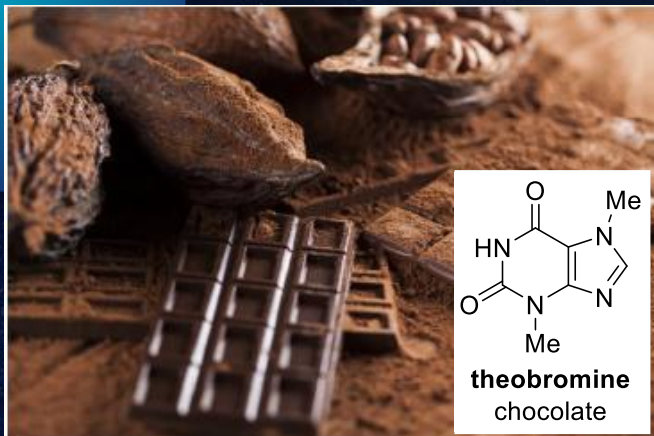




CHEM2010: Aromatic and Heteroaromatic Chemistry

Dr. Miriam O'Duill
miriam.oduill@nottingham.ac.uk





How is the course structured?

Lectures

- Mon, 10am (Pope C15): Neil Oldham – Spectroscopy
- Tue, 10am (X1): Miriam O'Duill – Synthesis.
- Attendance recorded via SEAtS app.
- Lecture recordings and handouts (**fill out the gaps!**) provided on Moodle.
- Don't fall behind!

Tutorials

- Tutorials are important exam prep.
- The question sheets have been designed for you to practice (and get personalised feedback on) exam-style questions.
- Using ChatGPT / AI to complete them wastes this opportunity.

Please scan the QR code in your SEAtS app to record your attendance.



Expectations

What I expect of you

- **You can't get good at a sport by watching it on TV! The same thing applies to chemistry.**
- Attend lectures and tutorials.
- **Self-study:**
A 10-credit course requires on average **100 hours of study.**
 - go over lecture notes;
 - attempt practice questions;
 - recommended reading:

Clayden, Organic Chemistry: free ebook
<https://ebookcentral.proquest.com/lib/notttingham/reader.action?docID=1591368>

What you can expect of me

- Lecture material provided on Moodle in a timely fashion.
- Short practice questions + model answers throughout to consolidate material and prepare you for exams.
- University can be hard, so don't be afraid to ask for support!



Course Overview

Topics

- 1 Introduction to Aromaticity
- 2 Properties of Aromatic Compounds (Acid/Base Chemistry)
- 3 Properties of Heteroaromatics
- 4 Reactivity: Electrophilic Aromatic Substitution
- 5 Reactivity: Electrophilic Aromatic Substitution of Heteroaromatics
- 6 Reactivity: Nucleophilic Aromatic Substitution
- 7 Synthesis of Heteroaromatics



Course Overview

Learning Outcomes

By the end of the course, you will be able to:

- define aromaticity and work out if a given compound is aromatic / heteroaromatic;
- discuss and compare the structure, properties and reactivity of aromatic and heteroaromatic compounds;
- describe (using curly arrow reaction mechanisms) how to synthesise important aromatic compounds.

Important:

- We will be building on foundations laid in 1st year – you need to be familiar with your 1st year chemistry!



Topic 1: Introduction to Aromaticity

Topic 1: Introduction to Aromaticity

Aromatic compounds: nomenclature, structure and bonding

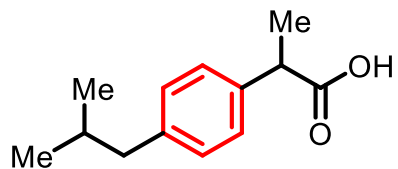
Learning outcomes

In this lecture, you will learn to:

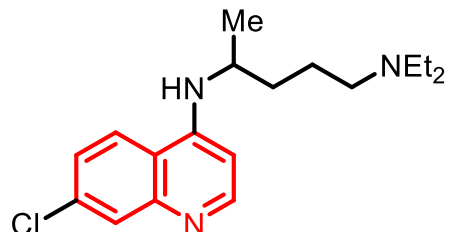
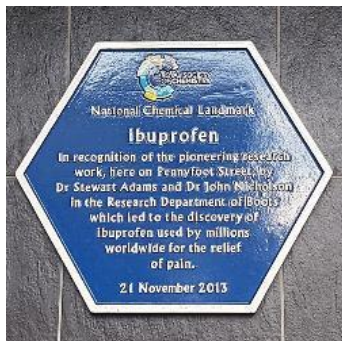
- Name common aromatic compounds;
- Define aromaticity and work out if a compound is aromatic;
- Describe the structure and bonding in aromatic compounds and explain how this affects their stability.



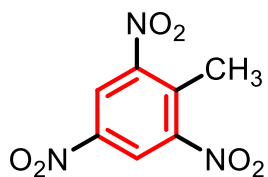
Aromatic compounds: Significance



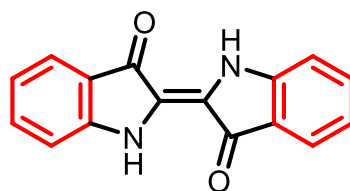
Ibuprofen
anti-inflammatory,
discovered at Boots,
Nottingham 1960



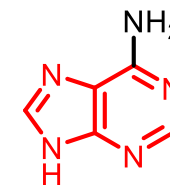
Chloroquine
anti-malarial/
anti-inflammatory



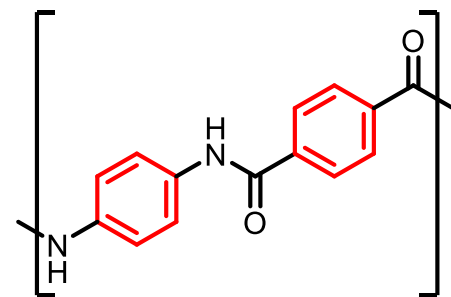
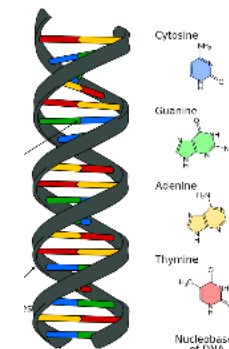
TNT
explosive, used as
standard comparative
convention of explosions



indigo
blue pigment
(e.g. jeans)



Adenine
DNA/RNA bases,
building blocks of life



Kevlar
strong, heat-resistant fibre,
used in sport equipment,
bulletproof vests,
engineering





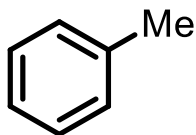
Aromatic compounds: Nomenclature, Structure and Bonding

Nomenclature

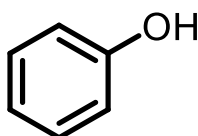
- Many aromatic compounds are known by their common names:



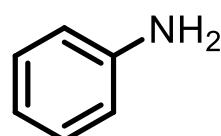
benzene



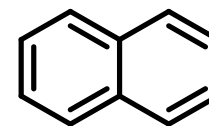
toluene



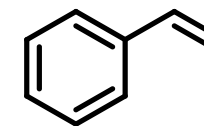
phenol



aniline

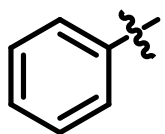


naphthalene

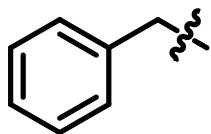


styrene

- Important abbreviations: aromatic substituents



Ph = phenyl



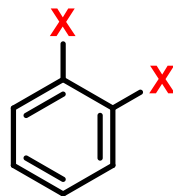
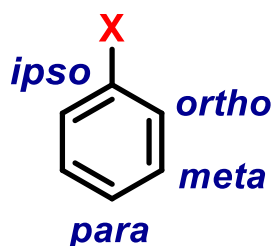
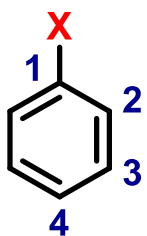
Bn = benzyl

Ar = any aromatic group

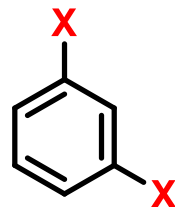


Nomenclature

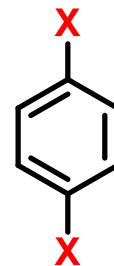
- For more than one substituent, the relative position on the ring must be indicated.
- For disubstituted arenes, there are three distinct isomers:



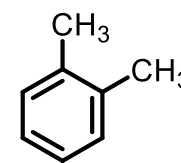
1,2- or *ortho*-disubstituted



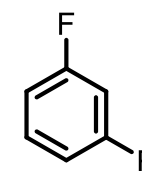
1,3- or *meta*-disubstituted



1,4- or *para*-disubstituted



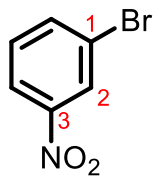
ortho-dimethylbenzene
or
1,2-dimethylbenzene



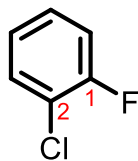
meta-difluorobenzene
or
1,3-difluorobenzene

- Different substituents are quoted in alphabetical order, priority (number 1, 2, etc.) is assigned by Cahn-Ingold-Prelog rules (highest priority for highest atomic number):

e.g.



1-bromo-3-nitrobenzene

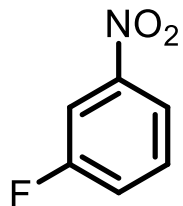


2-chloro-1-fluorobenzene



Question

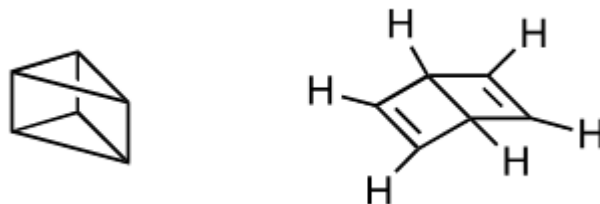
Q: What is the IUPAC name of this aromatic compound?





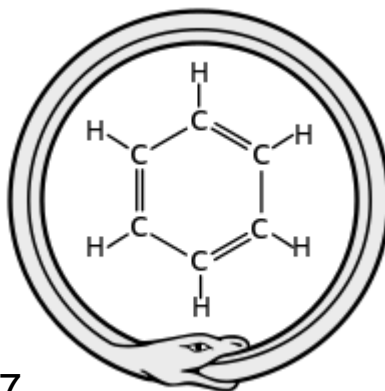
Structure and Bonding: Benzene C_6H_6

- Isolated by Michael Faraday in 1825 as a colourless, smelly ('aromatic') liquid
- Formula C_6H_6 , but structure initially unclear



Some early proposed structures for C_6H_6

- Cyclic structure proposed in 1865 by **August Kekulé** (apparently after a dream)





Structure and Bonding: Benzene C₆H₆

- 1929: **Kathleen Lonsdale** proves that the benzene ring is flat and that all C–C bonds have the same length by X-ray crystallography.
- What does this mean?

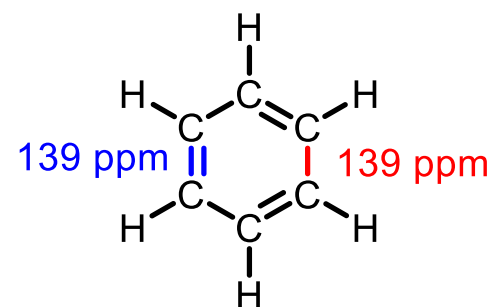
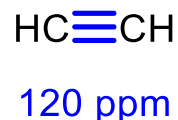
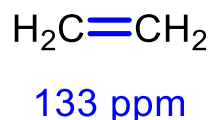
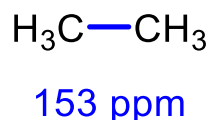


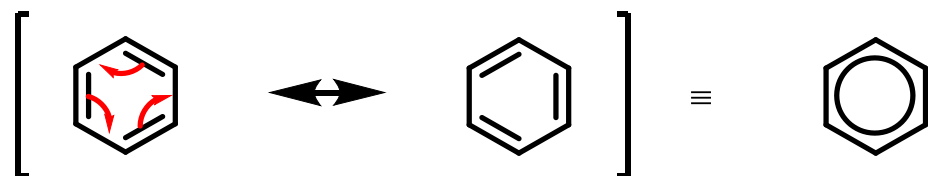
image: www.britannica.com

- Even though we draw the C–C bonds in benzene as alternating single and double bonds, this is not an exact representation of its true structure.



Structure and Bonding: Benzene C_6H_6

- Kekulé suggested that benzene rapidly changes between two forms; today we describe the structure as **delocalised**.



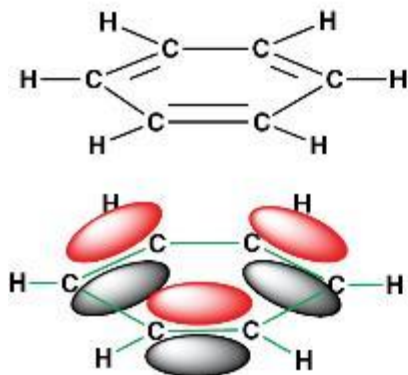
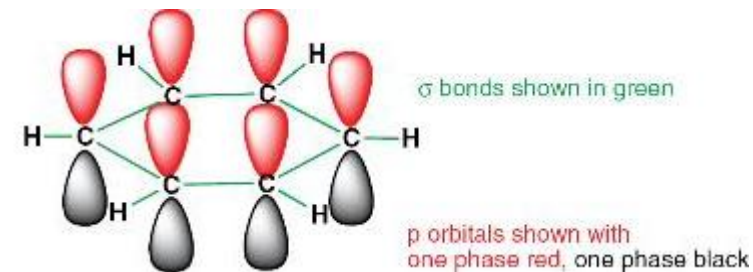
Two equivalent Kekulé
resonance structures

The circle represents the
delocalised electrons.
This representation is not useful
for showing reactivity: **do not use**

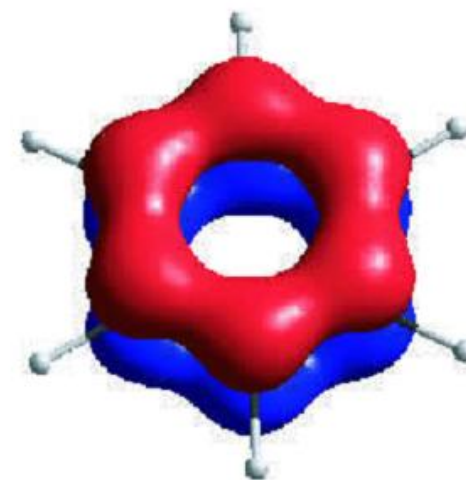
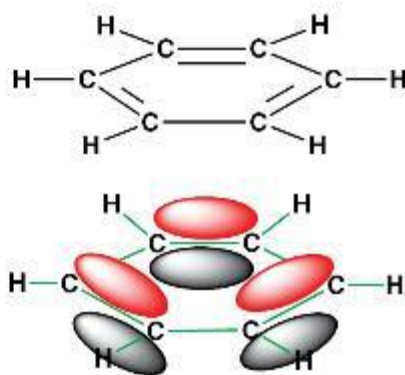


Delocalisation

- All carbons in benzene are sp^2 hybridised and all of the p orbitals overlap to form a continuous π -system, spreading (**delocalising**) electron density equally over each carbon atom in the ring: they form a **conjugated** system.



p-electrons are **not** isolated in localised double bonds.

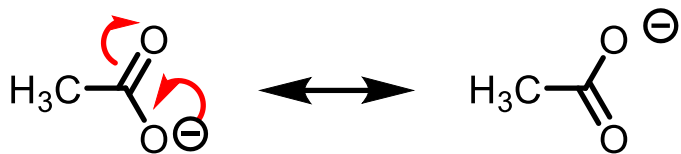


Instead, all of the p_z orbitals overlap to **spread electron density out** over the entire ring.

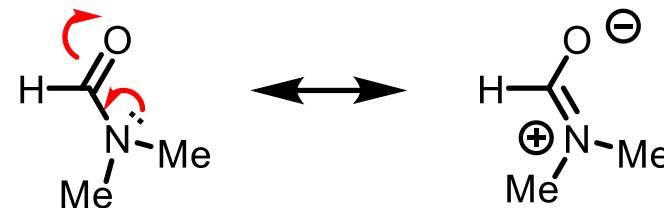


Delocalisation and conjugation

- Recap from 1st year:



Acidity of carboxylic acids:
resonance structures for ethanoate ion



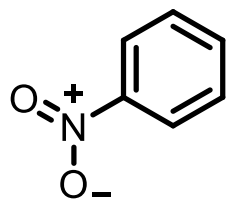
Amide resonance in DMF:
amides are quite stable & unreactive

Delocalisation stabilises molecules and charged intermediates: the more resonance structures you can draw of a cation/anion, and the more atoms you can delocalise electrons over in a neutral molecule, the more stable it is.

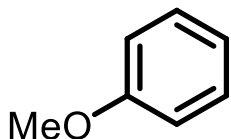


Delocalisation and conjugation

- **Practice question:** Draw resonance forms that show delocalisation / conjugation in nitrobenzene and methoxybenzene.



nitrobenzene



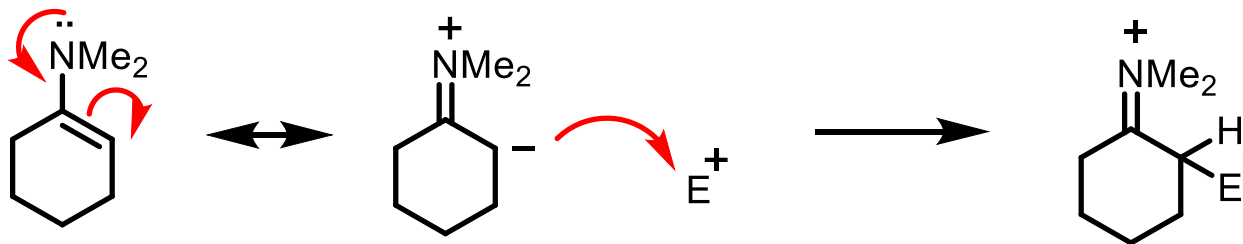
anisole /
methoxybenzene

- Revise electron-withdrawing and electron-donating groups!
(I have provided a one-page pdf on Moodle if you are unfamiliar with these concepts.)

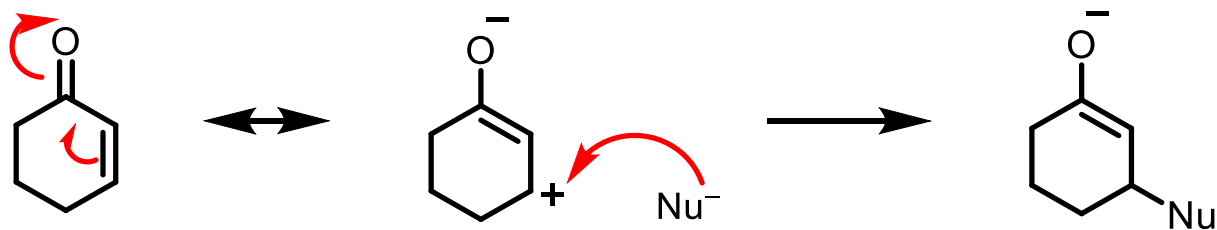


Delocalisation and conjugation

- Recap from 1st year: **delocalisation can explain reactivity**



Imines react with electrophiles



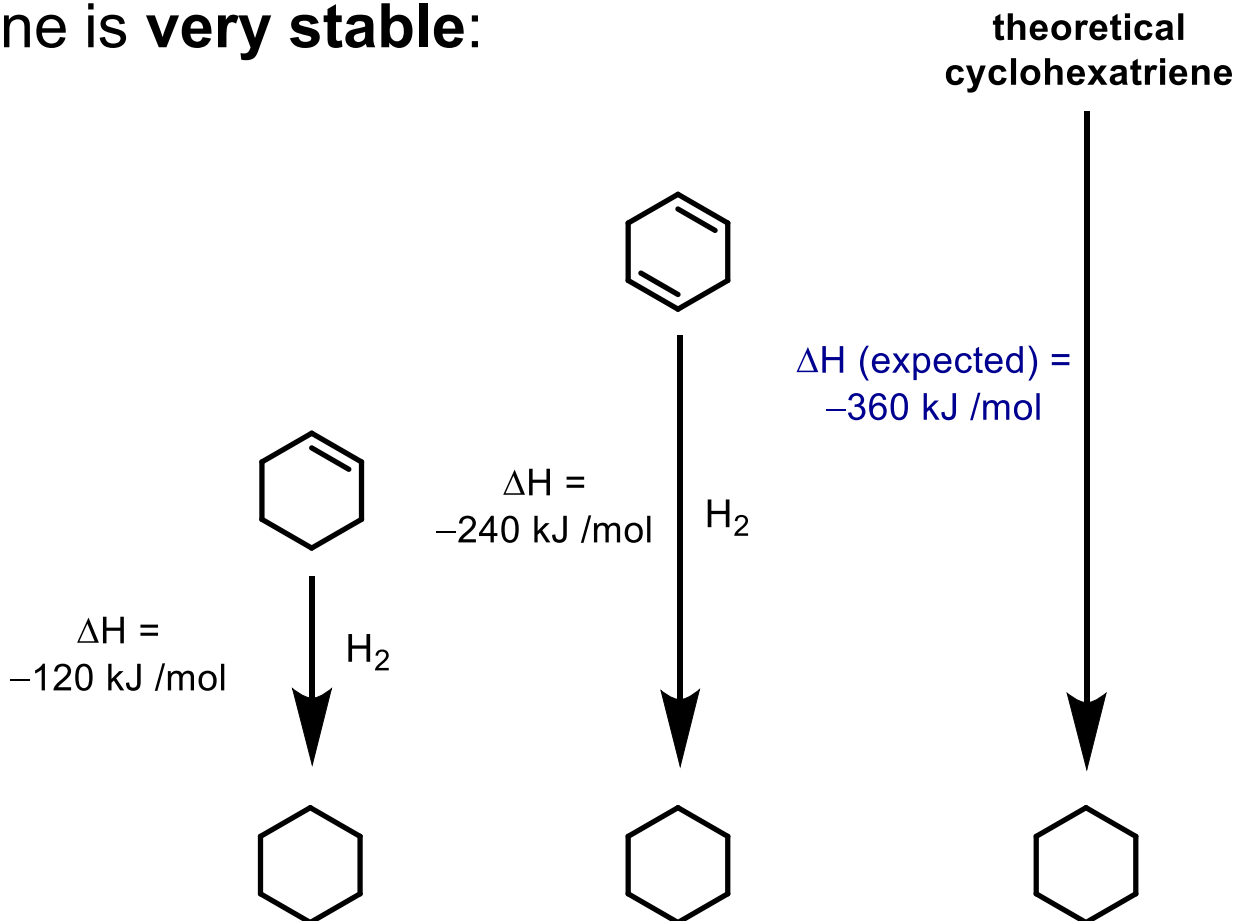
Enones react with nucleophiles

- How does benzene react?



Stability of benzene

- Benzene is **very stable**:

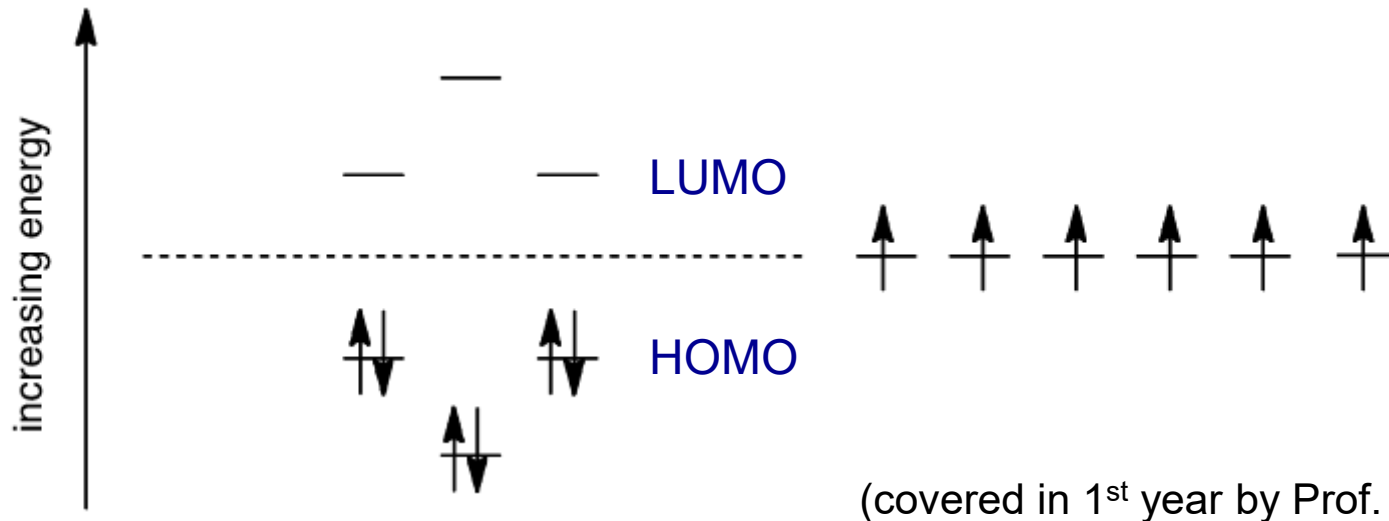


- Because of this resonance stabilisation, benzene is **relatively unreactive**.



Origin of benzene's stability: Molecular Orbitals

- The 6 p_z atomic orbitals (AOs) combine to form 6 molecular orbitals (MOs):

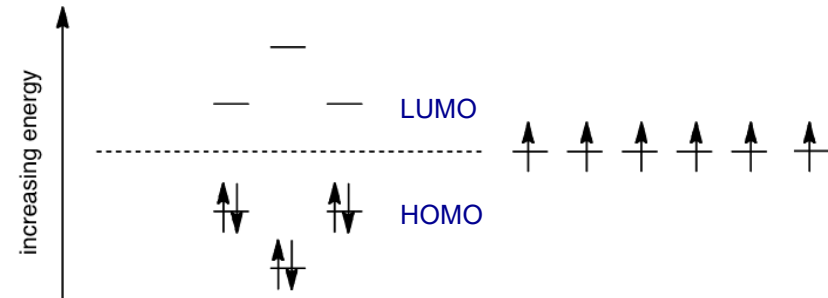


- The **bonding MOs are lower in energy than the individual, isolated p_z AOs**
- All **electrons occupy these low energy orbitals**, decreasing the overall energy of the system. This is the **origin of benzene's stability** and aromaticity.



More general: Origin of aromatic stability

- This is a general observation: Any cyclic system of delocalised electrons paired in purely bonding orbitals benefits from aromatic resonance stabilisation. These systems have **$(4n + 2) \pi$ electrons** ($n = \text{integer}$).



- This is known as **Hückel's rule of aromaticity**:

Planar, fully conjugated, cyclic systems with **$(4n + 2) \pi$ electrons** ($n = \text{integer}$) are exceptionally stable and are said to be **aromatic**.

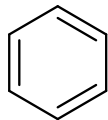


The four rules of aromaticity

For a compound to be aromatic, all four criteria must be met:

1. An aromatic compound must be **cyclic** (*i.e.* it is a ring)
2. Every carbon is sp^2 hybridised and all the p-orbitals overlap to give a **fully conjugated π -electron system**.
3. The ring atoms must be in a single plane (*i.e.* **planar**, sp^2 hybridised carbons)
4. Hückel Rule: there must be **$(4n+2)$ π -electrons** in the aromatic ring ($n = 0, 1, \dots$)

e.g.

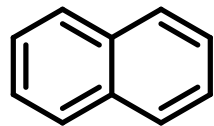


Benzene

- ✓ • Cyclic
- ✓ • sp^2 -hybridised carbons:
fully conjugated
- ✓ • planar
- ✓ • 6 π -electrons
($4n+2 = 6$ for $n = 1$)



Examples: Are these compounds aromatic?

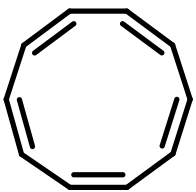


naphthalene

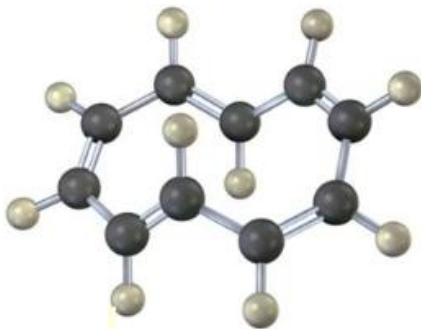
- ✓ 1. cyclic
 - ✓ 2. fully conjugated (all C sp^2 -hybridised)
 - ✓ 3. planar
 - ✓ 4. $(4n + 2)$ π -electrons
- aromatic**
- naphthalene has 10 π electrons
($4n + 2 = 10$ for $n = 2$)



Examples: Are these compounds aromatic?



cyclodecapentaene



- ✓ 1. cyclic
- ✓ 2. fully conjugated (all C sp^2 -hybridised)
- ✗ 3. planar
- ✓ 4. 10 π -electrons ($4n + 2 = 10$ for $n = 2$)

Rings with more than 7 atoms generally 'pucker' (i.e. become non-planar) to relieve strain.

not aromatic



Examples: Are these compounds aromatic?



cyclopentadienyl
anion

An anion is a filled
p-orbital (2 electrons)

- ✓ 1. cyclic
- ✓ 2. fully conjugated (all C sp^2 -hybridised)
- ✓ 3. planar
- ✓ 4. 6 π -electrons ($4n + 2 = 6$ for $n = 1$)

aromatic



cyclopentadienyl
cation

A cation is a vacant
p-orbital (0 electrons)

- ✓ 1. cyclic
- ✓ 2. fully conjugated (all C sp^2 -hybridised)
- ✓ 3. planar
- ✗ 4. 4 π -electrons ($4n + 2 \neq 4$ for $n = \text{integer}$)

not aromatic

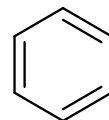
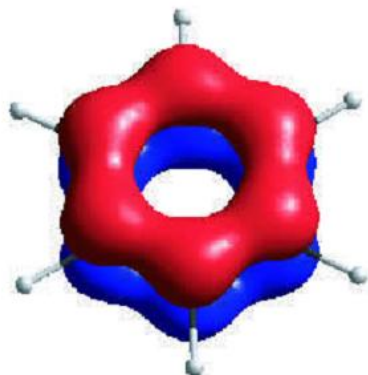
- Planar, fully conjugated, cyclic systems with **(4n) π electrons** are very unstable and are described as **anti-aromatic**.



Summary

In this lecture, you learned how to:

- Name aromatic compounds;
- Define aromaticity and work out if a compound is aromatic;
- Describe the structure and bonding in aromatic compounds and explain how this affects their stability and reactivity.



Benzene

Planar, fully conjugated, cyclic systems with **$(4n + 2)$ π electrons** (n = integer) are exceptionally stable and are said to be **aromatic**.

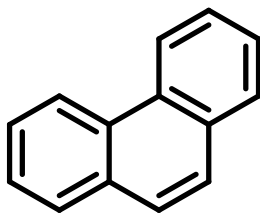
4 rules of aromaticity:

- ✓ • Cyclic
- ✓ • sp^2 -hybridised carbons: fully conjugated
- ✓ • planar
- ✓ • 6 π -electrons
($4n+2 = 6$ for $n = 1$)

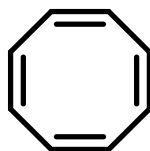


Topic 1: Practice questions

Are the following molecules aromatic? Provide reasoning for your answers.



