CHE202 Structure & Reactivity in Organic Chemistry: Reduction Reactions and Heterocyclic Chemistry

9 lectures, Semester B 2014

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Office hours:
9.30-10.30 am Tuesday
1.30-2.30 pm Thursday (by appointment only)
Course structure and recommended texts

- **Coursework:**
  - Semester B – week 9 5\% (‘Coursework 7’)
  - Semester B – week 11 5\% (‘Coursework 8’)

- **Test:**
  - Semester B – week 12 15\% (‘Test 4’)

- **Recommended text books:**

Don’t forget clickers
Overview of Reduction Chemistry lecture material

- **Reduction:**
  - Definition (recap.)
  - Reduction of carbon-carbon double and triple bonds
    - Heterogeneous hydrogenation
    - Homogeneous hydrogenation, including *stereoselective* hydrogenation
    - Dissolved metal reductions
    - Other methods of reduction
  - Reduction of carbon-heteroatom double and triple bonds
    - Reduction of carbonyl derivatives, addressing *chemoselectivity*
    - *Stereoselective* reduction of carbonyl derivatives
    - Reduction of imines and nitriles
  - Reductive cleavage reactions
    - Hydrogenolysis of benzyl and allyl groups
    - Dissolved metal reduction
    - Deoxygenation reactions
  - Reduction of heteroatom functional groups
    - *e.g.* azides, nitro groups, N-O bond cleavage
Reduction: definition

- Reduction of an organic substrate can be defined as:
  - The concerted addition of hydrogen.
    e.g.
    \[
    \text{Catalytic hydrogenation (e.g. H}_2\text{(g) & Pd)}
    \]
  - The ionic addition of hydrogen \textit{NB: Dr. Lebrasseur's & Dr Bray's carbonyl lectures.}
    e.g.
    \[
    \text{Hydride addition then protonation (e.g. LiAlH}_4\text{ then acid w/up)}
    \]
  - The addition of electrons.
    e.g.
    \[
    \text{Dissolved alkali metals}
    \]

\text{one electron added}
‘OIL RIG’: a helpful mnemonic...

- Consider the reaction from the point of view of the electrons:

  **OIL**  *Oxidation Is Loss*

  **RIG**  *Reduction Is Gain*
Question: reduction or not?

- Which of these transformations represent reductions?

- A. All of them
- B. 3, 4 and 5
- C. 1, 3, 4 and 5
- D. 1, 3 and 5
- E. 1, 4 and 5
• Reduction of carbon-carbon double and triple bonds
Reduction of carbon-carbon double and triple bonds

- **Catalytic hydrogenation**
  - Concerted addition of hydrogen across a π-bond.
  - Use hydrogen gas.
  - Transition metal (TM) catalyst promotes the reaction.
  - Catalyst can be *heterogeneous* or *homogeneous*.

- Hydrogenation has a different mechanism of reduction compared to hydride reducing agents (e.g. NaBH₄), therefore different *chemoselectivity* is often observed.

  *e.g.*

  ![Reaction Diagram](image-url)

  ![Reaction Diagram](image-url)

*Aldehyde not reduced*

*NB: 10 mol% = 0.1 equivalent*
Reduction of carbon-carbon double and triple bonds

- **Heterogeneous hydrogenation**
  - Catalyst insoluble in reaction medium.
  - TM (e.g. Pt, Pd, Rh) adsorbed onto a solid support, typically carbon or alumina ($\text{Al}_2\text{O}_3$).

- **Reduction of alkenes:**
  - Reactions generally proceed at r.t. and 1 atm. $\text{H}_2$ pressure, however, reaction rates increase when elevate $T$ and/or $P$.
  - Hydrogenation is typically selective for **syn-addition**.
  - Need a solvent that dissolves sufficient hydrogen (e.g. methanol, ethanol, acetic acid).

*NB: Very occasionally the product from anti-addition occurs, see p. 624 OC textbook for an explanation.*

\[\text{Ph} = \text{Ph} \]
\[\text{PtO}_2\text{(cat.)} \]
\[\text{H}_2 (1 \text{ atm.}) \]

\[\text{Ph} \quad \text{(S)} \quad \text{Ph} \]
\[\text{Ph} \quad \text{(S)} \quad \text{Ph} \]

\[\text{(Z)-alkene} \]
\[\text{(E)-alkene} \]
Reduction of carbon-carbon double and triple bonds

- **Mechanism:**
  - Complex and difficult to study (reaction occurs on metal surface and each catalyst is different).
  - Working model (explains syn-selectivity):
    i). $H_2$ dissociatively *adsorbed* onto metal surface.
    ii). Alkene π-bonds *coordinated* to catalyst surface.
    iii). Alkene π-bonds *adsorbed* onto catalyst surface.
    iv). A hydrogen atom is *added* sequentially onto both carbons.
    v). Reduced product can *dissociate* from catalyst surface.

- **Syn-selectivity** increases with increased hydrogen pressure.
- Reactivity decreases with increased alkene substitution.
**Reduction of carbon-carbon double and triple bonds**

- **Complete reduction of aromatic compounds:**
  - Lose aromaticity: more forcing conditions required *c.f.* isolated alkenes.
  - Rh, Ru & Pt are most effective catalysts (*i.e.* Pd less active so use Pd when require *chemoselectivity* for alkene reduction in presence of aromatic ring).
  - Carbocyclic and heterocyclic aromatic rings amenable.

![Carbocyclic ring](image1)

![Heterocyclic ring](image2)

**NB:** carboxylic acid untouched

**NB:** increased $H_2$ pressures

**NB:** syn-addition of hydrogen

![Example reaction](image3)
Question: reduction of carbon-carbon double and triple bonds

Which of these structures 1 to 5 is the correct reduction product?

- A. 1
- B. 2
- C. 3
- D. 4
- E. 5

[Diagram showing structures 1 to 5]
Reduction of carbon-carbon double and triple bonds

- **Reduction of alkynes to alkanes:**
  - Standard heterogeneous hydrogenation results in complete reduction to alkanes. 
  
  \[ \text{Ph} \equiv \text{CO}_2\text{Me} \rightarrow \text{Ph} \equiv \text{CO}_2\text{Me} + \text{H}_2 \]

  - Requires chemoselectivity to differentiate between reduction of alkyne and alkene.

  - Requires control over cis- or trans- geometry.

  \[ \text{Ph} \equiv \text{CO}_2\text{Me} \rightarrow \text{Ph} \equiv \text{CO}_2\text{Me} + \text{H}_2 \]

  - Alkynes to alkenes?

  - *Require chemoselectivity to differentiate between reduction of alkyne and alkene.*

  - *Require control over cis- or trans- geometry.*
Reduction of carbon-carbon double and triple bonds

- Reduction of alkynes to cis-alkenes
  - Lindlar’s catalyst: affords cis-alkenes.
  - Pd is poisoned with Pb and an amine – more active towards alkyne than alkene (NB: alkene reduction is still possible so reactions often require careful monitoring).
    e.g.

```
Ph C≡C H2 (1 atm.), quinoline, Pb(OAc)4, EtOAc
\text{Pd/CaCO}_3 (10 \text{ mol\%})
\text{CO}_2\text{Me}
\text{cis-(Z)-alkene}
```

- Mechanism: two hydrogens added to same face of alkyne (similar to slide 10), giving syn-addition.
Reduction of carbon-carbon double and triple bonds

- **Homogeneous hydrogenation:**
  - Metal-ligand complex is soluble in reaction medium.
  - Phosphines are common ligands (i.e. good donors).

  e.g. Wilkinson's catalyst, \((\text{Ph}_3\text{P})_3\text{RhCl}\)
  - Stereospecific *syn*-addition of hydrogen across alkene.
  - Less substituted and least sterically hindered double bonds reduced most easily.
  - *Chemoslectivity* (i.e. ketones, carboxylic acids, esters, nitriles, ethers and nitro groups all inert to these conditions.

*Least hindered alkene*

\[
\text{(Ph}_3\text{P})_3\text{RhCl (cat.), } \text{H}_2 (1 \text{ atm.}) \quad \text{benzene/EtOH} \quad 95\%
\]

*NB: Heterogeneous hydrogenation (e.g. } \text{H}_2, \text{ Pd/C} \text{ is non-selective and leads to over reduction}

*NB: This mechanism is beyond the scope of the course – for a full explanation see ‘Ox & Red in Org Synth’ p. 54*
**Reduction of carbon-carbon double and triple bonds**

- **Enantioselective hydrogenation:**
  - If metal-ligand complex (MLₙ) is chiral, then possible to control to which face of alkene H₂ is delivered.
  - Discrimination between enantiotopic faces of alkene can lead to single enantiomer of product.

**ANSWER:** use chiral ligand.

- e.g. BINAP is a chiral & bidentate ligand for TM.
- Commercially available as both (R)- and (S)- enantiomers (i.e. chose desired product enantiomer).

- Beyond hydrogenation, homogeneous catalysis is an extremely important area of organic chemistry and you will encounter numerous examples in future lecture courses…
Reduction of carbon-carbon double and triple bonds

- **Dissolved metal reductions:**
  - Alkali metals (e.g. Na, Li, K) dissolved in liquid ammonia.
  - ‘Free electrons’ add to low-lying π*-orbitals.

\[
\text{Na} \quad \text{NH}_3 (l) \quad \rightarrow \quad \text{Na}^+ + e^- \quad \text{Consider the solution as a source of ‘free electrons’}
\]

- **Reduction of alkene to alkane:**
  - Selectively reduces *electron deficient* alkenes to alkanes (i.e. no reaction with standard alkenes).

\[
\text{Reduces electron deficient alkene only}
\]

*NB: Low temperature as NH\textsubscript{3} is a gas at T > –33 °C.
NB: Stoichiometry of alcohol is crucial.*
Mechanism of alkene reduction:

i). Addition of electron to π-bond gives radical anion.

ii). Radical anion protonated by 1 equiv. of t-BuOH to give neutral radical.

iii). Addition of 2nd electron yields allylic anion.

iv). Proton transfer affords enolate (NB: no proton source so enolate stable under these conditions).

v). Addition of more acidic proton source, NH₄Cl (aq), protonates enolate to give ketone product.

