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

Semester A 2015

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

- **Coursework:**
  - Semester A – week 9 5% (‘Coursework 3’)
  - Semester A – week 11 5% (‘Coursework 4’)

- **Test:**
  - Semester A – week 12 15% (‘Test 2’)

- **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.  
    ```latex
catalytic hydrogenation (e.g. H_2(g) & Pd) 
\[
\text{H}_2 \text{(g) \rightarrow H}_2\text{O}_2 \text{H}
\]
```

- The ionic addition of hydrogen  
  *NB: Dr. Lebrasseur’s & Dr Bray’s carbonyl lectures.*  
  e.g.  
  ```latex
hydrde addition then protonation  
(e.g. LiAlH}_4 \text{ then acid w/up) }
\[
\text{H}_2\text{O}_2 \text{H} \text{ then } \text{H}_2\text{O}_2 \text{H}
\]
```

- The addition of electrons.  
  e.g.  
  ```latex
dissolved alkali metals  
\[
\text{H}_2\text{O}_2 \text{H} \leftrightarrow \text{H}_2\text{O}_2 \text{H}
\]
```

  *Overall two electrons 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*.

\[
\text{Metal Catalyst} \quad \text{H}_2 (g) \quad \text{H}_2 \quad \text{H}
\]

- Hydrogenation has a different mechanism of reduction compared to hydride reducing agents (e.g. NaBH\(_4\)), therefore different *chemoselectivity* is often observed.
  - e.g.

\[
\text{Catalyst: Pd/C (10 mol\%) } \quad \text{H}_2 (g) \quad \text{Aldehyde not reduced}
\]

*NB: 10 mol\% = 0.1 molar 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 (Al₂O₃).

- **Reduction of alkenes:**
  - Reactions generally proceed at r.t. and 1 atm. H₂ pressure, however, reaction rates increase when elevate T and/or P.
  - Hydrogenation is typically selective for *syn*-addition.
  
  ![Chemical structures](image)

  - 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.*
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). $\mathrm{H}_2$ dissociatively *adsorbed* onto metal surface.
    ii). Alkene $\pi$-bonds *coordinated* to catalyst surface.
    iii). Alkene $\pi$-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**

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

\[\text{Pt/C (cat.), } H_2 (4 \text{ atm.}) \quad \rightarrow \quad \text{AcOH}\]

**Heterocyclic ring**

\[
\begin{align*}
\text{Me} & \quad \text{Bu}^n \\
\text{Me} & \quad \text{Bu}^n
\end{align*}
\]

\[10\% \text{ PtO}_2 (10 \text{ mol%}) \quad H_2 (5 \text{ atm.}), \text{ HBr, r.t.}\]

\[\text{74\%}\]

\[\text{NB: carboxylic acid untouched}\]

\[\text{NB: increased } H_2 \text{ pressures}\]

\[\text{NB: syn-addition of hydrogen}\]

\[\text{(±)-monomorine}\]
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
Reduction of carbon-carbon double and triple bonds

- **Reduction of alkynes to alkanes:**
  - Standard heterogeneous hydrogenation results in complete reduction to alkanes.
  - e.g.

  \[
  \text{Ph} \equiv \text{CO}_2\text{Me} \xrightarrow{\text{Pd/C (10 mol%)}, \text{H}_2 (1 \text{ atm.}), \text{MeOH}} \text{Ph} - \text{CH}_2 - \text{CH}_2 - \text{CO}_2\text{Me}
  \]

  - 1 mole of \( \text{H}_2 \) added

  - 2 moles of \( \text{H}_2 \) added

- **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.

  \[
  \text{Ph} \equiv \overset{\equiv}{\text{C}} \overset{\equiv}{\text{C}} \text{Me} \overset{\equiv}{\text{CO}} \overset{\equiv}{\text{O}Me} \rightarrow \begin{array}{c}
  \text{Ph} \\
  \overset{\equiv}{\text{C}} \overset{\equiv}{\text{C}} \text{Me} \\
  \end{array} \overset{\equiv}{\text{CO}} \overset{\equiv}{\text{Me}} \overset{\equiv}{\text{H}} \overset{\equiv}{\text{H}} \]

  \[
  \text{Pd/CaCO}_3 (10 \text{ mol%}) \quad \text{H}_2 (1 \text{ atm.}), \text{ quinoline} \quad \text{Pb(OAc)}_4, \text{ EtOAc} \]

  \[\text{cis-}(Z)-\text{alkene}\]

  e.g.

  \[
  \begin{array}{c}
  \text{TBSO} \\
  \text{R} \\
  \text{O} \\
  \text{R} \\
  \text{O} \\
  \text{O} \\
  \text{O}
  \end{array} \rightarrow \begin{array}{c}
  \text{TBSO} \\
  \text{R} \\
  \text{O} \\
  \text{R} \\
  \text{O} \\
  \text{Z}
  \end{array}
  \]

  \[
  \text{Pd/CaCO}_3 (10 \text{ mol%}) \quad \text{H}_2 (1 \text{ atm.}), \text{ quinoline} \quad \text{Pb(OAc)}_4, \text{ hexane}, \text{ r.t.} \]

  \[86\%\]

- **Mechanism**: two hydrogens added to same face of alkyne, leading to *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).

- **Example:** 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.
- **Chemoselectivity** (*i.e.* ketones, carboxylic acids, esters, nitriles, ethers and nitro groups all inert to these conditions.

![Chemoselectivity example](image)

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

Sir Geoffrey Wilkinson
(Nobel Prize in Chemistry 1973)

**NB:** Heterogeneous hydrogenation (*e.g.* \(\text{H}_2, \text{Pd}/\text{C}\)) is non-selective and leads to over reduction.
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…
Pre-Lecture Diagnostic Test – Feedback


- Excellent – no obviously weak areas.
  - individuals are strongly encouraged to revise any specific areas of weakness that the test revealed.

Lowest scoring question was Q13 (although this may be logistical/operational rather than understanding – I have learnt that ‘drag and drop’ qns require extra care for QMplus quizzes!).

Revision:

**FEEDBACK:** each week please use QMplus to comment on which area of the last two lectures was least clear – I will then revise that topic at the start of the next lectures.
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 $\pi^*$-orbitals.

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

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

\[
\begin{align*}
\text{O} & \quad \text{CH}_2=\text{CH}\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2 \\
\text{i). Li, NH}_3 (l), \text{t-BuOH (1 equiv), –78 °C} & \quad \rightarrow \\
\text{O} & \quad \text{CH}_2=\text{CH}\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2
\end{align*}
\]

Reduces electron deficient alkene only

*NB: Low temperature as NH$_3$ is a gas at $T > –33$ °C.*

*NB: Stoichiometry of alcohol is crucial.*
Reduction of carbon-carbon double and triple bonds

- **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.

`Reduction of carbon-carbon double and triple bonds`
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

  - Provided it is not electron deficient, product alkene will not be reduced.
  - Vinyl anions are geometrically unstable and choose (*E*)-geometry.

Vinyl anions sufficiently basic to deprotonate NH$_3$
(c.f. enolate basicity on slide 18)
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
Reduction of carbon-carbon double and triple bonds

- **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.*

  ![Reaction Scheme]

  Pentadienyl anion has the highest electron density at the central position, hence kinetic protonation (at low T) affords *regioselectivity* for non-conjugated product.

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

- **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.
Reduction of carbon-carbon double and triple bonds

- Birch reduction of heterocycles:
  - Heterocycles bearing an electron withdrawing group can also be partially reduced. e.g.

\[
\begin{align*}
\text{i-PrO} & \quad \text{Na, NH}_3 (l), \text{t-BuOH, } -78 \, ^\circ C \\
\text{i-PrO} & \quad \text{Na, NH}_3 (l), \text{t-BuOH, } -78 \, ^\circ C \\
\end{align*}
\]

- Heterocycles are electron rich – electron withdrawing group required for reduction.
- Electron withdrawing group also stabilises radical anion formation, controls *regioselectivity*. 
Reduction of carbon-carbon double and triple bonds

- 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.
  
  e.g.

\[
\begin{align*}
\text{MeO} & \quad \text{O} \\
\text{O} & \quad \text{MeO} \\
\text{H} & \quad \text{H} \\
\text{K, NH}_3(\text{l}) & \quad \text{THF, } -70^\circ\text{C}
\end{align*}
\]
Question: Birch reduction

- Which of these substrates will be reduced the fastest under Birch conditions (i.e. dissolved metal, NH$_3$ (l), –78 °C)?

A. 1  
B. 2  **✓**  
C. 3  
D. 4  
E. 5
Reduction of carbon-carbon double and triple bonds

- **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).
  
  ![Diimide structure](image)

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

  ![Oxidation and Decarboxylation](image)

  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).

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

\[
\begin{array}{c}
\text{KO}_2\text{CN}=\text{NCO}_2\text{K} \\
\text{AcOH, CH}_2\text{Cl}_2 \\
