>
<td>$\text{HRC}=\text{CH}$&lt;sup&gt;\text{PdI}&lt;/sup&gt;</td>
<td>$\text{H}_2\text{C}=\text{C}$&lt;sup&gt;\text{I}&lt;/sup&gt;</td>
<td>$\text{C}=\text{CH}_2$</td>
</tr>
<tr>
<td>a&lt;sup&gt;1&lt;/sup&gt;</td>
<td>$\text{OH}$&lt;sup&gt;\text{H}_3\text{C}\text{C}^-\text{CH}_3&lt;/sup&gt;</td>
<td>$\text{H}_3\text{C}\text{C}=\text{CH}_3$</td>
<td>$\text{C}=\text{O}$</td>
</tr>
<tr>
<td>a&lt;sup&gt;2&lt;/sup&gt;</td>
<td>$\text{H}_2\text{C}=\text{C}$&lt;sup&gt;\text{H}_3\text{C}\text{C}^-\text{CH}_3&lt;/sup&gt;</td>
<td>$\text{Br}-\text{H}_2\text{C}\text{C}=\text{CH}_3$</td>
<td>$\text{C}=\text{O}$</td>
</tr>
<tr>
<td>a&lt;sup&gt;3&lt;/sup&gt;</td>
<td>$\text{H}_2\text{C}=\text{C}$&lt;sup&gt;\text{O}^-\text{H}_3\text{C}\text{C}^-\text{OR&lt;/sup&gt;}</td>
<td>$\text{H}_2\text{C}=\text{C}$&lt;sup&gt;\text{O}^-\text{H}_3\text{C}\text{C}^-\text{OR&lt;/sup&gt;}</td>
<td>$\text{C}=\text{OR}$</td>
</tr>
<tr>
<td>alkyl a</td>
<td>$\text{CH}_3$</td>
<td>$(\text{CH}_3)_3\text{S}^-\text{Br}$</td>
<td></td>
</tr>
</tbody>
</table>
The following obvious rules apply to the arrangement of functionality in the product ("target molecule") of synthesis:

<table>
<thead>
<tr>
<th>Reacting synthons</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>alkyl a + alkyl d</td>
<td>non-functional</td>
</tr>
<tr>
<td>alkyl a + d(^1) , alkyl d + a(^1)</td>
<td>monofunctional</td>
</tr>
<tr>
<td>a(^1) + d(^1)</td>
<td>1,2-difunctional</td>
</tr>
<tr>
<td>a(^1) + d(^2) , a(^2) + d(^1)</td>
<td>1,3-difunctional</td>
</tr>
<tr>
<td>a(^1) + d(^3) , a(^2) + d(^2) , a(^3) + d(^1)</td>
<td>1,4-difunctional</td>
</tr>
<tr>
<td>Reacting synthons</td>
<td>Products</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>alkyl a + alkyl d</td>
<td>non-functional</td>
</tr>
<tr>
<td>alkyl a + d¹ , alkyl d + a¹</td>
<td>monofunctional</td>
</tr>
<tr>
<td>a¹ + d¹</td>
<td>1,2-difunctional</td>
</tr>
<tr>
<td>a¹ + d² , a² + d¹</td>
<td>1,3-difunctional</td>
</tr>
<tr>
<td>a¹ + d³ , a² + d² , a³ + d¹</td>
<td>1,4-difunctional</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>synthon type</th>
<th>example</th>
<th>reagent</th>
<th>functional group</th>
</tr>
</thead>
<tbody>
<tr>
<td>d⁰</td>
<td>CH₃S</td>
<td>CH₃SH</td>
<td>──C─S─</td>
</tr>
<tr>
<td>d¹</td>
<td>C≡N</td>
<td>K CN</td>
<td>──C≡N</td>
</tr>
<tr>
<td>d²</td>
<td>CH₂-CHO</td>
<td>CH₃CHO</td>
<td>──CHO</td>
</tr>
<tr>
<td>d³</td>
<td>C≡C─C─NH₂</td>
<td>Li C≡C─C─NH₂</td>
<td>──C─NH₂</td>
</tr>
<tr>
<td>alkyl d</td>
<td>CH₃</td>
<td>LiCH₃</td>
<td>──</td>
</tr>
<tr>
<td>a⁰</td>
<td>P(CH₃)₃</td>
<td>(H₃C)₂P─Cl</td>
<td>──P(CH₃)₂</td>
</tr>
<tr>
<td>a¹</td>
<td>HRC=CH</td>
<td>H₂C=CH₁</td>
<td>──C=CH₂</td>
</tr>
<tr>
<td>a¹</td>
<td>H₃C─C─CH₃</td>
<td>H₃C─C─CH₃</td>
<td>──C=O</td>
</tr>
<tr>
<td>a²</td>
<td>H₂C─C=CH₃</td>
<td>Br─H₂C─C=CH₃</td>
<td>──C=O</td>
</tr>
<tr>
<td>a³</td>
<td>H₂C─C─C─OR</td>
<td>H₂C─C─C─OR</td>
<td>──C─OR</td>
</tr>
<tr>
<td>alkyl a</td>
<td>CH₃</td>
<td>(CH₃)₃S Br</td>
<td>──</td>
</tr>
<tr>
<td>Products</td>
<td>Reacting synthons</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-functional alkyl a+alkyl d</td>
<td>( \text{CH}_3^+ + \text{CH}_3^- )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mono functional alkyl a + d(^1)</td>
<td>( \text{CH}_3^+ + \text{C}≡\text{N} ) alkyl d + a(^1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,2-difunctional a(^1) + d(^1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,3-difunctional a(^1) + d(^2)</td>
<td>( \text{OH} + \text{CH}_2\text{-CHO} ) a(^2) + d(^1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,4-difunctional a(^1) + d(^3)</td>
<td>( \text{OH} + \text{C}≡\text{C}–\text{C}NH_2 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,4-difunctional a(^2) + d(^2)</td>
<td>( \text{O} + \text{CH}_2\text{-CHO} )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,4-difunctional a(^3) + d(^1)</td>
<td>( \text{H}_2\text{C}≡\text{C} + \text{C}≡\text{N} )</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Examples for arrangements of functionality in bisfunctional compounds:
If an open-chain organic molecule contains an electron acceptor and an electron donor site, the two reactive carbon atoms may be combined intramolecularly.