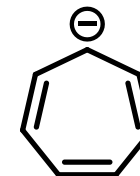
phenanthrene



cyclooctatetraene



cyclopropene
cation

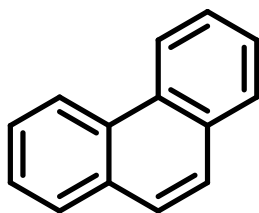


cycloheptatrienyl
anion



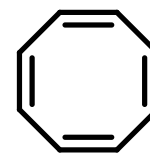
Topic 1 practice questions: Solution

2. Are the following molecules aromatic? Provide reasoning for your answers.

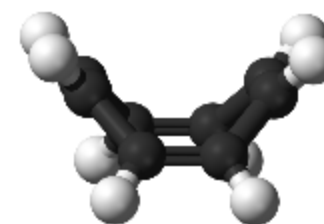


phenanthrene

- ✓ 1. cyclic
 - ✓ 2. fully conjugated (all C sp^2 -hybridised)
 - ✓ 3. planar
 - ✓ 4. 14 π -electrons ($4n + 2 = 14$ for $n = 3$)
- aromatic**



cyclooctatetraene



- ✓ 1. cyclic
 - ✓ 2. fully conjugated (all C sp^2 -hybridised)
 - ✗ 3. planar
 - ✗ 4. 8 π -electrons ($4n + 2 \neq 8$ for $n = \text{integer}$)
- not aromatic**



Topic 1 practice questions: Solution

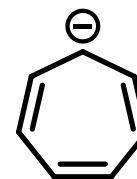
2. Are the following molecules aromatic? Provide reasoning for your answers.



cyclopropene
cation

- ✓ 1. cyclic
- ✓ 2. fully conjugated (all C sp^2 -hybridised)
- ✓ 3. planar
- ✓ 4. 2 π -electrons ($4n + 2 = 2$ for $n = 0$)

aromatic



cycloheptatrienyl
anion

- ✓ 1. cyclic
- ✓ 2. fully conjugated (all C sp^2 -hybridised)
- ✓ 3. planar
- ✗ 4. 8 π -electrons ($4n + 2 \neq 8$ for $n = \text{integer}$)
($4n = 8$ for $n = 2$)

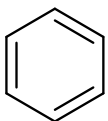
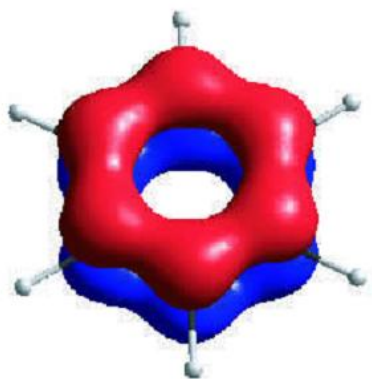
not aromatic (anti-aromatic)



Topic 2: Acid/Base Chemistry of Aromatic Compounds

Recap Topic 1: Introduction to Aromaticity

Planar, fully conjugated, cyclic systems with $(4n + 2)$ π **electrons** (n = integer) are exceptionally stable and are said to be **aromatic**.



Benzene

4 rules of aromaticity:

- ✓ • Cyclic
- ✓ • sp^2 -hybridised carbons: fully conjugated
- ✓ • planar
- ✓ • 6 π -electrons
($4n+2 = 6$ for $n = 1$)



Topic 2: Acid/Base Chemistry of Aromatic Compounds

Topic 2: Acid/Base Chemistry of Aromatic Compounds

2.1 Revision of acid/base chemistry

2.2 Acid/base chemistry of aromatic compounds

Learning outcomes

In this lecture, you will learn to:

- Define pK_a and pK_{aH} ;
- Describe which factors influence the acidity and basicity of an organic compound and compare the acidity or basicity of aromatic compounds.



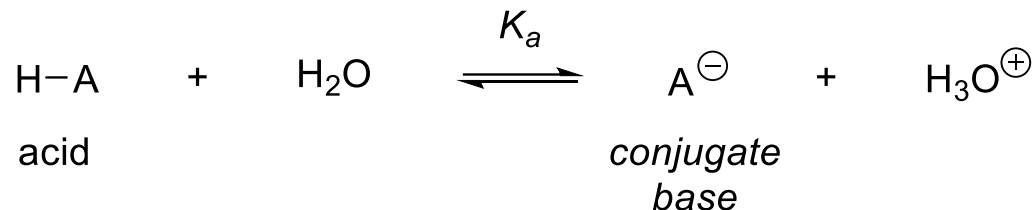
Revision: Acids and Bases



- pK_a is the measure of acidity and basicity.
- An **acid** is a species with a tendency to **lose a proton**.
- A **base** is a species with a tendency to **accept a proton**.



Revision: Acids



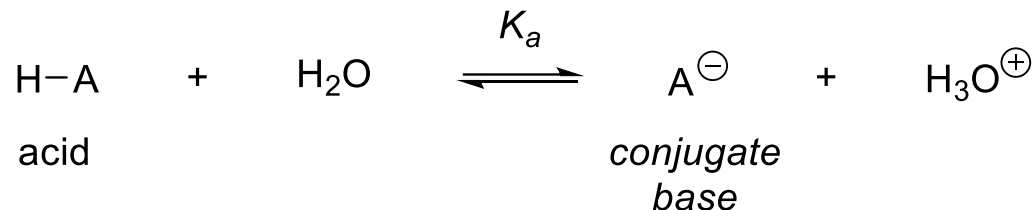
- An **acid** is a species with a tendency to **lose a proton**.
- The **pK_a** describes how much of the acid has been deprotonated and exists in its conjugate base form: it is a quantitative measure of acid strength in solution.

$$pK_a = -\log_{10} K_a$$

- The lower the pK_a, the stronger the acid.



Revision: Acids

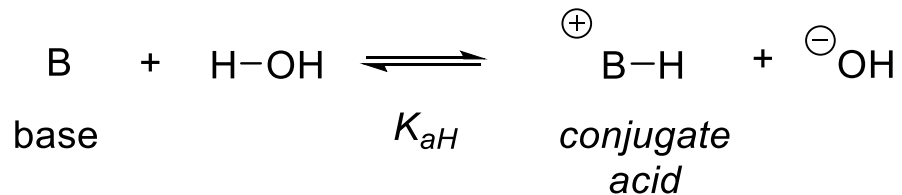


Three main factors affect the strength of an acid:

1. The **stability of the conjugate base** A^- :
 - (i) electronegative A and
 - (ii) inductively and mesomerically electron-withdrawing substituents stabilise A^- and make HA a stronger acid.
2. The **H–A bond strength**: H–A bond strengths decrease down the periodic table (size/energy mismatch of atomic orbitals), making the bond easier to break.
3. The **solvent**: The better the solvent is at solvating/stabilising ions, the easier it is for the acid to be deprotonated.



Revision: Bases



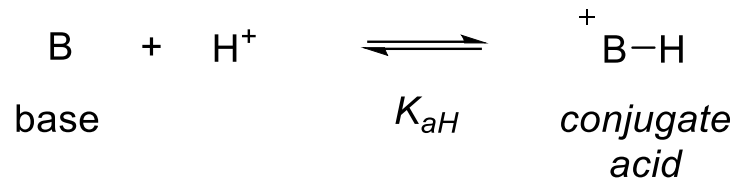
- A **base** is a species with a tendency to **accept a proton**.
- The strength of a base is traditionally measured by considering the pK_a of its conjugate acid: **pK_{aH}**

$$pK_{aH} = -\log_{10} K_{aH}({}^{\oplus}\text{BH})$$

- For the conjugate acid, a lower pK_a means a stronger acid and thus a weaker base:
The lower the pK_{aH} , the weaker the base.



Revision: Bases

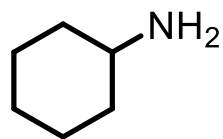


- Any factor that increases the strength of an acid usually decreases the strength of the corresponding conjugate base.
- The main factor that affects the strength of a base is the **availability of its lone pair** of electrons:
 - (i) electronegative B and
 - (ii) inductively and mesomerically electron-withdrawing substituentsmake the lone pair less available for reaction with H^+ , making B a weaker base.

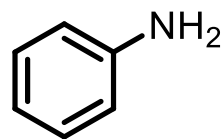


Acid/base chemistry of aromatic compounds

Basicity of Anilines

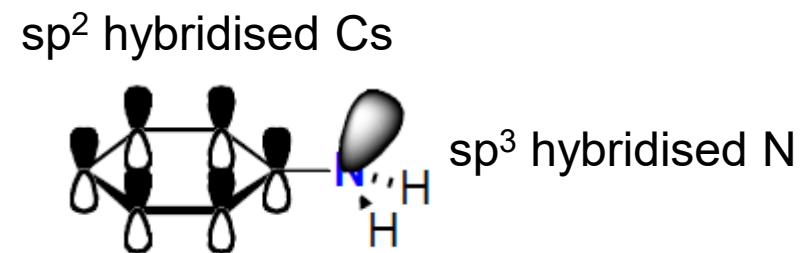
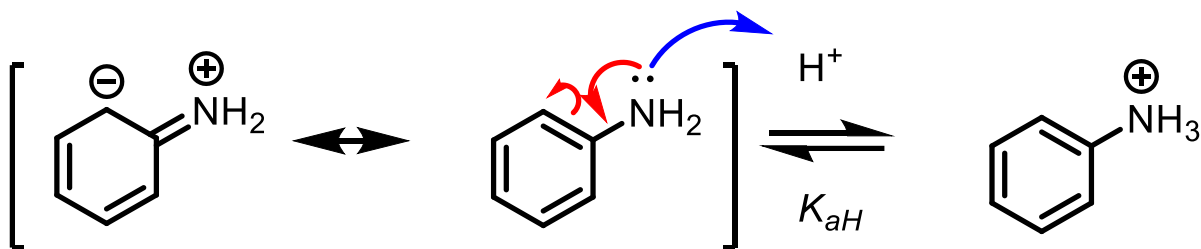


cyclohexylamine
 $\text{pK}_{\text{aH}} 10.7$



aniline
 $\text{pK}_{\text{aH}} 4.6$

- **Lower basicity** of aniline is due to **delocalisation of N lone pair** into aromatic ring

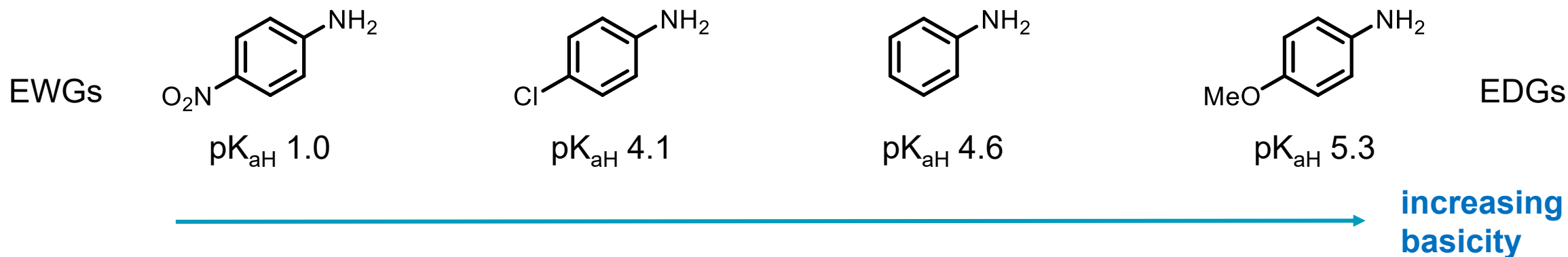


- However, the N lone pair is in an sp^3 orbital. Therefore, orbital overlap with the aromatic π -system is not optimal and **delocalisation is only partial**.



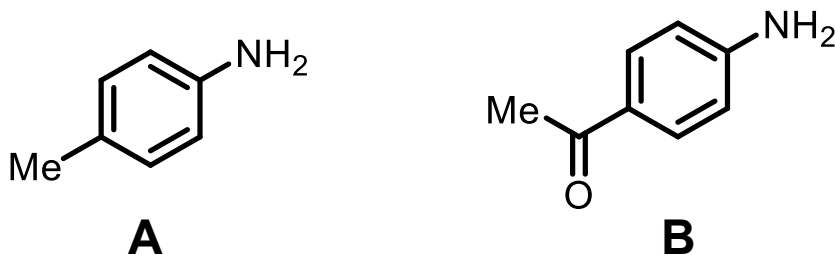
Basicity of anilines

Basicity of substituted anilines



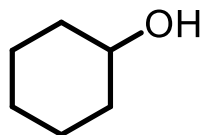
Electron-donating groups make the lone pair on N more nucleophilic, i.e. more available for reaction with H^+ , making the aniline a stronger base.

Question: Which of the two anilines (A or B) is the stronger base?

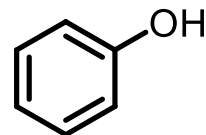




Acidity of phenols

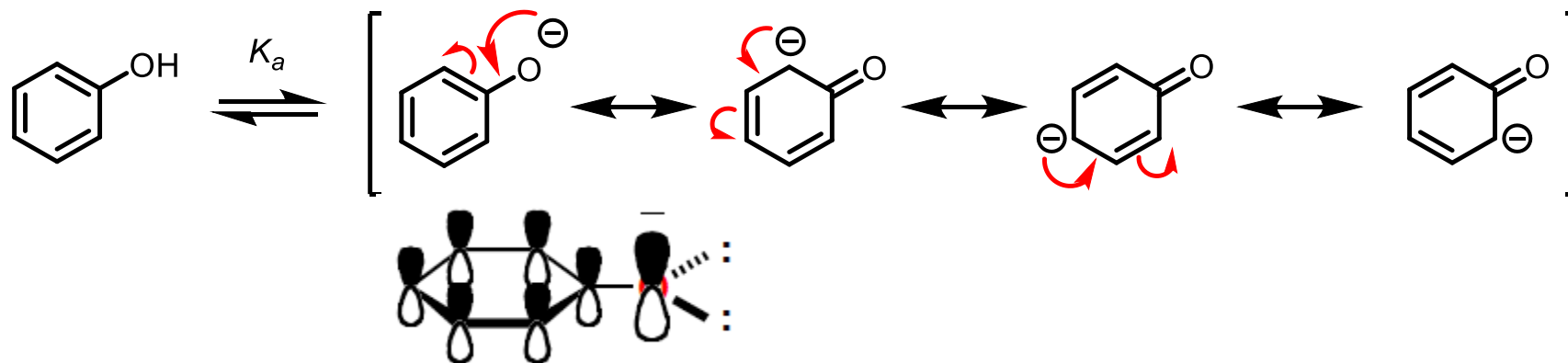


cyclohexanol
 pK_a 16



phenol
 pK_a 10

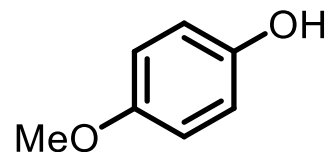
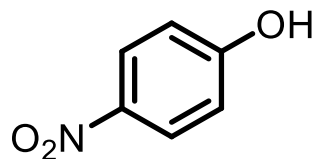
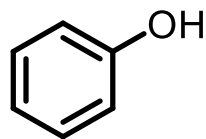
- **Higher acidity** of phenol is due to **resonance stabilisation of the conjugate base**:





Acidity of phenols: Example

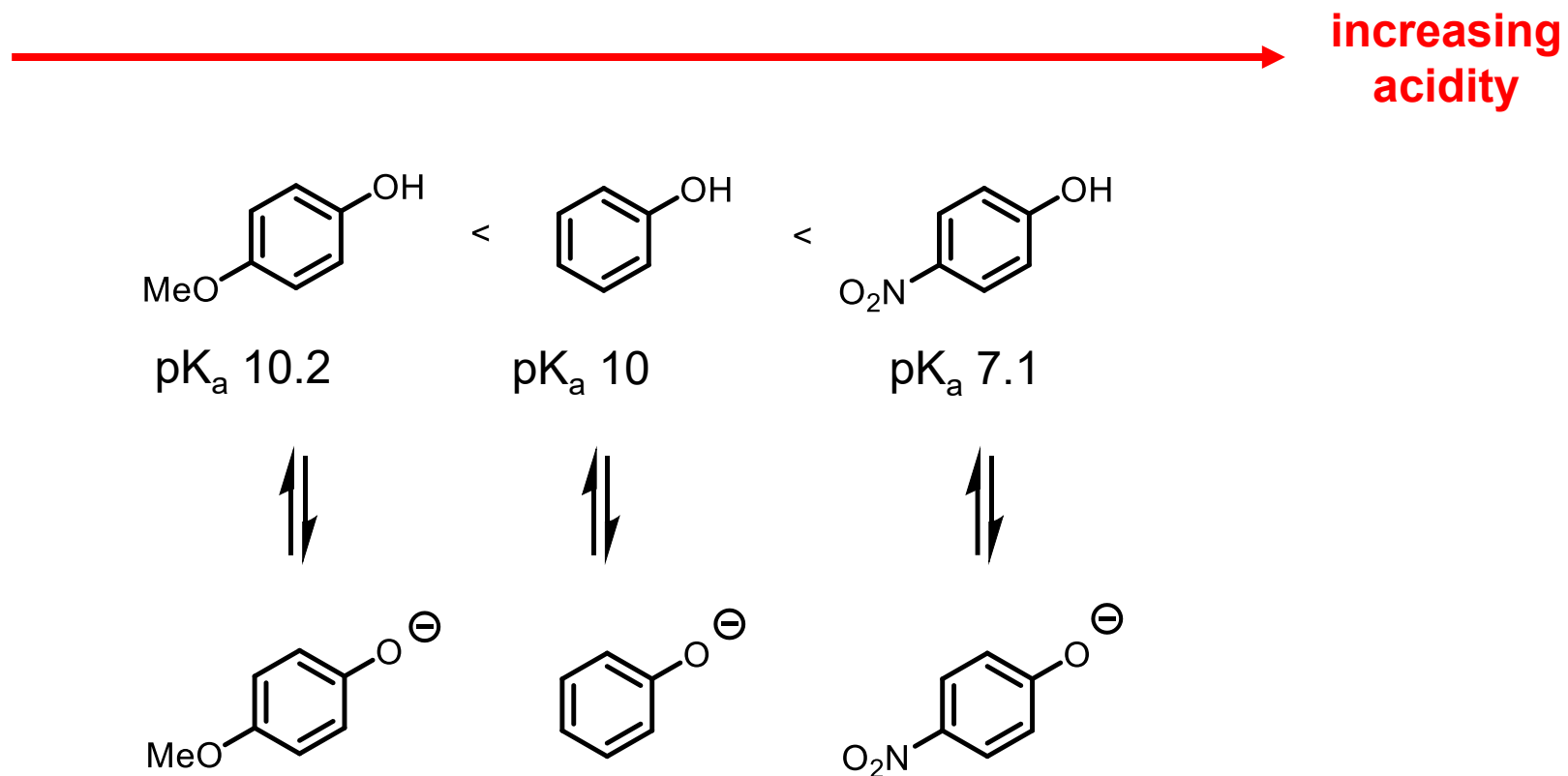
Rank the following molecules in order of increasing acidity, justifying your choice.





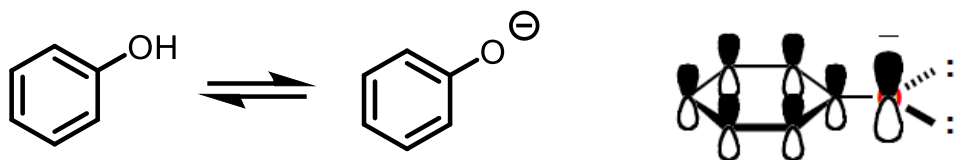
Acidity of phenols: example

To determine the strength of an acid, consider the stability of its conjugate base:

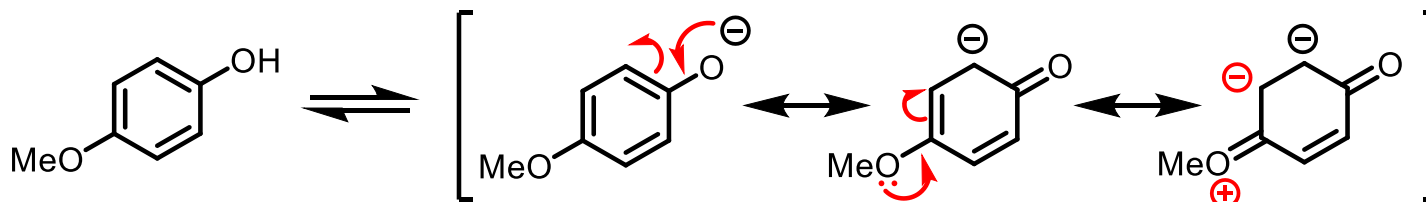




Acidity of phenols: example



conjugate base stabilised by delocalisation

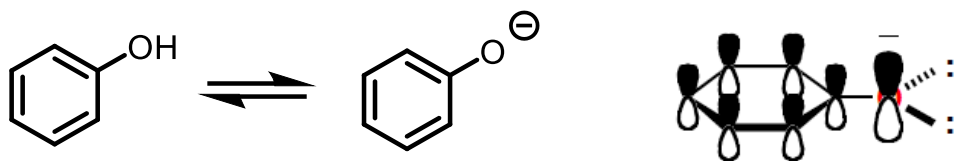


OMe: mesomerically
electron-donating

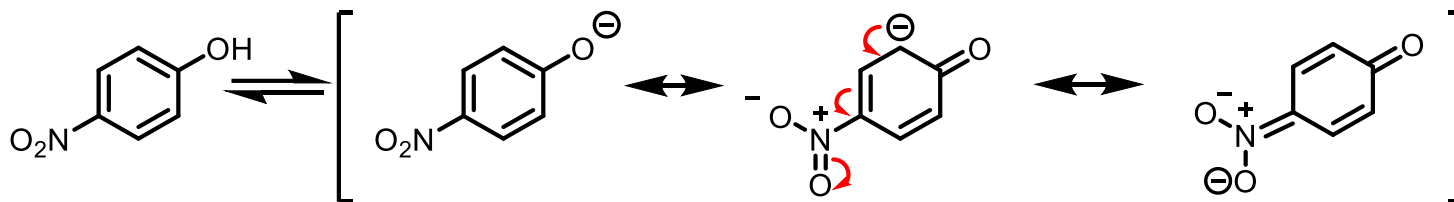
conjugate base (delocalised anion) **destabilised** by **mesomerically electron-donating** methoxy substituent: **weaker acid**



Acidity of phenols: example



conjugate base stabilised by delocalisation

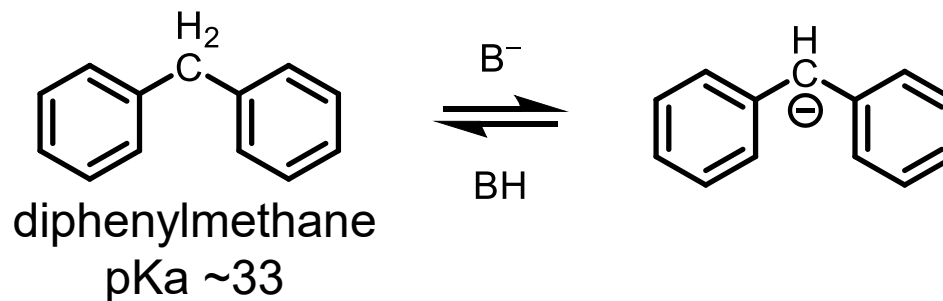
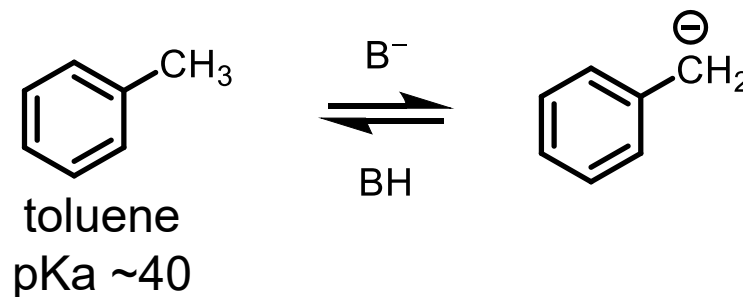
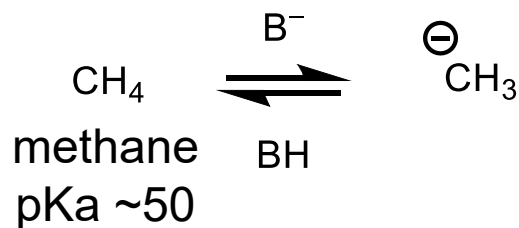


conjugate base (delocalised anion) **stabilised** by further delocalisation into **mesomerically electron-withdrawing** nitro substituent: **stronger acid**



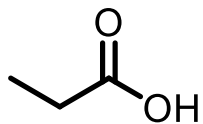
Alkylbenzenes

- In the same way that a phenoxide anion can be stabilised by delocalisation into the ring, so can other anions.
- Methyl groups attached to aromatic rings tend to be more reactive than simple aliphatic methyl groups:

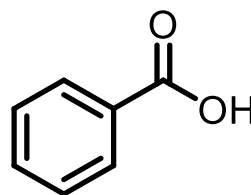




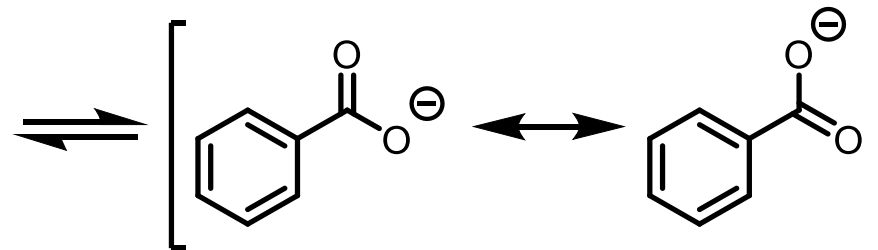
Acidity of benzoic acids



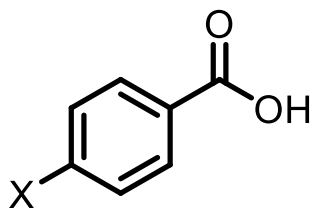
ethanoic acid
 pK_a 4.76



benzoic acid
 pK_a 4.20



- It is not possible to stabilise the benzoic acid anion by conjugation into the ring
- However, the **acidity of benzoic acids is affected by substituents:**



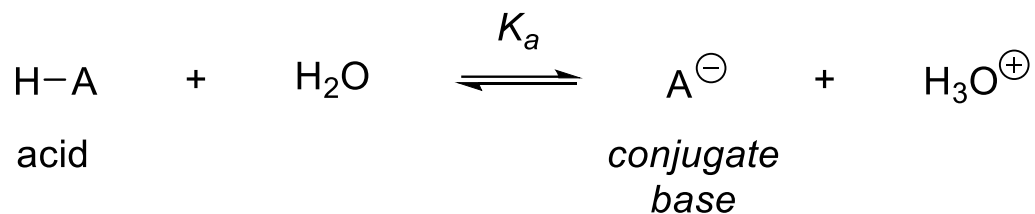
X	pK_a
H	4.20
NO_2	3.44
Cl	3.99
OMe	4.47



Summary

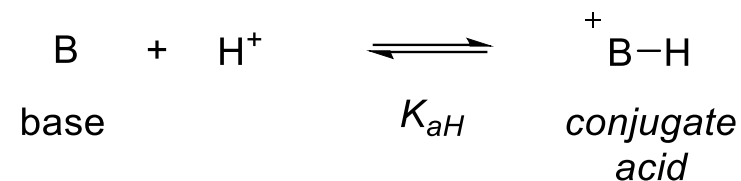
In this lecture, you learned how to:

- Describe which factors influence the acidity and basicity of an organic compound,



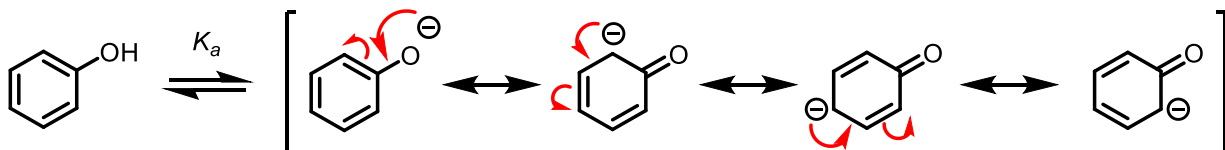
Strength of H–A bond?

Stabilisation of A[−] by EWGs?

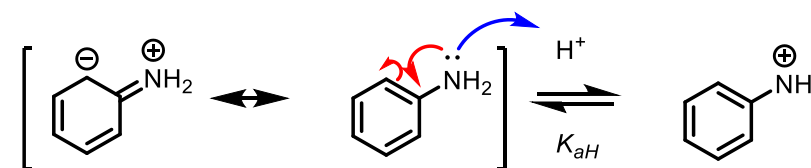


Availability of N lone pair?

- compare the acidity and basicity of different aromatic compounds.



Aromatic alcohols (phenols) are more acidic than aliphatic alcohols due to resonance stabilisation of the conjugate base.

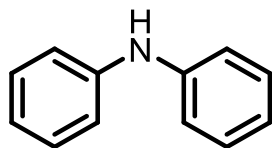
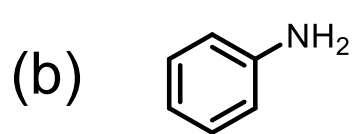
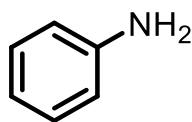
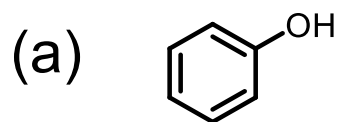


Aromatic amines (anilines) are less basic than aliphatic amines due to delocalisation of N lone pair into the aromatic ring.

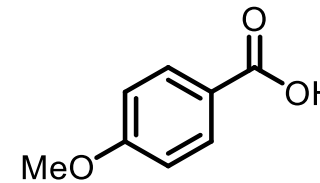
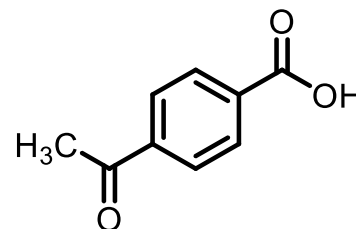
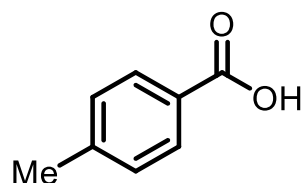
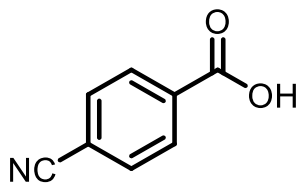


Topic 2 - Practice questions

1. In each pair, determine which of the two molecules is more basic. Provide reasoning for your choice.



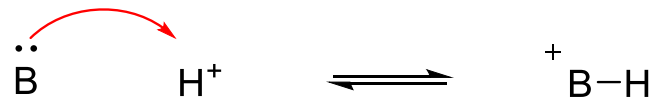
3. Rank the following benzoic acids in order of increasing acidity:



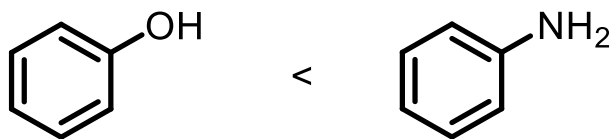


Topic 2 practice questions: Solutions

1. To determine the strength of a base, consider the availability of its lone pair.



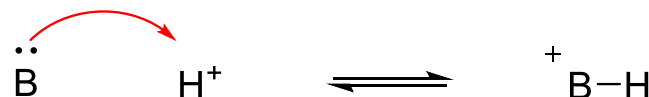
(a) Oxygen is more electronegative than nitrogen; the lone pair on oxygen is held closer to the nucleus and thus less available for reaction with H^+ making phenol a weaker base (stronger acid) than aniline.