\end{array}
\]

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

\[
\begin{array}{c}
\text{NH}_2\text{NH}_2 \\
\text{O}_2, \text{Cu(II)} \\
\end{array}
\]

\[ \text{NB: trans-alkenes reduced in preference to cis-alkene} \]
Birch reduction – recap.

- Initial electron addition – consider the stability of the subsequent radical anion.
  - These curly arrow mechanisms are discussed in all general organic chemistry textbooks.
  - e.g.

\[
\begin{align*}
\text{CO}_2\text{Me} & \quad \text{Na, NH}_3 (l), \text{t-BuOH, } -78 \degree \text{C} \\
\text{H} & \quad \text{H}
\end{align*}
\]

Radical is closest to stabilising group (i.e. ester)

NB: pentadienyl anion has largest coefficient of electron density at central position (kinetic protonation occurs here)
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.

  ![Reduction Mechanism Diagram](image)

  - LiAlH$_4$ deprotonates alcohol then complex forms between alkoxide and Lewis acidic AlH$_3$.
  - Intramolecular delivery of hydride.
  - Intramolecular coordination of vinyl anion to Lewis acidic Al species locks geometry of alkene.

  - *H$_2$ (g) evolution* due to stereospecific protonation of C-Al bond during workup.
Reduction of carbon-carbon double and triple bonds

**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 LiAlH$_4$ (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.
Questions: end of Lectures 1 & 2

Q1. What is the product of this Birch reduction? Draw a curly arrow mechanism to describe the reaction.

\[ \text{Me} \begin{array}{c}
\text{Li, NH}_3 (l), -78 \, ^\circ\text{C, t-BuOH}
\end{array} \rightarrow ? \]

Q2. Provide two different sets of reagents and conditions that would carry out this transformation. Draw curly arrow mechanisms for both.

\[ \text{Ph} \begin{array}{c}
\text{OH}
\end{array} \rightarrow ? \rightarrow \text{Ph} \begin{array}{c}
\text{OH}
\end{array} \]

Q3. Which two types of selectivity (i.e. chemo, regio, stereo) are observed in this Lindlar reduction and how do the reagents and conditions control these selectivities?

\[ \text{Ph} \begin{array}{c}
\text{CO}_2\text{Me}
\end{array} \xrightarrow{\text{Lindlar reduction}} \text{Ph} \begin{array}{c}
\text{CO}_2\text{Me}
\end{array} \]

Q4. Which of the two following hydrogenations would require the greater pressure of hydrogen, and why?

\[ \text{Pd/C (cat.), H}_2 (g), \text{MeOH} \]

\[ \text{Pd/C (cat.), H}_2 (g), \text{MeOH} \]
Aims: at the end of this section you will be able to...

- Understand the origin and reactivity of C-O and C-N multiple bonds.

- Draw curly arrow mechanisms for standard C-O and C-N multiple bond reductions.

- Understand the origin and predict the chemoselectivity of different hydride reducing agents (e.g. LiAlH₄, NaBH₄, LiBH₄, BH₃, DIBAL etc.)

- Understand the origin and predict the stereochemical outcome of ketone reduction using appropriate Felkin-Anh models of 1,2-stereinduction.
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 H₂ (g) and TM catalyst.
  - e.g.

  ![Catalytic hydrogenation reaction](image)

  \[ \text{NB: Pt more reactive metal than Pd} \]

  - 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*.

  ![Ionic hydrogenation reaction](image)

  \[ \text{NB: see Dr Lebrasseur’s & Dr Bray’s lectures on carbonyl chemistry} \]
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.

  
  \[ \text{LiAlH}_4, \text{NaBH}_4, \text{BH}_3, \text{LiBH}_4, \text{DIBAL, NaCNBH}_3, \text{Al(Oi-Pr)}_3. \]

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>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>✓</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 AMINE ALCOHOL
Reduction of carbon-oxygen double and triple bonds

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

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

\[
\text{Racemic product}
\]

\[
\text{NB: amide not reduced}
\]

\[
\text{w/up}
\]

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.

  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.**

  - Reaction completely reversible
  - Works via hydride transfer from the isopropoxy group (i.e. different mechanism c.f. NaBH₄ & LiAlH₄).

  6-membered transition state

  NB: a,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).
  
- **Luche reduction:**
  - Excellent *regioselectivity* for [1,2]-attack by using CeCl$_3$ in addition to NaBH$_4$.
  - Ce(III) activates carbonyl & promotes formation of alkoxyborohydrides from NaBH$_4$ and MeOH.
A. At room temperature LiAlH$_4$ is a solid
B. At room temperature LiAlH$_4$ is a liquid
C. At room temperature NH$_3$ is a liquid
D. At room temperature NH$_3$ is a gas
E. NaBH$_4$ will not reduce an ester
F. NaBH$_4$ 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.

    ![Chemical Reaction Diagram]

    - Li⁺ activates carbonyl group
    - 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.

  Intermediate collapses to aldehyde upon w/up, *but* excess DIBAL has already been quenched so no further reduction can occur

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

\[ \text{DIBAL reduces esters at } -70 \degree \text{C} \]

\[ \text{tetrahedral intermediate stabilised at low } T \]

\[ \text{NB: alkene not reduced} \]

\[ \text{hemiacetal} \]
Reduction of carbon-oxygen double and triple bonds

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

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

\[
\text{LiAlH}_4 \quad \text{LiAlH}_4, \text{Et}_2\text{O} \quad \text{88 %}
\]

- tetrahedral intermediate collapses by expelling best LG (i.e. O better than N)
- iminium ion reduced rapidly by LiAlH$_4$
Reduction of carbon-oxygen double and triple bonds

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

    ![Reduction mechanism diagram]

    - BH$_3$ donates hydride to reactive imidate.
    - Borate donates hydride to reactive imidate.
    - BH$_3$ reduces reactive iminium ion.
    - (c.f. 1st step of hydroboration mechanism)

NB: ester not reduced
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.

  ![Chemical reaction diagram](attachment:image.png)

  - Tetrahedral intermediate is difficult to stabilise and collapses *in situ* to iminium ion which is further reduced to amine (c.f. LiAlH₄).
  - No general reagent for amide reduction to aldehyde... BUT...
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

\[
\text{DIBAL, toluene} \quad 0^\circ C, \quad 74\%
\]

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

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

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

\[
\text{w/up reveals hemiaminal}
\]

\[
\text{hydrolysis to aldehyde}
\]
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.

    ![Reaction Diagram]

    - Stabilised chelated tetrahedral intermediate
    - NB: also works with Grignard reagents
    - Elimination of MeNHOMe

    Q: What would happen if this was a simple amide, rather than a Weinreb amide?
Reduction of carbon-oxygen double and triple bonds

- **Reduction of carboxylic acids to alcohols:**
  1. Use LiAlH₄ but require very forcing conditions, as form unreactive carboxylate salts. e.g. 1

  ![Chemical structure](image)

  - **Mechanism:** complexation with lone pair forms active reducing agent (see amide reduction).
  - **Milder conditions compared to using LiAlH₄.** e.g. 2

  ![Chemical structure](image)

  2. Use BH₃: Lewis acidic, so **chemoselective** for most electron rich carbonyl groups only (acids and amides).
  - **Mechanism:** complexation with lone pair forms active reducing agent (see amide reduction).
  - **Milder conditions compared to using LiAlH₄.** e.g. 2

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.
- Method for chemoselective reduction of acid in presence of ester.
  e.g. 3

acid → alcohol

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 (NB: imines more electrophilic than aldehydes).
  - e.g.

  ![Reduction of imines to amines](image)

  - **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.
  - e.g.

  ![Reductive amination](image)

  - *Aldehyde not reduced by NaCNBH₃*
  - *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.

  ![Mechanism diagram](image)

  - NB: iminium ion formation

  - **CO$_2$ (g) evolution**
Reduction of carbon-nitrogen double and triple bonds

- **Reduction of nitriles to amines:**
  - Complete reduction using LiAlH₄ (*i.e.* powerful reducing agent).
  - e.g.