No t-BuOH remaining – enolate stable until add NH₄Cl (aq)
Reduction of carbon-carbon double and triple bonds

- **Reduction of alkynes to trans-alkenes:**
  - Dissolved metal reduction forms trans-double bond with high levels of *stereoselectivity*.
  - e.g. *c.f. Lindlar catalyst gives cis-alkene*

  ![Reduction of alkynes to trans-alkenes](image)

  Vinyl anions sufficiently basic to deprotonate \( \text{NH}_3 \)
  *(c.f. enolate basicity on slide 18)*

  - Provided it is not electron deficient, product alkene will not be reduced.
  - Vinyl anions are geometrically unstable and choose \((E)\)-geometry.
Question: some $pK_a$ revision

- Put these anions in order of decreasing stability (i.e. most stable first and least stable last).

A. 1, 5, 2, 3, 4
B. 1, 5, 2, 4, 3
C. 5, 1, 2, 3, 4
D. 1, 2, 5, 4, 3
E. 5, 1, 4, 3, 2
Partial reduction of aromatic rings:
- Birch reduction: dissolved metal reduction of aromatic rings.
- Affords non-conjugated diene product.
- Similar mechanism: electron transfer, radical anion protonation…
  e.g.

Pentadienyl anion has the highest electron density at the central position, hence kinetic protonation (at low T) affords *regioselectivity* for non-conjugated product.
Regioselectivity of Birch reduction:
- Electron withdrawing groups promote *ipso*, *para* reduction.
  e.g.

- Electron withdrawing groups stabilise electron density at the *ipso* and *para* positions.
- Protonation favoured at C-4 as leaves a radical stabilised by conjugation with the carbonyl group.
Reduction of carbon-carbon double and triple bonds

- **Regioselectivity of Birch reduction:**
  - Electron donating groups promote *ortho*, *meta* reduction.
  - *e.g.*

- Electron donating groups stabilise electron density at the *ortho* and *meta* positions.
- Protonation favoured at C-2 as leaves a radical stabilised by conjugation with the methoxy group.
Birch reduction of heterocycles:
- Heterocycles bearing an electron withdrawing group can also be partially reduced.
  e.g.

- Heterocycles are electron rich – electron withdrawing group required for reduction.
- Electron withdrawing group also stabilises radical anion formation, controls *regioselectivity.*
Application of the Birch reduction in complex synthesis:
- Alkene is conjugated to the benzene ring, therefore electron deficient and can be reduced.
- Alkene reduced more rapidly than electron rich benzene ring.

\[
\begin{array}{c}
\text{MeO} \quad \text{O} \quad \text{O} \\
\end{array}
\]

\[
\begin{array}{c}
\text{K, NH}_3 \ (l) \\
\text{THF, } -70 \ ^\circ \text{C}
\end{array}
\]

\[
\begin{array}{c}
\text{MeO} \\
\end{array}
\]
Which of these substrates will be reduced the fastest under Birch conditions (i.e. dissolved metal, \( \text{NH}_3 \) (l), \(-78 \, ^\circ\text{C}\))?

A. 1  
B. 2  
C. 3  
D. 4  
E. 5  

Answer: B.
Diimide reduction of alkynes and alkenes to alkanes:
- Concerted syn-addition of hydrogen across π-bond using cis-diimide.
- Alkynes are reduced to alkanes (NB: iodoalkynes are an exception and cis-iodoalkenes produced).
  e.g.
  \[
  \text{cis-diimide} \quad \xrightarrow{\text{syn-addition}} \quad \text{Irreversible} \quad \text{N}_2 \text{ evolution}
  \]

- Diimide is unstable, can be generated in situ from oxidation of hydrazine or decarboxylation of potassium azodicarboxylate.

**Oxidation**
\[
\text{H}_2\text{NN} \xrightarrow{\text{Cu(II)}} \text{O}_2 \quad \rightarrow \quad \text{H} \quad \text{N} = \text{N}^{\dagger}
\]

**Decarboxylation**
\[
\text{KO}_2\text{C} \quad \text{N} = \text{N} \quad \xrightarrow{\text{AcOH}} \quad \text{N} = \text{N}^{\dagger}
\]

NB: trans-diimide most stable isomer, isomerise to reactive cis-diimide with acid catalysis or heat.

NB: The mechanisms for diimide formation are beyond the scope of the course.
Reduction of carbon-carbon double and triple bonds

- **Order of reactivity:** alkynes > terminal or strained alkenes > substituted alkenes.
- *trans*-Alkenes react faster than *cis*-alkenes.
- Will not reduce polarised double bonds (e.g. C=O).

**e.g.**

\[
\begin{align*}
&\text{KO}_2\text{CN}=\text{NCO}_2\text{K} \\
&\text{AcOH, CH}_2\text{Cl}_2 \\
\end{align*}
\]

\[\text{NB: O-O o-bond intact}\]

\[
\begin{align*}
&\text{NH}_2\text{NH}_2 \\
&\text{O}_2, \text{Cu(II)} \\
\end{align*}
\]

\[\text{NB: trans-alkenes reduced in preference to cis-alkene}\]
Reduction of carbon-carbon double and triple bonds

- **Reduction of propargylic alcohols to trans-allylic alcohols:**
  - Use LiAlH$_4$.
  - *Stereoselectivity* due to complexation of reducing agent to oxygen.
  - e.g.

  
  \[
  \text{LiAlH}_4, \text{THF}, 70 \degree C
  \]

  \[
  \text{Me}_3\text{Si}-\overset{\text{OH}}{\text{CHO}} \rightarrow \text{Me}_3\text{Si}-\overset{\text{OH}}{\text{CCH}}
  \]

  \[
  \text{LiAlH}_4 \text{ deprotonates alcohol then complex forms between alkoxide and Lewis acidic AlH}_3
  \]

  \[
  \text{H}_2 (g) \text{ evolution}
  \]

  \[
  \text{Intramolecular delivery of hydride}
  \]

  \[
  \text{Intramolecular coordination of vinyl anion to Lewis acidic Al species locks geometry of alkene}
  \]
Summary:
- C-C π-bonds typically reduced by hydrogenation or dissolved alkali metal.

- 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.

- Pd is less active and can be used for chemoselective alkene reduction in presence of aromatic ring.

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

- Homogenous hydrogenation can offer greater regioselectivity w.r.t. heterogeneous catalysis (e.g. alkene reduction more sensitive to steric requirements) and opportunities for enantioselectivity.

- 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
Reduction of carbon-heteroatom double and triple bonds

- **Catalytic hydrogenation:**
  - Possible to reduce C-heteroatom π-bonds with H\(_2\) (g) and TM catalyst.
  - e.g.

    \[
    \text{PtO}_2 \text{(5 mol\%)} \quad \text{H}_2 \text{(g) (1 atm.)}
    \]

    NB: Pt more reactive metal than Pd

  - BUT… chemoselectivity is big issue (i.e. many substrates contain C-C π-bonds that are also reduced).

- **Ionic hydrogenation:**
  - C-heteroatom π-bonds are polarised and susceptible to attack by nucleophilic ‘hydride’.
  - Opportunity to control chemoselectivity.

    \[
    \text{NaBH}_4, \text{MeOH} \quad 0 \degree \text{C}, 97 \% \quad \text{0}^\circ \text{C}, 97 \%
    \]

    NB: see Dr Lebrasseur’s & Dr Bray’s lectures on carbonyl chemistry
Reduction of carbon-heteroatom double and triple bonds

- **Functional groups:**
  - Wide range of FGs, with wide range of electrophilicities.
  
  - e.g.

  - NITRILE
  - AMIDE
  - KETONE
  - ACID CHLORIDE
  - ALDEHYDE
  - IMINE
  - CARBOXYLIC ACID
  - ESTER

- **Hydride reducing agents:**
  - Wide variety of reducing agents, with different reactivities.
  
  - e.g.

  - LiAlH₄, NaBH₄, BH₃, LiBH₄, DIBAL, NaCNBH₃, Al(Oi-Pr)₃.

Achieve *chemoselectivity* through careful selection of reducing agent for desired FG reduction.
Reduction of carbon-heteroatom double and triple bonds

- Put these functional groups in order of decreasing electrophilicity (i.e. most reactive first and least reactive last)

A. Aldehyde, Ketone, Imine, Ester, Amide, Acid
B. Imine, Ester, Amide, Ketone, Aldehyde, Acid
C. Acid, Amide, Ester, Ketone, Aldehyde, Imine
D. Imine, Aldehyde, Ketone, Ester, Amide, Acid
E. Imine, Aldehyde, Ketone, Ester, Acid, Amide
Reduction of carbon-heteroatom double and triple bonds

- Summary of FG reactivity with common reducing agents:

<table>
<thead>
<tr>
<th>Reducing Agent</th>
<th>IMINUM ION</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>
<td>slow</td>
</tr>
<tr>
<td>NaBH₄</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>slow</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>LiBH₄</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>DIBAL (-78 °C)</td>
<td>✓ slow (✗)</td>
<td>✓ (✗)</td>
<td>✓ (✓)</td>
<td>✓ (✓) aldehyde</td>
<td>✓ (✓) aldehyde</td>
<td>✓ (✓)</td>
</tr>
<tr>
<td>BH₃</td>
<td>✓ slow</td>
<td>slow</td>
<td>slow</td>
<td>slow</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>NaCNBH₃</td>
<td>✓ slow</td>
<td>slow</td>
<td>slow</td>
<td>slow</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Product: AMINE ALCOHOL ALCOHOL ALCOHOL AMINE ALCOHOL

Decreasing electrophilicity
Reduction of carbon-oxygen double and triple bonds

- Reduction of aldehydes and ketones to alcohols (recap.):
  - Use NaBH₄.
  - e.g.

  ![Chemical structure]

  \[ \text{NaBH}_4 \rightarrow \text{MeOH} \]

  \[ \text{NaBH}_3\text{OMe} + \text{H}_2 \]

  \[ \text{MeOH} \]

  \[ \text{NaBH}_2(\text{OMe})_2 + \text{H}_2 \]

  **NB: amide not reduced**

  **Racemic product**

  **More alkoxy ligands leads to more powerful reducing agent**
Reduction of carbon-oxygen double and triple bonds

- **Reduction of aldehydes and ketones to alcohols (recap.):**
  - Use LiAlH$_4$ (NB: stronger reducing agent than NaBH$_4$ – reduces amide too, no chemoselectivity).
  - e.g.

\[
\begin{align*}
\text{LiAlH}_4, \text{THF, } \Delta & \quad \rightarrow \\
\text{Li}^+ & \quad \rightarrow \\
\text{Li} & \quad \rightarrow \\
\text{LiAlH}_3
\end{align*}
\]

\[
\begin{align*}
\text{LiAlH}_4, \text{THF, } \Delta & \quad \rightarrow \\
\text{Li}^+ & \quad \rightarrow \\
\text{LiAlH}_3
\end{align*}
\]

*NB: mechanism of amide reduction covered later*

Li$^+$ functions as a Lewis acid (*i.e.* precoordination activates the carbonyl by lowering the LUMO energy)
Reduction of carbon-oxygen double and triple bonds

- Reduction of aldehydes and ketones to alcohols (alternative):
  - Meerwein-Ponndorf-Verley reduction.
  - High *chemoselectivity* for aldehydes and ketones over esters, alkenes etc.
  - Works *via* hydride transfer from the isopropoxy group (*i.e.* different mechanism *c.f.* NaBH₄ & LiAlH₄).

  e.g.