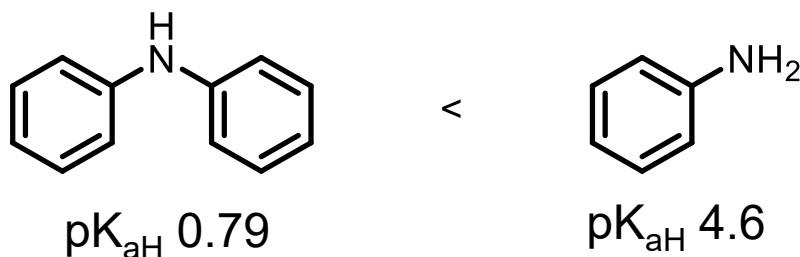


Topic 2 practice questions: Solutions

1. To determine the strength of a base, consider the availability of its lone pair.



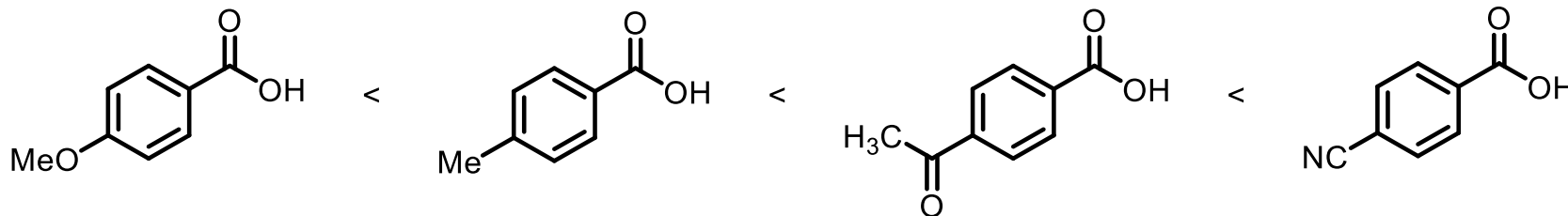
(b) The N lone pair in aniline is partially delocalised into the aromatic ring; the N lone pair in diphenylamine is partially delocalised into two aromatic rings making it more stable and less available to react with H^+ .





Topic 2 practice questions: Solutions

2. Rank the following benzoic acids in order of increasing acidity:



strongly electron-donating X:
destabilises carboxylate anion:
weaker acid

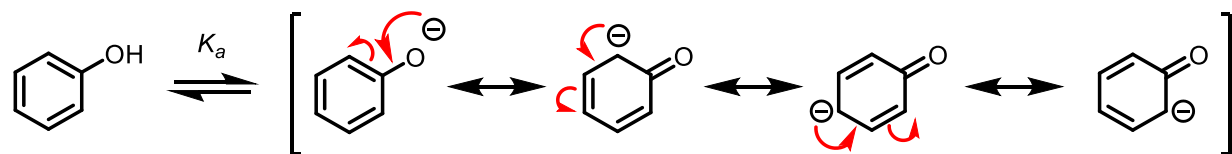
strongly electron-withdrawing X:
stabilises carboxylate anion:
stronger acid

X (para)	σ
CN	0.67
COCH ₃	0.49
CH ₃	-0.17
OCH ₃	-0.29

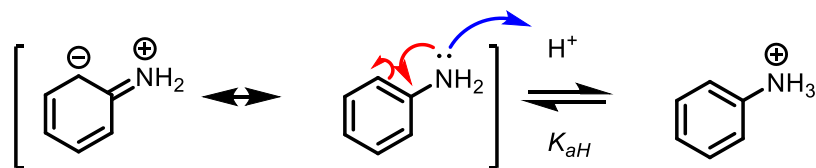


Recap Topic 2: Acid/Base Chemistry of Aromatics

In the last lecture, you learned how to compare the acidity and basicity of different aromatic compounds:



Aromatic alcohols (phenols) are more acidic than aliphatic alcohols due to resonance stabilisation of the conjugate base.



Aromatic amines (anilines) are less basic than aliphatic amines due to delocalisation of N lone pair into the aromatic ring.



Topic 3: Heteroaromatic Compounds

Topic 3: Heteroaromatic Compounds

3.1 6-Membered Heteroaromatics: Pyridine

3.2 5-Membered Heteroaromatics: Pyrrole

Learning outcomes

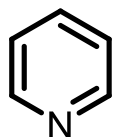
In this lecture, you will learn to:

- identify heteroaromatic compounds;
- describe the properties and reactivity of 5- and 6-membered heteroaromatic compounds.

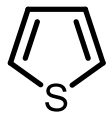
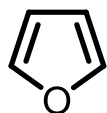
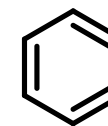


Heteroaromatics

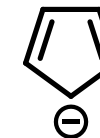
- Benzene derivatives are not the only class of aromatic compounds.
- Recap: planar, fully conjugated, cyclic systems with $(4n + 2)$ pi-electrons are aromatic.
- Carbon can be replaced with a heteroatom (e.g. O, N, S) in the ring – if all the above still hold, the compound is **heteroaromatics**
- Around two thirds of organic compounds are heteroaromatic.



pyridine is isoelectronic with benzene



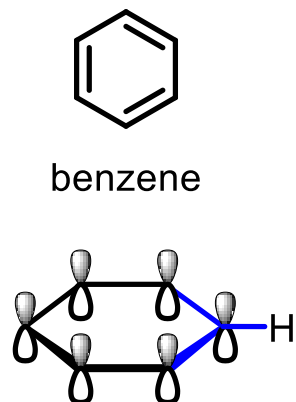
pyrrole, furan, thiophene are
isoelectronic with cyclopentadiene anion



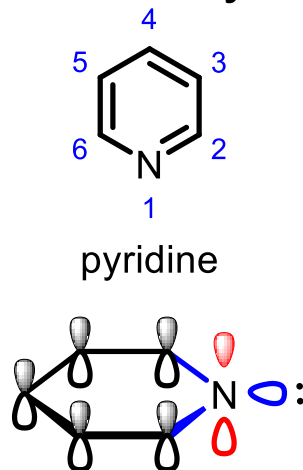


6-Membered Heteroaromatics: Pyridine

Pyridine is isoelectronic with benzene. Both have 6 electrons in 6 parallel p-orbitals that make up the 6 π -electrons for aromaticity:



- All carbons sp^2 hybridized
- six p-orbitals combine for delocalized π -system

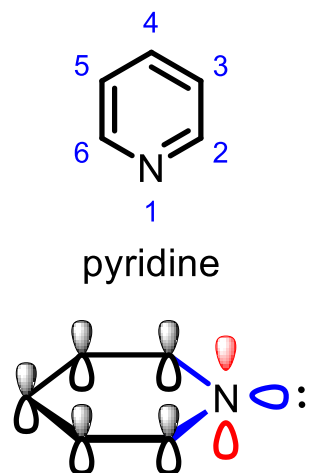


- All carbons *and nitrogen* sp^2 hybridized
- 1 electron in N p-orbital contributes to π -system
- **N lone pair in sp^2 orbital orthogonal to ring: not involved in delocalization (it is “available”)**



Pyridine: Aromaticity

Pyridine fulfils the 4 rules of aromaticity and is therefore (hetero)aromatic:



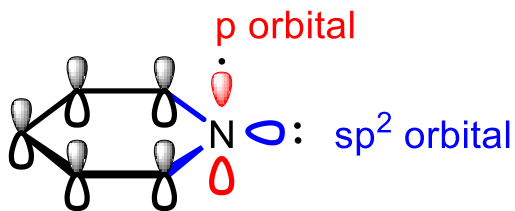
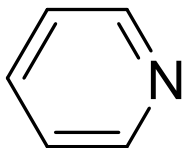
pyridine

- ✓ • Cyclic
- ✓ • All atoms sp^2 -hybridised:
fully conjugated
- ✓ • planar
- ✓ • 6 π -electrons
($4n+2 = 6$ for $n = 1$)
Nitrogen contributes one electron to π -system.



How many electrons does the heteroatom contribute to the pi system?

Question: How do you determine the number of electrons a heteroatom contributes to the pi system?

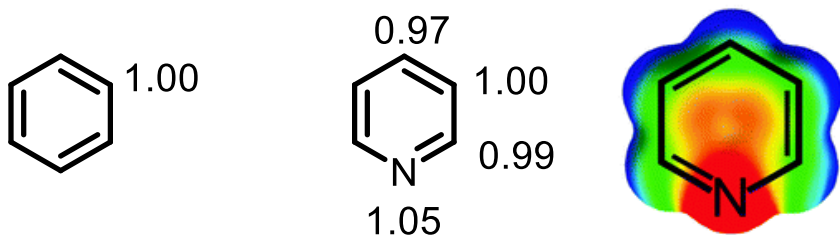


1. Determine the number of valence electrons on the heteroatom.
N: 5
 2. How many of those electrons are used to form sigma / single bonds to adjacent atoms?
2 bonding electrons – this leaves 3 valence electrons
 3. Draw any remaining empty orbitals on the heteroatom and fill them starting with the lowest energy orbital ($sp^2 < p$).
N is sp^2 hybridised (to fulfill rules of aromaticity): it has 3 sp^2 orbitals and one p orbital.
- This N contributes **one** electron to the pi-system.



Pyridine: Structure and Reactivity

- π -electron densities (calculated)



The presence of the **electronegative nitrogen atom** has an important effect on the structure and reactivity of pyridine (compared with benzene):

- weaker resonance stabilisation energy than benzene
- Lower HOMO/LUMO energies than benzene

- Resonance energy



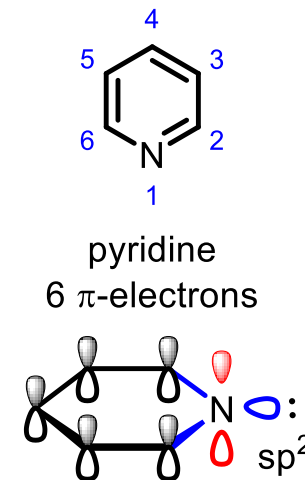
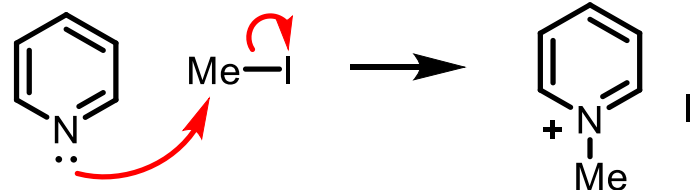
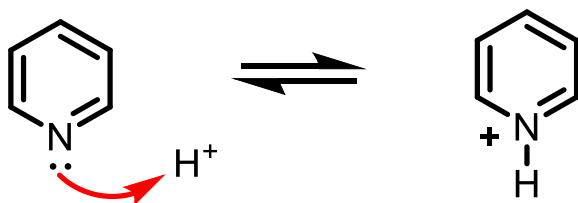
- Bond lengths (pm)





Pyridine: Structure and Reactivity

- Nomenclature: the heteroatom in the ring has priority #1
- The **lone pair** is **not delocalised** around the aromatic ring. It is available for reactions:
 - pyridine is a **weak base** and a **reasonable nucleophile**.

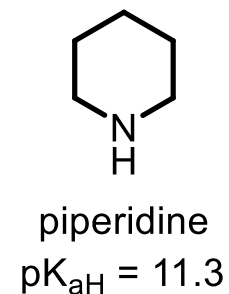
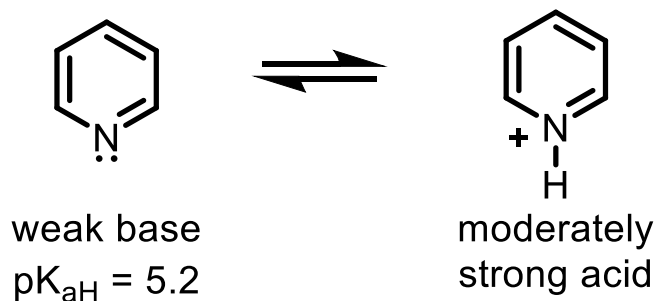


- The electronegative nitrogen atom lowers the (HOMO / LUMO) orbital energies compared to benzene
- Pyridine is **electron-deficient** (electronegative N), *i.e.* **electrophilic**.
 - electrophilic aromatic substitution is difficult.
 - nucleophilic aromatic substitution is easy.



Pyridine: Basicity

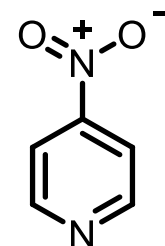
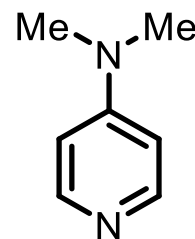
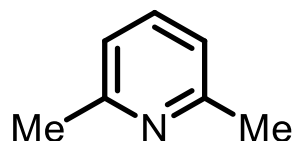
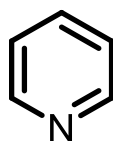
- The nitrogen in pyridine is sp^2 -hybridized (imine).
- Lone pairs in sp^2 orbitals are less available (held closer to the nucleus) than lone pairs in sp^3 orbitals (more p character), so imines are weaker bases than amines.





Pyridine: Basicity

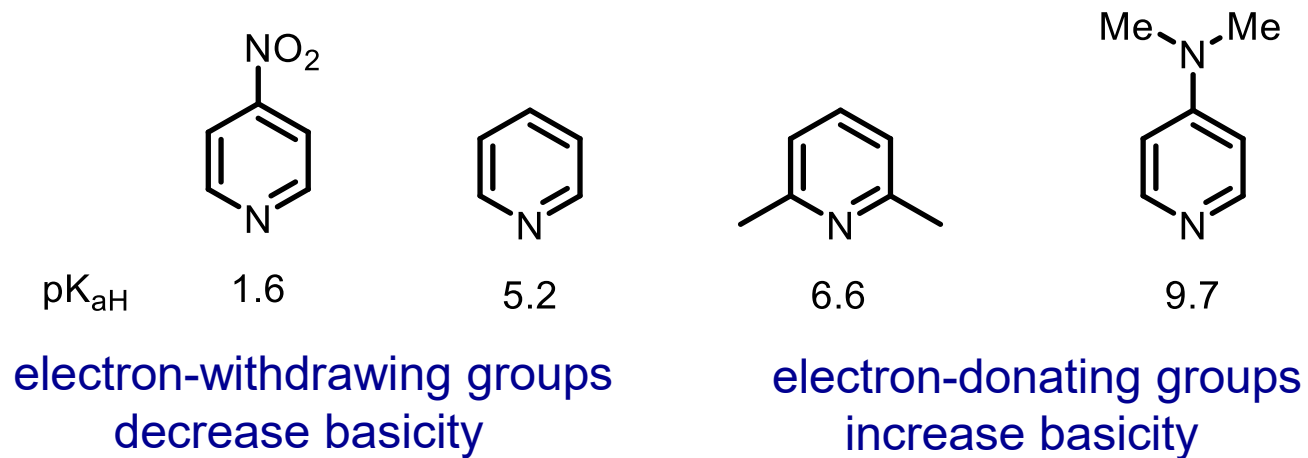
Question: Put the following pyridine molecules in order of increasing basicity:



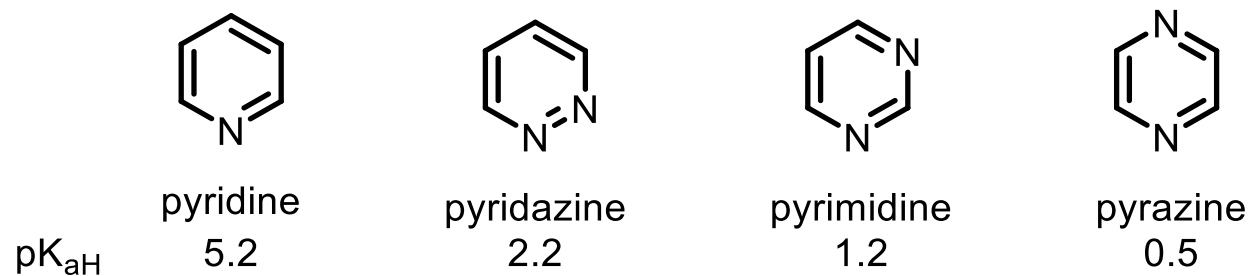


Pyridine: Basicity

- The basicity of pyridines is strongly influenced by the substituents on the ring:



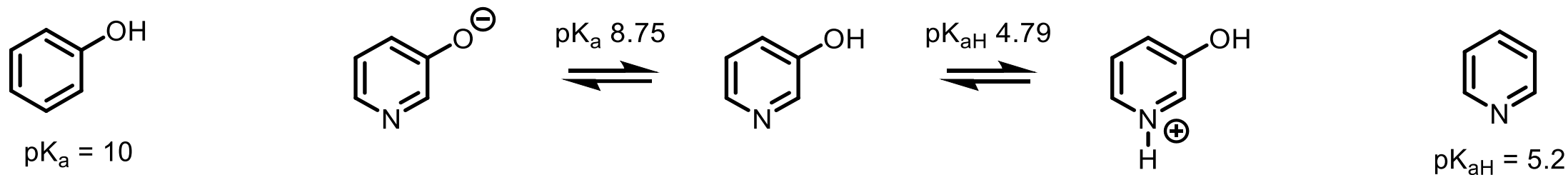
- Extra nitrogen atoms in the ring exert an electron-withdrawing effect, decreasing basicity:



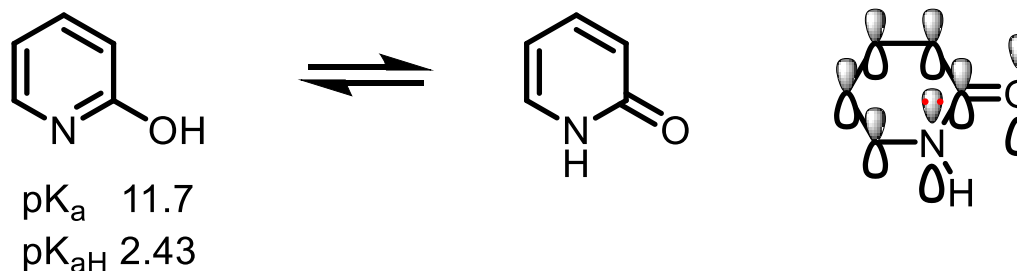


Hydroxypyridine: A special case

- Hydroxypyridines are both weak acids and bases



- 2-hydroxy- and 4-hydroxypyridine exist as two tautomeric forms, making them both less acidic and less basic than 3-hydroxypyridine:

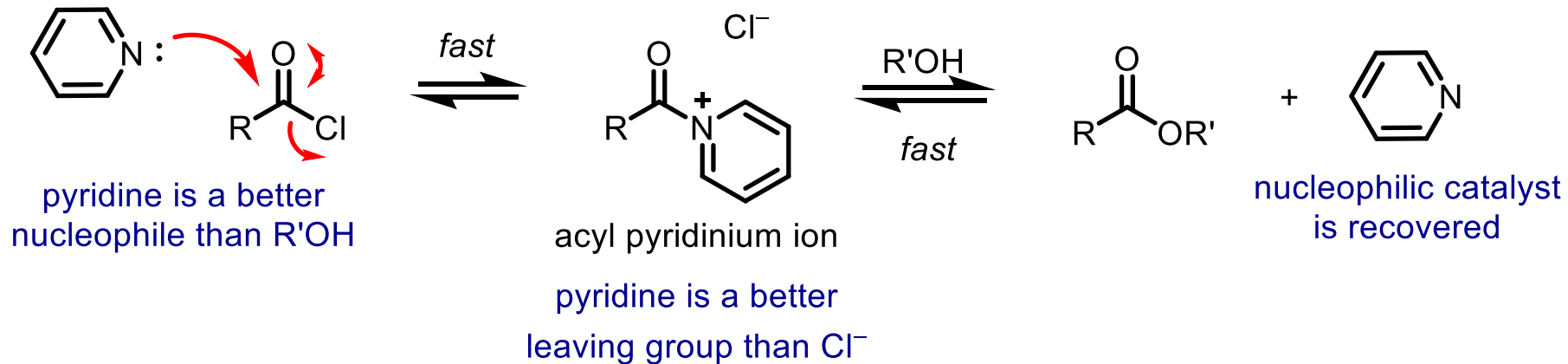
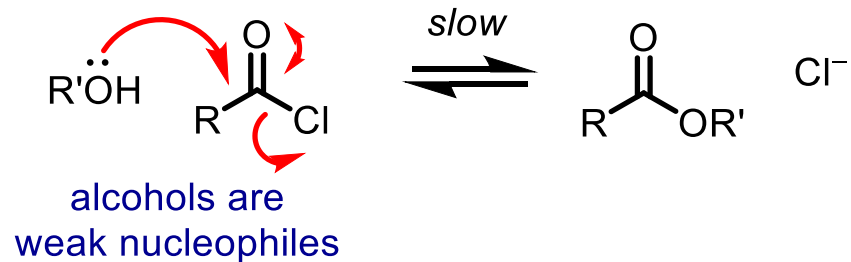


- Note: the pyridone form is still aromatic, as the lone pair of electrons on nitrogen can be delocalised into the ring.



Pyridine: Nucleophilicity

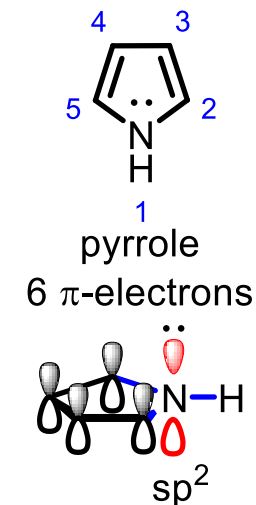
- The nitrogen lone pair is also available for nucleophilic attack on electrophiles
- Pyridine is often used as a **nucleophilic catalyst**, e.g. ester syntheses are often carried out with pyridine as the solvent:





5-Membered Heteroaromatics: Pyrrole

- Pyrrole is isoelectronic with cyclopentadiene anion.
- The nitrogen is sp^2 hybridised: the nitrogen lone pair is in the 2p orbital parallel to the carbon 2p orbitals and thus contributes 2 electrons to the π -system
- The **lone pair is delocalised** around the aromatic ring: it is unavailable for reactivity, making the pyrrole nitrogen **non-basic** and **non-nucleophilic**
- Pyrrole and other 5-membered heterocycles are **electron-rich** (delocalisation of lone pair: “pi-excessive”), *i.e.* **nucleophilic**
 - electrophilic aromatic substitution is very easy.
 - nucleophilic aromatic substitution is difficult.



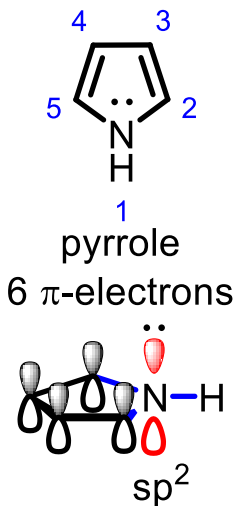
Weaker resonance stabilisation energy than benzene.

Higher HOMO/LUMO energies than benzene.



Pyrrole: Aromaticity

Pyrrole fulfils the 4 rules of aromaticity and is therefore (hetero)aromatic:

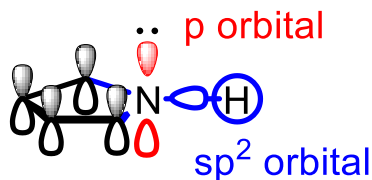


- ✓ • Cyclic
- ✓ • All atoms sp^2 -hybridised:
fully conjugated
- ✓ • planar
- ✓ • 6 π -electrons
($4n+2 = 6$ for $n = 1$)
Nitrogen contributes two electron to π -system.



How many electrons does the heteroatom contribute to the pi system?

Question: How do you determine the number of electrons a heteroatom contributes to the pi system?



1. Determine the number of valence electrons on the heteroatom. N: 5
2. How many of those electrons are used to form sigma / single bonds to adjacent atoms?

3 bonding electrons – this leaves 2 valence electrons

3. Draw any remaining empty orbitals on the heteroatom and fill them starting with the lowest energy orbital ($sp^2 < p$).

N is sp^2 hybridised (to fulfill rules of aromaticity): it has 3 sp^2 orbitals and one p orbital.

All three sp^2 orbital are used in the formation of sigma bonds (two N–C bonds, one N–H bond); the remaining 2 valence electrons must go in the p orbital.

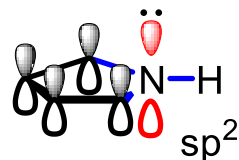
→ This N contributes **two** electron to the pi-system.



5-Membered Heteroaromatics



pyrrole

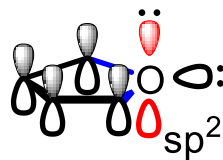


resonance
energy

90 kJ/mol



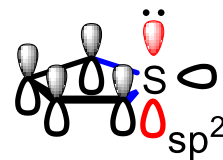
furan



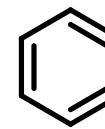
68 kJ/mol



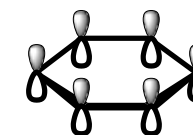
thiophene



122 kJ/mol



benzene



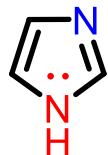
150 kJ/mol

- The structure of furan and thiophene is very similar to that of pyrrole.
- The differences stem mainly from **electronegativity** differences:
 - O and N are more electronegative than C: poor orbital overlap and electron delocalisation, decreased resonance stabilisation
 - Electronegativity of S is comparable to C: good orbital overlap, lone pair is fully delocalised into the π -system; strong resonance stabilisation



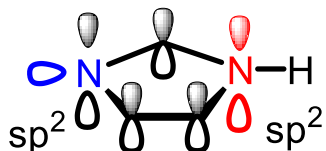
5-Membered Heteroaromatics with 2 heteroatoms

Question: Is imidazole aromatic?



imidazole

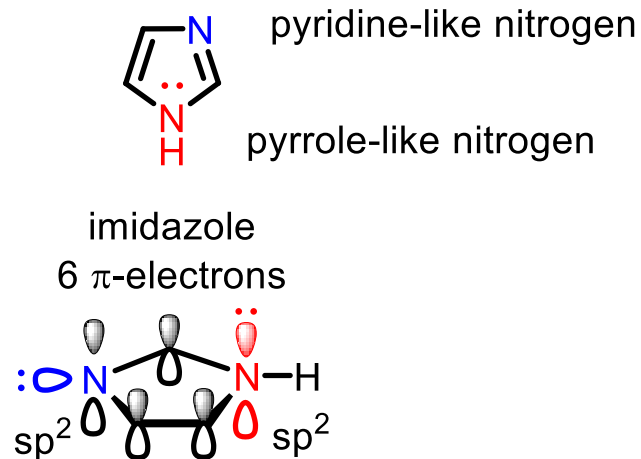
Imidazole **is** aromatic.



- ✓ • Cyclic
- ✓ • All atoms sp^2 -hybridised: fully conjugated
- ✓ • planar
- How many π -electrons? ($4n+2 = ?$)
- ✓ • Six π -electrons ($4n+2 = 6$ for $n = 1$)



5-Membered Heteroaromatics with 2 heteroatoms

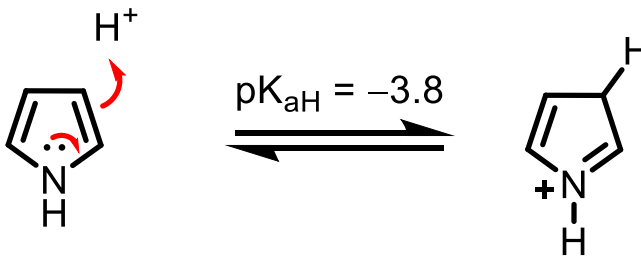


- Imidazole has one (non-basic, non-nucleophilic) **pyrrole-like nitrogen**, the lone pair of which is delocalised into the aromatic π -system.
- and one (basic, nucleophilic) **pyridine-like nitrogen**, the lone pair of which is orthogonal to the aromatic π -system.

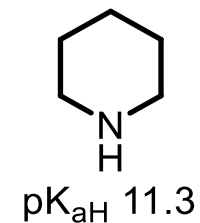
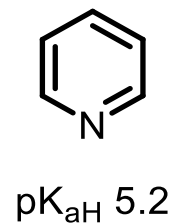
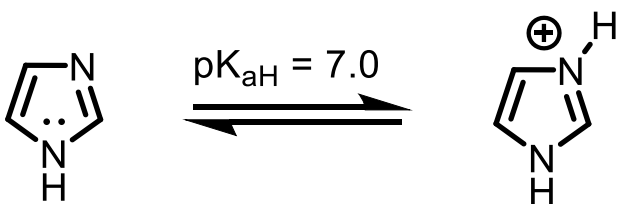


Basicity of 5-membered heteroaromatics

- The nitrogen **lone pair** in pyrrole is **delocalized** and therefore non-nucleophilic and **non-basic**.
- In very strong acid, pyrrole can be protonated, but it protonates on carbon, not nitrogen:



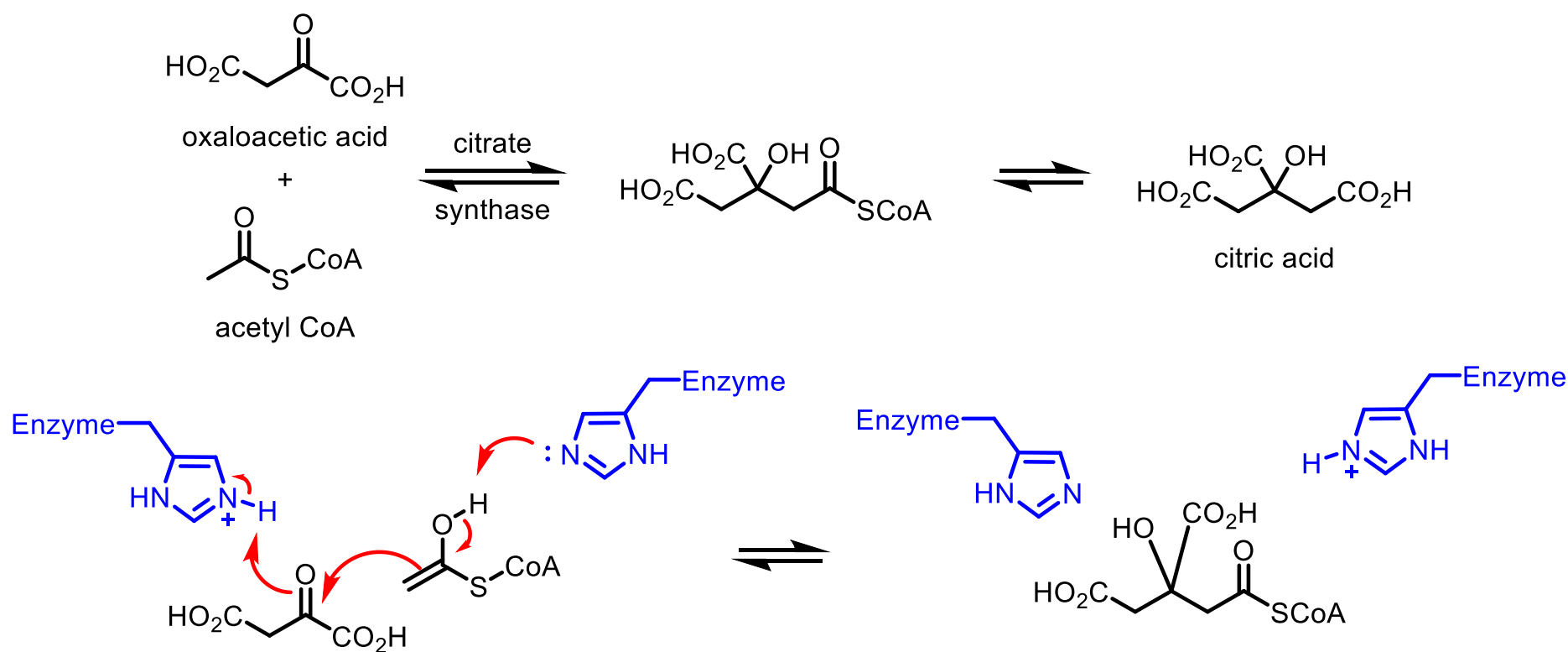
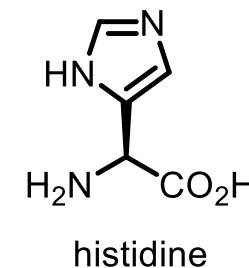
- Imidazole, on the other hand, has a 'pyridine-like' nitrogen and is moderately basic:





Imidazoles in Nature

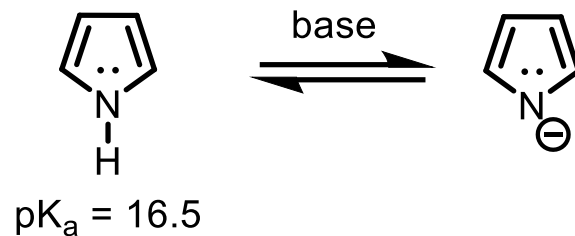
- Histidine is used as a **general acid/base catalyst** in **enzymes**
- e.g. citric acid cycle:



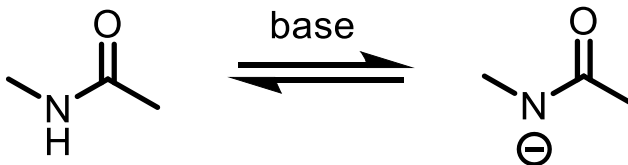


Acidity of 5-membered heteroaromatics

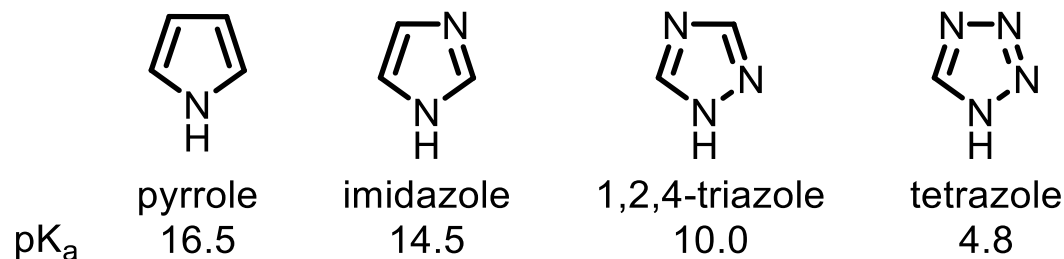
- An effect of the delocalization of the N lone pair is to make pyrrole weakly acidic



- Comparable to an amide:



- Azoles are also acidic, and the acidity increases dramatically as the number of ring nitrogens increases:





Summary

In this lecture, you learned how to identify heteroaromatic compounds.