  ```latex
  \text{Li}^+ \text{activates nitrile group}
  \text{LiAlH}_4 \rightarrow \text{imine intermediate}
  \text{LiAlH}_4, \text{THF} \rightarrow \text{reduction of intermediate imine followed by w/up}
  \text{LiAlH}_4, \text{then H}_3\text{O}^+ \rightarrow \text{Overall 2 equivalents of hydride added}
  ```
Reduction of carbon-nitrogen double and triple bonds

- **Reduction of nitriles to aldehydes:**
  - Partial reduction using DIBAL (note: 1 equivalent of reducing agent is crucial).
  - e.g.

  ![Reaction Mechanism]

  **NB:** Lewis acidic DIBAL coordinates to nitrile lone pair and ‘ate’ complex is hydride donor.

  - no DIBAL remaining
  - so iminoalane reduction cannot occur

  ![Additional Reaction]

  **iminoalane**
Reduction of carbon-heteroatom double and triple bonds

- **Summary of FG reactivity with common reducing agents:**

<table>
<thead>
<tr>
<th>Reducing Agent</th>
<th>Iminium Ion</th>
<th>Aldehyde</th>
<th>Ketone</th>
<th>Ester</th>
<th>Amide</th>
<th>Carboxylic Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>LiAlH$_4$</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓ (slow)</td>
</tr>
<tr>
<td>NaBH$_4$</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>slow</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>LiBH$_4$</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>BH$_3$</td>
<td>✓ slow</td>
<td>slow</td>
<td>slow</td>
<td>slow</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>NaCNBH$_3$</td>
<td>✓ slow</td>
<td>slow</td>
<td>slow</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
</tbody>
</table>

*Product*

<table>
<thead>
<tr>
<th>AMINE</th>
<th>ALCOHOL</th>
<th>ALCOHOL</th>
<th>ALCOHOL</th>
<th>AMINE</th>
<th>ALCOHOL</th>
</tr>
</thead>
</table>

*decreasing electrophilicity*
Stereoselective reduction of carbonyl groups
Diastereoselectivity with hydrides: 1,2-stereoinduction

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

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

*Felkin* product

- Drawing Newman projections (recap.).

\[ \text{Ph} \text{O} \text{Ph} \xrightarrow{\text{add substituents}} \text{Me} \text{O} \text{Ph} \]

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

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

\[
\begin{align*}
\text{Ph} & \quad \text{O} \\
\text{LiBH(s-Bu)}_3 & \quad \text{THF} \\
\rightarrow & \quad \text{Ph} \quad \text{OH}
\end{align*}
\]

- 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).

\[\text{Newman projection}\]

\[\text{Lowest energy conformations of chiral starting material}\]

\[\text{(i.e. place largest group 90° to C=O)}\]

*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.

  ![Reaction Scheme](image1)

  ![Newman Projection](image2)

  - 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.

  - $\pi^*$ C=O overlaps with $\sigma^*$ C-S; creates lower energy LUMO

  ![Overlap Diagram](image3)

  (i.e. most reactive in this conformation)
Diastereoselectivity with hydrides: 1,2-stereoinduction

- **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).
  - e.g.

    ![Chemical structure](image)

    - 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*
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

1. most reactive conformation
20. diastereoselectivity
Diastereoselectivity with hydrides: 1,2-stereoinduction

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

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

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

  - How do we explain *diastereoselectivity*? Consider reactive conformation.

  \[
  \begin{align*}
  &\text{‘R’ = Me} \\
  &\text{Chelation model} \\
  &\text{‘R’ = OSi(i-Pr)₃} \\
  &\text{Felkin polar model} \\
  \end{align*}
  \]

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

- **Summary: which model to use?**

```
\[
\begin{array}{c}
\text{X} \\
\text{Y} \\
\text{Z} \\
\text{R}
\end{array}
\]

- \text{\textit{a-}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)
Questions: end of Lectures 3 & 4

Q1. Provide a curly arrow mechanism for this reaction. What is the name of this transformation?

\[ \text{cyclohexanone} \xrightarrow{\text{Al(Oi-Pr)}_3, \ i-	ext{PrOH}} \xrightarrow{\Delta} \text{cyclohexanol} \]

Q2. What are the structures of A and B? Draw mechanisms for both reactions and rationalise the observed selectivity.