  ![Reduction of carbon-oxygen double and triple bonds](image)

  *Al is Lewis acid*

  ![Reaction reversibility](image)

  *Reaction completely reversible*

  ![Hydride transfer](image)

  *6-membered transition state*

  *NB: α,β-unsaturated carbonyls reduced to allylic alcohols*
Reduction of carbon-oxygen double and triple bonds

- **Reduction of α,β-unsaturated ketones:**
  - Two potential sites of attack leads to two possible products.
  - [1,2]-attack leads to allylic alcohols.
  - [1,4]-attack leads to fully reduced alcohol (i.e. via conjugate addition, enol tautomerism, reduction).
  e.g.

- **Luche reduction:**
  - Excellent *regioselectivity* for [1,2]-attack by using CeCl₃ in addition to NaBH₄.
  - Ce(III) activates carbonyl & promotes formation of alkoxyborohydrides from NaBH₄ and MeOH.
Question:

- **Identify which statements are correct** (more than one statement may be correct).

- ✓ A. At room temperature LiAlH₄ is a solid
- ✓ B. At room temperature LiAlH₄ is a liquid
- ✓ C. At room temperature NH₃ is a liquid
- ✓ D. At room temperature NH₃ is a gas
- ✓ E. NaBH₄ will not reduce an ester
- ✓ F. NaBH₄ will reduce an ester
Reduction of carbon-oxygen double and triple bonds

- **Reduction of esters to alcohols:**
  - Use LiAlH₄ (or LiBH₄ for a milder & *chemoselective* alternative; NB: NaBH₄ not reactive enough).
  - e.g.

  ![Reaction Scheme]

  - Li⁺ activates carbonyl group
  - LiAlH₄, THF, 0 °C
  - Tetrahedral intermediate collapses
  - Aluminate species eliminated, but are poorer hydride donors than parent LiAlH₄ (c.f. alkoxyborates)

  **NB:** DIBAL at r.t. will reduce esters to alcohols
  **NB:** Aluminate species eliminated, but are poorer hydride donors than parent LiAlH₄ (c.f. alkoxyborates)

**Can we stop the reduction at the aldehyde?**
Reduction of carbon-oxygen double and triple bonds

- **Reduction of esters to aldehydes:**
  - Require tetrahedral intermediate not to collapse to aldehyde *in situ*.
  - Use 1 equivalent of DIBAL at low temperature.
  - DIBAL forms Lewis acid-base complex with carbonyl group in order to become a reducing agent (*i.e.* reduces more electron rich C=O groups more quickly).

  e.g.

  ![Reduction of esters to aldehydes](image)

  - DIBAL reduces esters at –70 °C
  - Tetrahedral intermediate stabilised at low T
  - Intermediate collapses to aldehyde upon w/up, *but* excess DIBAL has already been quenched

  NB: alkene not reduced
Reduction of carbon-oxygen double and triple bonds

- Reduction of amides to amines:
  - Amides poor electrophiles, require LiAlH$_4$.
  - e.g.

\[
\text{Li}^+ \text{activates carbonyl group}
\]

\[
\begin{align*}
\text{LiAlH}_4, \text{Et}_2\text{O} & \quad 88\% \\
\text{tetrahedral intermediate} & \quad \text{collapses by expelling best LG (i.e. O better than N)} \\
\text{iminium ion reduced rapidly by LiAlH}_4
\end{align*}
\]
Reduction of carbon-oxygen double and triple bonds

- Reduction of amides to amines (alternative):
  - Use BH$_3$ (chemoselective for amide over ester).
  
  e.g.

  \[
  \text{MeO}_2\text{C} \quad \begin{array}{c} \text{N} \\ \text{Bn} \end{array} \quad \text{O} \\
  \rightarrow \quad \begin{array}{c} \text{N} \\ \text{Bn} \end{array} \\
  \text{MeO}_2\text{C} \\
  \]

  Like DIBAL, BH$_3$ forms Lewis acid-base complex

  Borate donates hydride to reactive imidate

  \[
  \text{MeO}_2\text{C} \quad \begin{array}{c} \text{N} \\ \text{Bn} \end{array} \quad \text{O} \\
  \rightarrow \quad \begin{array}{c} \text{N} \\ \text{Bn} \end{array} \\
  \text{MeO}_2\text{C} \\
  \]

  BH$_3$ reduces reactive iminium ion

  NB: ester not reduced

Borate donates hydride to reactive imidate
Reduction of carbon-oxygen double and triple bonds

- Reduction of amides to aldehydes?
  - Require stabilised tetrahedral intermediate following hydride addition (c.f. partial reduction of ester).
  - e.g.

  Tetrahedral intermediate is difficult to stabilise and collapses \textit{in situ} to iminium ion which is further reduced to amine (c.f. LiAlH$_4$).
  - No general reagent for amide reduction to aldehyde... BUT...

\[ \text{NMe}_2\text{O} \xrightarrow{\text{M-}[\text{H}]} \text{NMe}_2\text{O} \xrightarrow{\text{H}_3\text{O}^+} \text{NMe}_2\text{OH} \]
Reduction of carbon-oxygen double and triple bonds

- Reduction of amides to aldehydes:
  - Weinreb’s amides form stable chelated intermediates at low T with DIBAL and LiAlH₄.
  - e.g. with DIBAL

\[
\text{Reduction of amides to aldehydes:}
\]

\[
\begin{align*}
\text{DIBAL, toluene 0 °C, 74 %}
\end{align*}
\]

\[
\text{Al is Lewis acid}
\]

\[
\text{hydrolysis to aldehyde}
\]

\[
\text{Borate donates hydride to reactive imidate}
\]

\[
\text{stabilised chelated tetrahedral intermediate}
\]

\[
\text{w/up reveals hemiaminal}
\]
Question: apply this understanding to a new situation

- Weinreb amides and organolithium reagents (a quick aside):
  - Considering the previous slide, determine the product of the following reaction:
  e.g.

\[
\begin{align*}
\text{MeLi, THF} & \quad 0 \degree C \\
\text{MeLi} & \quad \text{MeLi} \\
\text{MeNHOMe} & \quad \text{MeNHOMe}
\end{align*}
\]

\[
\begin{align*}
\text{ketone} & \quad \text{elimination of MeNHOMe} \\
\text{stabilised chelated tetrahedral intermediate} & \quad \text{NB: also works with Grignard reagents}
\end{align*}
\]
Reduction of carbon-oxygen double and triple bonds

- Reduction of carboxylic acids to alcohols:
  1). Use LiAlH$_4$ but require very forcing conditions, as form unreactive carboxylate salts.
    e.g. 1

\[
\text{OH} \quad \text{LiAlH}_4 \quad \text{heat} \quad \rightarrow \quad \text{H}_2 \quad \text{g} \quad \text{OH} \quad \text{LiAlH}_4 \quad \text{unreactive}
\]

2). Use BH$_3$: Lewis acidic, so chemoselective for most electron rich carbonyl groups (acids and amides).
   - Mechanism: complexation with lone pair forms active reducing agent (see amide reduction).
   - Milder conditions w.r.t. LiAlH$_4$.
   e.g. 2

\[
\text{OH} \quad \text{BH}_3\cdot\text{THF} \quad \rightarrow \quad \text{OH} \quad \text{BH}_3\cdot\text{THF}
\]

NB: for further explanation see ‘OC’ textbook p. 619.
Reduction of carbon-oxygen double and triple bonds

3). Via more reactive intermediate: convert carboxylic acid to mixed anhydride, then reduce with NaBH₄.
- 2 steps, but generally quick and high yielding procedures.
- Chemoselective reduction of acid in presence of ester.
e.g. 3

\[
\text{acid} \rightarrow \text{alcohol}
\]

\[
\text{BocHN} \quad \text{OH} \quad \text{Cl} \quad \text{OEt} \rightarrow \quad \text{BocHN} \quad \text{OH} \quad \text{O} \quad \text{EtO} \quad \text{MeOH, } 0 \, ^{\circ} \text{C} \rightarrow \quad 97 \% \text{ yield over 2 steps}
\]

\[
\text{BocHN} \quad \text{OH} \quad \text{O} \quad \text{EtO} \quad \text{MeOH, } 0 \, ^{\circ} \text{C} \rightarrow \quad \text{BocHN} \quad \text{CH}_\text{2} \text{Cl} \quad \text{EtO} \quad \text{MeOH, } 0 \, ^{\circ} \text{C} \rightarrow \quad \text{BocHN} \quad \text{CH}_\text{2} \text{Cl} \quad \text{EtO} \quad \text{MeOH, } 0 \, ^{\circ} \text{C} \rightarrow \quad \text{BocHN} \quad \text{CH}_\text{2} \text{Cl} \quad \text{EtO} \quad \text{MeOH, } 0 \, ^{\circ} \text{C} \rightarrow
\]

NB: most reactive at C=O that originated from carboxylic acid, as other C=O π-system has overlap from two oxygens.

Eliminate CO₂ (g) and EtO⁻
Reduction of carbon-nitrogen double and triple bonds

- **Reduction of imines to amines:**
  - Use NaBH₄ or LiAlH₄.
  - Example:
    - Reaction of an imine with NaBH₄ in MeOH at 0 °C, 95% yield:
      - **NB:** analogous to mechanism of aldehyde reduction

- **Reductive amination:**
  - Convert carbonyl group to amine through *in situ* imine formation.
  - Add acid to increase imine reactivity w.r.t. carbonyl group, can now use much weaker hydride reducing agent (e.g. NaCNBH₃) to *chemoselectively* reduce iminium ion in presence of carbonyl.
  - Example:
    - **NB:** can also use NaBH(OAc)₃
Question: reductive amination

- **Eschweiler-Clark reaction:**
  - Introduced in 1st year.
  - Can you draw the mechanism for this reductive amination?
  e.g.

\[
\begin{align*}
\text{NH}_2 & \quad \text{HCHO} \quad \text{HCO}_2\text{H} \\
\text{N} & \quad \text{H} \quad \text{H} \quad \text{O} \\
\text{N} & \quad \text{H} \quad \text{H} \quad \text{O} \\
\text{N} & \quad \text{H} \quad \text{H} \quad \text{O} \\
\end{align*}
\]

\[\text{CO}_2 (g) \text{ evolution}\]

**NB:** iminium ion formation
Reduction of carbon-nitrogen double and triple bonds

- **Reduction of nitriles to amines:**
  - Complete reduction using LiAlH$_4$ (*i.e.* powerful reducing agent).
  - e.g.