4 rules of aromaticity:

(i) cyclic, (ii) all atoms sp^2 -hybridised: fully conjugated, (iii) planar, (iv) $4n+2$ π -electrons:

How many electrons does the heteroatom contribute to the π -system?

If lone pair is parallel to / part of the π -system: 2 electrons,

if lone pair is orthogonal to / not part of the π -system: 1 electron

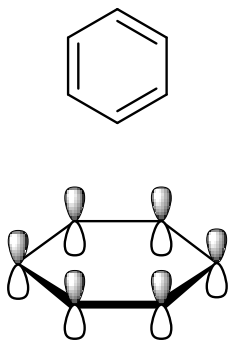




Summary

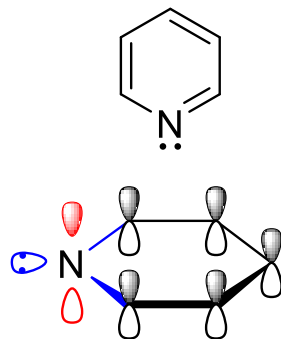
In this lecture, you also learned how to:

- Describe the properties of heteroaromatic compounds compared to benzene:



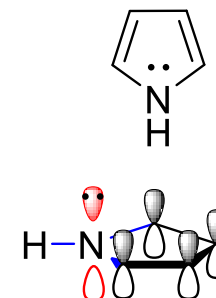
Benzene

- Good size and energy match of C 2p orbitals: strong resonance stabilisation
- Very difficult to disrupt aromaticity



Pyridine

- Lone pair not part of aromatic π -system
- Nucleophilic on nitrogen
- Lower HOMO energy than benzene: electrophilic π -system (electronegative N)



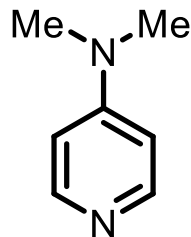
Pyrrole

- Lone pair is part of aromatic π -system
- Not nucleophilic on nitrogen
- Higher HOMO energy than benzene: nucleophilic π -system (electron-rich)



Topic 3 – Practice questions

1. When pyridine is used as a nucleophilic catalyst in ester syntheses, stoichiometric amounts are necessary. DMAP, however, can be used in catalytic amounts. Why do you think this is the case? (Draw a reaction mechanism to support your answer.)

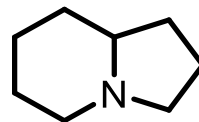


DMAP
dimethylaminopyridine



Topic 3 – Practice questions

2. Can you draw an aromatic heterocycle based on the following ring system?

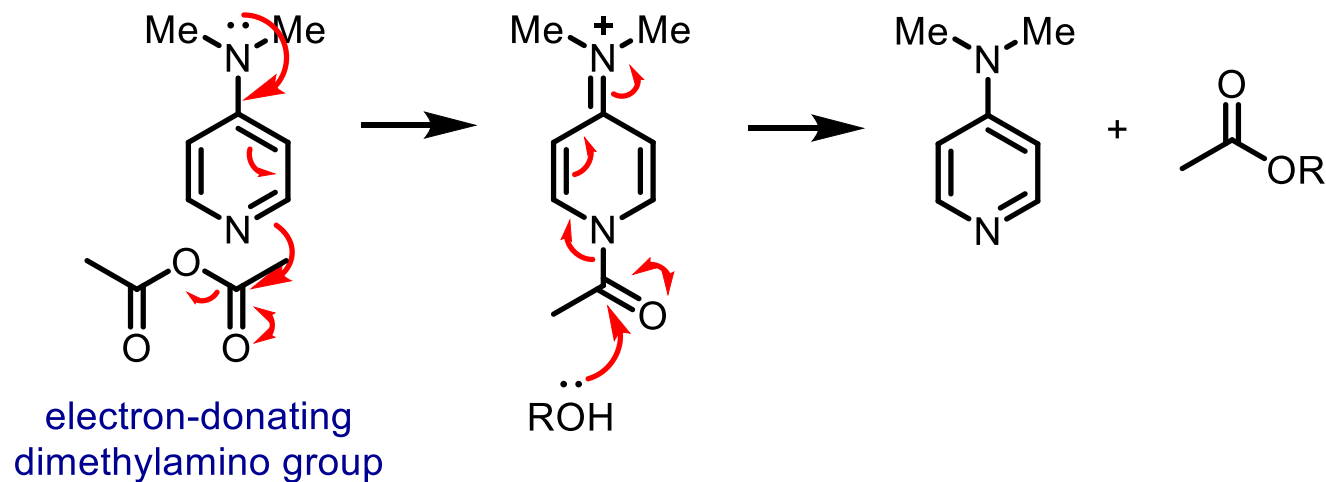


- a) Does the compound you have drawn fulfill Hückel's rule of aromaticity?
- b) Would you predict the nitrogen in your heteroaromatic compound to be basic or non-basic?



Topic 3 practice questions: Solution

1. When pyridine is used as a nucleophilic catalyst in ester syntheses, stoichiometric amounts are necessary. DMAP, however, can be used in catalytic amounts. Why do you think this is the case? (Draw a reaction mechanism to support your answer.)

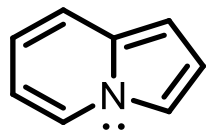


The dimethylamino substituent in DMAP is electron-donating, increasing electron-density on the nitrogen, increasing the energy of its HOMO and making its lone pair 'more available' for nucleophilic attack compared to pyridine. DMAP is therefore a stronger nucleophile than pyridine and a more efficient nucleophilic catalyst.

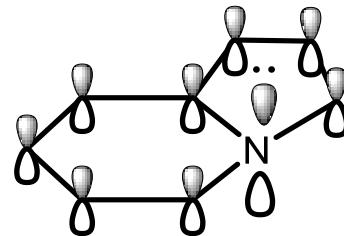


Topic 3 practice questions: Solution

2. Can you draw an aromatic heterocycle based on the following ring system?



pyrrocoline /
indolizine



10 π -electrons
 $(4n+2)=10$ for $n=2$

a) Does the compound you have drawn fulfill Hückel's rule of aromaticity?

Yes, the nitrogen contributes to the π -system.

b) Would you predict the nitrogen in your heteroaromatic compound to be basic or non-basic?

The nitrogen is pyrrole-like: the lone pair is conjugated into the aromatic ring, and therefore unavailable for nucleophilic attack. The compound is not basic on nitrogen.



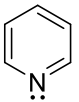
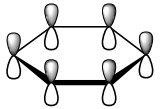
Recap Topic 3: Heteroaromatic Compounds

In the last two lectures, you learned about aromatic and heteroaromatic compounds:



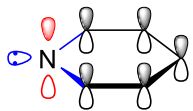
Benzene

- Good size and energy match of C 2p orbitals: strong resonance stabilisation
- Very difficult to disrupt aromaticity



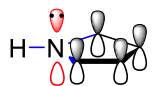
Pyridine

- Lone pair orthogonal to / not part of aromatic π -system: nucleophilic on nitrogen
- Electronegative N: electron-poor aromatic, lower HOMO energy than benzene



Pyrrole

- Lone pair is part of aromatic π -system: electron-rich aromatic, higher HOMO energy than benzene
- Not nucleophilic on nitrogen





Topic 4: Electrophilic Aromatic Substitution

Learning outcomes

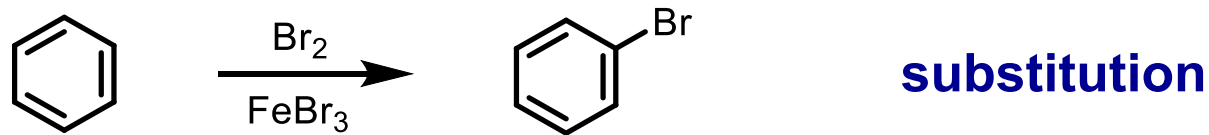
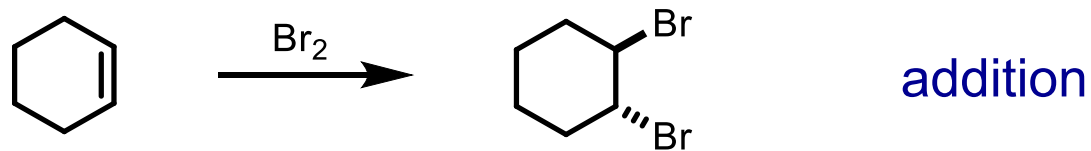
In this lecture, you will learn to:

- describe the reaction of benzene with electrophiles (electrophilic aromatic substitution);
- predict the effects of pre-existing substituents on the rate and selectivity of these reactions;
- propose the synthesis of aromatic compounds from simple starting materials using electrophilic aromatic substitution reactions.



Reactivity of aromatic compounds

- Recap: Because of the **high stability of aromatic systems** (resonance stabilisation), they are **relatively unreactive**. ('Breaking' aromaticity requires a lot of energy.)
- Because of delocalisation, benzene reacts very differently to an isolated alkene:

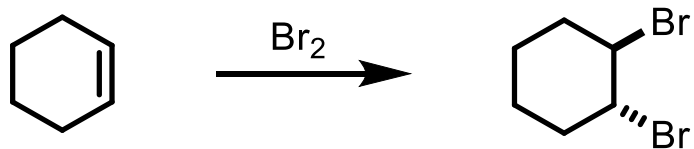


- Electron-rich aromatics react with electrophiles (this topic: electrophilic aromatic substitution), while electron-poor aromatics react with nucleophiles (next topic: nucleophilic aromatic substitution).



Electrophilic addition to alkenes

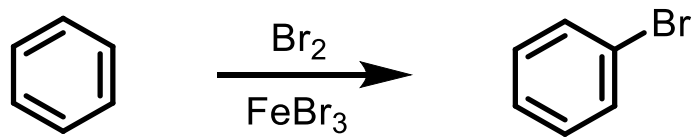
- Closer look at mechanism: for both alkenes and aromatics, a cationic intermediate is formed





Electrophilic aromatic substitution

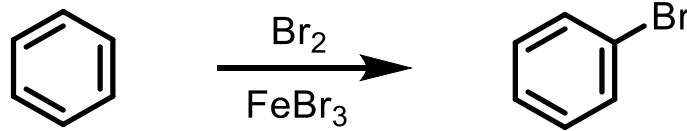
- Closer look at mechanism: for both alkenes and aromatics, a cationic intermediate is formed



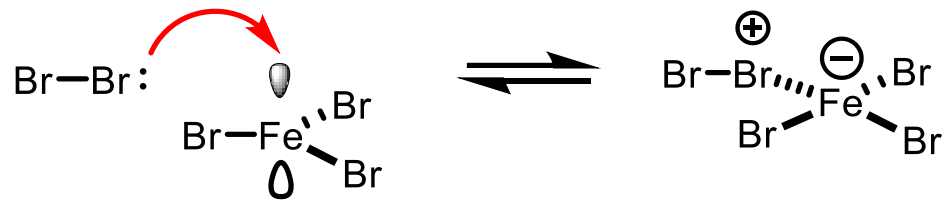


Electrophilic aromatic substitution

- Closer look at mechanism: for both alkenes and aromatics, a cationic intermediate is formed

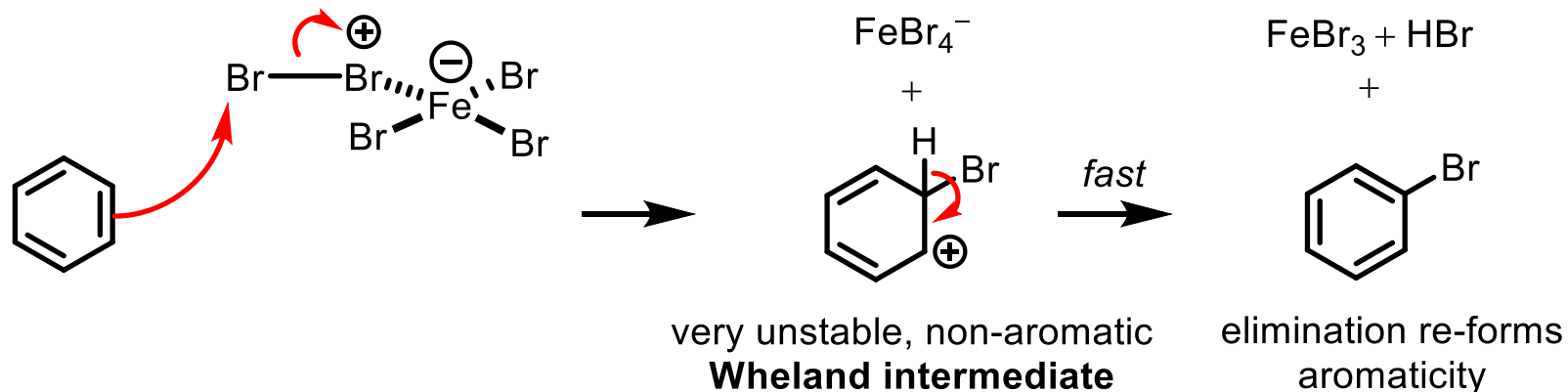


1) Generation of the electrophile



Benzene is very stable (unreactive), so the reactivity of the electrophile needs to be increased by reaction with a Lewis acid.

2) Electrophilic aromatic substitution

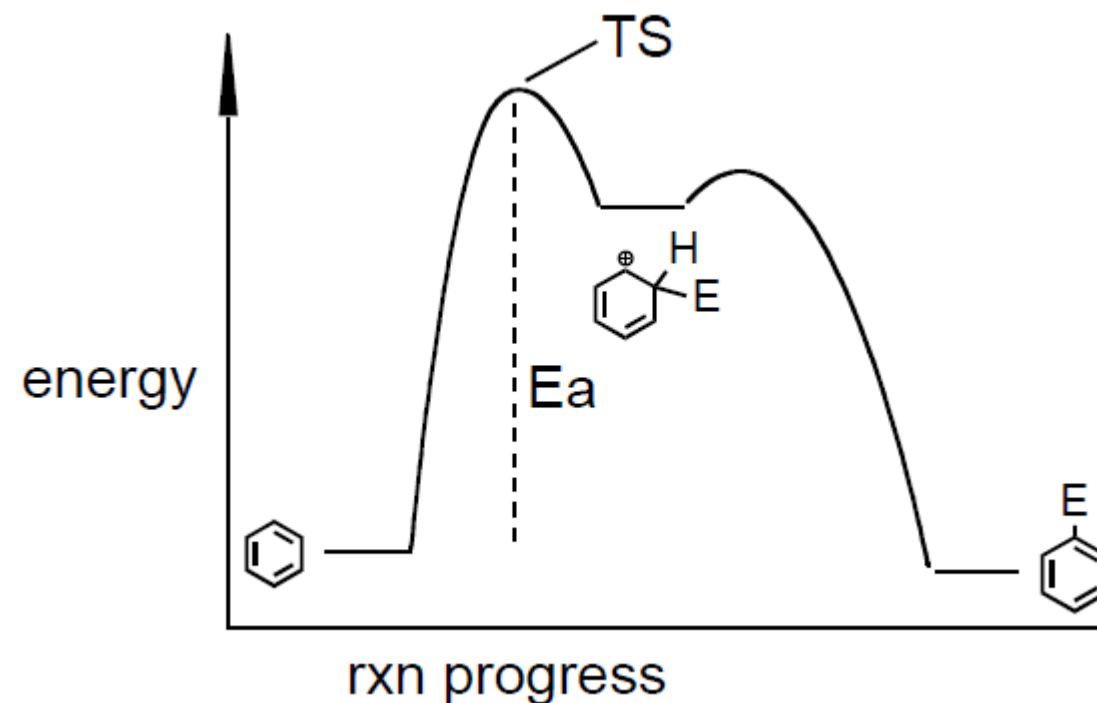
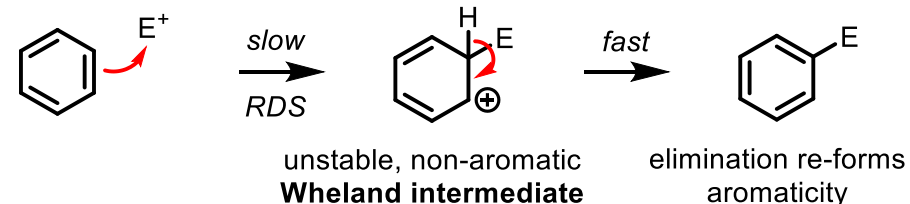


The aromatic pi-electrons act as the nucleophile, attacking the activated electrophile.



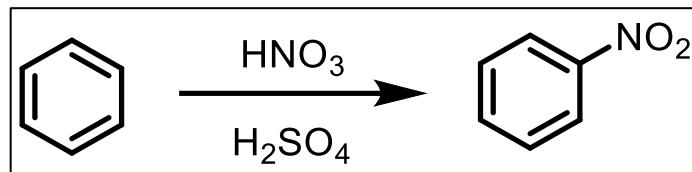
Electrophilic aromatic substitution

- Disrupting aromaticity requires a lot of energy: formation of the Wheland intermediate is the rate determining / slow step (high activation energy)
- The (Wheland) intermediate is unstable and has a much higher energy than the starting materials or the products
- The two transition states are similar in structure to the intermediate, so we can use the intermediate as a model for the transition states





Nitration



Typical conditions: conc. HNO_3 and conc. H_2SO_4 1:1

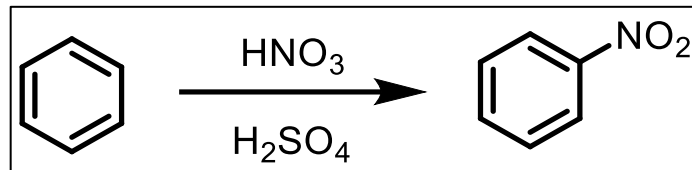
When you draw mechanism of any electrophilic aromatic substitution reaction, always consider the following **two steps**:

- 1) Generation of the electrophile
- 2) Electrophilic aromatic substitution



Nitration

Reaction Mechanism



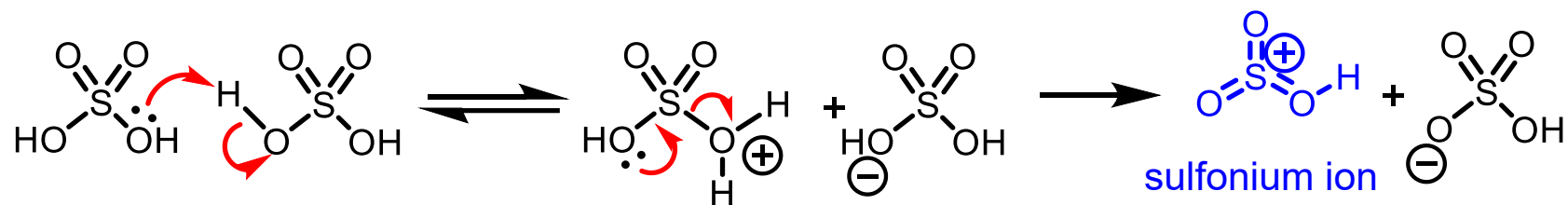


Sulfonation

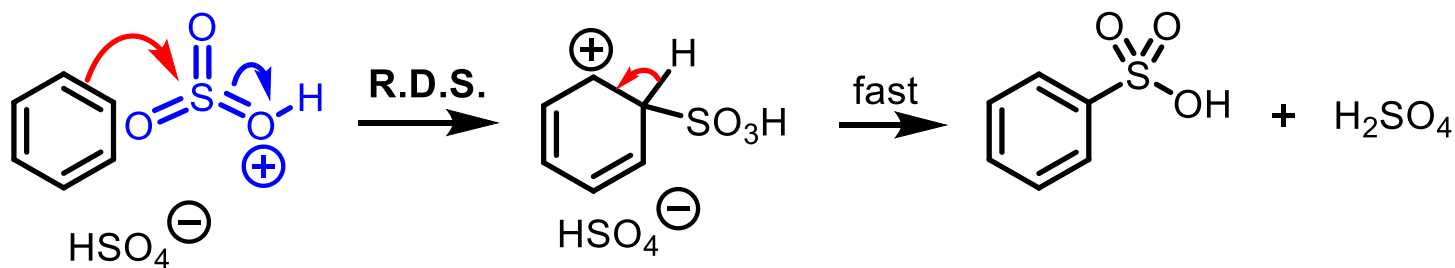


Typical conditions: conc. H_2SO_4 saturated with SO_3 (oleum).

1) Generation of the electrophile

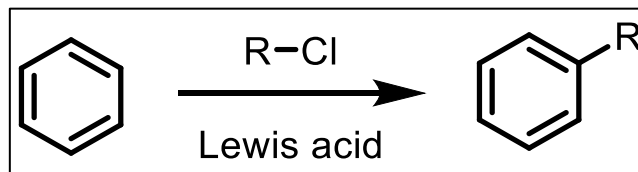


2) Electrophilic aromatic substitution





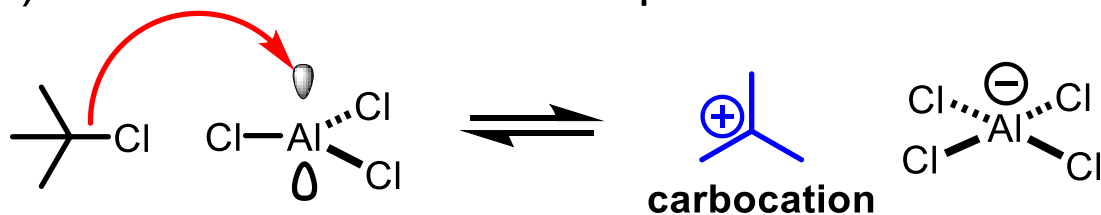
Friedel-Crafts alkylation



R = alkyl; typical Lewis acids: FeCl_3 , FeBr_3 , AlCl_3

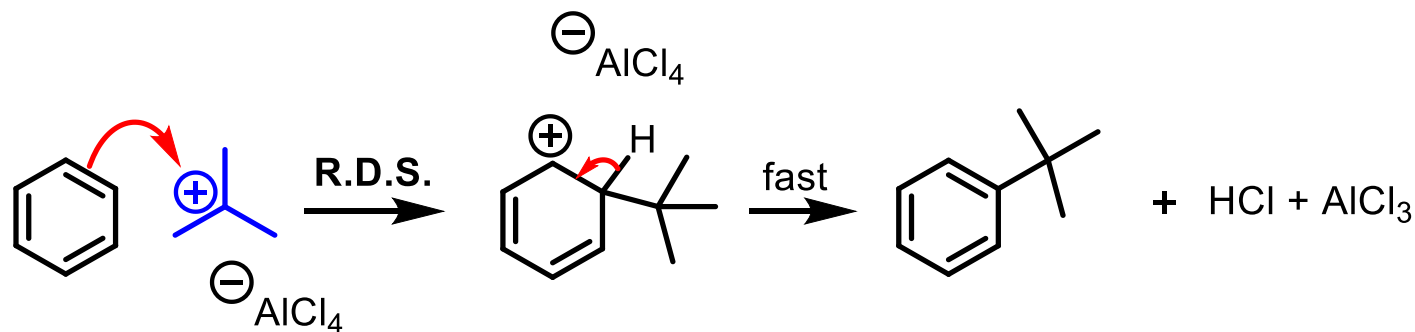
Mechanism:

1) Generation of the electrophile



Q: Draw a curly arrow reaction mechanism for step 2 (electrophilic aromatic substitution).

2) Electrophilic aromatic substitution

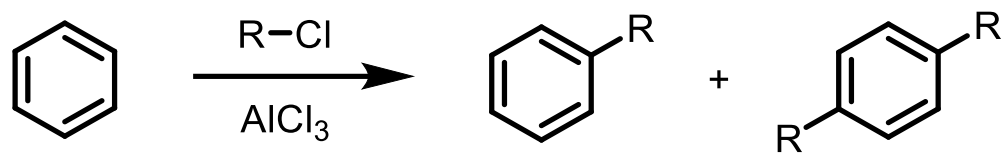




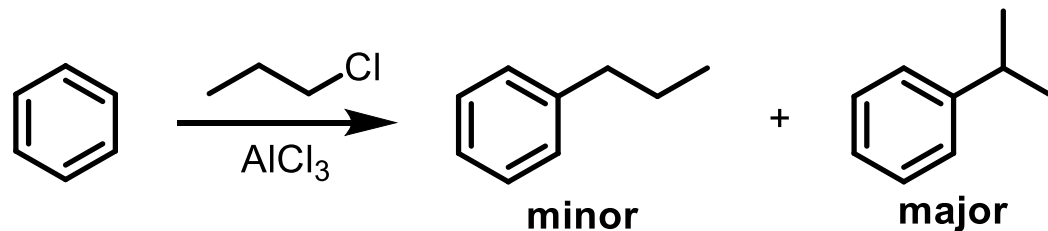
Friedel-Crafts alkylation

Disadvantages:

- The products of Friedel-Crafts alkylation reactions are more reactive than the starting materials because alkyl groups are electron-donating (see later: *activated substrates*): **over-alkylation** can occur.

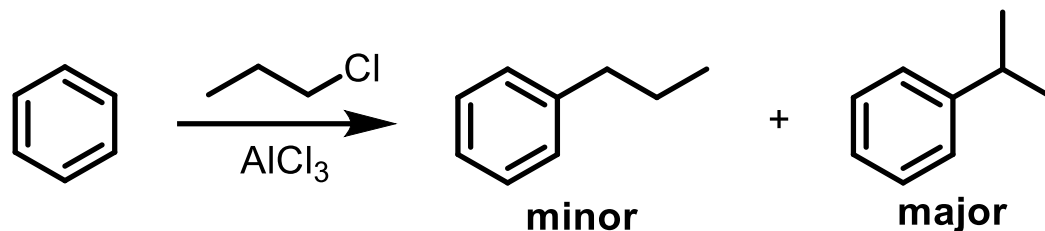


- Friedel-Crafts alkylation is only useful with tertiary alkyl halide electrophiles. **Rearrangement** occurs with secondary alkyl halides:

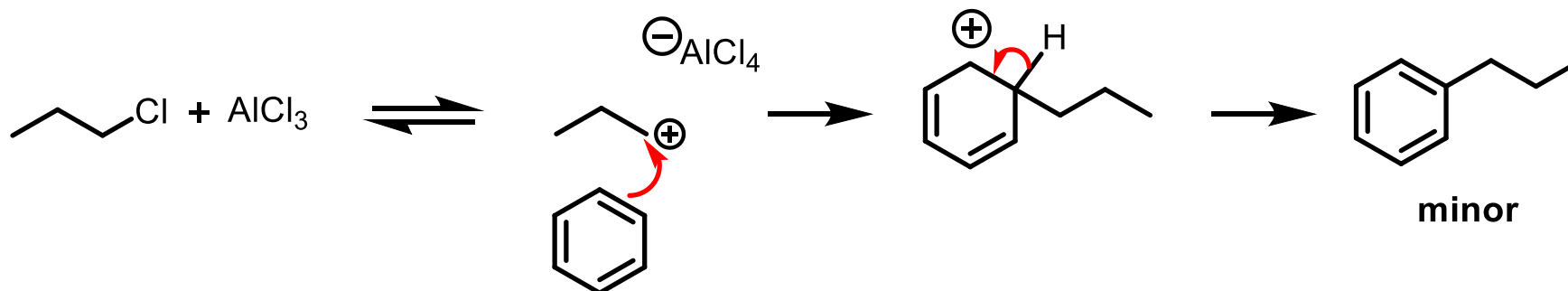




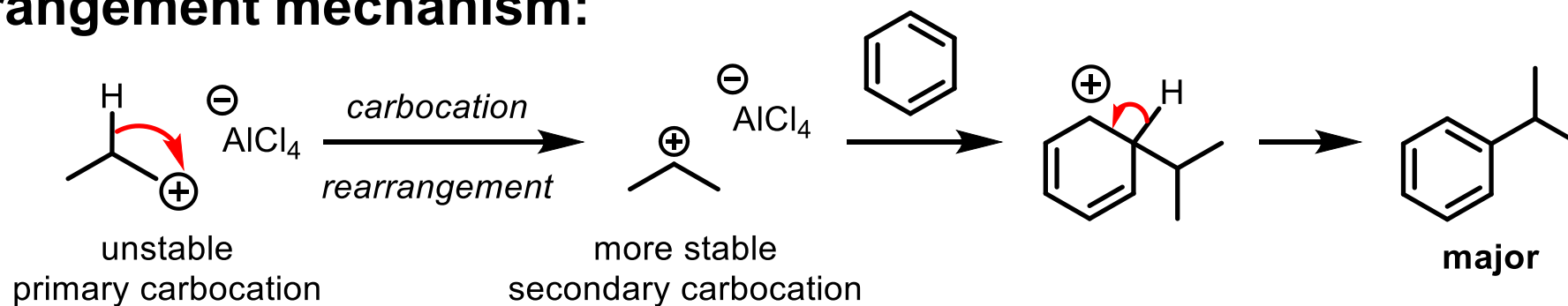
Friedel-Crafts alkylation



Expected mechanism:



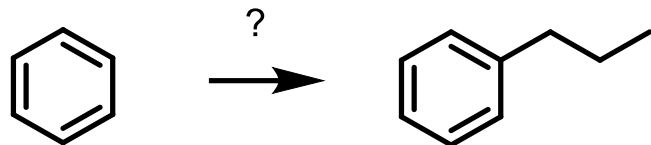
Rearrangement mechanism:



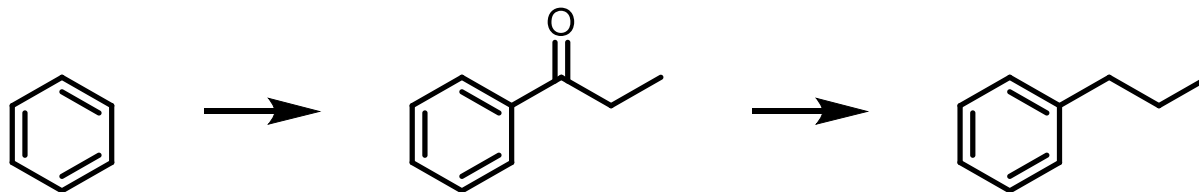


Friedel-Crafts acylation

So, can we convert benzene into n-propylbenzene?