A \xleftarrow{\text{LiBH}_4} \xrightarrow{\text{LiAlH}_4} B

Q3. Put these FGs into their order of increasing reactivity with DIBAL (i.e. least first, most reactive last).

ESTER  KETONE  ALDEHYDE  AMIDE

Q4. What is the product of this reaction? Draw a mechanism to describe the formation.

\[ \text{cyclohexanone} \xrightarrow{1. \triangleleft \text{NH}_2, \ HCl, \ MeOH} \xrightarrow{2. \text{NaCNBH}_3} ? \]

Q5. What is the stereochemistry of the product in this reaction? Explain how you came to your choice.

\[ \text{Ph} - \text{cyclohexanone} \xrightarrow{\text{NaBH}_4, \ \text{MeOH}} \text{Ph} - \text{cyclohexanol} \]
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.

- Identify heterocycles, explain their importance and be aware of aspects concerning nomenclature.

Note: Reagents & conditions in questions – reagents are most important part of reaction to remember/apply (solvent is less important to answers, unless it has been specifically mentioned in lecture notes e.g. polar & protic for hydrogenations)
Diastereoselectivity with hydrides: 1,3-stereoinduction

- **1,3-Polyols:**
  - Important motif found in many natural products.

- How do we control *diastereoselectivity*?

![Diagram of 1,3-Polyols with 1,3-syn and 1,3-anti configurations]

![Chemical structures of 1,3-Polyols with reaction arrow and product configurations]
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.

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

NB: for further explanation see ‘OC’ textbook p. 370-374.
Diastereoselectivity with hydrides: 1,3-stereoinduction

- **1,3-syn Diols:**
  - Use a Lewis acid (e.g. \( \text{Bu}_2\text{BOMe}, \text{BF}_3 \)).
  - 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

Why does hydride attack from this face?...consider in 3D

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.

![Chemical structure and reaction diagram](attachment:diastereoselectivity.png)

- Intramolecular hydride delivery
- 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.

1,3-anti
Diastereoselectivity with hydrides: addition to cyclohexanones

**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).

![Diagram showing axial and equatorial attack with small and bulky hydrides.](image-url)
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’:

  (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).

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

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

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

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

\[
\begin{align*}
\text{1} & : \text{BnO} \quad \text{OH} \\
\text{2} & : \text{BnO} \quad \text{OH} \\
\text{3} & : \text{BnO} \quad \text{OH} \\
\text{4} & : \text{BnO} \quad \text{OH}
\end{align*}
\]
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.

Boron in catalyst is Lewis acidic and activates C=O group

BH$_3$ used to regenerate active catalyst

Boat-like arrangement controls facial selectivity

Binding of BH$_3$ and ketone to exo face of catalyst

Hydride delivered from ‘top’ face

(R)-alcohol, 97 % ee

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

Cl\(\text{Ph}\)\(\text{Me}\) 1 mol% \(\text{BH}_3\), THF

\[
\text{Cl}\cdots\text{OH}\cdots\text{Ph}
\]

\[96\%\text{ ee}\]

- e.g. 2

\[
\text{TBSO}\cdots\text{OH}\cdots\text{Me}
\]

\[94\%\text{ de}\]

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.

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

**Hydrogenolysis**
- Reductive cleavage of a carbon-heteroatom (C-X) single bond through the addition of hydrogen.
- Most commonly used to cleave benzylic (PhCH\(_2\))– groups attached to oxygen or 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 Lecture 1).

*E.g.*

\[
\text{N} \quad \text{Ph} \quad \xrightarrow{\text{Pd/C (10 mol%), } \text{H}_2 \ (1 \ \text{atm.})} \quad \text{EtOH} \quad \text{NH}
\]

\[
\text{O} \quad \text{Ph} \quad \xrightarrow{\text{Pd/C (10 mol%), } \text{H}_2 \ (1 \ \text{atm.})} \quad \text{EtOAc} \quad \text{O} \quad \text{OH}
\]

*Ease of formation and removal means that the benzyl group is commonly used as a ‘protecting group’ in organic synthesis for more reactive FGs such as 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:**
  - $C_{sp3}$-Hal and $C_{sp2}$-Hal bonds are amenable to hydrogenolysis.
  - Typically use Pd and a base (NB: produce HX acid as a byproduct which may retard reaction if it isn’t neutralised by base).

  e.g. 

  ![Diagram of reductive dehalogenation example](image)

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

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

  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. 

  ![Diagram of dissolved metal example](image)

  $\text{Na, NH}_3 (l), \text{t-BuOH, \text{-78 °C}}$

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

- Deoxygenation – ketones and aldehydes to alkanes:
  e.g. 1 Reduction to alcohol, make into good LG, displace with hydride.

- Can use Super-Hydride™ for less reactive displacement steps (i.e. LiEt₃BH).
- Electron-donating alkyl groups make it the most nucleophilic hydride source.

NB: Especially effective for challenging S₂N₂ reactions on activated LG
Reductive cleavage reactions

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

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

Hydrazine

Nitrogen gas evolution (irreversible)

Azine

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

- Which conditions break which bond?

  **Benzyl group cleavage**

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

  Use Pd/C, H₂, or dissolved metal

  X = O or N

  **Reductive dehalogenation**

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

  Use Pd/C, H₂

  X = Halogen (i.e. I, Br, Cl, F)

  **Deoxygenation**

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

  Wolf-Kischner or 3 step sequence (i.e. reduction, activation, reduction)
The question asks which set of reagents and conditions A to E will deliver the reduction product.

A. $\text{H}_2$ (1 atm.), Pd/C, MeOH, r.t.
B. $\text{H}_2$ (1 atm.), Pd/BaSO$_4$, Pb(OAc)$_4$, quinoline, r.t.
C. Na, NH$_3$, r.t.
D. Li, NH$_3$, $-78^\circ$C
E. $\text{H}_2$ (1 atm.), Pd/C, MeOH, 50 °C

The correct answer is D. Li, NH$_3$, $-78^\circ$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.

- Strategic aside: azide is an excellent nucleophile (better than NH$_3$ and easier to handle), 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.
Reduction of nitrogen-containing functional groups

2). Staudinger reduction:
- use PPh₃ as another *chemoselective* method for azide reduction in the presence of an alkene.
e.g.

\[
\begin{align*}
\text{N}_3 & \quad \text{PPh}_3, \text{THF} \quad \rightarrow \\
\text{amine} & \quad \text{amine}
\end{align*}
\]

*NB: Pd/C & H₂ would also reduce alkene*

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.
  
  e.g.
  