  ![Reduction of nitriles to amines](image)

  Li$^+$ activates nitrile group
  Overall 2 equivalents of hydride added
Reduction of carbon-nitrogen double and triple bonds

- Reduction of nitriles to aldehydes:
  - Partial reduction using DIBAL (1 equiv.).
  - e.g.

\[
\begin{align*}
\text{DIBAL (1 equiv.), Toluene, } -78^\circ C \\
\text{then } H_3O^+ \\
\text{w/up}
\end{align*}
\]

\[
\begin{align*}
\text{N} & \text{O} \\
\text{DIBAL (1 equiv.), } & \text{Toluene, } -78^\circ C \\
\text{then } H_3O^+ & \text{w/up}
\end{align*}
\]

\[
\begin{align*}
\text{iminoalane}
\end{align*}
\]

NB: Lewis acidic DIBAL coordinates to nitrile lone pair and ‘ate’ complex is hydride donor
Reduction of carbon-heteroatom double and triple bonds

- Summary of FG reactivity with common reducing agents:

<table>
<thead>
<tr>
<th>Reducing Agent</th>
<th>IMINUM ION</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>
<td>slow</td>
</tr>
<tr>
<td>NaBH₄</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>slow</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>LiBH₄</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>DIBAL (−78 °C)</td>
<td>✓ slow</td>
<td>✓ (✓)</td>
<td>✓ (✓)</td>
<td>✓ (✓ aldehyde)</td>
<td>✓ (✓ aldehyde)</td>
<td>✓ (✓)</td>
</tr>
<tr>
<td>BH₃</td>
<td>✓ slow</td>
<td>slow</td>
<td>slow</td>
<td>slow</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>NaCNBH₃</td>
<td>✓ slow</td>
<td>slow</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

Product: AMINE ALCOHOL ALCOHOL ALCOHOL AMINE ALCOHOL
Stereoselective reduction of carbonyl groups
Diastereoselectivity with hydrides: 1,2-stereoinduction

- Felkin-Anh model (recap.):

\[ \text{Ph} \quad \text{O} \quad \text{LiBH}(s-\text{Bu})_3 \quad \text{THF} \quad \text{Ph} \quad \text{OH} \]

*Felkin* product

- Drawing Newman projections (recap.).

*Look down highlighted C-C bond*  
*Convert to Newman projection*  
*Ensure configuration around chiral centre is correct*
Diastereoselectivity with hydrides: 1,2-stereoisoduction

- **Felkin-Anh model (recap.):**
  - e.g.

  ![Chemical Structure]

  $\text{Ph} - \text{O} \quad \overset{\text{LiBH}(s-\text{Bu})_3}{\underset{\text{THF}}{\rightarrow}} \quad \text{Ph} - \text{OH}$

  'Felkin' product

- Reactive confirmation (*i.e.* least sterically hindered).
- Nu approaches along Bürgi-Dunitz trajectory (107° O=C···Nu).
- Least hindered approach is past ‘H’ and away from large group (e.g. Ph).

**NB:** see Dr Bray’s 1st year lectures notes
Diastereoselectivity with hydrides: 1,2-stereoinduction

- **Felkin polar model:**
  - Use when α-substituent is electron withdrawing but not a good LG (NB: competing $S_N2$ reaction).
  - e.g.
  
  ![Diastereoselectivity with hydrides: 1,2-stereoinduction](image)

  - Reactive conformation (i.e. $\pi^*$ and $\sigma^*$ combine to lower LUMO).
  - Electronegative group 90° to C=O group (*even if it isn’t the largest group*).
  - Approach along Bürgi-Dunitz trajectory (107°).
  - Least hindered approach is past ‘H’ and away from electronegative group.

  ![Felkin polar model](image)

  ![Newman projection](image)
**Felkin chelation model:**
- Can reverse selectivity when (i) α-substituent contains lone pairs and (ii) use chelating metal.
- Require Lewis acid metal that chelates to more than one heteroatom at once (*i.e.* to the carbonyl group and α-substituent).

\[ \text{MeO} - \text{Me} - \text{O} \quad \xrightarrow{\text{Zn(BH}_4)_2\text{, THF}} \quad \text{MeO} - \text{Me} - \text{OH} \]

'Felkin' product

- Reactive conformation (*i.e.* Lewis acid coordination lowers LUMO).
- Electronegative group almost eclipses C=O to enable chelation with the metal (*even if electronegative group is the largest*).
- Approach along Bürgi-Dunitz trajectory (107°).
- Least hindered approach is past ‘H’ and away from group at 90°.

**Chelating metals**
- Li⁺ (sometimes)
- Mg²⁺
- Zn²⁺
- Cu²⁺
- Ti⁴⁺
- Ce³⁺
- Mn²⁺

**NB:** Na⁺ and K⁺ do not chelate

**Newman projection**
Diastereoselectivity with hydrides: 1,2-stereoinduction

- **Examples:**
e.g. 1 Key step in synthesis of anticancer agent, dolastatin.

- How do we explain *diastereoselectivity*? Consider reactive conformation.
  1. No chelation so electronegative group goes 90° to C=O
  2. Approach alongside H

**Visualisation aid:** draw product in same orientation, then rotate to put longest chains in same plane

*most reactive conformation*
Diastereoselectivity with hydrides: 1,2-stereoinduction

- **Examples:**
e.g. 2 Chelation or not?

\[ 	ext{Me}_2\text{Mg} \quad \text{THF, } -70 \, ^\circ\text{C} \]

\[ \begin{align*}
\text{OR} & \quad \rightarrow \quad \text{Me} \quad \text{OR} \\
\text{Ph} & \quad + \quad \text{OMe} \quad \text{Ph}
\end{align*} \]

\[ \text{diastereoselectivity} \]

- How do we explain diastereoselectivity? Consider reactive conformation.

\[ \begin{align*}
R = \text{Me} & \quad 99 & \quad 1 \\
R = \text{OSi(i-Pr)}_3 & \quad 42 & \quad 58
\end{align*} \]

- Chelation model
- Felkin polar model

Large group disrupts efficient chelation
Diastereoselectivity with hydrides: 1,2-stereoinduction

**Summary: which model to use?**

- **α-chiral carbonyl compound**

1. **Is there a heteroatom at the chiral centre?**
   - **No**
     - Use **Felkin polar model** (i.e. conformations with the electronegative group 90° to C=O)
   - **Yes**
     - **Is there a metal ion capable of chelation?**
       - **No**
         - Use **Felkin-Anh model** (i.e. conformations with the largest group 90° to C=O)
       - **Yes**
         - Use **Felkin chelation model** (i.e. conformations with the heteroatom and C=O almost eclipsed)
Aims: at the end of this section you will be able to...

- Understand the origin and predict the stereochemistry of reductions that form 1,3-diols.

- Understand the origin and predict the stereochemistry of reductions of cyclohexanones (i.e. axial or equatorial attack?).

- Understand the origin and predict the stereochemistry of the enantioselective CBS reduction of ketones.

- Understand the term ‘reductive cleavage’ and be familiar with suitable reagents and conditions.

- Understand the different mechanisms and methods to reduce heteroatom functional groups.
1,3-Polyols:
- Important motif found in many natural products.

- How do we control diastereoselectivity?
**Diastereoselectivity with hydrides: 1,3-stereoinduction**

- **Conformations of 6-membered rings (recap.):**
  - Cyclohexane is not flat… puckered to enable tetrahedral carbon atoms.
  - Two most common conformers are the ‘chair’ (lowest energy) and ‘boat’.

  e.g.

  [Diagrams of Cyclohexane, Chair, and Boat conformations]

- Cyclohexene adopts a ‘half chair’ in its lowest energy conformation.

  [Diagram of Cyclohexene and Half chair conformations]

NB: for further explanation see ‘OC’ textbook p. 370-374.
- **1,3-syn Diols:**
  - Use a Lewis acid (e.g. Bu₂BOMe, BF₃).
  - Chelates to carbonyl and alcohol in a 6-membered ring (*i.e.* half chair conformation).
  - Favours *intermolecular* hydride delivery from less hindered face of C=O.

Lewis acidic boron:
(i) chelates C=O and C-OH
(ii) activates C=O group

1,3-syn

Axial attack ensures smallest group is in axial position on chair
Diastereoselectivity with hydrides: 1,3-stereoinduction

- **1,3-anti Diols:**
  - Use weakly Lewis acidic reducing agent to disfavour chelation.
  - *Intramolecular* delivery of hydride.
  - Use weak reducing agent to minimise competition from intermolecular delivery.
  - Chair-like 6-membered ring T.S. controls stereochemistry.

[Diagram showing the reaction with Me₄NBH(OAc)₃ and AcOH, leading to 1,3-anti diols]

- **Lewis acidic boron chelates**
  - C-OH group
- **AcOH solvent activates**
  - C=O group

- Place substituents in lowest energy pseudo-equatorial positions within chair-like 6-membered ring T.S.
Axial or equatorial attack?
- When reducing cyclohexanones, the hydride can end up in an axial or equatorial position.
- *Can we achieve this selectively?*

- ‘Axial attack’ favoured with a small hydride source (e.g. LiAlH₄, NaBH₄).
- ‘Equatorial attack’ favoured by bulky hydride sources (e.g. L-selectride Na(s-Bu)₃BH).
Diastereoselectivity with hydrides: addition to cyclohexanones

- **Why does ‘axial attack’ occur at all?**
  - If ‘axial attack’ is more hindered then why is it even favoured with small hydride sources?
  - *Need to consider the transition state leading to the alkoxy intermediate from ‘axial attack’.*

  ![Diagram of axial and equatorial attack](image.png)

  (i.e. more hindered approach)

  - ‘Axial attack’: oxy substituent moves away from neighbouring C-H bond.
  - ‘Equatorial attack’: oxy substituent moves towards neighbouring C-H bond, leading to higher torsional strain in T.S (*i.e.* disfavoured).