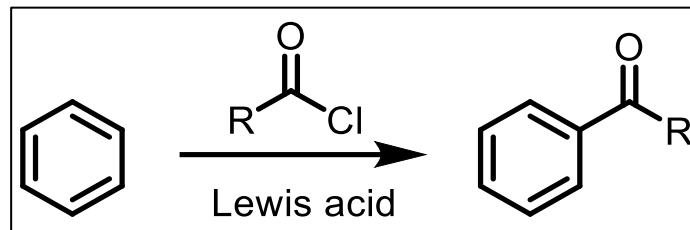


Solution: make the ketone via Friedel-Crafts acylation, then reduce to the alkane (e.g. Clemmenson or Wolff-Kishner reduction)

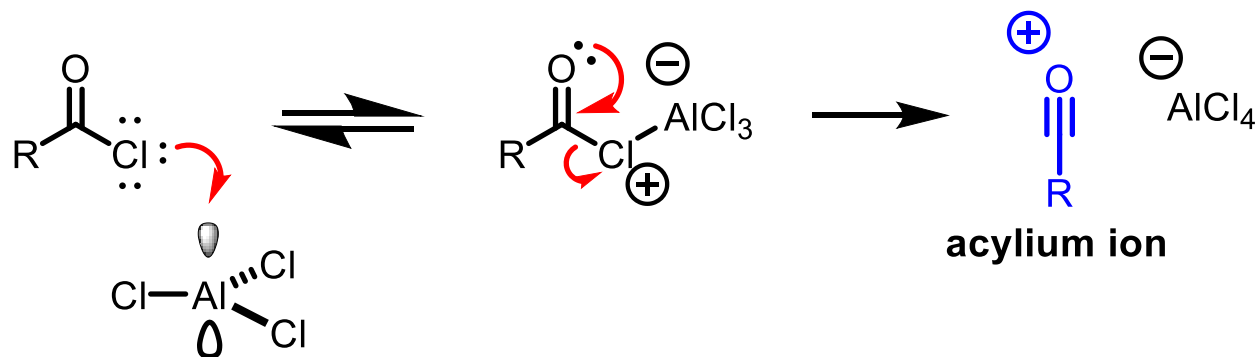




Friedel-Crafts acylation

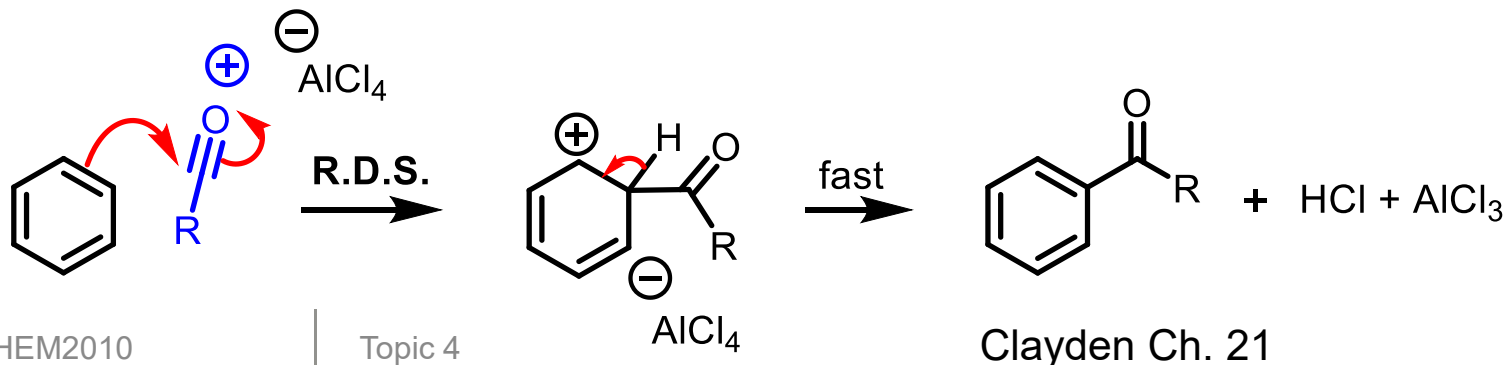


1) Generation of the electrophile



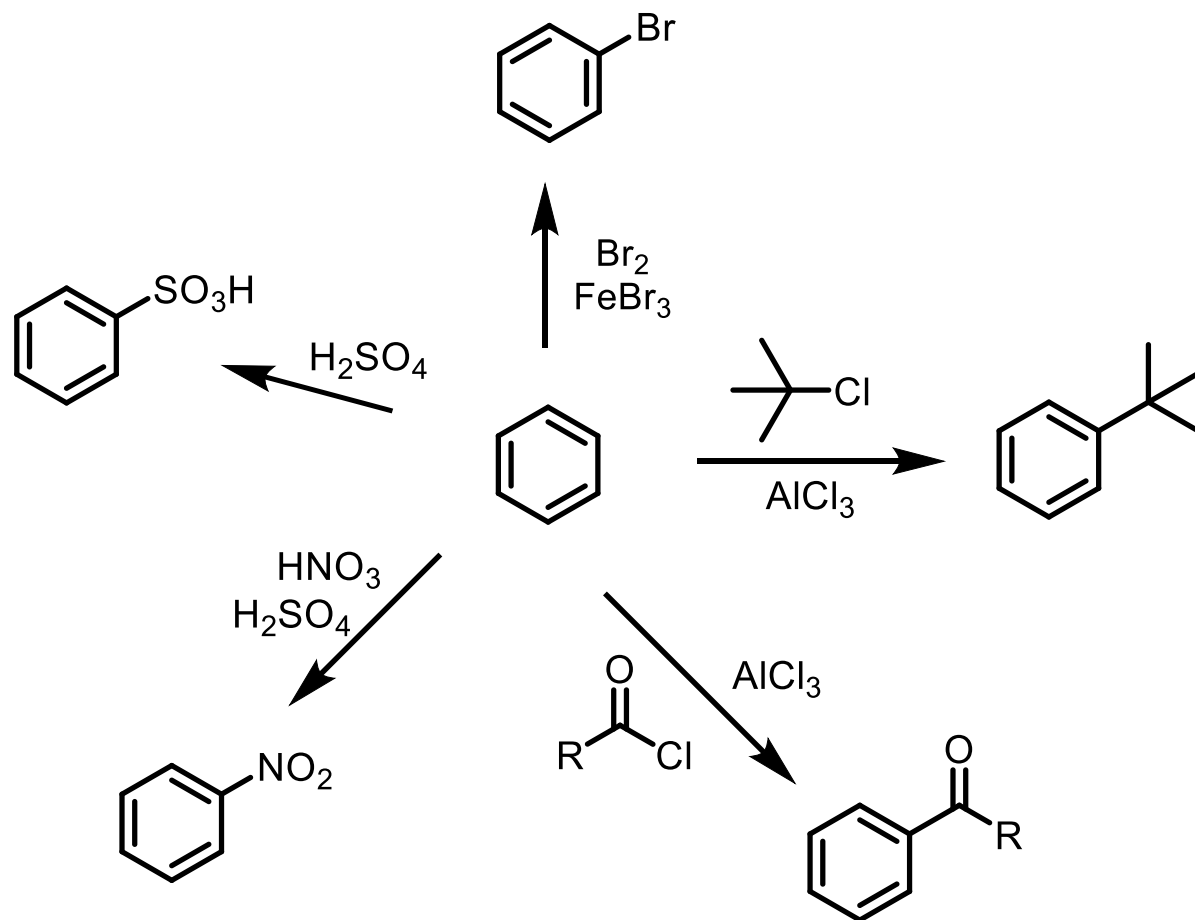
More general and reliable
than Friedel-Crafts alkylation:
no over-acylation, no rearrangements.

2) Electrophilic aromatic substitution





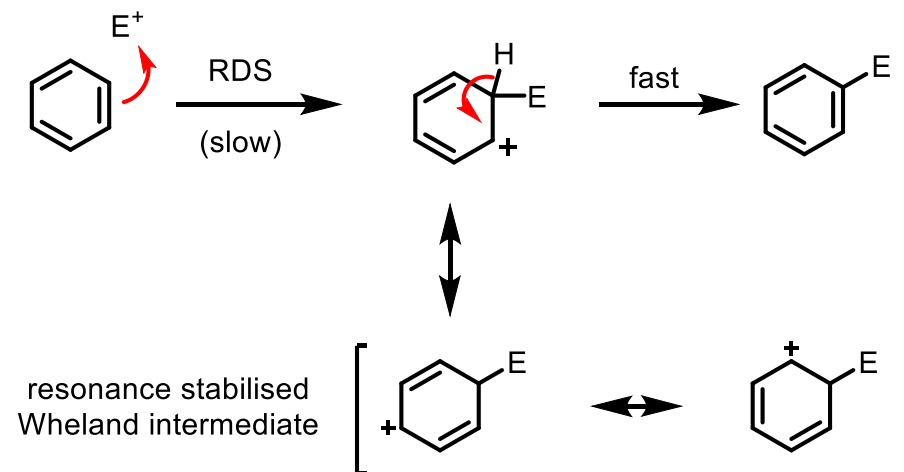
Summary: Electrophilic aromatic substitution reactions



You need to be able to draw curly arrow reaction mechanisms for these transformations.

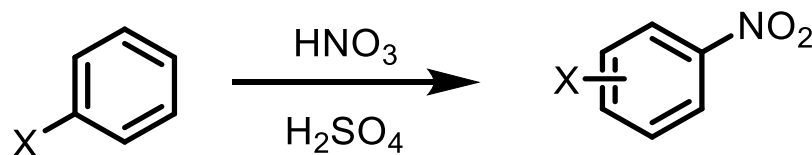
Remember:

- 1) Formation of the electrophile (E^+)
- 2) Electrophilic aromatic substitution:





Electrophilic aromatic substitution: substituent effects



So far, we have only seen examples of unsubstituted benzene molecules undergoing electrophilic aromatic substitution.

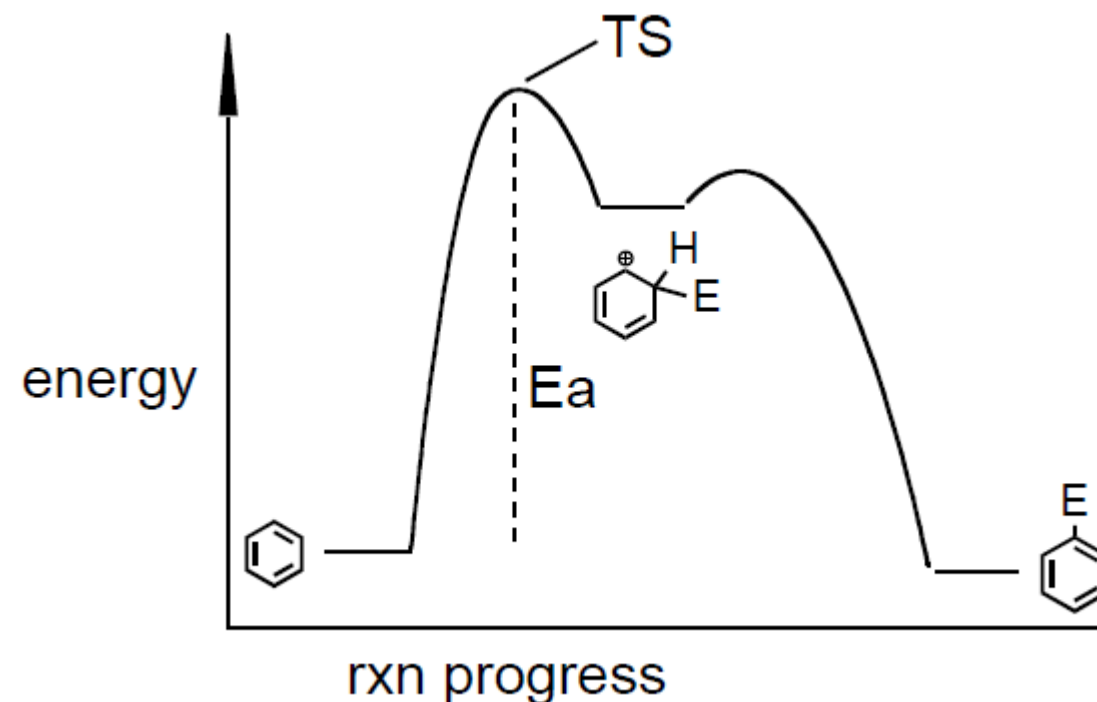
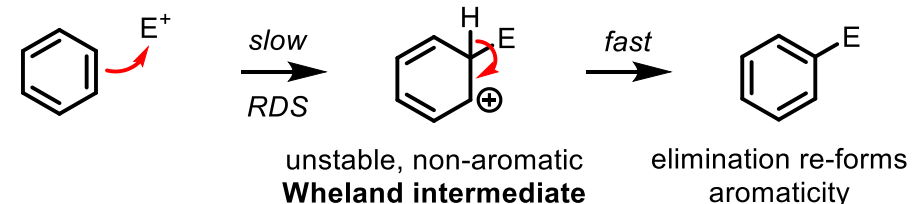
What happens when there is already a substituent X on our aromatic molecule?

Answer: X will have an effect on the **rate** and **selectivity** of the reaction.



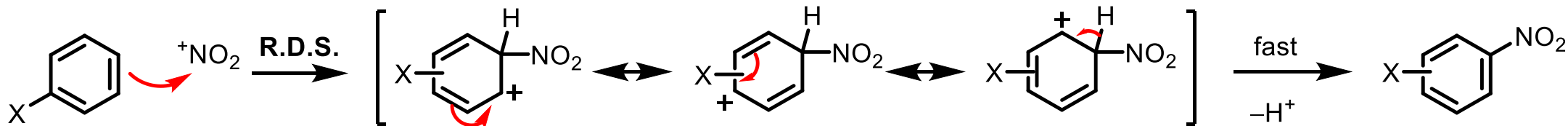
Electrophilic aromatic substitution

- Disrupting aromaticity requires a lot of energy: formation of the Wheland intermediate is the rate determining / slow step (high activation energy)
- The (Wheland) intermediate is unstable and has a much higher energy than the starting materials or the products
- The two transition states are similar in structure to the intermediate, so we can use the intermediate as a model for the transition states





Substituent effects on reaction rate



X	σ	Relative rate
OH	-0.38	1000
CH ₃	-0.17	25
H		1
Cl	+0.22	0.033
NO ₂	+0.77	6×10^{-8}
⁺ NMe ₃	+0.82	6×10^{-1}

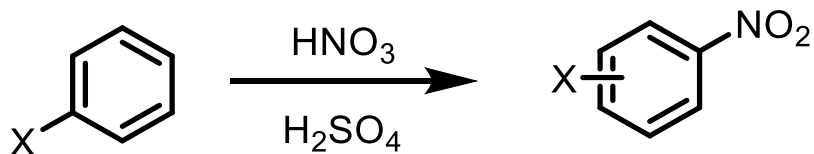
electron-rich aromatics are **more nucleophilic** and **react faster** in electrophilic aromatic substitution reactions

electron-poor aromatics are **less nucleophilic** and **react slower**

σ = Hammett sigma constant: quantifies how electron-donating ($-ve \sigma$) or $-$ withdrawing ($+ve \sigma$) a substituent is. Note: Mesomeric effects are stronger than inductive effects.

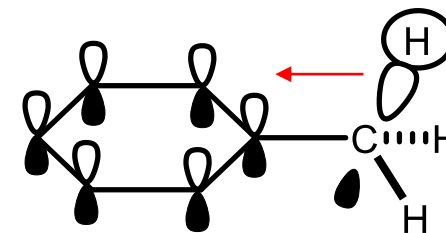


Substituent effects on reaction rate



X	σ	Relative rate
CH ₃	-0.17	25
H		1

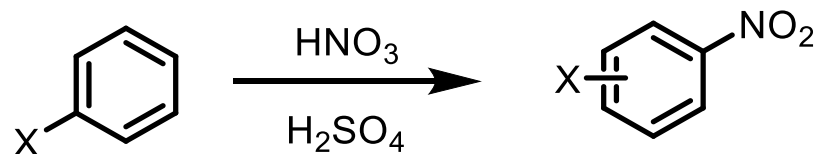
- Toluene is nitrated faster than benzene: the methyl group increases nucleophilicity and activates the ring towards reaction with electrophiles.
- Alkyl groups **donate electrons** by hyperconjugation (σ -conjugation) (weak effect).
- This is the reason over-alkylation can occur in Friedel-Crafts alkylation (alkylated aromatics are more reactive than the non-alkylated starting material).



hyperconjugation: C-H σ -bond donates electron-density into π -system

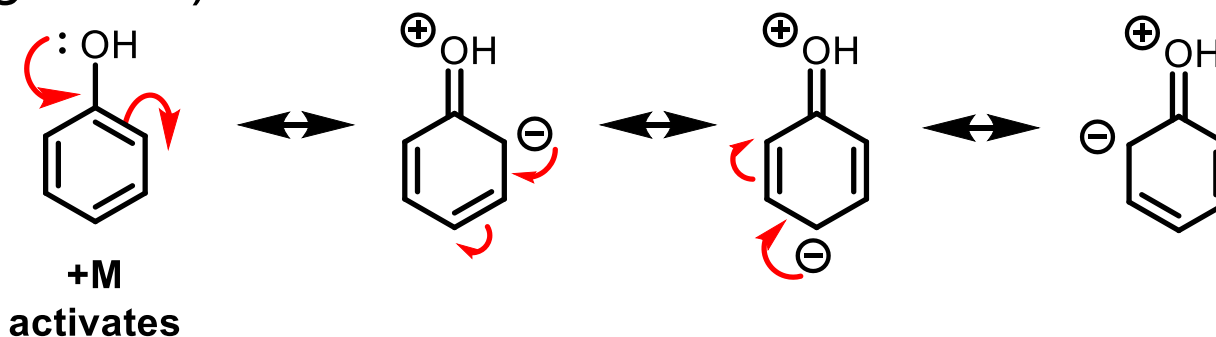


Substituent effects on reaction rate

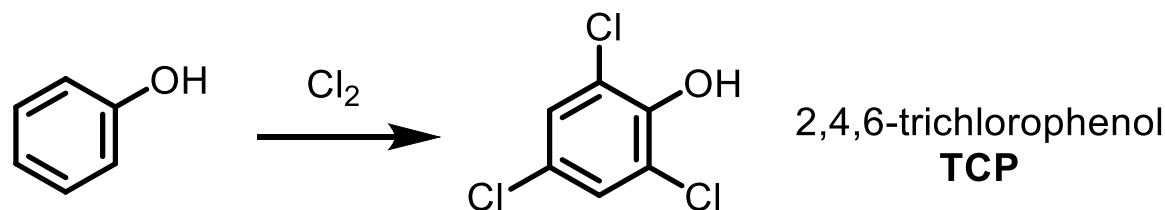


X	σ	Relative rate
OH	-0.38	1,000
H		1

- Phenol reacts much faster than benzene: the **mesomerically electron-donating** hydroxy group increases nucleophilicity and activates the ring towards reaction with electrophiles (strong effect).

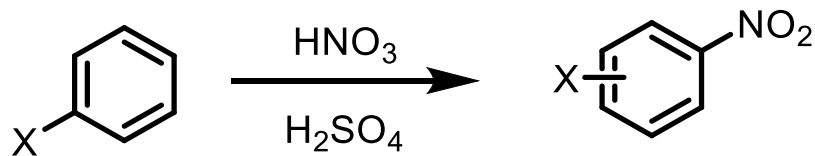


- Because phenol is so electron-rich, over-substitution occurs:



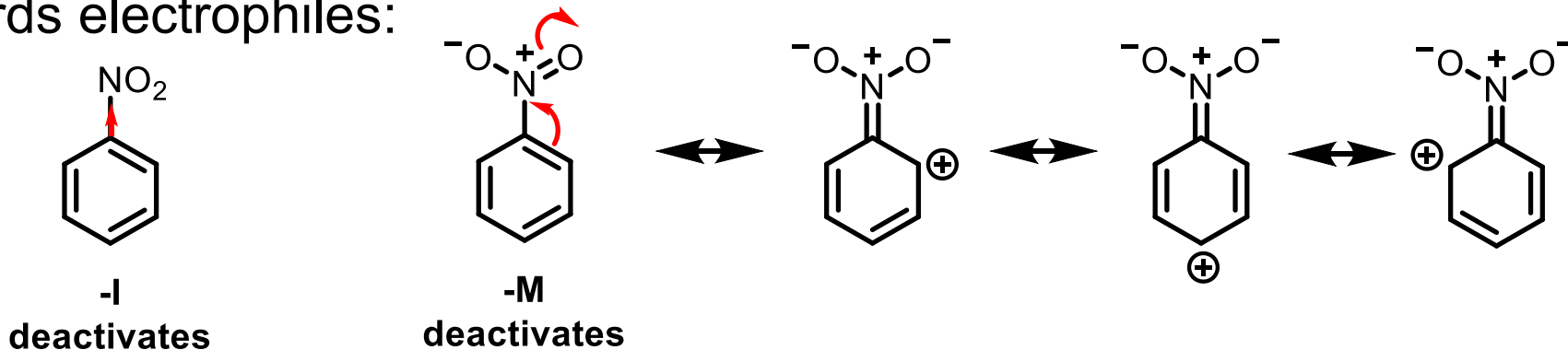


Substituent effects on reaction rate

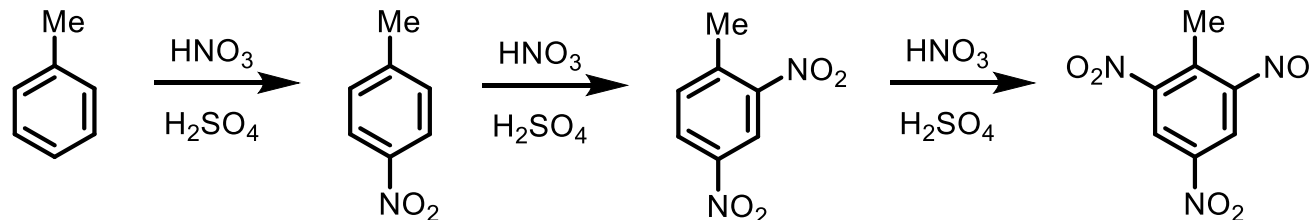


X	σ	Relative rate
H		1
NO ₂	+0.77	6×10^{-8}

- Nitrobenzene reacts much slower than benzene: the nitro group is **mesomerically (–M) and inductively (–I) electron-withdrawing**, decreasing nucleophilicity and making the ring less reactive towards electrophiles:



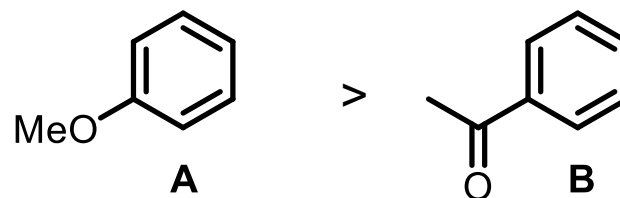
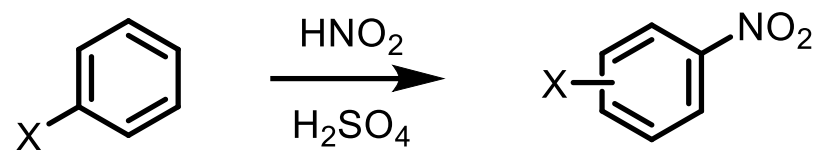
- TNT is made by nitration of toluene. The nitro group is strongly deactivating, so the last nitration requires high temperatures:





Question

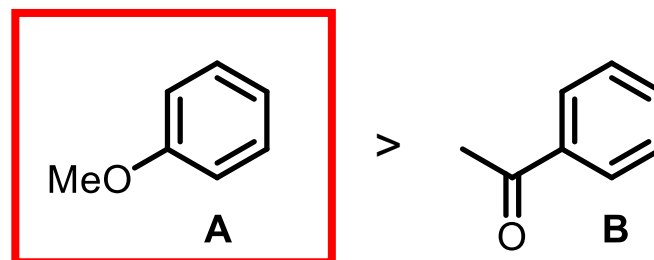
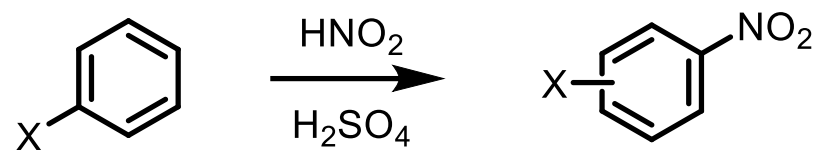
Which molecule will react faster in an electrophilic aromatic nitration: A or B?





Question

Which molecule will react faster in an electrophilic aromatic nitration: A or B?

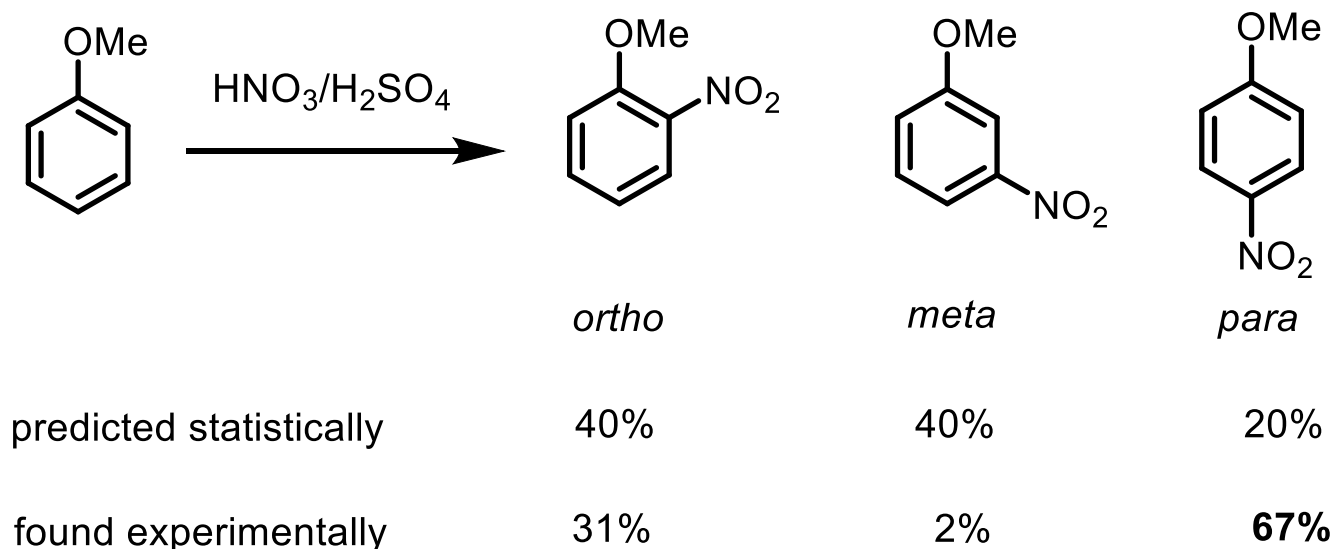




Substituent effects on selectivity

If there is already a substituent X on the aromatic molecule, it will have an effect on the **regioselectivity** of electrophilic aromatic substitution, *i.e.* at which site (carbon) the aromatic ring reacts with the electrophile.

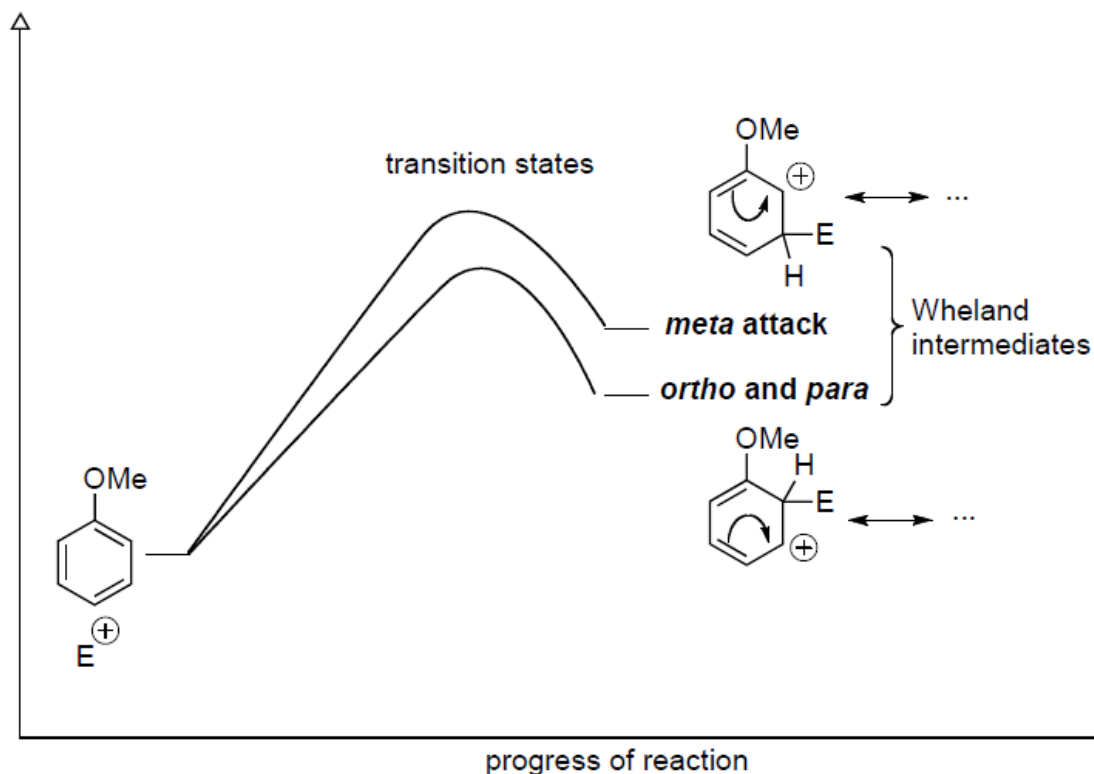
Electron-donating groups





Substituent effects on selectivity: EDGs

- Most electrophilic substitutions are under **kinetic control**: fastest product (lowest energy transition state) predominates.
- *Ortho*- and *para*-products are formed upon electrophilic attack on methoxybenzene, because the TS from *ortho* and *para* attack is lower in energy: smaller activation energy E_a .
- *Para* attack is favoured over *ortho* due to sterics.



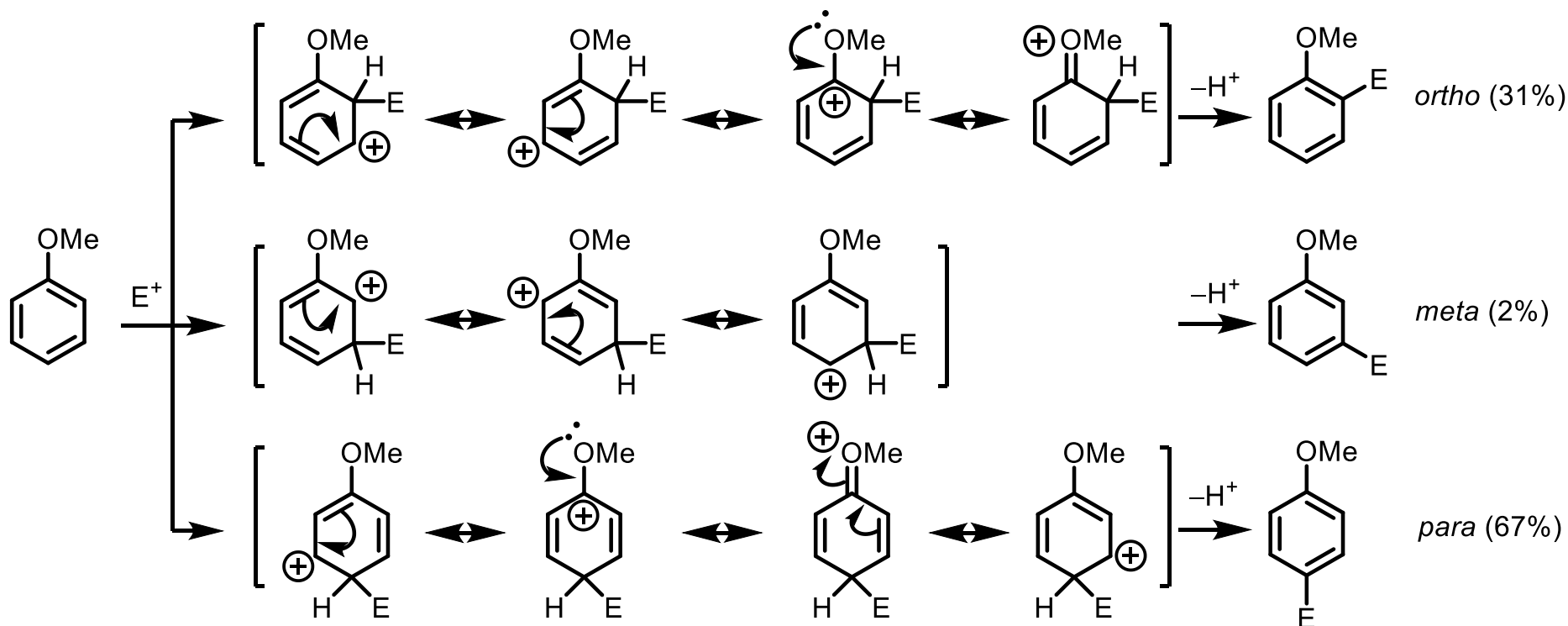
Summary:

- EDG makes aromatic ring more nucleophilic.
- EDG stabilises positively charged intermediate.
- This stabilisation is most effective when electrophile adds *ortho* or *para* to the EDG.