  - Many different 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.

\[
\begin{align*}
\text{MeO} & \quad \text{N} \\
\text{N}_3 & \quad \text{O} \\
\text{H}_2\text{N} & \quad \text{N} \\
\text{Me} & \quad \text{Me} \\
\text{O} & \quad \text{OMe} \\
\text{Br} & \quad \text{Bn} \\
\text{O} & \quad \text{OMe} \\
\text{OMe} & \quad \text{OMe} \\
\text{Br} & \quad \text{Bn} \\
\text{N}_3 & \quad \text{N} \\
\text{H}_2\text{N} & \quad \text{N} \\
\text{Me} & \quad \text{Me} \\
\text{O} & \quad \text{OMe} \\
\text{OMe} & \quad \text{OMe} \\
\text{Br} & \quad \text{Bn} \\
\text{N}_3 & \quad \text{N} \\
\text{H}_2\text{N} & \quad \text{N} \\
\text{Me} & \quad \text{Me} \\
\text{O} & \quad \text{OMe} \\
\text{OMe} & \quad \text{OMe} \\
\text{Br} & \quad \text{Bn} \\
\end{align*}
\]

\[10\% \text{ Pd/C, } \text{H}_2 (1 \text{ atm.}) \xrightarrow{\text{MeOH:EtOAc}} ?\]

A. 1

\[\checkmark\] B. 2

C. 3
Questions: end of Lectures 5 & 6

Q1. What is the product of this reduction? Assign the stereochemistry of the new stereocentre and use Newman projections to explain how you arrived at this assignment. What happens if NaCl is used instead of MgBr₂?

\[
\text{Ph} \quad \text{O} \quad \text{Ph} \quad \text{NaBH}_4, \text{MgBr}_2, \text{MeOH} \quad \text{?}
\]

Q2. What is the stereochemistry at C*? Use conformational drawings to explain your answer.

\[
\text{Na(s-Bu)}_3\text{BH}, \text{THF} \quad \text{OH}
\]

Q3. Provide reagents and conditions to complete the following transformation in 2 steps.

\[
\text{Br} \quad \text{NO}_2 \quad \text{Reagents?} \quad \text{2 steps} \quad \text{NH}_2
\]

Q4. What is the stereochemistry at C*. Use conformational drawings to explain your answer.

\[
\text{F} \quad \text{C} \quad \text{I} \quad \text{Catalyst A (1 mol%)} \quad \text{BH}_3\cdot\text{THF} \quad \text{F} \quad \text{C} \quad \text{I} \quad \text{OH}
\]

\[
\text{A}
\]
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)
- BENZENE (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](image1)
  ![Deoxyadenosine](image2)
  ![Quinine](image3)
  ![Omeprazole](image4)
  ![Ranitidine](image5)
  ![Nicotine](image6)
How many heterocycles are in this pharmaceutical compound? (NB: count any fused rings separately)

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

Sildenafil ('Viagra')
Aims for the final lectures

- **Heterocycles:**
  - Heterocyclic nomenclature.
  - 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?).
  - Summary & comparison of pyrrole and pyridine structure & reactivity.
  - Consider epoxide ring opening under acidic and basic conditions.
  - Synthesis of pyridine and pyrrole.
### Top 20 global best-selling drugs in 2009

#### 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 ($bil)</th>
<th>Compound type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipitor</td>
<td>Atorvastatin</td>
<td>Cholesterol</td>
<td>Pfizer</td>
<td>12.45</td>
<td>pyrrole</td>
</tr>
<tr>
<td>Plavix</td>
<td>Clopidogrel</td>
<td>Atherosclerosis</td>
<td>BMS</td>
<td>9.29</td>
<td>thiophene-tetra-H-pyridine</td>
</tr>
<tr>
<td>Enbrel</td>
<td>Etanercept</td>
<td>Arthritis</td>
<td>Amgen</td>
<td>8.00</td>
<td>protein</td>
</tr>
<tr>
<td>Advair</td>
<td>Fluticasone salmeterol</td>
<td></td>
<td>Pfizer</td>
<td>7.70</td>
<td>aromatic-steroid</td>
</tr>
<tr>
<td>Remicade</td>
<td>Infliximab</td>
<td>Inflammation</td>
<td>J&amp;J</td>
<td>6.91</td>
<td>antibody</td>
</tr>
<tr>
<td>Diovan</td>
<td>Valsartan</td>
<td>Hypertension</td>
<td>Novartis</td>
<td>6.01</td>
<td>tetrazole</td>
</tr>
<tr>
<td>Avastin</td>
<td>Bevacizumab</td>
<td>Colon cancer</td>
<td>Roche</td>
<td>5.92</td>
<td>antibody</td>
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<td>Rituxan</td>
<td>Rituximab</td>
<td>Rheumatoid arthritis</td>
<td>Roche</td>
<td>5.80</td>
<td>antibody</td>
</tr>
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<td>Abilify</td>
<td>Aripiprazole</td>
<td>Schizophrenia</td>
<td>BMS</td>
<td>5.60</td>
<td>quinolone-piperazine</td>
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<td>Humira</td>
<td>Adalimumab</td>
<td>Several</td>
<td>Abbott</td>
<td>5.49</td>
<td>antibody</td>
</tr>
<tr>
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<td>Trastuzumab</td>
<td>Breast cancer</td>
<td>Roche</td>
<td>5.02</td>
<td>benzimidazole - pyridine</td>
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<td>Esmoprazole</td>
<td>Nexium</td>
<td>Ulcers</td>
<td>AZ</td>
<td>4.96</td>
<td>thiazepine - diazepine</td>
</tr>
<tr>
<td>Zyprexa</td>
<td>Olanzapine</td>
<td>Anti-psychotic</td>
<td>Eli Lilly</td>
<td>4.91</td>
<td>piperazine</td>
</tr>
<tr>
<td>Seroquel</td>
<td>Quetiapine</td>
<td>Schizophrenia</td>
<td>AZ</td>
<td>4.89</td>
<td>pyrimidine</td>
</tr>
<tr>
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<td>Rosuvastatin</td>
<td>Cholesterol</td>
<td>AZ</td>
<td>4.74</td>
<td>quinoline</td>
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<tr>
<td>Singular</td>
<td>Omeprazole</td>
<td>Asthma</td>
<td>Merck</td>
<td>4.66</td>
<td>aromatic</td>
</tr>
<tr>
<td>Effexor</td>
<td>Venlafaxine</td>
<td>Depression</td>
<td>Pfizer</td>
<td>4.30</td>
<td>pyrrole</td>
</tr>
<tr>
<td>Lantus</td>
<td>Insulin glargine</td>
<td>Diabetes</td>
<td>Sanofi-Aventis</td>
<td>4.22</td>
<td>insulin</td>
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<tr>
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<td>Enoxaparin</td>
<td>Anti-coagulant</td>
<td>Sanofi-Aventis</td>
<td>4.17</td>
<td>carbohydrate</td>
</tr>
<tr>
<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 \((X = Se)\)
  etc.

- indole

- benzofuran \((X = O)\)
- benzothiophene \((X = S)\)
  etc.

- isoindole \((X = N)\)
- isobenzofuran \((X = O)\)
  etc.
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
Heterocycles: nomenclature

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

- nb: aromatic

- nb: non-aromatic

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

- 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
- NB: aromatic

- piperazine
- morpholine
- 1,4-dioxane
- NB: non-aromatic
Heterocycles: nomenclature

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

\[
\text{epoxide} \\
\text{aziridine} \\
oxetane \\
\text{azetidine} \\
\beta\text{-lactam}
\]

\[\text{(+)-Roxicarin} \]

**NB: macrocycle**
Heterocycles: key reactions (recap.)

- **Enol formation:**
  - NB: acidic conditions.
  - e.g.