  (i.e. less hindered approach)

  ![](image.png)

  alkoxy intermediate from ‘axial attack’

**NB:** for further explanation see ‘OC’ textbook p. 471.
Question: reduction of cyclohexanones

- What is the stereochemistry of the product of the following reduction?

```
+-----------------+------------+-----------------+------------+
|                 | NaBH₄      | MeOH            |           |
|                 |           |                 |           |
| O               |           |                 |           |
| BnO             |           |                 |           |
|                 |           |                 |           |
| BnO             |           |                 |           |
|                 |           |                 |           |
| BnO             |           |                 |           |
|                 |           |                 |           |
```

A. 1
B. 2
C. 3
D. 4

![Options 1, 2, 3, 4](image)
**Enantioselective reduction of ketones**

- **In general:**
  - Reagent determines from which face of carbonyl group the hydride approaches.
  - Selective synthesis of one enantiomer of secondary alcohol over the other.
  - Require a chiral reagent in order to introduce a chiral environment for the reduction.
  - Highly desirable but difficult to achieve in practice.

- Can the reagent be used in catalytic amounts (*i.e.* chiral and non-racemic compounds are often more expensive than racemic mixtures, so want to use as little as possible)?
Enantioselective reduction of ketones

- **Corey-Bakshi-Shibata (‘CBS’) reduction:**
  - Uses a chiral reducing agent.
  - CBS reagent used in catalytic quantities (also need BH$_3$ as the stoichiometric source of hydride).
  - Reduce unsymmetrical ketones to chiral secondary alcohols.
  - Catalyst binds to both BH$_3$ and substrate in an ordered manner, resulting in high enantioselectivity.

"CBS" reagent with BH$_3$ bound

*NB: for further explanation see ‘Ox and Red’ textbook p. 69.*
Enantioselective reduction of ketones

- Predict the stereochemistry of the products of these ‘CBS’ reductions:
  e.g. 1

\[
\text{Cl} \quad \text{H}_2\text{C-} \quad \text{Ph} \quad \overset{\text{Me}}{\text{1 mol\%}} \quad \text{BH}_3, \text{THF} \quad \rightarrow \quad \text{Cl} \quad \text{H}_2\text{C-} \quad \text{Ph} \\
\]

\[
\text{e.g. 2}
\]

\[
\text{TBSO} \quad \text{H}_2\text{C-} \quad \text{Me} \quad \overset{\text{Me}}{\text{1 mol\%}} \quad \text{BH}_3, \text{THF} \quad \rightarrow \quad \text{TBSO} \quad \text{H}_2\text{C-} \quad \text{Me} \\
\]

NB: require good size differentiation between two ketone substituents for high levels of enantioselectivity.
Reductive cleavage reactions
**Reductive cleavage reactions**

- **Definition**: Break single bonds between carbon and electronegative elements and replace with bonds to hydrogen.

\[
\text{C} - \text{X} \quad \xrightarrow{\text{REDUCTION}} \quad \text{C} - \text{H} \quad X = \text{N, O, S, halogen}
\]

- **Hydrogenolysis**
  - Reductive cleavage of a carbon-heteroatom (C-X) single bond through the addition of hydrogen.
  - Most commonly used to cleave benzylic and allylic groups from oxygen and nitrogen.
  - Pd is usual choice of metal catalyst as it reduces the C-X bond faster than the aromatic ring π-bonds. (c.f. Pt, Rh, Ru – see slide 9).
  - e.g.

\[
\begin{align*}
\text{Ph} & \quad \xrightarrow{\text{Pd/C (10 mol%), } \text{H}_2 (1 \text{ atm.})} \quad \text{EtOH} \quad \text{NH} \\
\text{Ph} & \quad \xrightarrow{\text{Pd/C (10 mol%), } \text{H}_2 (1 \text{ atm.})} \quad \text{EtOAc} \quad \text{OH}
\end{align*}
\]

*Ease of formation and removal means that the benzyl group is commonly used as a ‘protecting group’ in organic synthesis for amines, amides, alcohols and carboxylic acids.*

NB: This cleavage mechanism is beyond the scope of the course – for an explanation see ‘Ox & Red in Org Synth’ p. 77
Reductive cleavage reactions

- **Reductive dehalogenation:**
  - Typically use Pd and a base (NB: produce HX acid as a byproduct which may retard reaction if it isn’t neutralised by base).
  - $C_{sp^3}$-Hal and $C_{sp^2}$-Hal bonds are amenable to hydrogenolysis.

  e.g.

  $\text{Br} \quad \text{OBn} \quad \text{OMe} \quad \text{Pd/C (10 mol\%)} \quad \text{H}_2 (1 \text{ atm.}), \text{Et}_3\text{N} \quad \text{MeOH, r.t., 97\%}$

  $\text{Weaker bonds reduced more easily: } C-I > C-Br > C-Cl > C-F$

  NB: This mechanism is beyond the scope of the course – for an explanation see ‘Ox & Red in Org Synth’ p. 76

- **Dissolved metal:**
  - An alternative method to cleave $N$-benzyl and $O$-benzyl groups.

  e.g.

  $\text{Bn} \quad \text{N} \quad \text{H} \quad \text{Bn} \quad \text{O} \quad \text{H} \quad \text{Bn} \quad \text{Na, NH}_3 (l), \text{t-BuOH, } -78^\circ \text{C}$

  NB: This mechanism is beyond the scope of the course – for an explanation see ‘Ox & Red in Org Synth’ p. 76
Deoxygenation – ketones and aldehydes to alkanes:

- e.g. 1 Reduction to alcohol, make into good LG, displace with hydride.

- Use Super-Hydride™ for displacement step (i.e. LiEt₃BH).
- Electron-donating alkyl groups make it the most nucleophilic hydride source.

NB: Especially effective for challenging S_N₂ reactions on activated LG
Reductive cleavage reactions

*e.g. 2 Wolff-Kischner reduction:*
- Use hydrazine and KOH.
- Requires elevated temperatures (up to 200 °C).

\[
\text{NH}_2\text{NH}_2, \text{KOH} \quad \text{ethylene glycol, } \Delta \\
\]

**Hydrazone**

**Ethylene glycol is a high boiling point solvent (197 °C)**

**Nitrogen gas evolution** (irreversible)

**Azine**

NB: see ‘Ox & Red in Org Synth’ p. 82
Reactive cleavage reactions: summary

- Which conditions break which bond?

**Benzyl group cleavage**

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

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

*Use Pd/C, \(H_2\); or dissolved metal*

**Reductive dehalogenation**

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

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

*Use Pd/C, \(H_2\)*

**Deoxygenation**

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

*Wolf-Kischner or 3 step sequence (i.e. reduction, activation, reduction)*
Question

- Which set of reagents and conditions A to E will deliver the reduction product?

A. H₂ (1 atm.), Pd/C, MeOH, r.t.
B. H₂ (1 atm.), Pd/BaSO₄, Pb(OAc)₄, quinoline, r.t.
C. Na, NH₃, r.t.
D. Li, NH₃, −78 °C
E. H₂ (1 atm.), Pd/C, MeOH, 50 °C
- Reduction of heteroatom functional groups
Reduction of nitrogen-containing functional groups

- **Reduction of azides (-N$_3$) to amines (-NH$_2$):**
  1. Use H$_2$ & Pd/C to reduce azide (NB: if alkene also present in substrate then use Lindlar’s catalyst as does not reduce alkenes, *chemoselectivity*).

  *e.g.*

  

  - **Strategy:** azide is excellent nucleophile, especially for S$_{N2}$ (*i.e.* charged, small size, low basicity), so good method of introducing amine into a molecule is azide displacement reaction then reduction.
2). **Staudinger reduction:**
- Use PPh₃ as another chemoselective method for azide reduction in the presence of an alkene. e.g.

\[
\begin{align*}
\text{azide} & \xrightarrow{\text{PPh₃, THF}} \text{amine} \\
\text{NB: Pd/C & H₂ would also reduce alkene}
\end{align*}
\]

NB: This mechanism is beyond the scope of the course, for further details see ‘Ox & Red in Org Synth’ p. 47
Reduction of nitrogen-containing functional groups

- Reduction of nitro groups (-NO₂) to amine (-NH₂):
  - H₂ & Pd/C is most common method.
  - Aromatic and aliphatic nitro groups are reduced.
  - Many reagents reduce nitro group (NB: choose conditions for desired chemoselectivity).

\[ \text{Ar} - \overset{\text{N}}{\overset{\text{O}}{\overset{\text{O}}{\text{O}}}} \stackrel{\text{H₂ addition}}{\longrightarrow} \text{Ar} - \overset{\text{N}}{\overset{\text{O}}{\overset{-\text{H}_2\text{O}}{\text{O}}}} \stackrel{\text{H₂ addition}}{\longrightarrow} \text{Ar} - \overset{\text{N}}{\overset{\text{O}}{\overset{\text{O}}{\text{H}}}} \stackrel{\text{H₂ addition}}{\longrightarrow} \text{Ar} - \overset{\text{N}}{\overset{\text{O}}{\overset{\text{H}}{\text{H}}}} \stackrel{\text{H₂ addition}}{\longrightarrow} \text{Ar} - \overset{\text{N}}{\overset{\text{H}}{\overset{\text{H}}{\text{H}}}} \]

- Many reagents reduce nitro group (NB: choose conditions for desired chemoselectivity).
  e.g. Fe & HCl; FeCl₃ & H₂O; SnCl₂ & HCl; Zn & HCl

NB: For details of this mechanism via SET see ‘Ox & Red in Org Synth’ p. 46
Question: reduction as a tool in total synthesis

- Identify the correct product of this reaction.

A. 1
B. 2
C. 3
Heterocyclic Chemistry
Aims for this session

- Heterocycles:
  - Definition.
  - Why heterocycles are important.
  - Nomenclature of common heterocycles.
  - Recap. of key reactions of ketones, enols, imines and enamines.
What is a heterocycle?

- A cyclic system (or ‘ring’) that contains one or more heteroatoms.
  - Can be aromatic or non-aromatic.

  e.g.

  **CARBOCYCLIC**
  - CYCLOPENTANE
    - (non-aromatic)

  **HETEROCYCLIC**
  - PYRROLIDINE
    - (non-aromatic)
  - 2,3-DIHYDROIMIDAZOLE
    - (non-aromatic)
  - PYRIDINE
    - (aromatic)
  - PYRIMIDINE
    - (aromatic)

  *NB: multiple heteroatoms*
Why are heterocycles important?

- Heterocycles are an extremely common motif.
  - Found in almost half of all known organic compounds.
  - Key constituents of natural products, DNA, amino acid proline (i.e. proteins), medicines, agrochemicals, materials and dyes.
  e.g.