Substituent effects on selectivity: EDGs

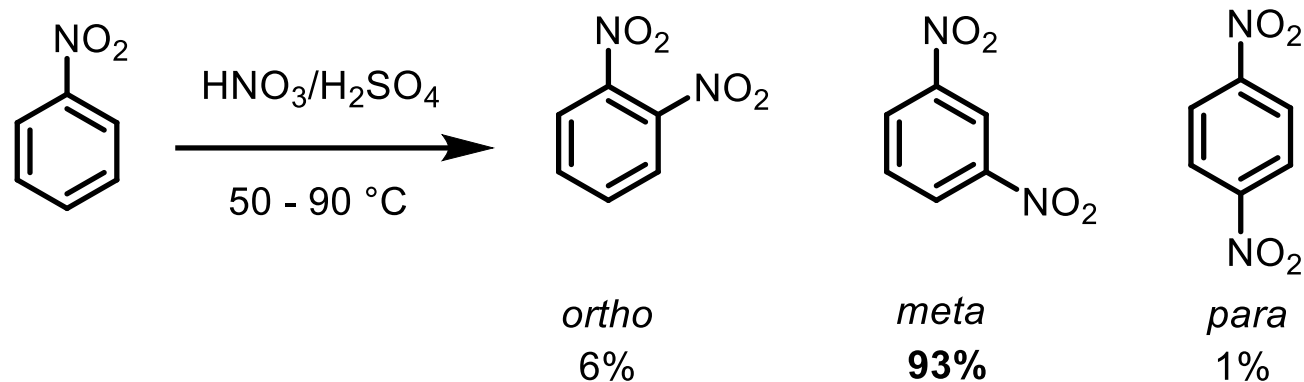
- The transition state is similar in structure and energy to the Wheland intermediate: consider the positively charged intermediate to find the lowest energy TS:
- The **intermediate is more stable** (more resonance forms) when the EDG is ortho or para to the site of attack.





Substituent effects on selectivity: EWGs

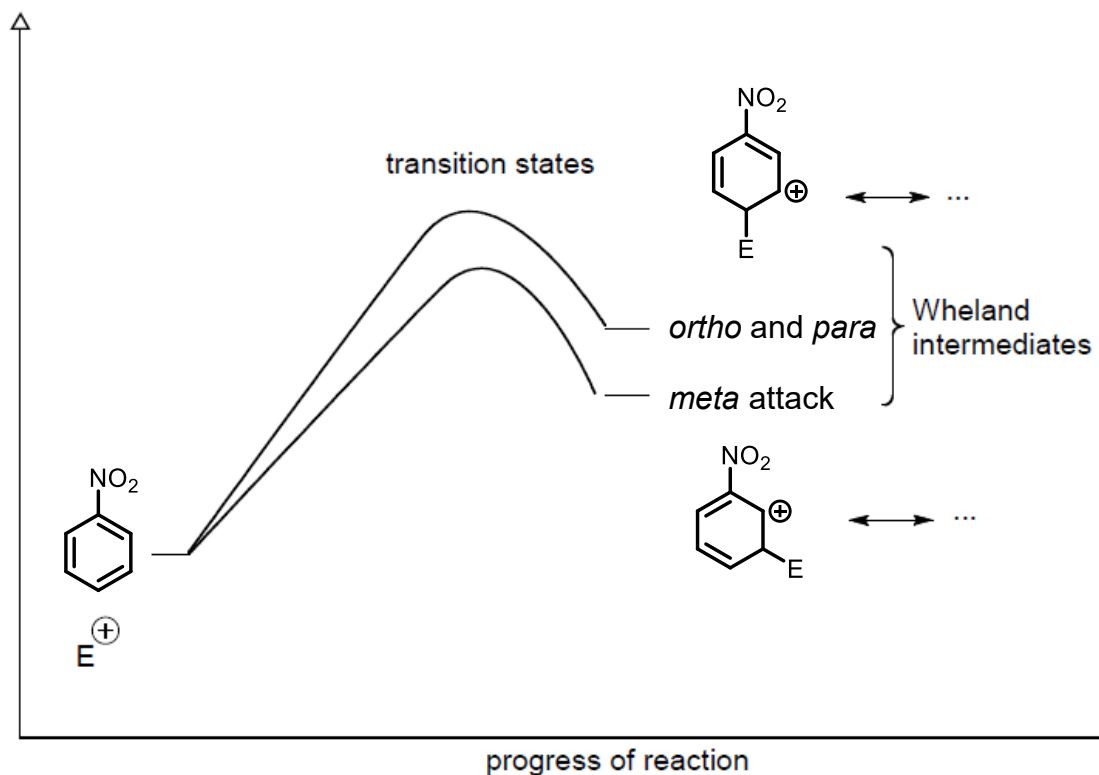
Electron-withdrawing groups





Substituent effects on selectivity: EWGs

- Meta*-products are formed upon electrophilic attack on nitrobenzene, because the TS from *meta* attack is lower in energy: smaller activation energy E_a .



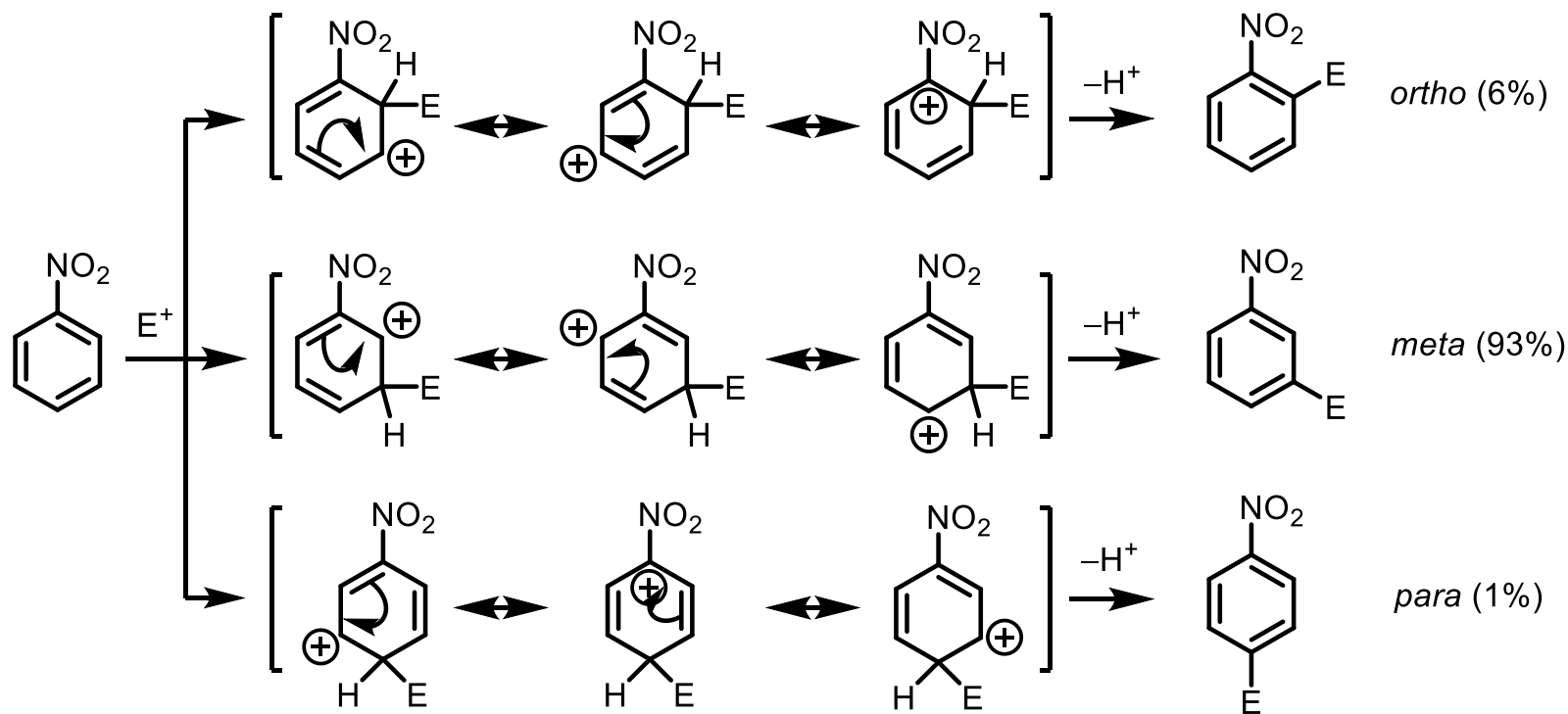
Summary:

- EWG makes aromatic ring less nucleophilic.
- EWG destabilises positively charged intermediate.
- This destabilisation is least effective (giving the most stable of all the destabilised options) when electrophile adds meta to the EWG.



Substituent effects on selectivity

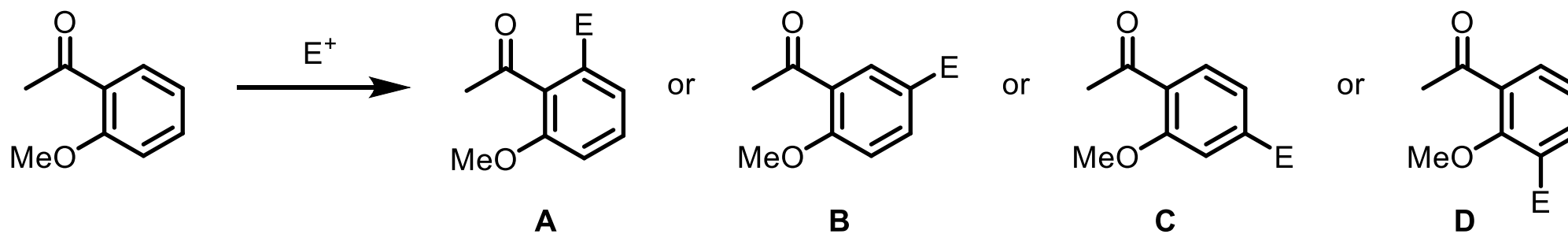
- The transition state is similar in structure and energy to the Wheland intermediate: consider the positively charged intermediate to find the lowest energy TS:
- The **intermediate is more stable** (least electron density withdrawn from carbocationic intermediate) when the EWG is *meta* to the site of attack.





Question

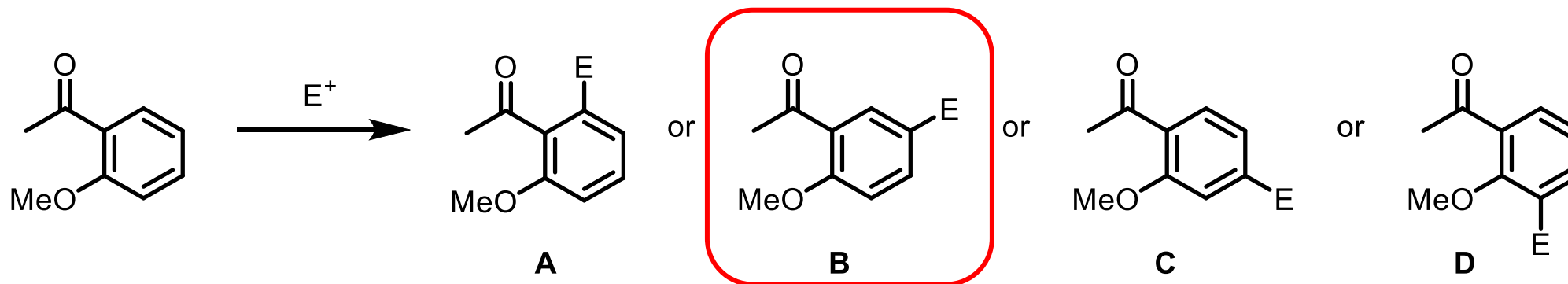
What is the major product in this electrophilic aromatic substitution reaction?





Question

What is the major product in this electrophilic aromatic substitution reaction?

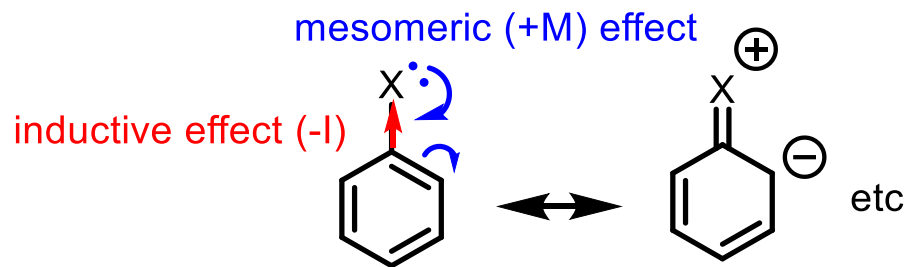


- If there are two substituents present, they can either reinforce each other / direct to the same position (as in this example), or oppose each other (giving a mix of products).



Substituent effects on selectivity

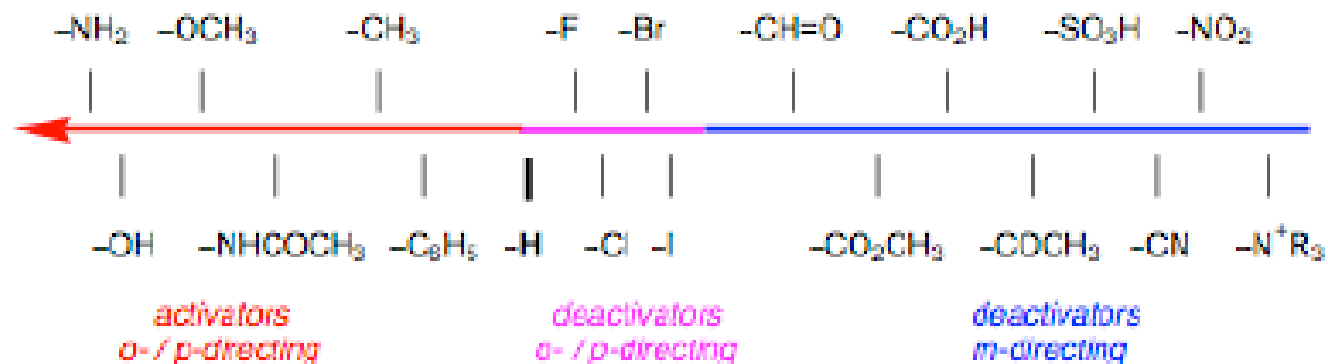
Halogens



- Halogens are inductively electron-withdrawing: **deactivating** (halobenzenes react at a slower rate than benzene)
- Halogens are mesomerically electron-donating: ***o*-/*p*-directing**
- The mesomeric effect in halobenzenes is very weak (poor orbital overlap between halogen and carbon p orbitals). It controls *o/p*-selectivity, but does not have a great influence on reaction rate.



Substituent effects: Summary



Electronic effect	Example	Rate cf. benzene	Where does “E” go?
electron-donating groups	$-\text{NR}_2$, $-\text{OR}$, alkyl	faster	<i>ortho/para</i>
halogens	F, Cl, Br, I	slower	<i>ortho/para</i>
electron-withdrawing groups	$-\text{NO}_2$, $-\text{COR}$, $-\text{SO}_3\text{R}$	slower	<i>meta</i>



Substituent effects in action

Substituent	Rate cf. benzene	Selectivity
EDG	fast	<i>ortho/para</i>
Halogens	slow	<i>ortho/para</i>
EWG	slow	<i>meta</i>

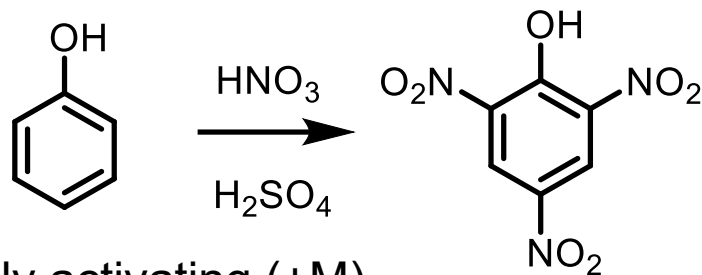
Consider:

- Is E^+ reactive enough? (loss of aromaticity when arene attacks electrophile)
- What substituents are present? M and I effects: *ortho* / *para* or *meta* directing?
- If two substituents are present, will they reinforce or oppose each other?
- Will introduction of E activate or deactivate the ring w.r.t. further substitution?
- Any **steric effects**? E.g. both *ortho* and *para* favoured electronically, but large groups favour *para* substitution.



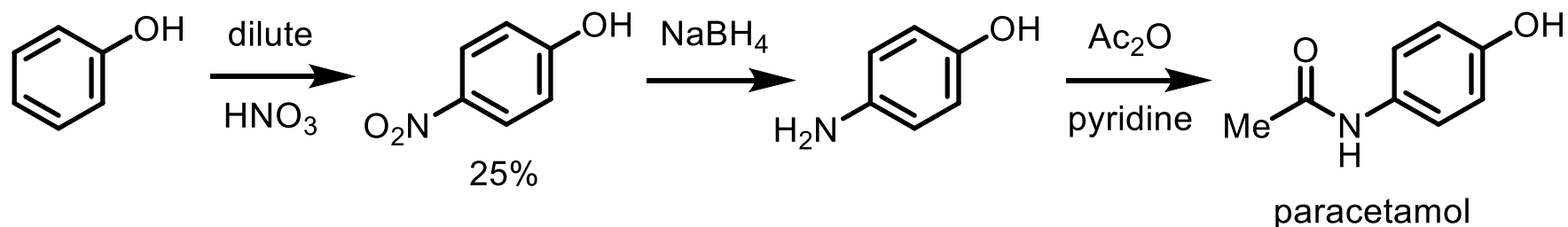
Substituent effects in action

The synthesis of paracetamol



- highly activating (+M)
- *ortho/para* directing

Very mild nitration conditions required for synthesis of paracetamol

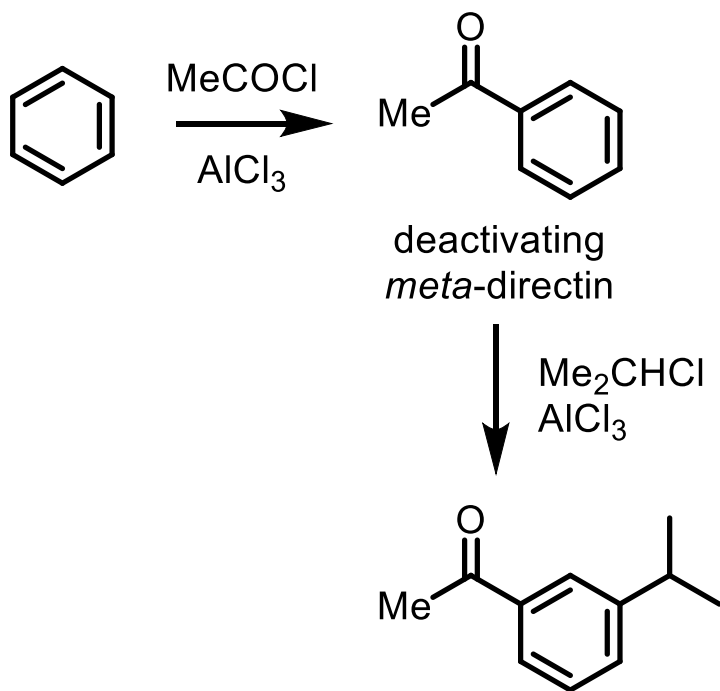
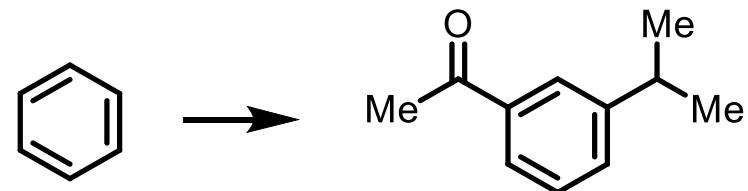




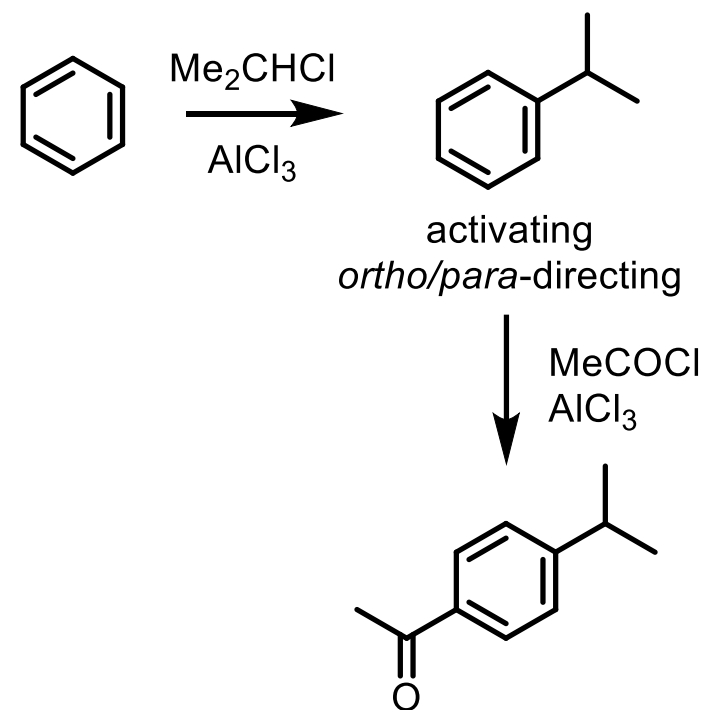
Substituent effects in action

The synthesis of ibuprofen

Which order do these substituents need to be added in?



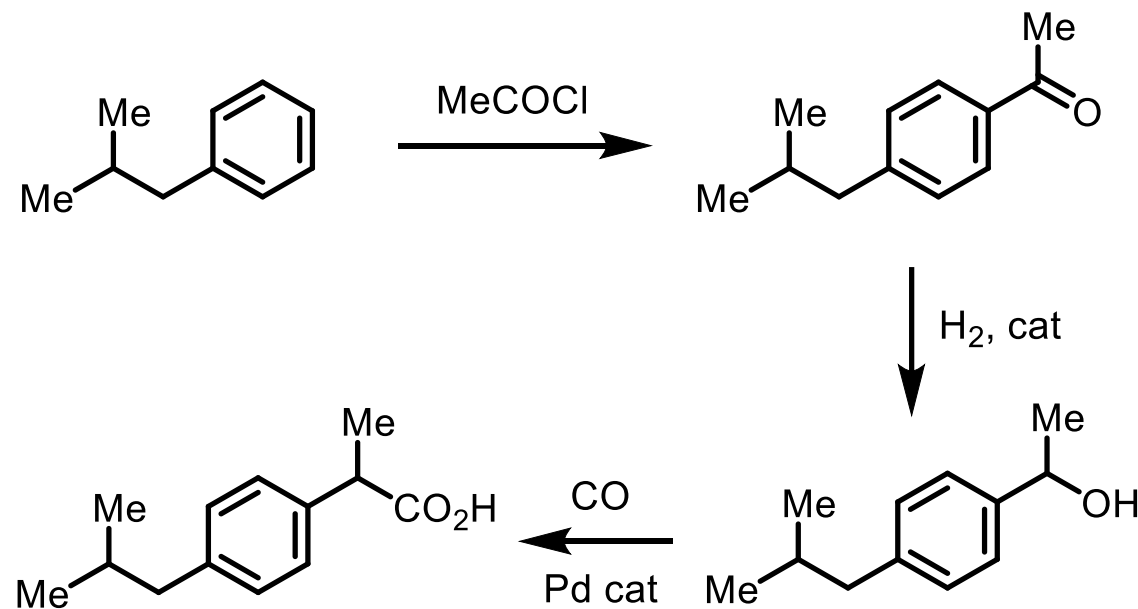
or





Substituent effects in action

The synthesis of ibuprofen

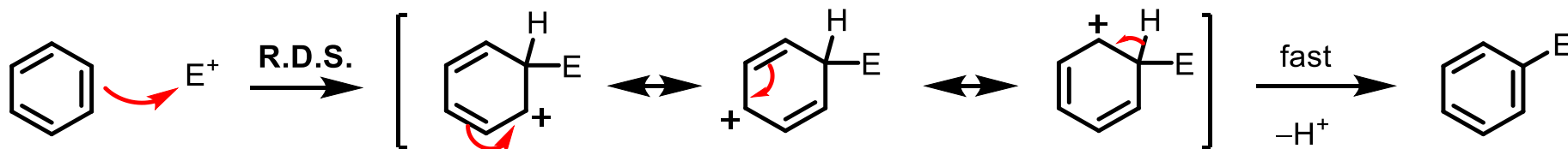




Summary

In this lecture, you have learned how to:

- draw the mechanism of electrophilic aromatic substitution reactions with various electrophiles (halogenation, nitration, sulfonation, Friedel-Craft alkylation and acylation).



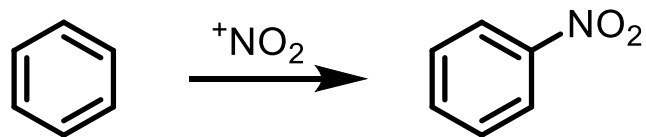
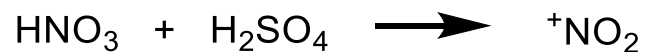
- predict the effects of pre-existing substituents on the rate and selectivity of electrophilic aromatic substitution reactions (the order of steps matters!)

Substituent	Rate cf. benzene	Selectivity
EDG	fast	<i>ortho/para</i>
Halogens	slow	<i>ortho/para</i>
EWG	slow	<i>meta</i>

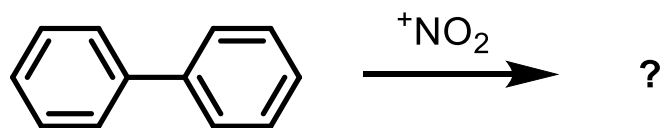


Topic 4 practice questions

1. Write a detailed mechanism for the following reaction:



2. Deduce the structure of the product formed in the following nitration reaction based on the product's ^1H NMR spectrum.

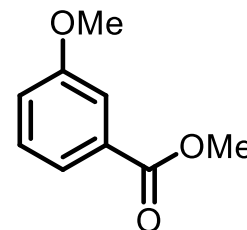
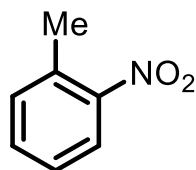
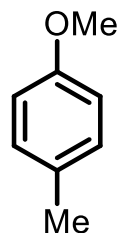


δ_{H}
7.77 (4H, d, $J = 10$ Hz)
8.26 (4H, d, $J = 10$ Hz)

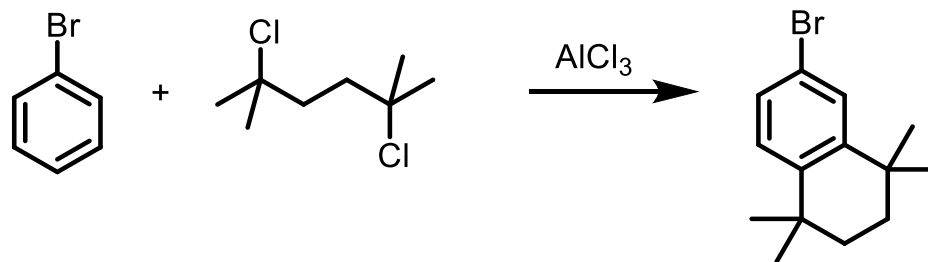


Topic 4 practice questions

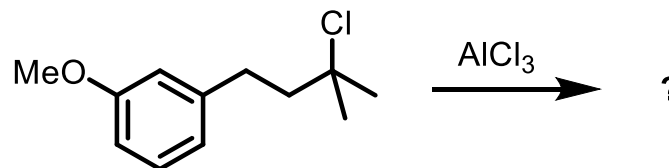
3. Predict where electrophilic aromatic substitution will occur on each of the following molecules.



4. Draw a mechanism for the following reaction and explain the position of the substitution:



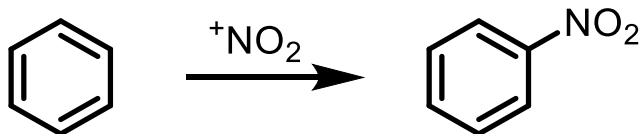
5. What are the two possible isomeric products from this reaction? Which isomer would you expect to be major product? Why?





Topic 4 practice questions – solutions

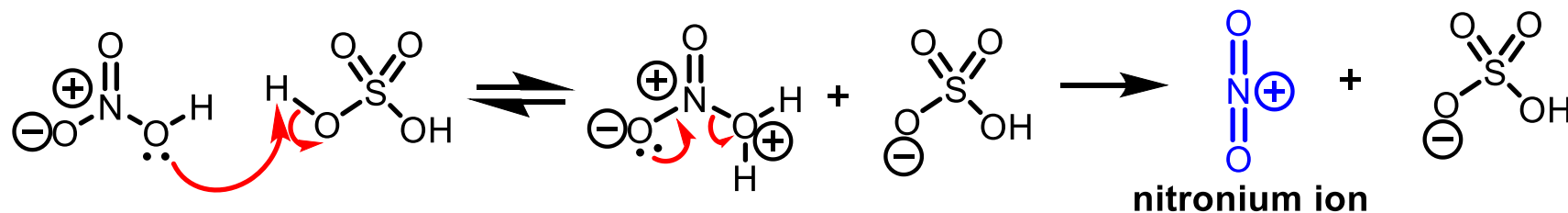
1. Write a detailed mechanism for the following reaction:



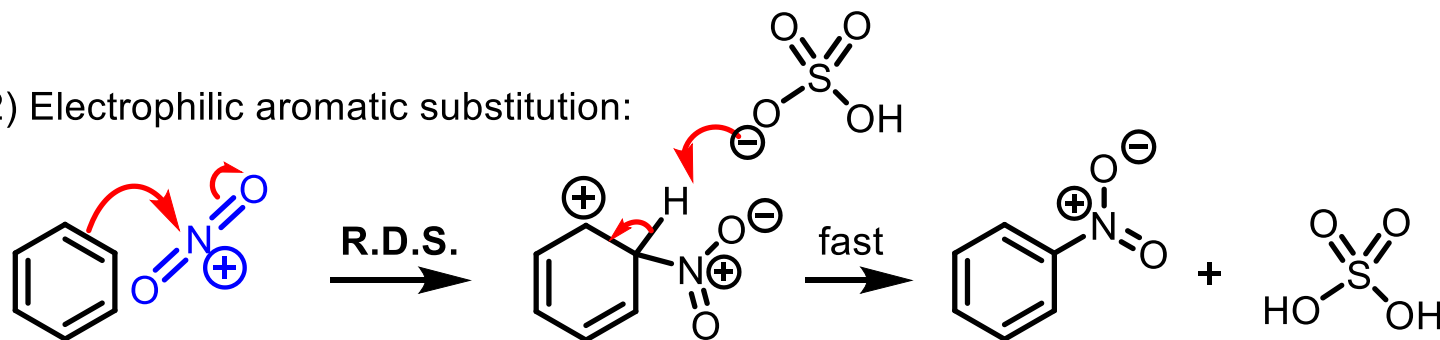
Tip:

Always draw the **full** structure of all functional groups (no abbreviations such as $-\text{NO}_2$)

1) Generation of the electrophile



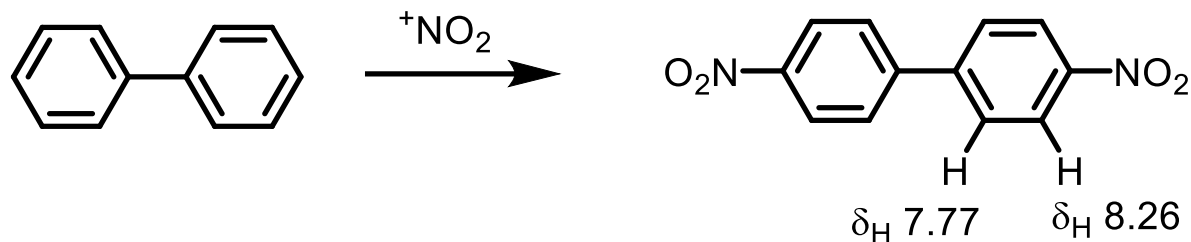
2) Electrophilic aromatic substitution:





Topic 4 practice questions – solutions

2. Deduce the structure of the product formed in the following nitration reaction based on the product's ^1H NMR spectrum.