  ![Enol formation diagram](image1)

  *NB: consider $pK_a$ of α-proton*

- **Enolate formation:**
  - NB: basic conditions.
  - e.g.

  ![Enolate formation diagram](image2)

  *NB: consider $pK_a$ of α-proton*  

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

NB: for a comprehensive list of $pK_a$ values, see: [http://evans.harvard.edu/pdf/evans_pka_table.pdf](http://evans.harvard.edu/pdf/evans_pka_table.pdf)
Question: $pK_a$ (again!)

What are the $pK_a$ values of the two $\alpha$-protons highlighted below?

- A. They are both the same
- B. 43 and 26
- C. 26 and –6
- D. 43 and –6

Correct answer: C. 26 and –6
Heterocycles: key reactions (recap.)

- **Formation of imines:**
  - NB: typically require catalytic acid.
  - e.g.

  \[
  \text{ketone} \quad \stackrel{\text{cat. } H^+}{\longrightarrow} \quad \text{imine} + \text{H}_2\text{O}
  \]

- **Enamine formation:**
  - NB: occurs under acidic or basic conditions.
  - e.g.

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

  *c.f. enol and enolate formation*

  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
Heterocycles: key reactions (recap.)

- **Aldol:**
  - NB: formation of thermodynamically favoured $\alpha,\beta$-unsaturated product drives reaction.
  - e.g.

![Chemical structure](image)

\[ \text{enol} + \text{aldehyde} \rightarrow \text{cat. H}^+ \rightarrow \text{$\alpha,\beta$-unsaturated product} \]
**Heterocycles: key reactions (recap.)**

- **Mannich reaction:**
  - NB: electrophile is imine rather than aldehyde in Aldol reaction.
  - 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)*
Aims for the final lectures

- **Heterocycles:**
  - Heterocyclic nomenclature.
  - 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?).
  - Summary & comparison of pyrrole and pyridine structure & reactivity.
  - Consider epoxide ring opening under acidic and basic conditions.
  - Synthesis of pyridine and pyrrole.
**Aromaticity (recap.)**

- **Hückel’s Rule:**
  e.g. aromatic compounds

  
  - Planar structures which have a cyclic array of $[4n + 2]$ delocalisable $\pi$-electrons

  
  - **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 heterocycles that are not aromatic

A. A
B. B
C. C
D. D
E. E
F. F
**Pyridine**

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

  - Benzene:
    - One electron in each p orbital
    - sp² hybridised carbon: one electron in sp² orbital σ-bonding to H

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

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

- $^1\text{H}$ NMR spectroscopic chemical shifts (i.e. $\delta_H$ in ppm):
  - i.e. how deshielded is each environment?
  
  
  ![diagram](image)
  
  e.g.

  $\delta_H$ in aromatic region of $^1\text{H}$ NMR spectrum
  (N.B. more deshielding in pyridine due to electronegative $N$ atom)

- $^{13}\text{C}$ NMR spectroscopic chemical shifts (i.e. $\delta_C$ in ppm):
  - i.e. how deshielded is each environment?
  
  ![diagram](image)
  
  e.g.

  $\delta_C$ in aromatic region of $^{13}\text{C}$ NMR spectrum
  (N.B. more deshielding in pyridine due to electronegative $N$ atom)

**YES, pyridine is aromatic**
Question: hybridisation states in heterocycles

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

A. \( p \)
B. \( sp \)
C. \( sp^2 \)  
D. \( sp^3 \)
In which hybrid atomic orbital is the nitrogen lone pair located?

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

Correct answer: D. sp^3
Pyridine: general reactivity trends

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

- **Benzene-like reactivity:**
  - Attack on π-system.
  - Electrophilic substitution.

  NB: S$_e$Ar is less likely than with benzene (remember deshielded signals in NMR)

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

  NB: behaves like an imine
Pyridine: lone pair reactivity

- **Basicity:**
  - Consider $pK_a$ of conjugate acid (i.e. $pK_{aH}$)...

- 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 (i.e. like an imine), hence weak base.
- Piperidine lone pair in sp$^3$ orbital, hence stronger base (i.e. greater ‘$p$’ character so higher energy molecular orbital and therefore more reactive).

- Pyridine $pK_a$ 5.2
- Piperidine $pK_a$ 11.5

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

- Which pyridine is the strongest base?

1. \( \text{pK}_a^\text{H} 5.2 \)
2. \( \text{pK}_a^\text{H} 6.8 \)
3. \( \text{pK}_a^\text{H} 0.7 \)

A. 1  
B. 2  
C. 3  

Correct answer: B. 2
**Pyridine: lone pair reactivity**

- **Nucleophilicity:**
  - NB: lone pair cannot be delocalised around the ring (i.e. sp² orbital orthogonal to the ring).

  ![Pyridine structure](image)

- Hence lone pair is a good nucleophile as it is available (e.g. readily alkylated or acylated).
  - e.g. acylation

  ![Acylation reaction](image)

- Typically, the more basic a pyridine, the more nucleophilic (except when sterically crowded).
  - 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

Correct answer: C. Nucleophilic catalysis
**Pyridine: benzene-like reactivity**

- **Electrophilic aromatic substitution ($S_{E}Ar$):**
  - Readily occurs on benzene, but much less favourable on unsubstituted 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.
  
  e.g. 

  \[
  \begin{array}{c}
  \text{N} \\
  \text{N} \\
  \end{array}
  \quad \begin{array}{c}
  \text{E} \\
  \text{E} \\
  \end{array}
  \quad \begin{array}{c}
  \text{N} \\
  \text{N} \\
  \end{array}
  \\
  \text{nitrogen makes pyridine ring electron deficient (i.e. less nucleophilic).}
  \\
  \text{pyridines preferentially react with electrophiles on nitrogen}
  \\
  \\
  \text{Yields from $S_{E}Ar$ reactions are typically poor:}
  \\
  \text{e.g. 1. **Friedel-Crafts** reactions normally fail.}
  \\
  \text{e.g. 2. **Nitration** with $HNO_3 + H_2SO_4$ at 300 °C gives < 5% of 3-nitropyridine.}
  \\
  \text{e.g. 3. **Halogenation** with $Cl_2 + AlCl_3$ at 130 °C gives only moderate yields of 3-chloropyridine.}
  \\
  \]
  
  NB: benzene reacts readily under these conditions (see 1st Year lecture notes).
**Pyridine: benzene-like reactivity**

- **Electrophilic aromatic substitution:**
  - Electronegative nitrogen atom withdraws electron density; C-2, C-4 and C-6 most affected.
  
  e.g.

  ![Diagram of pyridine with electrophilic substitution](image)

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

  ![Diagram of pyridine with electrophilic substitution](image)

  - C-3 & C-5 substitution least disfavoured (but still unlikely to occur).
  
  e.g.