This corresponds to the synthesis of a monocyclic compound.

Intramolecular reactions of electron donor and acceptor sites in cyclic starting materials produce spirocyclic, fused, or bridged polycyclic compounds.
1.3 Umpolung

- Reagents with carbonyl-type groupings exhibit $a^1$ or (if $\alpha,\beta$-unsaturated) $a^3$ properties.
- In the presence of acidic or basic catalysts they may react as enol-type electron donors ($d^2$ or $d^4$ reagents).
- This reactivity pattern is considered as "normal".
- It allows, for example, syntheses of 1,3- and 1,5-difunctional systems via aldol-type ($a^1+d^2$) or Michael-type ($a^3+d^2$) additions.
If hetero atoms are introduced or exchanged, the "normal" reactivity of a carbon atom may be inverted (e.g. \( a^1 \rightarrow d^1 \), \( d^2 \rightarrow a^2 \)), or a given reactivity may shift from one carbon atom to another (e.g. \( a^3 \rightarrow a^4 \)).

It is also possible to change reactivity by adding carbon fragments (e.g. \( \text{CN}^- \), \( \text{RC}≡\text{C}^- \), carbenoids) to functional groups. All these processes leading to changes of the synthon type have been called "umpolung" (German: dipole inversion; Wittig, 1951).

In rare cases the polarity of hetero atoms may also be inverted, e.g. \( \text{R-S}_{(d)\text{-H-}} \rightarrow \text{R-S}_{(a)\text{-S}_{(a)}\text{-R}} \).
Tab. 1.2 summarizes some typical umpolung reactions and some specific synthons with their equivalent reagents (Seebach, 1979).

<table>
<thead>
<tr>
<th>umpolung type</th>
<th>chemical reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>( a^1 \rightarrow d^1 )</td>
<td>exchange of hetero atoms or reduction</td>
</tr>
<tr>
<td>( a^1 \rightarrow d^1 )</td>
<td>( \ce{HC-Br} \quad + \ce{Ph_3P} \quad -\ce{HBr} \quad \ce{C=PPh_3} )</td>
</tr>
<tr>
<td>( a^1 \rightarrow d^1 )</td>
<td>( \ce{C-X} \quad + \ce{Mg or 2M} \quad -\ce{MX} \quad \ce{C-MgX, C-M} )</td>
</tr>
<tr>
<td>( a^1 \rightarrow d^1 )</td>
<td>( \ce{CHO} \quad + \ce{SH SH} \quad -\ce{H_2O} \quad -\ce{H} \quad \ce{C=S} )</td>
</tr>
<tr>
<td>( a^1 \rightarrow d^1 )</td>
<td>( \ce{CO} \quad + \ce{Fe(CO)_4} \quad -\ce{X} \quad \ce{Fe(CO)_4} )</td>
</tr>
<tr>
<td>( a^1 \rightarrow a^3 )</td>
<td>( \ce{R=O} \quad + \ce{MgBr} \quad +\ce{H} \quad \ce{R=O} )</td>
</tr>
<tr>
<td>( a^1 \rightarrow d^3 )</td>
<td>( \ce{HOR} \quad + \ce{RSH} \quad +\ce{2O} \quad \ce{S=O} )</td>
</tr>
<tr>
<td>( a^3 \rightarrow a^4 )</td>
<td>( \ce{\ce{CH_2} \quad [::CH_2]} \quad \ce{CO} \quad \ce{CH_2} )</td>
</tr>
</tbody>
</table>
In retro-synthetic analyses, it is often useful to consider an "umpolung" of a given reagent, especially if the target molecule contains 1,2- or 1,4-difunctional systems.

<table>
<thead>
<tr>
<th>umpolung type</th>
<th>chemical reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>$d^{1,2} \rightarrow a^{1,2}$</td>
<td>oxidation of alkenes</td>
</tr>
<tr>
<td>$d^2 \rightarrow a^2$</td>
<td></td>
</tr>
<tr>
<td>$a^1 \rightarrow d^1$</td>
<td>addition of carbon fragments</td>
</tr>
<tr>
<td>$a^1 \rightarrow d^3$</td>
<td></td>
</tr>
</tbody>
</table>