Reduction of carbon-carbon double and triple bonds

- **Summary:**

  - Heterogeneous catalysts of Pd, Pt, Rh, Ru etc. are effective at C-C π-bond hydrogenation (alkene, alkyne, aromatic).

  - Hydrogenation of C-C π-bond involves *stereoselective* syn-addition of hydrogen.

  - Mechanism of action means hydrogenation can be *chemoselective* for C-C π-bond over other FGs (e.g. ketone, nitrile, ester, amide etc.).

  - cis-Alkenes formed *stereoselectively* from alkynes using Lindlar’s catalyst.

  - trans-Alkenes formed *stereoselectively* from alkynes using dissolved alkali metal or LiAlH₄ (if O atom).

  - *Regioselectivity* of Birch reduction determined by substituents (EWG gives *ipso, para*; EDG gives *ortho, meta*).

  - Diimide is an alternative to TM catalysed hydrogenation and dissolved metal reductions, *stereoselective* syn-addition of hydrogen, *chemoselective* for C-C π-bonds.
Reduction of carbon-heteroatom double and triple bonds

- Summary of FG reactivity with common reducing agents:

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Aldehyde</th>
<th>Ketone</th>
<th>Ester</th>
<th>Amide</th>
<th>Carboxylic Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>LiAlH₄</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>NaBH₄</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>slow</td>
<td>✓</td>
</tr>
<tr>
<td>LiBH₄</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>DIBAL (–78 °C)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>BH₃</td>
<td>✓</td>
<td>slow</td>
<td>slow</td>
<td>slow</td>
<td>✓</td>
</tr>
<tr>
<td>NaCNBH₃</td>
<td>✓</td>
<td>slow</td>
<td>slow</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Product: AMINE | ALCOHOL | ALCOHOL | ALCOHOL | ALCOHOL | AMINE | ALCOHOL

Decreasing electrophilicity
Diastereoselectivity with hydrides: 1,2-stereoinduction

- Drawing Newman projections (recap.).

Felkin-Anh model (recap.):

e.g.

Lowest energy conformations of chiral starting material

(i.e. place largest group 90° to C=O)
Diastereoselectivity with hydrides: 1,2-stereoinduction

- **Summary:** which model to use (i.e. Felkin-Anh etc.)?

- **α-chiral carbonyl compound**

- **Is there a heteroatom at the chiral centre?**
  - **No**
    - Use **Felkin-Anh model** (i.e. conformations with the largest group 90° to C=O)
  - **Yes**
    - Is there a metal ion capable of chelation?
      - **No**
        - Use **Felkin polar model** (i.e. conformations with the electronegative group 90° to C=O)
      - **Yes**
        - Use **Felkin chelation model** (i.e. conformations with the heteroatom and C=O almost eclipsed)
Enantioselective CBS reduction of ketones

10 mol% catalyst BH$_3$, THF
Reactive cleavage reactions: summary

- Which conditions break which bond?

  **Benzyl group cleavage**

  ![Chemical structure](image)

  \[
  X^\text{Ph} \rightarrow X^\text{H}
  \]

  Use Pd/C, H\textsubscript{2} or dissolved metal

  \(X = \text{O or N}\)

  **Reductive dehalogenation**

  ![Chemical structure](image)

  \[
  \text{C}^\text{X} \rightarrow \text{C}^\text{H}
  \]

  Use Pd/C, H\textsubscript{2}

  \(X = \text{Halogen} \)  
  (i.e. I, Br, Cl, F)

  **Rosenmund reduction**

  ![Chemical structure](image)

  \[
  \text{Cl}^\text{H} \rightarrow \text{H}^\text{R}
  \]

  Use Lindlar catalyst

  **Deoxygenation**

  ![Chemical structure](image)

  \[
  \text{O}^\text{R} \rightarrow \text{H}^\text{R}
  \]

  Wolf-Kischner or 3 step (reduction, activation, reduction)
Reduction of nitrogen-containing functional groups

- Summary:

**Azide reduction**

\[ R\text{N}_3 \rightarrow R\text{NH}_2 \]

*Use Pd/C, H\textsubscript{2} or PPh\textsubscript{3}*

**Nitro reduction**

\[ R\text{NO}_2 \rightarrow R\text{NH}_2 \]

*Use Pd/C, H\textsubscript{2} or SnCl\textsubscript{2} & HCl etc.*
Pyrrole vs pyridine

- **Structure:**
  - Lone pair on pyridine in sp² orbital (basic) c.f. lone pair on pyrrole in p orbital (non-basic).
  - e.g.

  - **basic**
    - Pyridine
    - sp² hybridised nitrogen: lone pair of electrons in sp² orbital, orthogonal to plane of π-system
  
  - **non-basic**
    - Pyrrole
    - One electron in each carbon p orbital

Location of nitrogen lone pair has major effect on reactivity and properties of pyrrole w.r.t pyridine
Pyrrole & pyridine: schematic reactivity summary

- **Pyrrole**: 
  - **Base (very easy)**: 
  - **E⁺ (easy)**: 
  - **Nu⁻ (difficult)**: 

- **Pyridine**: 
  - **Base (difficult)**: 
  - **E⁺ (difficult)**: 
  - **Nu⁻ (easy)**: 

- **Activated Pyridine**: 
  - **Nu⁻ (very easy)**: 
  - **E⁺ (very easy)**: 

- **Benzene**: 
  - **Base (difficult)**: 
  - **E⁺ (easy)**: 
  - **Nu⁻ (difficult)**:
Epoxide ring openings & heterocycle synthesis

- **Summary:**

  - Under *acidic conditions*, epoxides open at end best able to stabilise +ve charge (*i.e.* loose $\text{S}_{\text{N}}2$ T.S.).

  - Under *basic conditions*, epoxides open at the less hindered end (*i.e.* minimise steric crowding in T.S.).

  - Synthesise pyrroles and pyridines using standard carbonyl chemistry (*e.g.* aldol reaction, conjugate addition, imine & enamine formation etc.).

  - Can use *Paal-Knorr* pyrrole synthesis to make pyrroles from 1,4-dicarbonyl compounds.

  - Can use *Hantzsch* pyridine synthesis to make pyridines *via* a 4 component coupling reaction.