  ![Diagram of pyridine with electrophilic substitution](image)
Electrophilic aromatic substitution:
- Does occur if electron donating group present (i.e. increases electron density within heterocycle).
  e.g.

\[
\text{Pyridine: benzene-like reactivity}
\]

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

\[
\begin{align*}
\text{Pyridine} & \quad \xrightarrow{mCPBA} \quad \text{Pyridine N-oxide} \\
\text{nitrogen lone pair is easily oxidised} & \quad \text{NB: stable solid}
\end{align*}
\]

*NB: This mechanism is beyond the scope of the course*
**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 due to steric effects).
  
  e.g.

  ![Reaction Diagram](image)

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

  ![Cleavage Diagram](image)

  - Formation of strong P=O double bond drives reaction

**NB:** This mechanism is beyond the scope of the course

**NB:** Obtain 2-chloropyridine if use PCl₃ (for further details see ‘OC’ textbook p 730)
Nucleophilic substitution (S\textsubscript{N}Ar):
- C-2 and C-4 halo-pyridines react easily with nucleophiles (i.e. electron poor ring readily accepts e\textsuperscript{-}).
- C-3 halo-pyridines less reactive (i.e. negative charge cannot be delocalised onto nitrogen).

\textit{e.g.}

\begin{equation}
\text{Pyridine: imine-like reactivity}
\end{equation}

\textit{Activated}\n\begin{equation}
(i.e. \text{N-protonated})
\end{equation}
Pyridine reactivity in action

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

  - **oxidation**
  - **nitration**

  **Omeprazole**
  **(proton pump inhibitor)**
Pyridine: summary

- Electronic structure of pyridine.

- Difference between structure & chemistry of pyridine and benzene.

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

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

- **S\text{E}Ar:** position of substitution; rate of reaction w.r.t. benzene; why unreactive?

- **Nucleophilic attack:** easy with halo-pyridines & activated pyridines.
**Pyrrole**

- **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.

  - cyclopentadiene anion
  - pyrrole

  \[ \text{sp}^2 \text{ hybridised carbon: negative charge in } p \text{ orbital, parallel to plane of } \pi \text{-system} \]
  \[ \text{sp}^2 \text{ hybridised nitrogen: lone pair of electrons in } p \text{ orbital, parallel to plane of } \pi \text{-system} \]

  - one electron in each neutral carbon p orbital
  - one electron in each carbon p orbital
**Pyrrole vs pyridine**

- **Structure:**
  - Lone pair on pyridine in $sp^2$ orbital (mild base) c.f. lone pair on pyrrole in $p$ orbital (non-basic).
  
  e.g.

  - **mild base**
    - Pyridine
    - $sp^2$ hybridised nitrogen: lone pair of electrons in $sp^2$ orbital, orthogonal to plane of $\pi$-system.
    - One electron in each $p$ orbital.

  - **non-basic**
    - Pyrrole
    - $sp^2$ hybridised nitrogen: lone pair of electrons in $p$ orbital, parallel to plane of $\pi$-system.
    - 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.
Imidazole: more than one nitrogen hybridisation state in the ring

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

imidazole

pyridine-like nitrogen

*mild base*

pyrrole-like nitrogen

*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 diagram](image)

  \[\begin{align*}
  \text{N} & 6.5 \\
  \text{H} & 6.2 \\
  6 & \approx 10
  \end{align*}\]

  \[\begin{align*}
  \text{H} & 7.2 \\
  \text{H} & 7.5 \\
  \text{H} & 8.5 \\
  \end{align*}\]

  *NB: not as big a difference in δ_H around ring 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 diagram](image)

  \[\begin{align*}
  \text{H} & 118.0 \\
  \text{N} & 107.7 \\
  \end{align*}\]

  \[\begin{align*}
  \text{H} & 128.5 \\
  \text{H} & 135.7 \\
  \text{H} & 149.8 \\
  \end{align*}\]

  *electron rich c.f. benzene*  
  *electron poor c.f. benzene*
Question: hybridisation states in heterocycles

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

![Chemical structure of a heterocycle with nitrogen and hydrogen atoms]

A. p  
B. sp  
C. sp²  
D. sp³
In which hybrid atomic orbital is the nitrogen lone pair located?

A. \( p \)  
B. \( sp \)  
C. \( sp^2 \)  
D. \( sp^3 \)
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 $S_NAr$ on an activated pyrrole, see ‘OC’ textbook p 738*
Pyrrole: lone pair reactivity

- **Basicity:**
  - Pyrrole lone pair in p orbital and delocalised around ring, hence non-basic.
  - Pyrrolidine lone pair in sp$^3$ orbital, hence stronger base.

\[
\begin{align*}
\text{PYRROLE} & \quad pK_a = 3.8 \\
\text{PYRROLIDINE} & \quad pK_a = 11.0
\end{align*}
\]
Pyrrole: lone pair reactivity

- **Acidity:**
  - Pyrrole has N-H present (NB. no N-H in pyridine).
  - Weakly acidic (i.e. lone pair delocalised around ring so less electron density located at nitrogen c.f. pyrrolidine).

  e.g.

  ![Diagram showing the reaction between pyrrole and base](image)

  \[ \text{pK}_a = 16.5 \]

  - Pyrrolidine is much less acidic.

  e.g.

  ![Diagram showing the reaction between pyrrolidine and base](image)

  \[ \text{pK}_a = 44.0 \]
Pyrrole: electrophilic substitution

- **S<sub>E</sub>Ars:**
  - 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<sub>E</sub>Ars as this is ‘pyridine-like’
Pyrrole: electrophilic substitution

- **S<sub>E</sub>A 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<sup>+</sup>).

  e.g.

\[
\text{N} \quad \text{H} \quad \text{E} \\
\text{H} \quad \text{N} \quad \text{H} \\
\text{E} \quad \text{H} \quad \text{E} \\
\text{H} \quad \text{E} \quad \text{H} \\
\text{N} \quad \text{H} \quad \text{E} \\
\text{H} \quad \text{E} \quad \text{H} \\
\text{N} \quad \text{H} \quad \text{E} \\
\text{H} \quad \text{E} \quad \text{H} \\
\]

**Linear conjugated intermediate**

\[
\text{N} \quad \text{H} \quad \text{E} \\
\text{H} \quad \text{N} \quad \text{H} \\
\text{E} \quad \text{H} \quad \text{E} \\
\text{H} \quad \text{E} \quad \text{H} \\
\]

**3 resonance forms of intermediate**

\[
\text{N} \quad \text{H} \quad \text{E} \\
\text{H} \quad \text{E} \quad \text{H} \\
\]

**C-2 product**
Pyrrole: electrophilic substitution

- $S_{E}Ar$ 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$^+$, less stable than linear conjugated intermediate).