  - Caffeine
  - Deoxyadenosine
  - Omeprazole
  - Ranitidine
  - Quinine
  - Nicotine
Question: identify the heterocycles

- How many heterocycles are in this pharmaceutical compound? (NB: count any fused rings separately)

![Chemical structure of Sildenafil ('Viagra')](image)

A. 0
B. 1
C. 2
D. 3
E. 4
F. 5

Correct answer: D. 3
### The World's Top-Selling Drugs 2009

<table>
<thead>
<tr>
<th>Brand Drug®</th>
<th>Generic name</th>
<th>Indications</th>
<th>Maker</th>
<th>Sales (billion)</th>
<th>Compound type</th>
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<tr>
<td>Lipitor</td>
<td>Atorvastatin</td>
<td>Cholesterol</td>
<td>Pfizer</td>
<td>12.45</td>
<td>pyrrole</td>
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<td>Clopidogrel</td>
<td>Atherosclerosis</td>
<td>BMS, Sanofi-Aventis</td>
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<td>thiophene-tetra-H-pyridine</td>
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<td>Etanercept</td>
<td>Arthritis</td>
<td>Amgen, Pfizer</td>
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<td>Inflammation</td>
<td>J&amp;J Merck</td>
<td>6.91</td>
<td>antibody</td>
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<td>AZ</td>
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<td>Eli Lilly</td>
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<td>Venlafaxine</td>
<td>Depression</td>
<td>Pfizer</td>
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<td>aromatic</td>
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<td>Diabetes</td>
<td>Sanofi-Aventis</td>
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<td>insulin</td>
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<td>Enoxaparin</td>
<td>Anti-coagulant</td>
<td>Sanofi-Aventis</td>
<td>4.17</td>
<td>carbohydrate</td>
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<td>Actos</td>
<td>Pioglitazone</td>
<td>Diabetes</td>
<td>Takeda</td>
<td>4.11</td>
<td>thiazolidinone</td>
</tr>
</tbody>
</table>

**NB:** Drugs containing **heterocycles** indicated in bold
**Five membered rings with one heteroatom:**
- NB: we will only study the highlighted compounds in more detail.
  
e.g.

- pyrrole
- furan
- pyrrolidine
- tetrahydrofuran ("THF")
- pyrrolidinone

- thiophene \(X = S\)
- selenophene \(X = Se\)
  
- indole
- benzofuran \(X = O\)
- benzothiophene \(X = S\)

- isoindole \(X = N\)
- isobenzofuran \(X = O\)
- Five membered rings with more than one heteroatom:
  - NB: we will not study these heterocycles in detail, but you should be aware of these compounds.
  e.g.

- imidazole
- pyrazole
- 1,2,3-triazole
- 1,2,4-triazole
- tetrazole

- oxazole
- thiazole
- isoxazole
- isothiazole
- benzoxazole
Six membered rings with one heteroatom:
- NB: we will only study the highlighted compounds in more detail.
  e.g.

- pyridine
- quinoline
- isoquinoline
- pyrylium cation
- piperidine
- 1,2,3,4-tetrahydropyridine
- pyridone
- tetrahydropyran

NB: aromatic

NB: non-aromatic
Six membered rings with more than one heteroatom:
- NB: we will not study these heterocycles in detail, but you should be aware of these compounds.
e.g.

- pyridazine
- pyrimidine
- 1,3,5-triazine
- quinazoline
- piperazine
- morpholine
- 1,4-dioxane

NB: aromatic

NB: non-aromatic
Beyond five and six membered rings:
- NB: we will only study the highlighted compound in more detail.
e.g.

- epoxide
- aziridine
- oxetane
- azetidine
- β-lactam

(+)-Roxaticin

NB: macrocycle

Penicillins
Heterocycles: key reactions (recap.)

- **Enol formation:**
  - NB: acidic conditions.
  e.g.
  
  \[
  \text{ketone} \rightleftharpoons \text{enol}
  \]

  *NB: consider pK\textsubscript{a} of α-proton*

  \[
  \begin{align*}
  \text{protonation} & : R - COH \\
  \text{deprotonation} & : R - COH \rightleftharpoons R - CH\equiv O \\
  \end{align*}
  \]

- **Enolate formation:**
  - NB: basic conditions.
  e.g.
  
  \[
  \text{ketone} \rightleftharpoons \text{enolate}
  \]

  *NB: consider pK\textsubscript{a} of α-proton*

  \[
  \begin{align*}
  \text{protonation} & : R - COH \\
  \text{deprotonation} & : R - COH \rightleftharpoons R - CH\equiv O \\
  \end{align*}
  \]

  *NB: need a strong base to effect complete irreversible deprotonation of a ketone (i.e. use LDA)*

NB: for a comprehensive list of pK\textsubscript{a} values, see: [http://evans.harvard.edu/pdf/evans_pka_table.pdf](http://evans.harvard.edu/pdf/evans_pka_table.pdf)
What are the $pK_a$ values of the two α-protons highlighted below?

A. They are both the same
B. 43 and 26
C. 26 and –6
D. 43 and –6
Aims for this session

- **Heterocycles:**
  - Continue recap. of key reactions of ketones, enols, imines and enamines.
  - Recap. of aromaticity.
  - Look at pyridine: structure and reactivity (how does it compare to benzene?).
  - Look at pyrrole: structure and reactivity (how does it compare to benzene?).
- **Formation of imines:**
  - NB: typically require catalytic acid.
  - e.g.

  ![Chemical reaction diagram](image)

  \[ \text{ketone} \xrightarrow{\text{cat. } H^+} \text{imine} + \text{H}_2\text{O} \]

- **Enamine formation:**
  - NB: occurs under acidic or basic conditions.
  - e.g. *c.f. enol and enolate formation*

  ![Chemical reaction diagram](image)

  \[ \text{imine} \xrightarrow{\text{tautomerisation}} \text{enamine} \]

  - NB: C=N bond weaker than C=O, therefore easier to form enamine compared to enol or enolate

  NB: enamines react with electrophiles on carbon and *not* nitrogen
**Aldol:**
- NB: formation of thermodynamically favoured $\alpha,\beta$-unsaturated product drives reaction.
  e.g.

\[
\text{enol} + \text{aldehyde} \xrightarrow{\text{cat. } H^+} \text{\(\alpha,\beta\)-unsaturated product}
\]
**Mannich reaction:**
- NB: electrophile is imine rather than aldehyde.
- Amine is poorer LG (c.f. alcohol in Aldol reaction), therefore intermediate does not eliminate.

  e.g.

  ![Mannich reaction diagram]

**Conjugate addition:**
- NB: orbital-controlled [1,4]-nucleophilic addition.
- NB: called a “Michael addition’ when carbon-based nucleophile such as enol or enolate.

  e.g.

  ![Conjugate addition diagram]

_NB: favoured when using ‘soft’ nucleophiles (i.e. uncharged and/or diffuse orbitals)_
Aromaticity (recap.)

- Hückel’s Rule:
  e.g.

  - **PYRROLE**
    - isoelectronic and isolobal with cyclopentadiene anion
    - 6\(\pi\) electrons

  - **PYRIDINE**
    - isoelectronic and isolobal with benzene
    - 6\(\pi\) electrons

Planar structures which have a cyclic array of \([4n + 2]\) delocalisable \(\pi\)-electrons
Question: heteroaromatic?

- Identify the heterocycle that is not aromatic

A. A
B. B
C. C
D. D
E. E
F. F

✓ F. F
Pyridine

- Structure:
  - Isoelectronic with benzene (i.e. 6π electrons, one in each of 6 parallel p orbitals).
  - E.g.

Nitrogen atom has major effect on reactivity and properties of pyridine w.r.t benzene.
Pyridine: is it really aromatic?

- **Resonance energy (kJ/mol):**
  - i.e. energy gained through delocalisation around the ring.
  e.g.

  \[
  \begin{array}{c}
  \text{苯} \quad 150 \\
  \text{吡啶} \quad 117 \\
  \end{array}
  \]

  i.e. benzene gains more energy through resonance

- **Bond lengths (pm):**
  - pyridine has different bond lengths within ring system.
  e.g.

  \[
  \begin{array}{c}
  \text{苯} \quad 140 \\
  \text{吡啶} \quad 139.4 \quad 139.5 \\
  \end{array}
  \]

  i.e. shorter bond lengths in pyridine
Pyridine: is it really aromatic?

- **1H NMR spectroscopic chemical shifts (i.e. δ_H in ppm):**
  - i.e. how deshielded is each environment?
  - e.g.

  ![Chemical shifts for benzene and pyridine](image)

  - More deshielding in pyridine

- **13C NMR spectroscopic chemical shifts (i.e. δ_C in ppm):**
  - i.e. how deshielded is each environment?
  - e.g.

  ![Chemical shifts for benzene and pyridine](image)

  - More deshielding in pyridine

**YES, pyridine is aromatic**
In which hybrid atomic orbital is the nitrogen lone pair located?

A. p
B. sp
C. sp²
D. sp³

Question: hybridisation states in heterocycles
Question: hybridisation states in heterocycles

- In which hybrid atomic orbital is the nitrogen lone pair located?

A. $p$
B. $sp$
C. $sp^2$
D. $sp^3$

[Chemical structure of a heterocycle with a nitrogen atom]
Pyridine: general reactivity trends

- **Lone pair reactivity:**
  - Basic (*i.e.* can be easily protonated).
  - Nucleophilic (*i.e.* can be alkylated or acylated).
  - \(N\)-oxidation (form \(N\)-oxides, see later).

- **Benzene-like reactivity:**
  - Attack on \(\pi\)-system.
  - Electrophilic substitution.

- **Imine-like reactivity:**
  - Susceptible to nucleophilic attack (*e.g.* displacement of halo-pyridines).

NB: \(S_E\)Ar is less likely than with benzene

NB: behaves like an imine
**Pyridine: lone pair reactivity**

- **Basicity:**
  - Consider $pK_a$ of conjugate acid...

  - The **stronger** the conjugate acid the **lower** the $pK_a$ and the **weaker** the base.
  - The **weaker** the conjugate acid the **higher** the $pK_a$ and the **stronger** the base.

- Pyridine lone pair in sp$^2$ orbital (c.f. imine), hence weak base.
- Piperidine lone pair in sp$^3$ orbital, hence stronger base (i.e. greater ‘p’ character).

\[
\begin{align*}
\text{Pyridine} & \quad \text{p}K_a \ 5.2 \\
\text{ Piperidine} & \quad \text{p}K_a \ 11.5
\end{align*}
\]

NB: for a recap. of $pK_a$, see ‘OC’ p 197.
Question: pyridine basicity

- Which pyridine is the strongest base?