δ_{H}
7.77 (4H, d, $J = 10$ Hz)
8.26 (4H, d, $J = 10$ Hz)

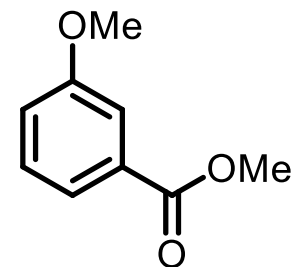
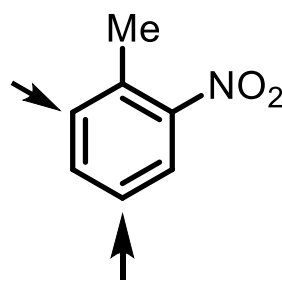
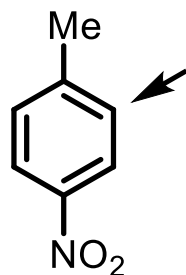
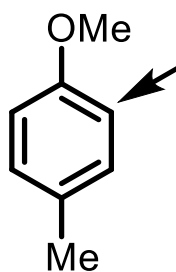
Information from ^1H NMR:

- Only two hydrogen environments: The product is a symmetrical molecule.
- 8 Hydrogens in total (integration data: 2x 4H): 2 nitro groups must have added to the molecule (double nitration).
- Coupling constants: Vicinal (*ortho*) coupling constants in benzene rings are typically 8–10 Hz, *meta* coupling constants are typically < 2 Hz: This data ($J=10$ Hz) suggest that the two proton environments are next to each other (*ortho*).
- Chemical shifts: One of the protons is shifted downfield due to the deshielding NO_2 group.



Topic 4 practice questions – solutions

3. Predict where electrophilic aromatic substitution will occur on each of the following molecules.



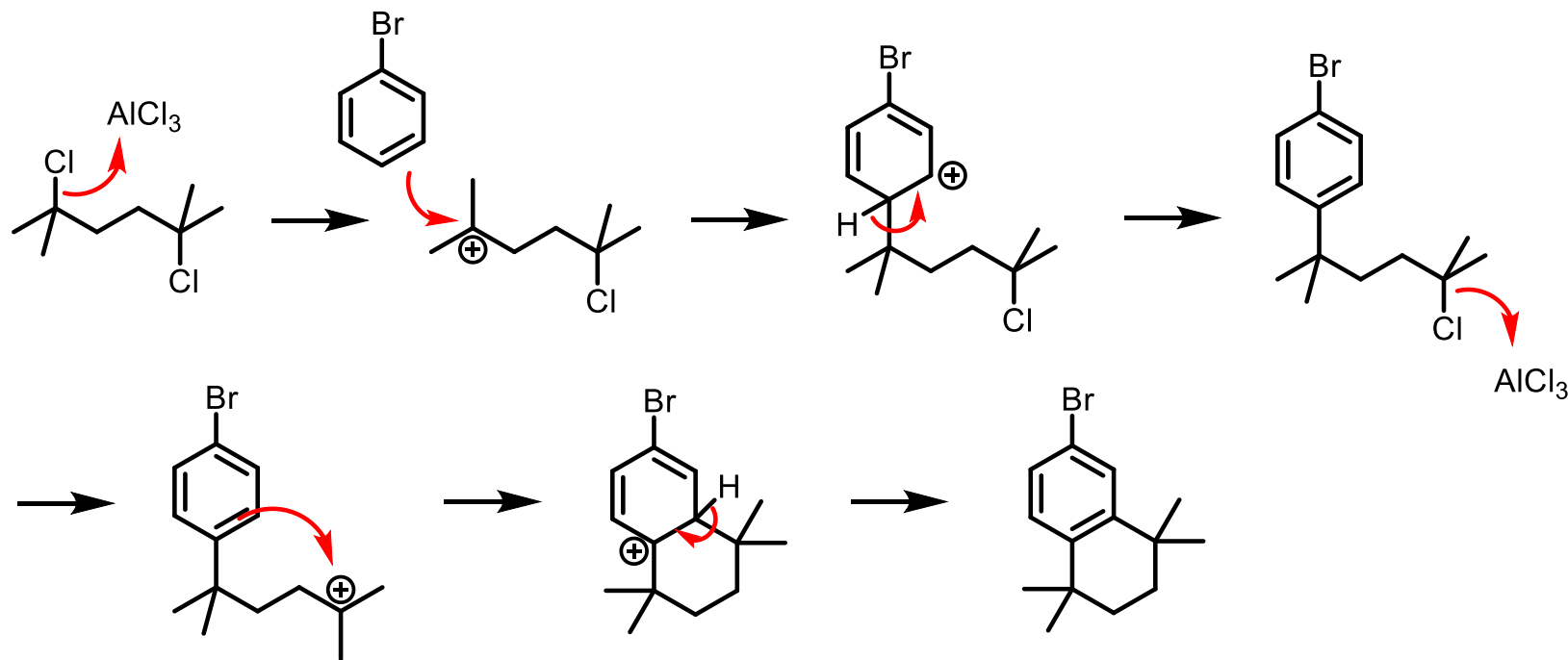
not selective
("horrible mixture")

- **Electron-donating groups:** activating, *ortho* / *para* directing
- **Electron-withdrawing groups:** deactivating, *meta* directing
- **Halogens:** deactivating, *ortho* / *para* directing
- Mesomeric effects are stronger, i.e. they “win out” over inductive effects.
- The effect of multiple groups is additive.



Topic 4 practice questions – solutions

4. Draw a mechanism for the following reaction and explain the position of the substitution:

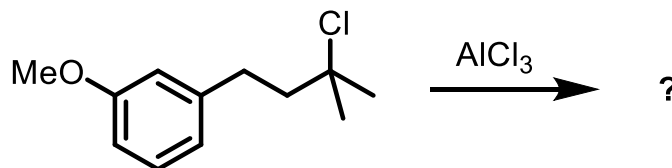


Bromine is *ortho/para* directing. The first Friedel-Craft substitution occurs at the sterically less hindered *para* position. The second is a cyclisation; the new ring cannot stretch any further than the next atom.

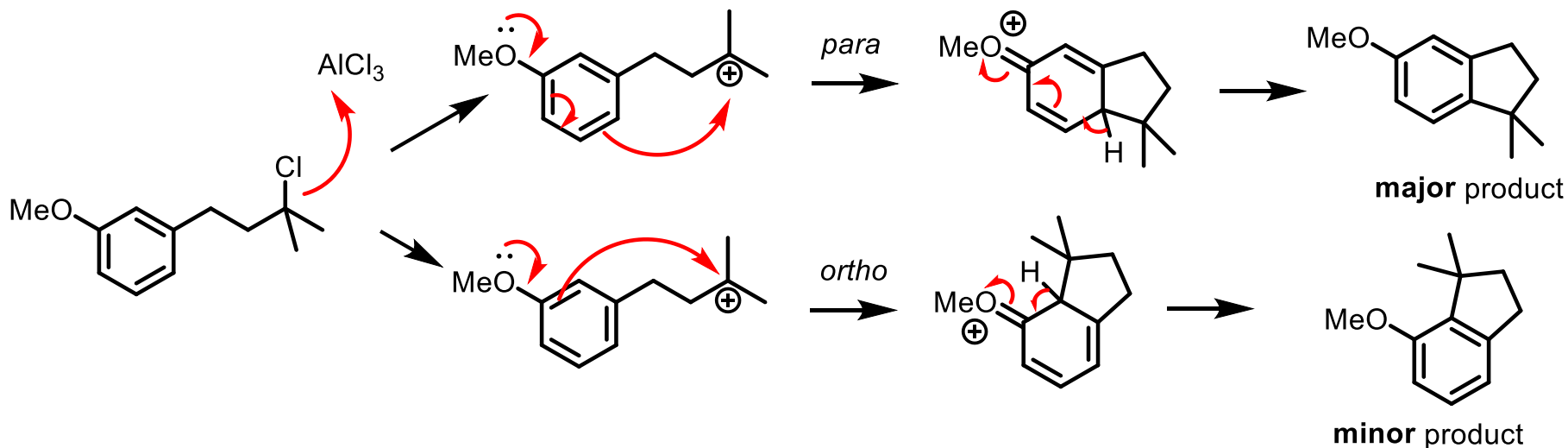


Topic 4 practice questions – solutions

5. What are the two possible isomeric products from this reaction? Which isomer would you expect to be major product? Why?

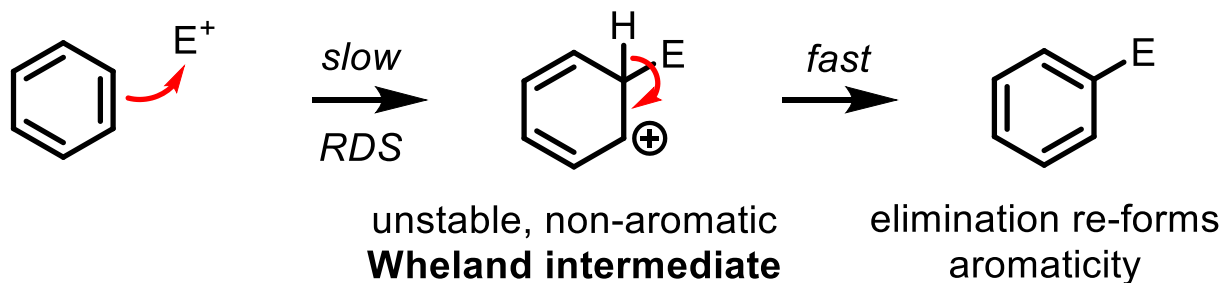


Methoxy groups are activating and *ortho/para* directing. Friedel-Craft cyclisation occurs preferentially *para* to the methoxy group due to steric hindrance.





Recap Topic 4: Electrophilic Aromatic Substitution



Electron-donating substituents: activating, *ortho/para* directing
Electron-withdrawing substituents: deactivating, *meta* directing
Halogens: deactivating, *ortho/para* directing



Topic 5: Reactivity of Heteroaromatic Compounds I

Topic 5: Electrophilic aromatic substitution of heteroaromatics

5.1 Electrophilic aromatic substitution reactions of 6-membered heteroaromatics

5.2 Electrophilic aromatic substitution reactions of 5-membered heteroaromatics

Learning outcomes

In this lecture, you will learn to:

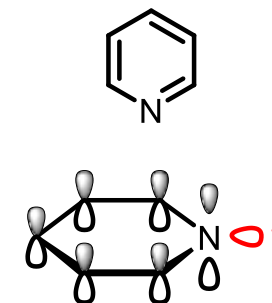
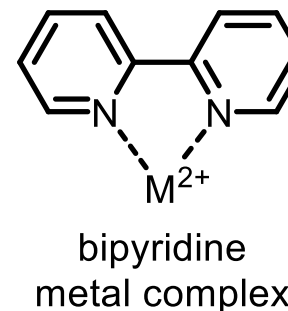
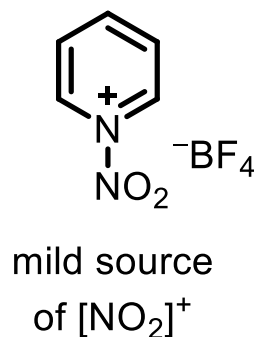
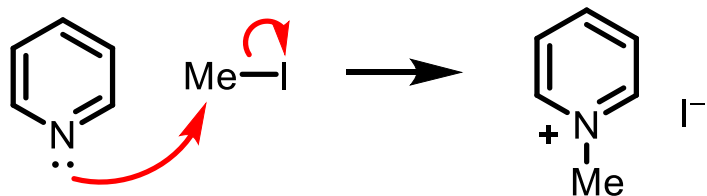
- describe the reaction of 6- and 5-membered heteroaromatics with electrophiles.



Electrophilic aromatic substitution of 6-membered heteroaromatics

Pyridine

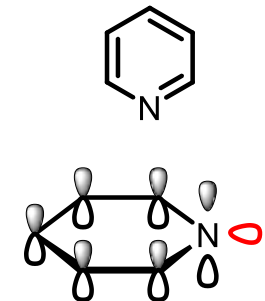
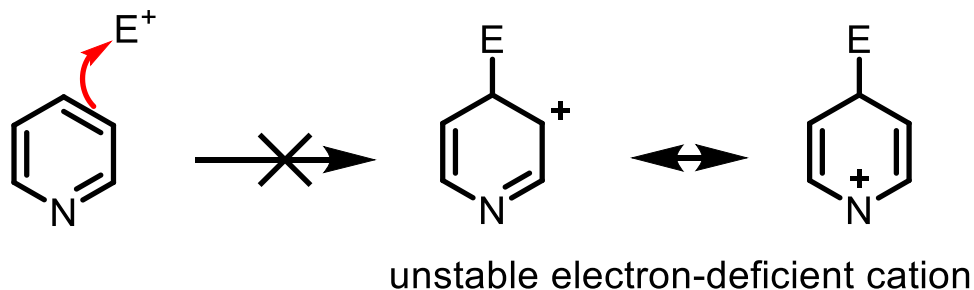
- Recap: Pyridine is **nucleophilic on nitrogen**: it reacts with a variety of electrophiles, Lewis acids and metals



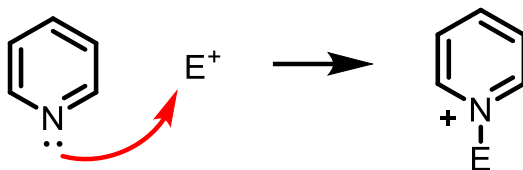


Electrophilic aromatic substitution of Pyridines

- Pyridine generally **does not readily undergo electrophilic aromatic substitution**



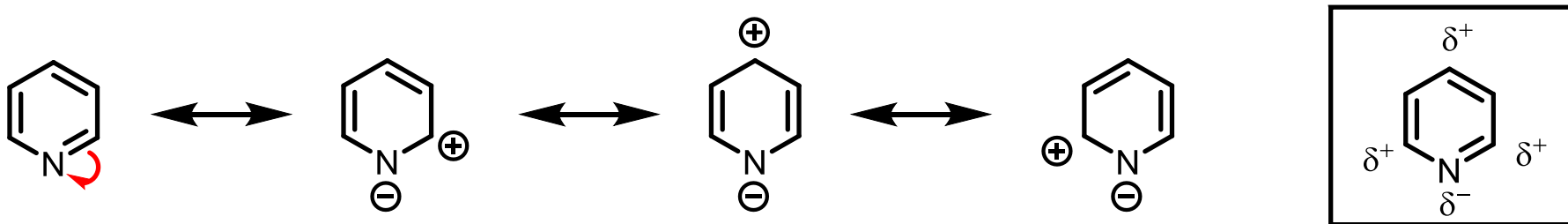
- **Thermodynamics:** the nitrogen in the ring lowers the HOMO compared to benzene, making the ring electron-deficient and less nucleophilic
- Pyridine is similar to a *deactivated* benzene (e.g. nitrobenzene) in its reaction with electrophiles.
- **Kinetics:** kinetic product is attack at N (forms a cationic intermediate that is inert to further electrophilic attack)





Electrophilic aromatic substitution of Pyridines

- The electronegative N atom effectively withdraws electron density away from the carbons: **low reactivity towards electrophiles**.

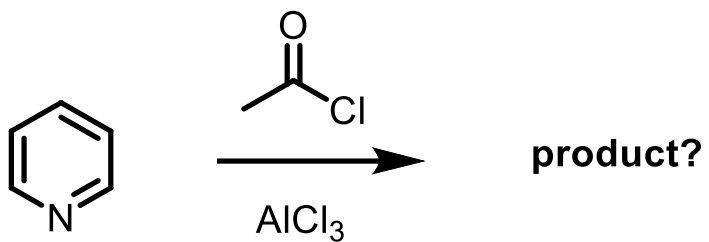


- When electrophilic aromatic substitution does occur, the **3-position** is the **favoured site of electrophilic attack**, but yields are often poor:
 - Friedel-Crafts reactions usually fail;
 - nitration with fuming sulfuric acid and KNO_3 at $300\text{ }^\circ\text{C}$ gives only 5% yield of 3-nitropyridine;
 - chlorine plus AlCl_3 only gives moderate yield of 3-chloropyridine, although bromine in fuming sulfuric acid at $130\text{ }^\circ\text{C}$ gives a reasonable yield of 3-bromopyridine.



Question

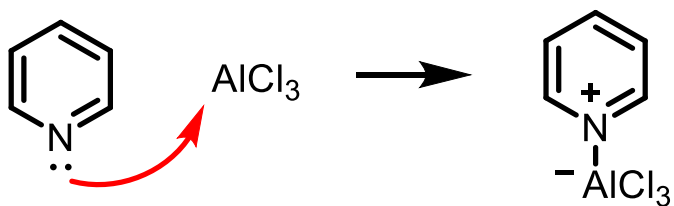
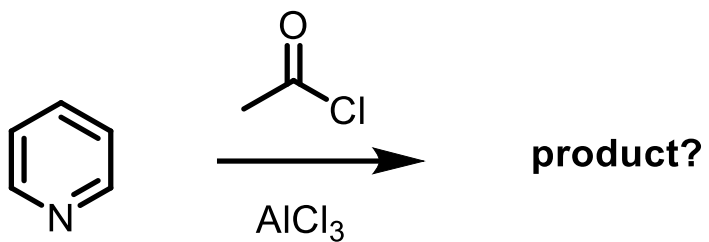
Draw the product of the following Friedel-Crafts reaction:





Question

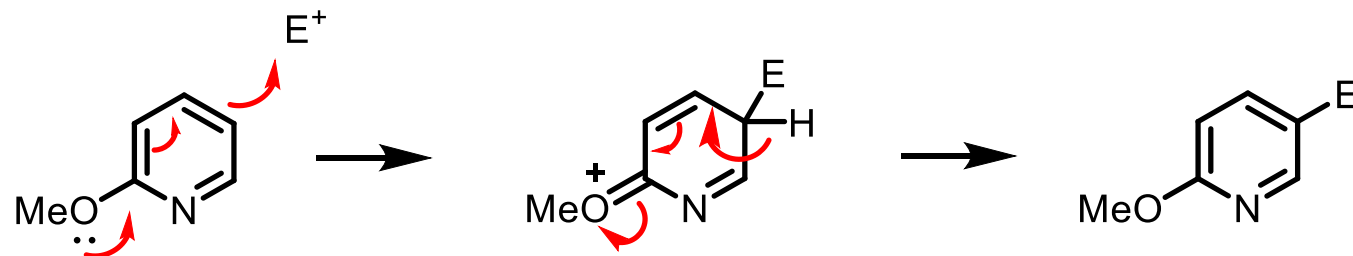
Draw the product of the following Friedel-Crafts reaction:





Electrophilic aromatic substitution of Pyridines

- Useful electrophilic substitution occurs on **activated** pyridines
e.g. **electron-donating groups:**

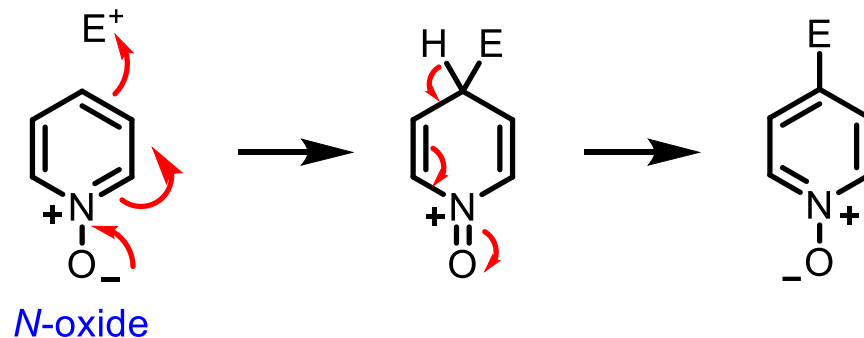




Electrophilic aromatic substitution of Pyridines

- Useful electrophilic substitution occurs on **activated** pyridines

e.g. **N-oxides**:

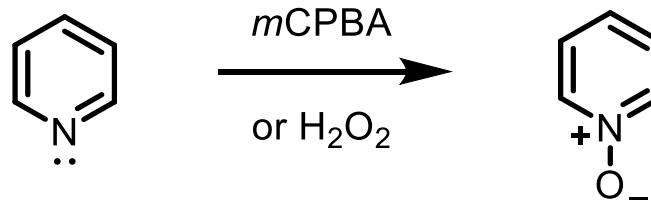


- stable dipolar species
- Oxygen acts as a **protecting group** (blocks reaction on nitrogen) and **activating group** (O electrons are delocalised around the ring: raises HOMO, increases nucleophilicity)
- nucleophilic on *para*- and *ortho*-position

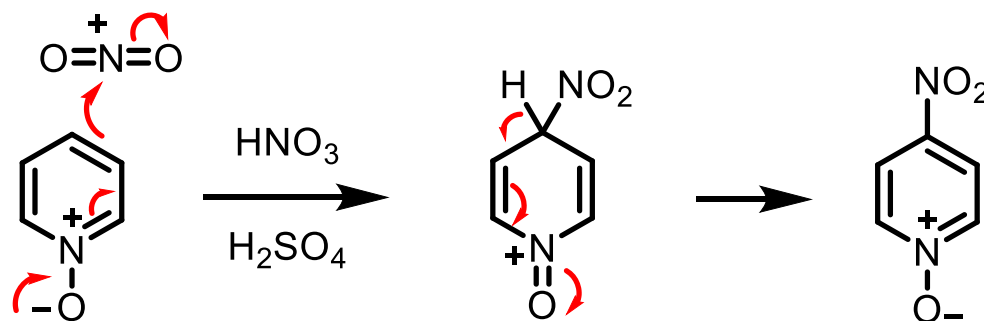


Electrophilic aromatic substitution of pyridine N-oxides

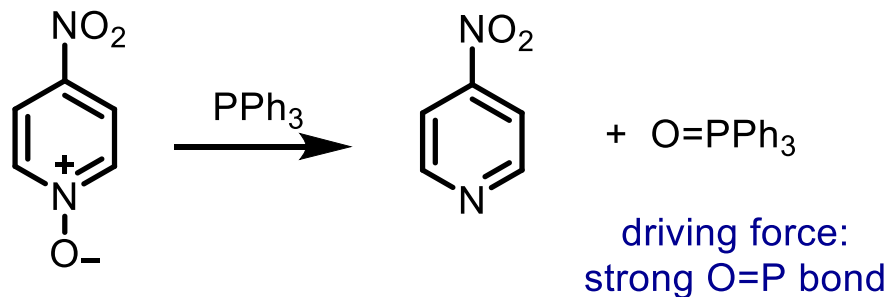
Protection: oxidation of nitrogen



Electrophilic aromatic substitution



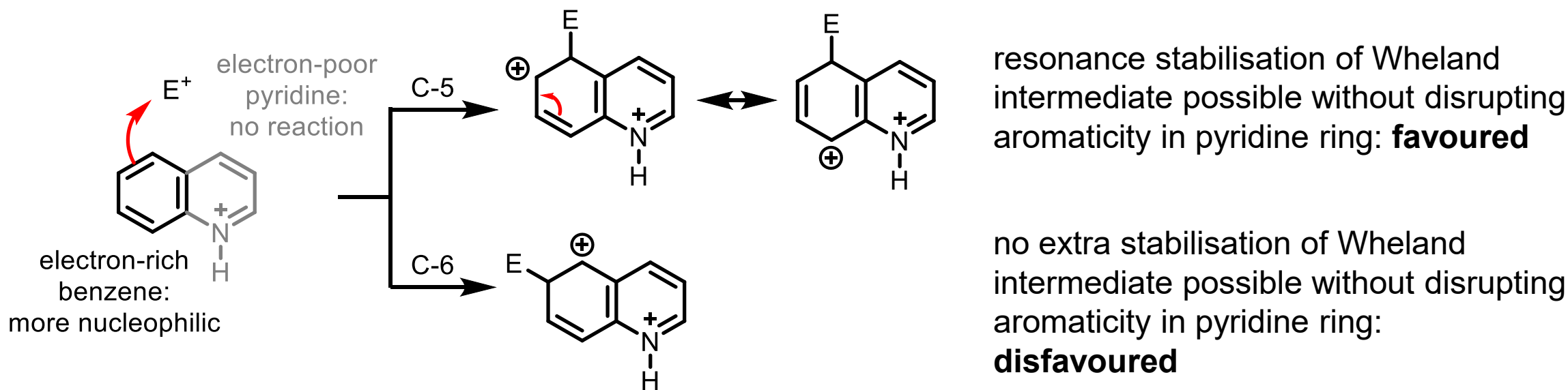
Deprotection: reduction with PPh_3 , PCl_3 , or P(OMe)_3





Electrophilic aromatic substitution of fused 6-membered heteroaromatics

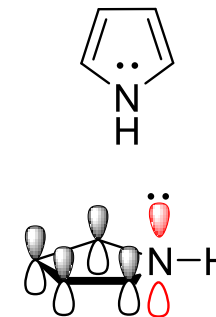
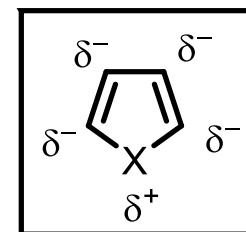
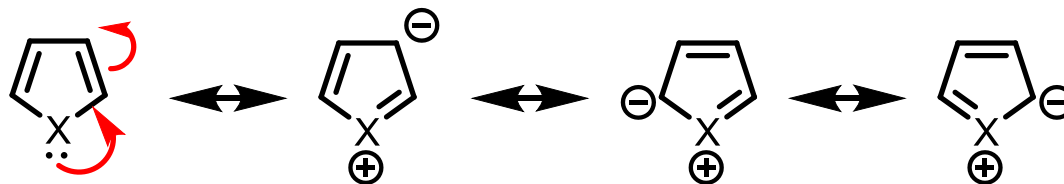
- Quinoline and isoquinoline undergo electrophilic aromatic substitution on the more electron-rich benzene ring – mainly at positions 5 and 8.



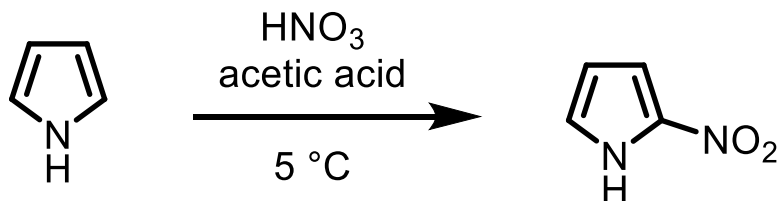


Electrophilic aromatic substitution of 5-membered heteroaromatics

- Recap: Pyrrole, furan and thiophene are **electron-rich** compared to benzene: they **readily undergo electrophilic aromatic substitution**



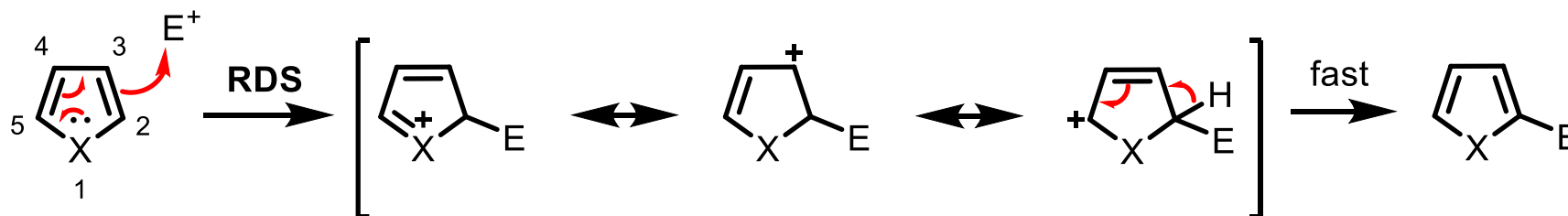
- Question:** Draw a curly arrow reaction mechanism for the nitration of pyrrole:



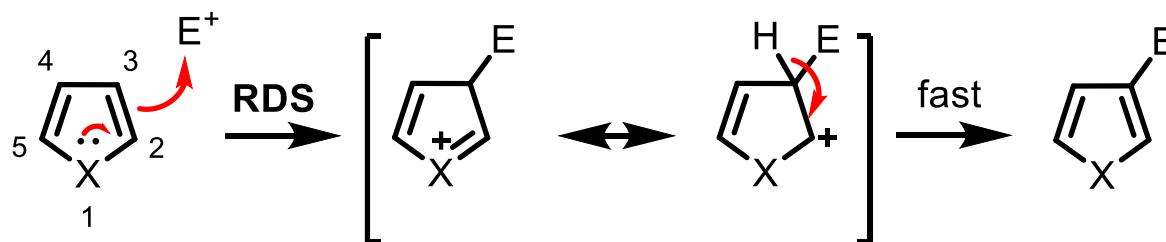


Electrophilic aromatic substitution of 5-membered heteroaromatics

- **2-Substitution** is generally preferred
- Consider stabilisation of carbocation:
 - Attack on 2-position: **3 resonance forms**: more stable



- Attack on 3-position: **only 2 resonance forms**: less stable

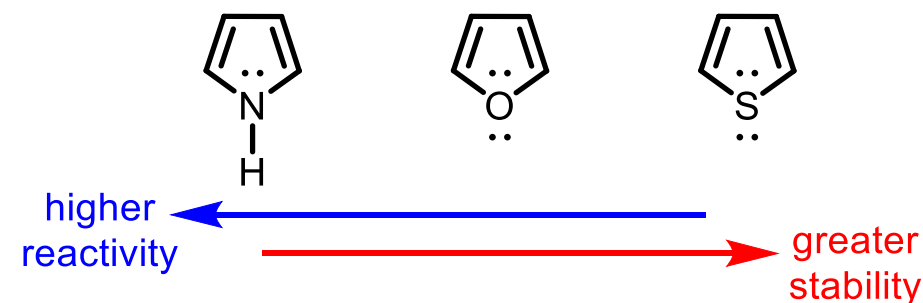




Electrophilic aromatic substitution of 5-membered heteroaromatics

- Relative rates of electrophilic substitution:
- Differences in reactivity mainly due to donation of lone pair electrons into the aromatic π -system (more efficient donation = more nucleophilicity)

pyrrole > furan > thiophene

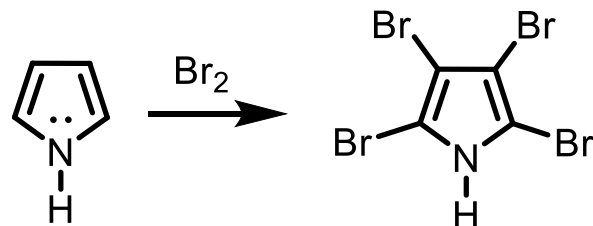


- Thiophene: least reactive (poor orbital overlap between S 3p and C 2p orbitals)
- Pyrrole: most reactive (nitrogen is the most powerful electron donor)

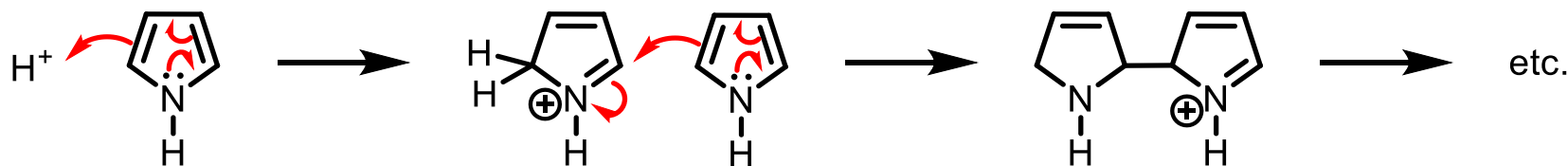


Electrophilic aromatic substitution of 5-membered heteroaromatics

- In fact, pyrrole is so reactive, that it can be difficult to selectively functionalise :



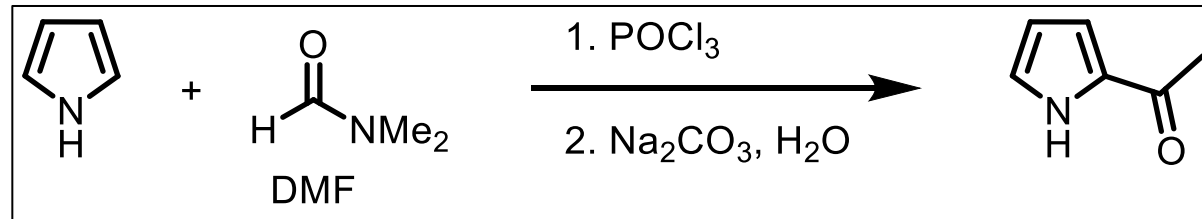
- It even self-polymerises in the presence of strong acids (which are often required in electrophilic aromatic substitution reactions):





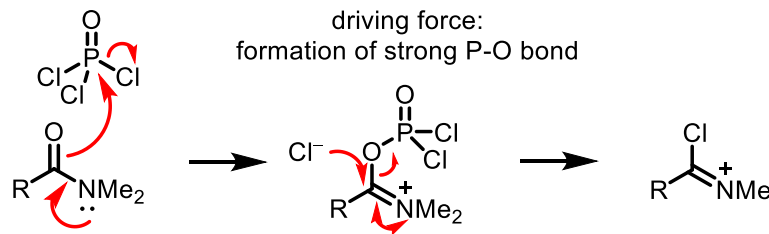
Vilsmeier-Haak reaction

- (Lewis) acid-free alternative to the Friedel-Crafts reaction
- Can be used to **selectively mono-formylate** electron-rich aromatics

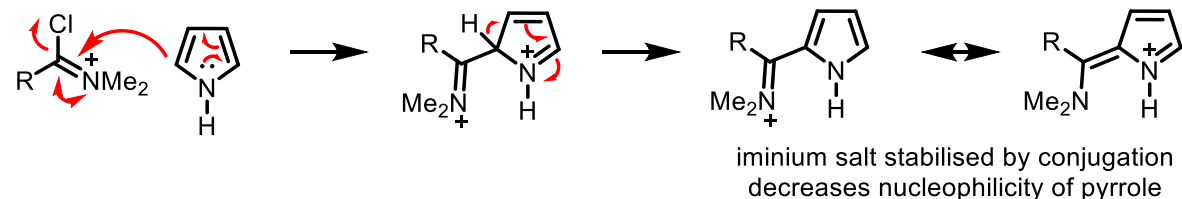


- **Mechanism**

Step 1a: formation of the carbon electrophile:



Step 1b: electrophilic aromatic substitution

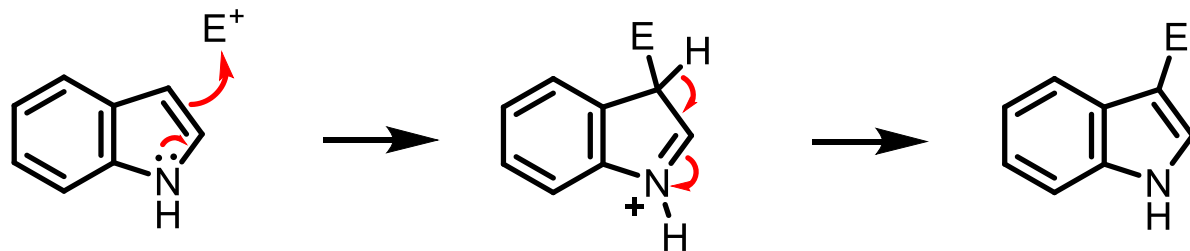


Step 2: hydrolysis of the imine: See last year's lecture notes.