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

\[ \text{cross conjugated intermediate} \]

\[ \text{2 resonance forms of intermediate} \]

\[ \text{C-3 product} \]
Pyrrole: electrophilic substitution

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

Anton Vilsmeier

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

iminium ion hydrolysis (e.g. Na₂CO₃, H₂O)
Question: electrophilic substitution of pyrrole

What is the product of this Mannich reaction?

\[
\text{HCHO} + \text{Me}_2\text{NH} \rightarrow \begin{bmatrix} \text{H} & \text{H} \end{bmatrix}^{\ominus} \text{NMe}_2
\]

\[
\text{N} \quad \text{H} \quad \text{H} \quad \text{NMe}_2
\]

\[
\text{N} \quad \text{Me} \quad \text{N}\quad \text{Me}_2
\]

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

Answer: C. 3
Pyrrole: reaction at nitrogen

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

\[
\text{N-alkylation}
\]

\[
\text{N-acylation}
\]

\(\text{NB: without deprotonation would get reaction solely at carbon}\)

- e.g. 1.

\[
\text{N-alkylation}
\]

- e.g. 2.
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).

- \( S_{\text{E}Ar} \): 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

**BENZENE**
- **E+ (easy)**
- **Base (difficult)**
- **Nu- (difficult)**

**PYRIDINE**
- **E+ (difficult)**
- **Base (difficult)**

**PYRROLE**
- **E+ (very easy)**
- **Base (very easy)**

**PYRROLE ANION**
- **E+ (very easy)**

**ACTIVATED PYRIDINE**
- **Nu- (very easy)**
Useful reactions of another heterocycle: epoxides

- **Epoxide ring-opening:**
  - 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.

  ![Epoxide ring-opening diagram](image)

  - $S_N2$ mechanism may lead to inversion of stereochemistry at reacting carbon centre.

  NB: inversion of stereochemistry at reacting carbon centre

  NB: acidic work-up to protonate alkoxylate

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

  ![Unsymmetrical epoxide diagram](image)

  - Unsymmetrical epoxides can lead to regioselectivity issues.

  - Attack at most hindered end or attack at less hindered end.
Epoxide ring-opening in base:
- Attack less hindered end of epoxide (i.e. minimise steric interactions between Nu\(-\) and E\(^+\)).
- Pure S\(_{N2}\) mechanism, inversion of stereochemistry at reaction centre (i.e. stereospecific).
  
  e.g.

\[ \text{Nu}^- + \text{S} \xrightarrow{\text{MeOH}} \text{Nu}^- \text{SN} \]

\text{NB: epoxide oxygen is a poor LG (i.e. RO\(-\)), so needs a strong Nu for S\(_{N2}\) reaction}

\text{Pentacoordinate T.S. in S\(_{N2}\) reaction hence minimise steric interactions}

\text{NB: for further details on epoxide ring opening, see ‘OC’ textbook p 438}
Useful reactions of other heterocycles

**Epoxide ring-opening in acid:**
- Attack more hindered end of epoxide (i.e. epoxide oxygen protonated in acid, so build up of positive charge in T.S. stabilised at most substituted end).
- ‘Loose’ $S_N2$ transition state, still inversion of stereochemistry at reaction centre (i.e. stereospecific).

*NB: inversion*

- Attack more hindered end (i.e. epoxide oxygen protonated in acid)
- ‘Loose’ $S_N2$ transition state
- Inversion of stereochemistry at reaction centre

**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.

\[
\text{MeOH, HCl} \rightarrow ?
\]

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

```
\[
\begin{align*}
\text{pyrrole} & \quad \text{1,4-dicarbonyl compound} \\
\text{pyrrole} & \quad \text{1,5-dicarbonyl compound}
\end{align*}
\]
```

- **Pyridine**

```
\[
\begin{align*}
\text{pyridine} & \quad \text{1,5-dicarbonyl compound} \\
\text{pyridine} & \quad \text{NH}_3
\end{align*}
\]
```

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).

\[
\begin{align*}
R\text{-}C\equiv\text{O} & \quad \text{AcOH} \\
\rightarrow & \\
R\text{-}N\text{H}_2 \quad R \quad \text{pyrrole}
\end{align*}
\]

\[R = \text{H, alkyl, aryl}\]

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

\[
\begin{align*}
\text{AcOH} & \\
\rightarrow & \\
\text{R'NH}_2
\end{align*}
\]

\[\text{NB: enamine formation}\]

\[
\begin{align*}
\text{NH}_2 & \quad \text{O} \\
\rightarrow & \\
\text{O} \quad \text{H} \quad \text{cyclisation}
\end{align*}
\]

\[\text{NB: overall, lose 2 moles of water}\]
**Question: synthesis of pyrroles**

- Identify the correct pyrrole product from this reaction

\[
\text{Ketone + H}_2\text{NCH}_2\text{CH}_2\text{NH}_2 + \text{AcOH} \rightarrow ?
\]

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

1. ![Structure 1](image1.png)
2. ![Structure 2](image2.png)
3. ![Structure 3](image3.png)
4. ![Structure 4](image4.png)
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.
  - Requires basic conditions.

  e.g.

  \[
  \begin{align*}
  \text{EtO}_2\text{C} & \text{CO}_2\text{Et} \quad \text{pH 8.5} \quad \text{EtOH} \quad \text{EtO}_2\text{C} \text{CO}_2\text{Et} \\
  \text{R} & \quad \text{1,4-dihydropyridine} \quad [\text{O}] \quad \text{oxidation} \quad \text{R} \quad \text{pyridine}
  \end{align*}
  \]

  \text{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 \( \alpha,\beta \)-unsaturated product (c.f. aldol reaction).

- \( \alpha,\beta \)-Unsaturated product is good electrophile (i.e. conjugate acceptor), so Michael reaction occurs.

*NB: 2nd equivalent of enolate used*

*NB: enamine formation*

*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 (driven to become aromatic).
- 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.
Summary of the lecture

- 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.
Questions: end of heterocyclic chemistry lectures

Q1. In what hybrid atomic orbital is the lone pair of the nitrogen atoms in both pyrrole and pyridine?

Q2. Identify the product from the following Vilsmeier-Haack reaction and draw a curly arrow mechanism to describe its formation. Explain the regioselectivity observed here.

\[
\text{Me} \quad \text{H} \\
\text{N} \\
\text{Me} + \text{H} \quad \text{O} \quad \text{NMe}_2 \quad 1. \text{POCl}_3 \\
\text{2. Na}_2\text{CO}_3, \text{H}_2\text{O} \rightarrow ?
\]

Q3. Identify the correct product A to E from the following nitration, explaining the regioselectivity.

\[
\text{Me} \quad \text{H} \\
\text{N} \\
\text{Me} + \text{HNO}_3 \quad \text{H}_2\text{SO}_4 \rightarrow ?
\]

\[
\begin{array}{c}
\text{A} \\
\text{B} \\
\text{C} \\
\text{D} \\
\text{E}
\end{array}
\]

Q4. What is the product of this ring-opening? Include a reaction mechanism with curly arrows to explain the regio and stereochemistry of the product.

\[
\begin{array}{c}
\text{Et} \\
\text{i-Pr}
\end{array} \quad \text{Me} \quad \text{HCl, MeOH} \rightarrow ?
\]
Exam Questions

- **Representative questions**

  This a relatively new course and hence there is only one past exam paper and one mock exam paper (see QMplus) that relate 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.

  **Make sure to revise workshops, quizzes and end-of-lecture questions.**