A. 1  
B. 2  
C. 3  

A. 1  
B. 2  
C. 3  

$\text{pK}_{aH} \text{ for 1: 5.2}$  
$\text{pK}_{aH} \text{ for 2: 6.8}$  
$\text{pK}_{aH} \text{ for 3: 0.7}$
**Pyridine: lone pair reactivity**

- **Nucleophilicity:**
  - NB: lone pair cannot be delocalised around the ring (i.e. sp$^2$ orbital orthogonal to the ring).

- Hence lone pair is a good nucleophile and readily alkylated or acylated.
  
  - **Example:**
    
    \[
    \text{H} \xrightarrow{\text{Cl}} \text{R} \xrightarrow{\text{Cl}^{-}} \text{N}^{+} \text{R}^{\text{acylated}}
    \]

- Typically, the more basic a pyridine, the more nucleophilic (except when sterically crowded).
  
  - **Example:** 2,6-di-tert-butyl pyridine (good base, poor nucleophile)
Question: DMAP as a catalyst

- *N,N*-Dimethyl-4-amino pyridine (DMAP) is a useful pyridine-based catalyst for acylation reactions. What type of catalysis is this an example of? (hint: what is the pyridine doing and why might DMAP be better than pyridine?)

A. Acid catalysis  
B. Base catalysis  
C. Nucleophilic catalysis

A.

B.

C. Nucleophilic catalysis
Electrophilic aromatic substitution:
- $S_{E}Ar$ readily occurs on benzene, but much less favourable on pyridine.
- Electronegative nitrogen atom lowers energy of $p$ orbitals within pyridine ring (w.r.t. benzene), hence pyridine ring less nucleophilic (i.e. lower HOMO) but more electrophilic (i.e. lower LUMO).
- Pyridine: nucleophilic lone pair leads to reaction with $E^+$ on nitrogen rather than carbon.

\[
\begin{array}{c}
\text{Pyridine: benzene-like reactivity} \\
\vdots
\end{array}
\]

- Yields from $S_{E}Ar$ reactions are typically poor:

\textbf{e.g. 1.} \textit{Friedel-Crafts} reactions normally fail.

\textbf{e.g. 2.} \textit{Nitration} with $HNO_3 + H_2SO_4$ at $300 \, ^{\circ}C$ gives $< 5\%$ of 3-nitropyridine.

\textbf{e.g. 3.} \textit{Halogenation} with $Cl_2 + AlCl_3$ at $130 \, ^{\circ}C$ gives only moderate yields of 3-chloropyridine.

\textbf{NB:} benzene reacts readily under these conditions (see 1st Year lecture notes).
Electrophilic aromatic substitution:
- Electronegative nitrogen atom withdraws electron density; C-2, C-4 and C-6 most affected.
  e.g.

- C-2 or C-4 substitution results in $\delta^+$ localised on nitrogen atom (highly disfavoured).
  e.g.

- C-3 & C-5 substitution least disfavoured (but still unlikely to occur).
  e.g.
**Pyridine: benzene-like reactivity**

- **Electrophilic aromatic substitution:**
  - Can occur if electron donating group present.
  
  e.g.

  ![Reaction scheme for electrophilic aromatic substitution on pyridine](image)

  - If no activating groups present, can convert pyridine into **pyridine N-oxide**.
  
  e.g.

  ![Reaction scheme for pyridine N-oxide formation](image)

  *nitrogen lone pair easily oxidised*

  *NB: stable solid*

  *NB: can also use H₂O₂ in AcOH*

  Pyridine N-oxides readily undergo SₐAr
**Pyridine: benzene-like reactivity**

- **Electrophilic aromatic substitution:**
  - Negative charge on oxygen delocalised into pyridine π-system (i.e. makes ring more electron rich).
  - Reaction with electrophiles occurs at C-2 or C-4 (but mainly at C-4).

  e.g.

- Easily cleave N-oxide with P(III) compounds (e.g. PCl₃, P(OMe)₃) to regain pyridine.

  e.g.

  *Phosphorus acts as a nucleophile (lone pair) and an electrophile (vacant d orbital)*

  *Formation of strong P=O double bond drives reaction*

  *NB: obtain 2-chloropyridine if use PCl₃ (for further details see ‘OC’ textbook p 730)*
Nucleophilic substitution:
- C-2 and C-4 halo-pyridines react easily with nucleophiles (c.f halobenzenes are relatively inert).
- C-3 halo-pyridines less reactive (i.e. negative charge cannot be delocalised onto nitrogen).

e.g.

\[ \begin{align*}
\text{Pyridine: imine-like reactivity} \\
\text{Activated (i.e. N-protonated)}
\end{align*} \]

NB: 2-chloropyridine is $3 \times 10^8$ times more reactive than chlorobenzene

- Pyridine will react with strong nucleophiles (e.g. LiAlH$_4$, Grignard reagents etc.).
- Activated pyridine will react with weaker nucleophiles (e.g. NaBH$_4$, -CN).

e.g.
Pyridine reactivity in action

- **Synthesis of Omeprazole:**
  - $\$\text{Billion-selling drug: proton pump inhibitor to treat stomach ulcers.}$
  - e.g.

  - [Chemical structures and reactions](image)

  - **Omeprazole**
Pyridine: summary

- Electronic structure of pyridine.

- Difference between structure & chemistry of pyridine and benzene.

- **Basicity**: strength relative to non-aromatic amines; effect of substituents.

- **Nucleophilicity**: react through lone pair.

- **$S_{EAr}$**: position of substitution; rate of reaction w.r.t. benzene; why unreactive?
  - **Pyridine N-oxides**: reactions, methods for synthesis & removal.

- **Nucleophilic attack**: easy with halo-pyridines & activated pyridines.
**Structure:**
- Isoelectronic with cyclopentadiene anion (i.e. 6π electrons, one in each of 4 parallel p orbitals on the carbons and lone pair in a parallel p orbital on nitrogen).

  e.g.

\[
\begin{align*}
\text{cyclopentadiene anion} & \quad \text{sp}^2 \text{ hybridised carbon:} \\
& \quad \text{negative charge in } p \text{ orbital, parallel to plane of } \pi\text{-system} \\
\text{pyrrole} & \quad \text{sp}^2 \text{ hybridised nitrogen:} \\
& \quad \text{lone pair of electrons in } p \text{ orbital, parallel to plane of } \pi\text{-system}
\end{align*}
\]
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*
  - one electron in each carbon p orbital
  - sp² hybridised nitrogen: lone pair of electrons in sp² orbital, orthogonal to plane of π-system

  **non-basic**
  - *pyrrole*
  - one electron in each p orbital
  - sp² hybridised nitrogen: lone pair of electrons in p orbital, parallel to plane of π-system

Location of nitrogen lone pair has major effect on reactivity and properties of pyrrole w.r.t pyridine
Imidazole: more than one nitrogen in the ring

- **Structure:**
  - Imidazole has 6π electrons, hence one nitrogen is pyridine-like and one nitrogen pyrrole-like.
  - e.g.

```
N
H
```

imidazole

```
N
N

N
```

pyridine-like nitrogen

```
N
N

N
```

pyrrole-like nitrogen

**basic**

**non-basic**
Pyrrole: NMR spectroscopic properties

- **1H NMR spectroscopic chemical shifts (i.e. δ_H in ppm):**
  - Pyrrole is electron rich from lone pair donation, hence greater shielding.
  - e.g.

  ![Pyrrole NMR Shifts](image)

  \[ \begin{align*}
  \delta_H &\approx 10 \\
  6.2 &\quad 6.5 \\
  7.1 &\approx 10 \\
  7.2 &\quad 7.5 \\
  
  \end{align*} \]

  \( \text{NB: not as big a difference in shifts c.f. pyridine} \)

- **13C NMR spectroscopic chemical shifts (i.e. δ_C in ppm):**
  - Pyrrole is electron rich from lone pair donation, hence greater shielding.
  - e.g.

  ![Pyrrole NMR Shifts](image)

  \[ \begin{align*}
  \delta_C &\quad 107.7 \\
  118.0 \\
  123.6 &\quad 128.5 \\
  135.7 &\quad 149.8 \\
  
  \end{align*} \]
In which hybrid atomic orbital is the nitrogen lone pair located?

A. p
B. sp
C. sp²
D. sp³
Question: hybridisation states in heterocycles

- In which hybrid atomic orbital is the nitrogen lone pair located?

A. p  
B. sp  
C. sp$^2$  
D. sp$^3$  

[Diagram of a nitrogen atom with a lone pair]
Pyrrole: general reactivity trends

- **Lone pair reactivity:**
  - Non-basic (i.e. $pK_a \approx -3.8$), in strong acid pyrrole protonates on carbon *not* nitrogen.
  - Nucleophilic on carbon rather than nitrogen (i.e. lone pair delocalised into ring).
  - Does not undergo $N$-oxidation (c.f. pyridine).

- **Electrophilic substitution:**
  - Electron rich ring is highly reactive to $S_{E}Ar$ (more so than benzene).

- **Nucleophilic substitution:**
  - Electron rich ring unreactive towards nucleophilic attack.
  - Require electron withdrawing substituent to activate ring.

*NB: for an example of $S_{N}Ar$ on an activated pyrrole, see ‘OC’ textbook p 738*
Pyrrole: lone pair reactivity

- **Basicity:**
  - Pyrrole lone pair delocalised around ring, hence non-basic.
  - c.f. Pyrrolidine lone pair in sp³ orbital, hence stronger base.

\[
\begin{align*}
\text{Pyrrole} & : \quad pK_a = -3.8 \\
\text{Pyrrolidine} & : \quad pK_a = 11.0
\end{align*}
\]
**Acidity:**
- Pyrrole has N-H present (c.f. pyridine).
- Weakly acidic (i.e. lone pair delocalised around ring so less electron density located at nitrogen c.f. pyrrolidine).

  e.g.  
  \[
  \begin{align*}
  &\text{N-H bond uses nitrogen sp}^2 \text{ orbital} \\
  &\text{negative charge in nitrogen sp}^2 \text{ orbital & lone pair delocalised into aromatic ring}
  \end{align*}
  \]

  - Pyrrolidine is much less acidic.

  e.g.  
  \[
  \begin{align*}
  &\text{negative charge in nitrogen sp}^3 \text{ orbital & lone pair fully localised on nitrogen}
  \end{align*}
  \]
Pyrrole: electrophilic substitution

- **$S_E Ar$:**
  - Pyrrole is electron rich, reacts readily with electrophiles (NB: more reactive than benzene).
  - Nitrogen lone pair delocalisation increases electron density at each carbon in ring.
  - e.g.

  - Is substitution at C-2 or C-3 favoured?

- NB: adding another heteroatom into the ring deactivates towards $S_E Ar$ as this is ‘pyridine-like’
S\textsubscript{E}Ar at C-2 position:
- Generally favoured.
- Cation resulting from electrophilic attack is more stabilised (i.e. 3 resonance forms).
- Linear conjugated intermediate (i.e. both double bonds conjugated with N\textsuperscript{+}).

\textit{e.g.}

Pyrrole: electrophilic substitution
- **S<sub>E</sub>Ar at C-3 position:**
  - Less favoured.
  - Cation resulting from electrophilic attack is less stabilised (i.e. 2 resonance forms).
  - *Cross conjugated* intermediate (i.e. only one double bond conjugated with N<sup>+</sup>, less stable than linear conjugated intermediate).

  *e.g.*

  ![Diagram](image_url)
Pyrrole: electrophilic substitution

e.g. Formylation in the absence of a strong Lewis acid: Vilsmeier-Haack reaction.

\[
\text{POCl}_3 + \text{DMF} \rightarrow [\text{H}^+\text{NMe}_2]^{\ominus} + \text{NMe}_2\text{H}\text{Cl} \rightarrow \text{NMe}_2\text{H}\text{Cl} + \text{POCl}_3
\]

NB: formation of intermediate driven by strong P=O bond formed

\[
\text{H}^+\text{NMe}_2 + \text{NMe}_2\text{H}\text{Cl} \rightarrow [\text{H}^+\text{NMe}_2]^{\ominus} + \text{NMe}_2\text{H}\text{Cl}
\]

\[
\text{S}_\text{E}\text{Ar}
\]

iminium ion hydrolysis
Aims for this lecture

- Heterocycles:
  - Continue look at pyrrole reactivity.
  - Summary & comparison of pyrrole and pyridine structure & reactivity.
  - Consider epoxide ring opening under acidic and basic conditions.
  - Synthesis of pyridine and pyrrole.
Pyrrole: electrophilic substitution

e.g. Recap.: Vilsmeier-Haack reaction.
Question: electrophilic substitution of pyrrole

- What is the product of this Mannich reaction?

\[ \text{HCHO} + \text{Me}_2\text{NH} \rightarrow \begin{array} {c} \text{NMe}_2 \end{array} \]

A. 1  
B. 2  
C. 3  
D. 4  

[Images of chemical structures 1, 2, 3, and 4]
Pyrrole: reaction at nitrogen

- **Pyrrole anion undergoes** *N*-alkylation and *N*-acylation:
  - Anion in sp² orbital (90° to plane of π-system), so cannot overlap with ring & subsequent reaction occurs at nitrogen.
  - 2 steps: (1). Deprotonate pyrrole (NB: pKₐ 16.5), (2) Add electrophile.
  - e.g. 1.

- **e.g. 2.**

**NB:** without deprotonation would get reaction solely at carbon

\[
\text{N-acylation}
\]

\[
\text{N-alkylation}
\]
**Pyrrole: Diels-Alder reactions**

- **Pyrrole functions as a diene:**
  - NB: benzene does not function as a diene for Diels-Alder reactions (i.e. pyrrole is “less aromatic”).
  - e.g. Synthesis of analgesic compound epibatidine, a natural product.

  **NB: see Dr Lebrasseur’s course on pericyclic chemistry**

\[ \text{[4+2]} \]

**NB: furan also takes part in Diels-Alder cycloadditions.**
Pyrrole: summary

- Electronic structure of pyrrole.

- Difference between structure & chemistry of pyrrole w.r.t. pyridine and benzene.

- Recognise pyrrole-like nitrogens and pyridine-like nitrogens in heterocycles.

- **Basicity:** pyrrole is not basic; protonate at C-2 in strong acid (leads to polymerisation).

- **Acidity:** pyrrole is weakly acidic; comparison to non-aromatic amines; electrophilic attack at nitrogen through pyrrole anion.

- **Nucleophilicity:** nitrogen lone pair delocalisation makes pyrrole ring electron rich; high nucleophilicity (at carbon).

- **SEAr:** position of substitution (i.e. C-2); rate of reaction w.r.t. benzene; why more reactive?
  - Vilsmeier-Haack reaction; Mannich reaction.

- **Nucleophilic attack:** unreactive, require electron withdrawing substituents to activate pyrrole ring.
Pyrrole & pyridine: schematic reactivity summary

- **Pyrrole**
  - Base (very easy)
  - $E^+$ (very easy)

- **Pyrrole Anion**
  - Base (very easy)
  - $E^+$ (very easy)

- **Pyridine**
  - Base (difficult)
  - $E^+$ (difficult)

- **Activated Pyridine**
  - Base (difficult)
  - $E^+$ (easy)
Epoxide ring-opening:
- Strained 3-membered ring, but requires either a good nucleophile or acid catalysis to react well.
- $S_N2$ mechanism, hence inversion of stereochemistry at reaction centre (i.e. stereospecific).
  e.g.

![Diagram of epoxide ring-opening](image1)

- Unsymmetrical epoxides lead to issues of regioselectivity (i.e. which end reacts?).
  e.g.

![Diagram of regioselectivity](image2)
Useful reactions of other heterocycles

- Epoxide ring-opening in base:
  - Attack less hindered end of epoxide (i.e. minimise steric interactions between Nu\(^-\) and E\(^+\)).
  - Pure S\(_N\)2 mechanism, inversion of stereochemistry at reaction centre (i.e. stereospecific).
  - e.g.

\[ \text{NB: epoxide oxygen is a poor LG (i.e. RO}^-\text{), so needs a strong Nu}\]

Pentacoordinate T.S. in S\(_N\)2 reaction hence minimise steric interactions

NB: for further details on epoxide ring opening, see ‘OC’ textbook p 438
**Epoxide ring-opening in acid:**
- Attack more hindered end of epoxide (i.e. epoxide oxygen protonated in acid, so build up of postive charge in T.S. stabilised at most substituted end).
- ‘Loose’ $S_N2$ transition state, inversion of stereochemistry at reaction centre (i.e. **stereospecific**).
  
  e.g.

**NB:** epoxide oxygen is protonated, so it is a good LG (i.e. ROH) and does not need a strong Nu.

**NB:** inversion

**attack at more hindered end**

**NB: for further details on epoxide ring opening, see ‘OC’ textbook p 438**
Question: epoxide opening

- Identify the correct product from this epoxide ring opening.

\[
\text{Epoxide ring opening with MeOH, HCl:} \quad ?
\]

- A. 1
- B. 2
- C. 3
- D. 4

Options:

- 1. \(\text{OMe} \quad \text{OH}\)
- 2. \(\text{OH} \quad \text{OMe}\)
- 3. \(\text{OH} \quad \text{OMe}\)
- 4. \(\text{OMe} \quad \text{OH}\)
Synthesis of heterocyclic rings

- **In general:**
  - Based on simple carbonyl chemistry (see previous recap. of key reactions).
  - Can disconnect the main bonds to reveal simple *linear* precursors.

  e.g. **Pyrrole**

  ![Pyrrole reaction](image)

  *pyrrole* → *1,4-dicarbonyl compound* + *R'NH₂*

  e.g. **Pyridine**

  ![Pyridine reaction](image)

  *pyridine* → *1,5-dicarbonyl compound* + *NH₃*

  NB: for a further summary of 5- and 6-membered ring synthesis, see ‘OC’ textbook p 785 & 786.
Synthesis of pyrroles

- **Paal-Knorr synthesis:**
  - Uses a 1,4-dicarbonyl compound and either ammonia or a 1° amine.
  - Requires weak acid (NB: strong acid will lead to formation of the corresponding furan).
  - e.g.

- **Mechanism:**
  - e.g.

**NB:** overall, lose 2 moles of water
Question: synthesis of pyrroles

- Identify the correct pyrrole product from this reaction

\[
\text{O} \quad \text{H} \quad 2 \quad \text{N}
\]

\[
\text{AcOH} \quad ?
\]

- A. 1
- B. 2
- C. 3
- D. 4
**Synthesis of pyridines**

- **Hantzsch synthesis:**
  - 4 component reaction (NB: 3 different substrates).
  - Initially affords a 1,4-dihydropyridine, but readily oxidises in air to give the pyridine.
  
  e.g.

  \[
  \text{EtO}_2\text{C} \quad \text{O} \quad \text{H} \quad \text{CO}_2\text{Et} \quad \text{pH 8.5} \quad \text{EtOH} \quad \text{EtO}_2\text{C} \quad \text{CO}_2\text{Et} \quad [\text{O}] \quad \text{oxidation} \quad \text{EtO}_2\text{C} \quad \text{CO}_2\text{Et} 
  \]

  1,4-dihydropyridine

  pyridine

  *NB: aldehyde provides extra carbon for pyridine ring (c.f. pyrrole synthesis)*

  NB: for further details of the Hantzsch pyridine ring synthesis, see ‘OC’ textbook p 763.
Synthesis of pyridines

- **Mechanism:**
  - Condensation with aldehyde to form α,β-unsaturated product (c.f. aldol reaction).

  ![Chemical structures](image)

  - α,β-unsaturated product is good conjugate acceptor, so Michael reaction occurs.

  **NB:** 2\(^\text{nd}\) equivalent of enolate used

  ![Chemical structures](image)

  **NB:** enamine formation

  ![Chemical structures](image)

  NB: for further details of the Hantzsch pyridine ring synthesis, see ‘OC’ textbook p 763.
Synthesis of pyridines

- **Mechanism (continued):**
  - Enamine formation, then intramolecular cyclisation of nitrogen onto other ketone.

- Final oxidation step is facile.
- Occurs in air, or with chemical reagents such as DDQ.

NB: The mechanism for oxidation is beyond the scope of this course, but for further details see ‘OC’ textbook p 764.
- Under *acidic conditions*, epoxides open at the more hindered end (i.e. loose S_N2 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.
Representative questions

This a new course and hence there is only one mock exam paper (see QMplus) that relates specifically to this course (and the exclusion of any other). However, much of the material is what I would class as core material that will crop up across a range of examination questions.

With regards to older lecture courses, particular attention should be paid to parts of the SBC703 course, ‘Synthesis of Pharmaceutically Active Molecules’.

Access to past papers can be made via the library webpage.

For general practice, many textbooks contain questions that will relate to the topics covered.