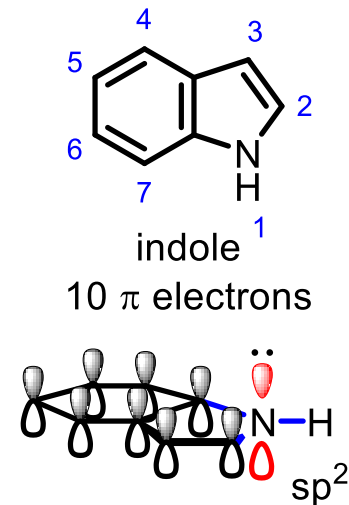
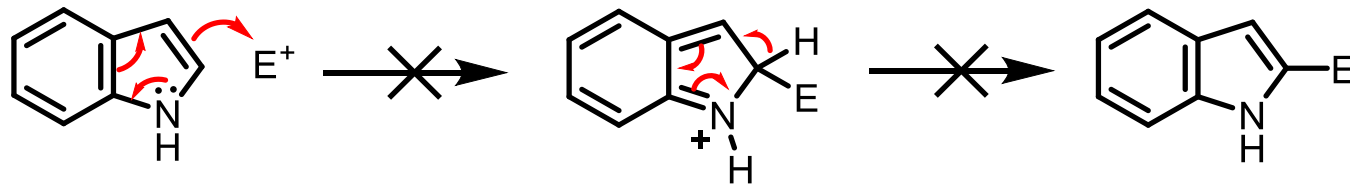


Electrophilic aromatic substitution of indoles

- Reactive pyrrole ring, relatively **unreactive benzene** ring
- Electrophilic aromatic substitution occurs on the pyrrole ring, favouring the **3-position** (aromaticity of benzene ring is not disturbed):



not breaking the aromaticity of the benzene ring:





c1cc[nH]1 > c1ccoc1 > c1ccsc1 > c1ccccc1 > c1ccccn1

$\approx$

COc1ccccc1 [O-][N+](=O)c1ccccc1

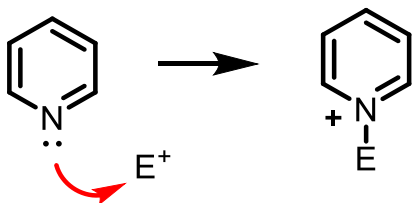


Summary

In this lecture, you learned how to describe the reaction of 6-membered heteroaromatics with electrophiles:

Pyridine

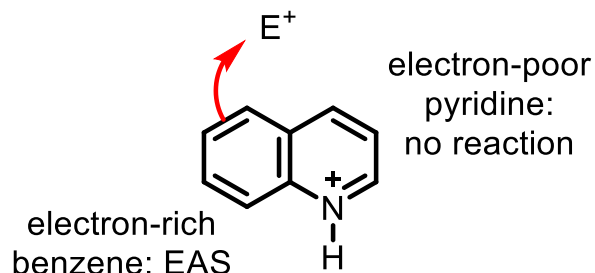
- Nucleophilic on N, no electrophilic aromatic substitution (EAS)



- activation (EDG or N-oxide) required for EAS

Quinoline

- EAS occurs on the more electron-rich benzene ring



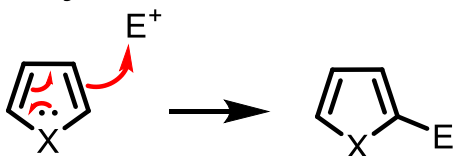


Summary

You also learned how to describe the reaction of 5-membered heteroaromatics with electrophiles:

5-membered heteroaromatics

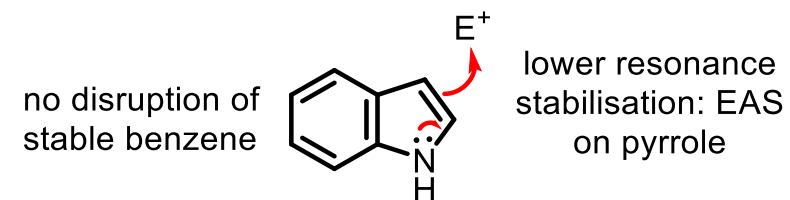
- very fast EAS



- pyrrole > furan > thiophene

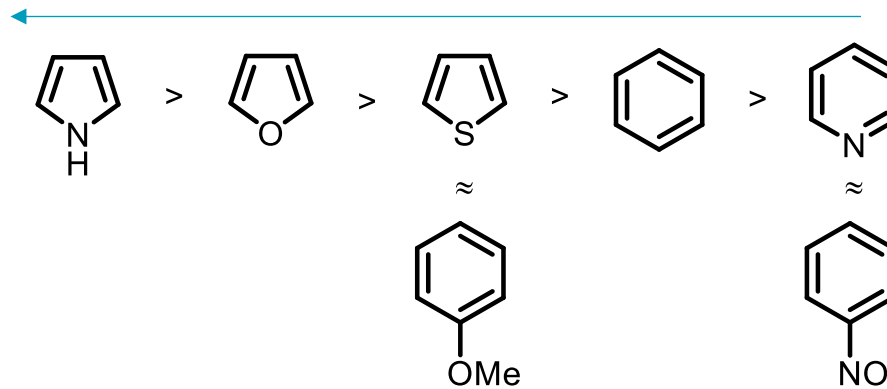
Indoles

- EAS on 'less aromatic' pyrrole ring



The reactivity of (hetero)aromatic molecules towards electrophiles covered in topics 4&5 is summarised below:

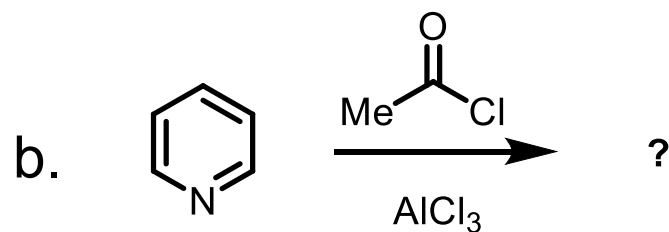
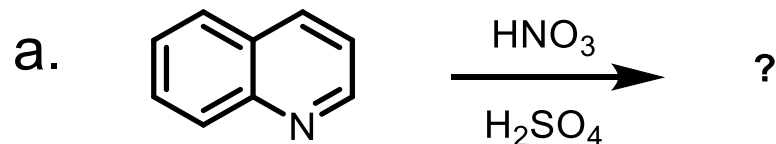
increasing reactivity
towards electrophiles





Topic 5 – Practice questions

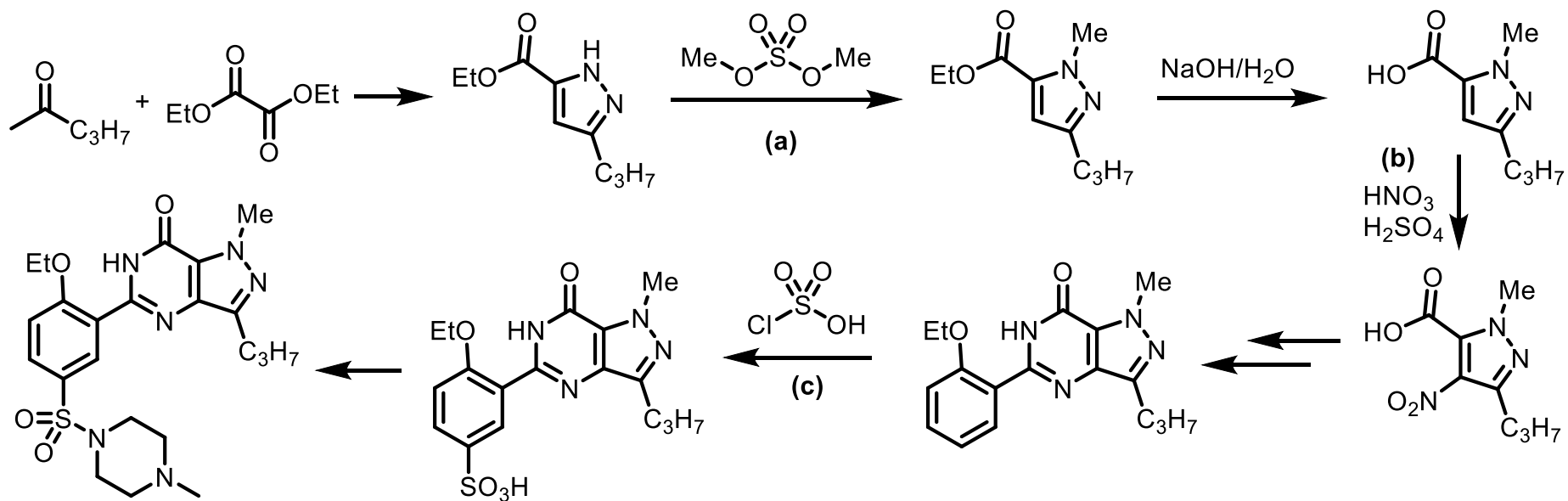
1. For both of the following reactions, draw a curly arrow reaction mechanism and explain the selectivity of the reaction (*i.e.* where does the electrophile attach?).





Topic 5 – Practice questions

2. You are already familiar with a lot of the chemistry in this synthesis of Sildenafil (Viagra) and we will cover more of it in the next lectures.



a) Provide a mechanism for the reaction with Me_2SO_4 .

b) Provide a mechanism for the nitration.

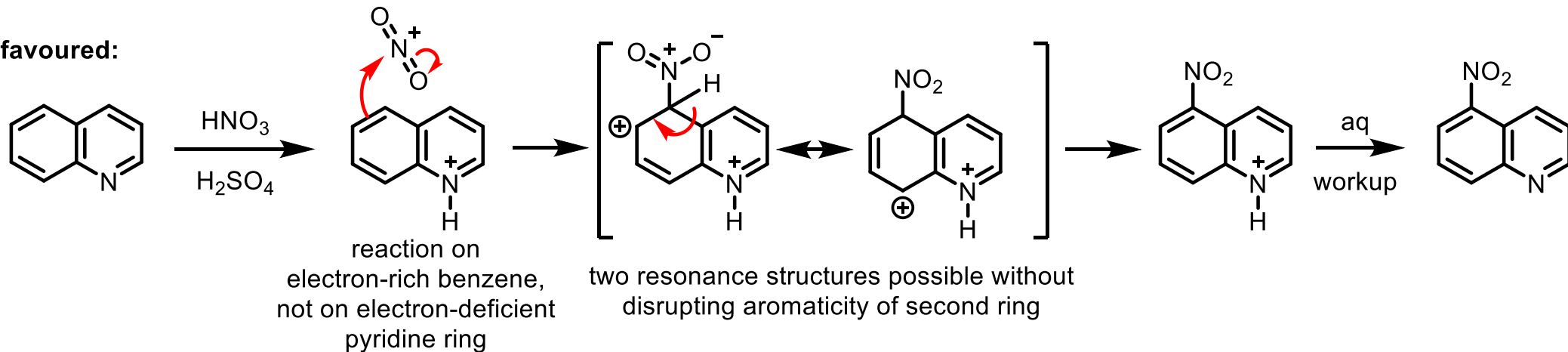
c) Provide a mechanism for the sulfonation and explain why this isomer of the product is formed.



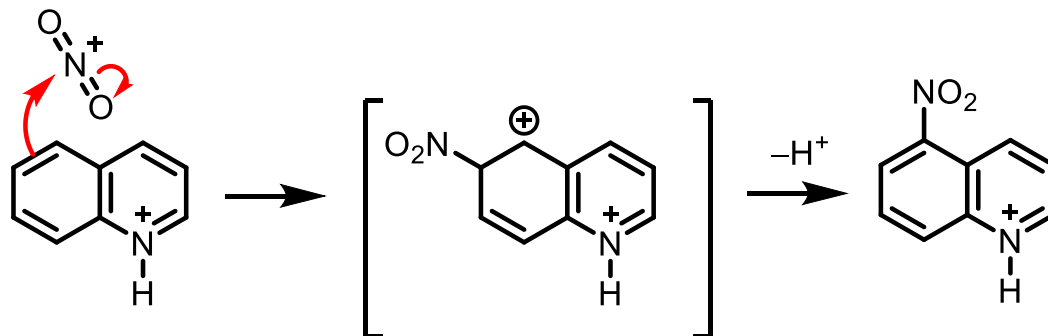
Topic 5 practice questions: Solutions

1a.

favoured:



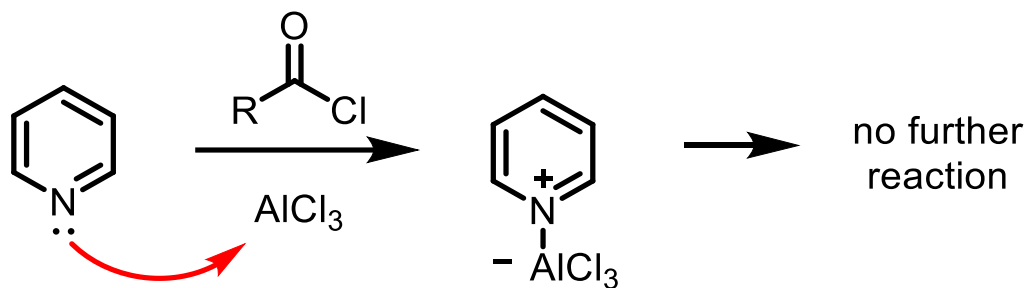
disfavoured:





Topic 5 practice questions: Solutions

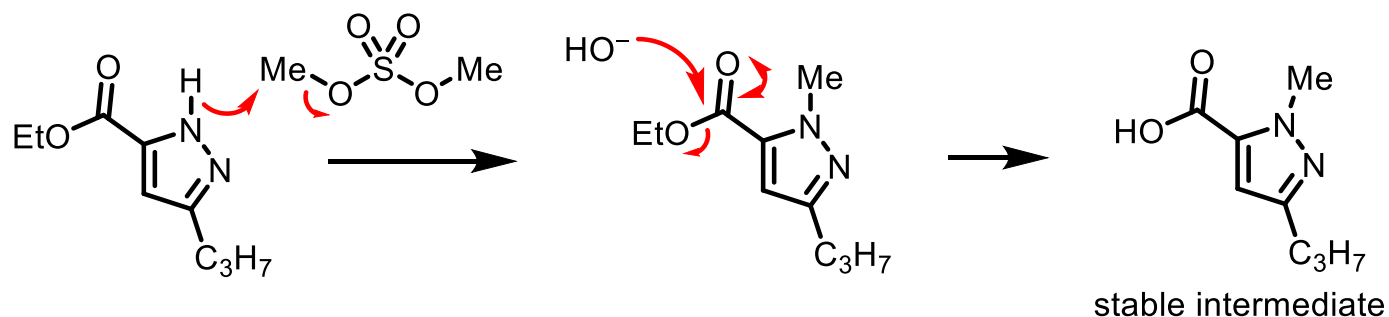
1b.



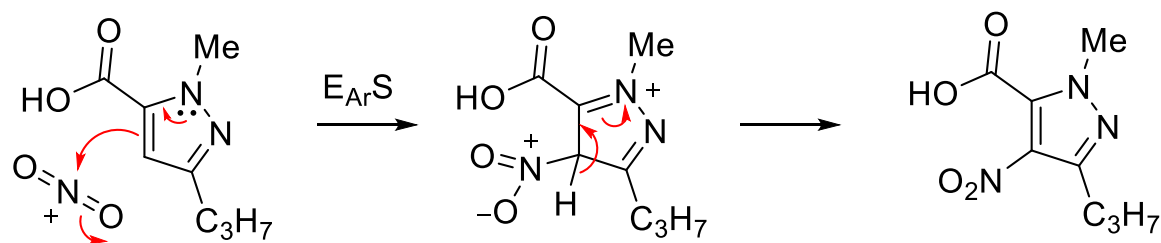


Topic 5 practice questions: Solutions

2a. Provide a reaction mechanism for the reaction with Me_2SO_4 .



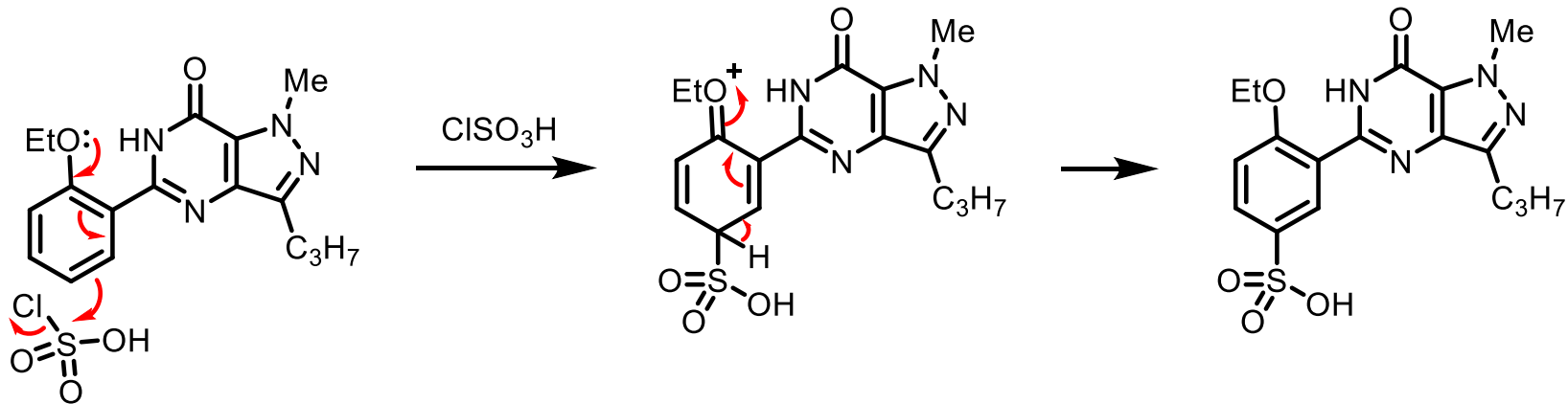
b. Provide a reaction mechanism for the nitration.





Topic 5 practice questions: Solutions

2c. Provide a reaction mechanism for the sulfonation and explain why this isomer of the product is formed.



OEt is mesomerically electron-donating: *ortho/para*-directing (*para* favoured for steric reasons).

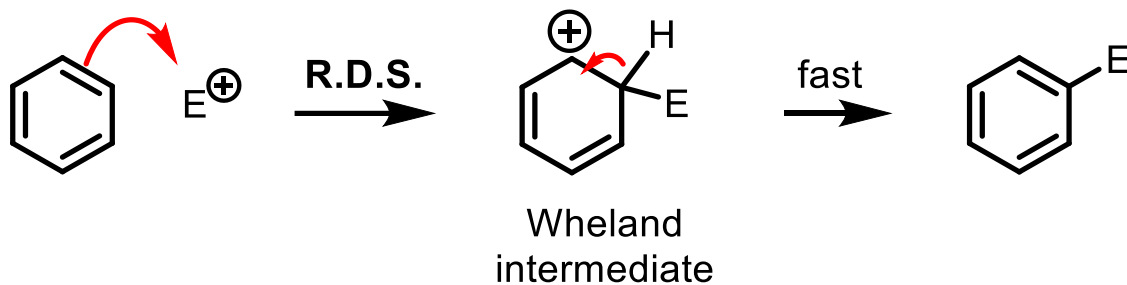
The heterocycle is mesomerically electron-withdrawing: *meta*-directing.

Both substituents on the benzene ring direct sulfonylation to the position shown above, resulting in the selective formation of one product isomer.



Topic 6: Reactivity of Aromatic Compounds II

Recap topic 4: Electrophilic Aromatic Substitution





Topic 6: Reactivity of Aromatic Compounds II

Topic 6: Nucleophilic Aromatic Substitution

6.1 Nucleophilic Aromatic Substitution by Addition–Elimination Mechanism

6.2 Nucleophilic Aromatic Substitution by S_N1 Mechanism

6.3 Nucleophilic Aromatic Substitution by Aryne Mechanism

6.4 Nucleophilic Aromatic Substitution of Heteroaromatics

Learning outcomes

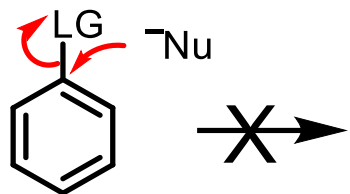
In this lecture, you will learn to

- describe the reaction of aromatic compounds with nucleophiles;
- describe the reactivity of 6- and 5-membered heteroaromatics with nucleophiles.

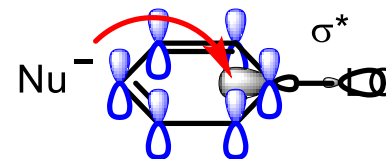


Nucleophilic Aromatic Substitution

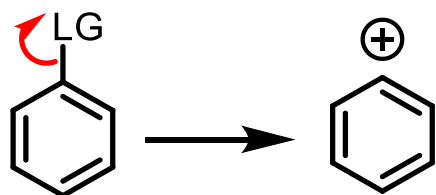
- While electrophilic aromatic substitution reactions are well known and dominate the chemistry of benzene, nucleophilic aromatic substitution is **much less common**.
- Mechanistically, it does not occur via familiar substitution processes:



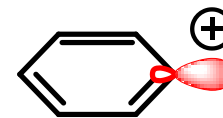
S_N2 *impossible*



addition to anti-bonding orbital not possible



S_N1 *very unfavourable*
although it is possible with
very good leaving groups

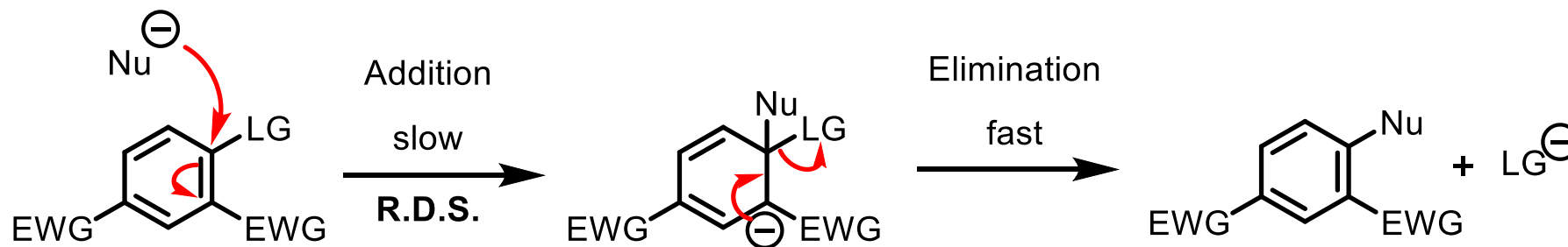


empty sp^2
orbital orthogonal
to π -system



Nucleophilic aromatic substitution by addition - elimination

- However, a **two-step addition elimination reaction** is possible for electron-poor aromatic compounds with $-M$ substituents (e.g. nitro groups).



LG = leaving group; EWG = mesomerically electron-withdrawing group
e.g. NO₂, CN, COR, CO₂R

- Rate-determining step is nucleophilic addition** to form an anionic intermediate known as a **Meisenheimer complex**

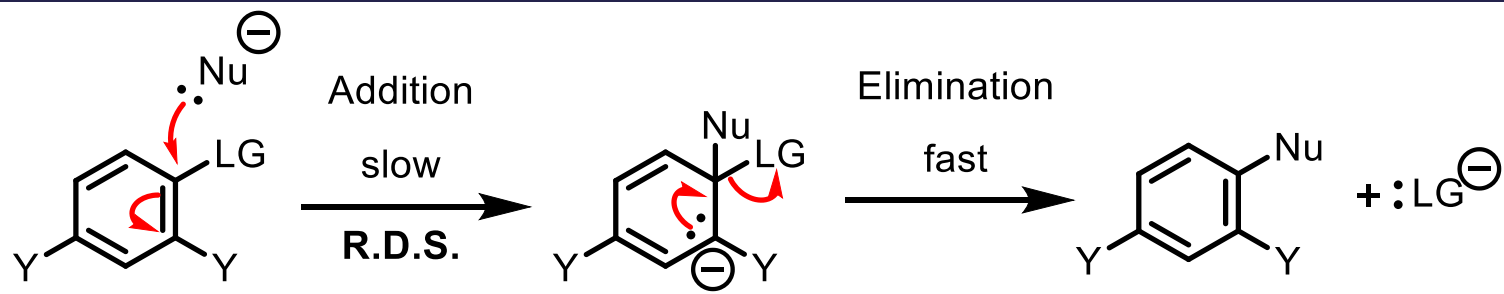


Nucleophilic aromatic substitution by addition - elimination

- Mechanistically, nucleophilic aromatic substitution is directly **akin to conjugate addition-elimination** reactions in aliphatic systems:



Leaving group ability



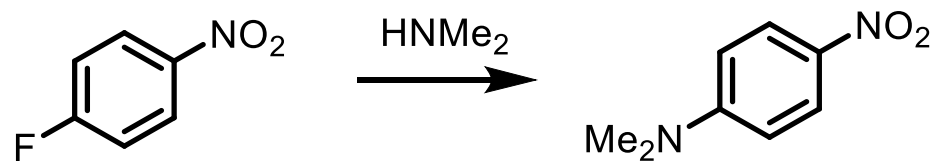
LG: $F \gg Cl > Br > I$

- Rate determining step is addition of the nucleophile.
- Although F slows down the 2nd step (relative to other halogens), its inductive effect and small size accelerates the first (rate determining) step. The C-halogen bond is not broken in the R.D.S.
- Summary: to do nucleophilic aromatic substitution you need:
 - An O, N, or CN nucleophile
 - A halide leaving group, ideally fluoride
 - A –M group (e.g. nitro, cyano) *ortho* or *para* (or both) to the leaving group



Question

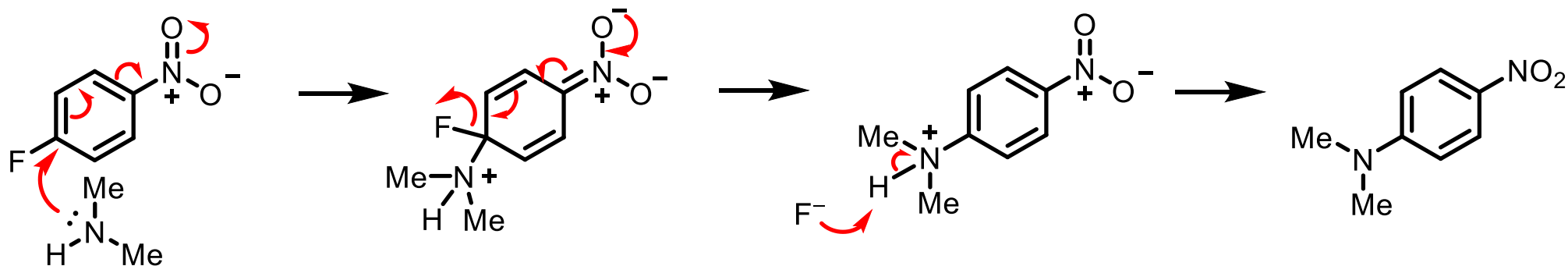
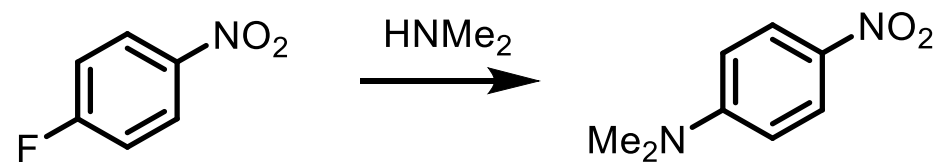
Draw a curly arrow reaction mechanism for the following reaction:





Question

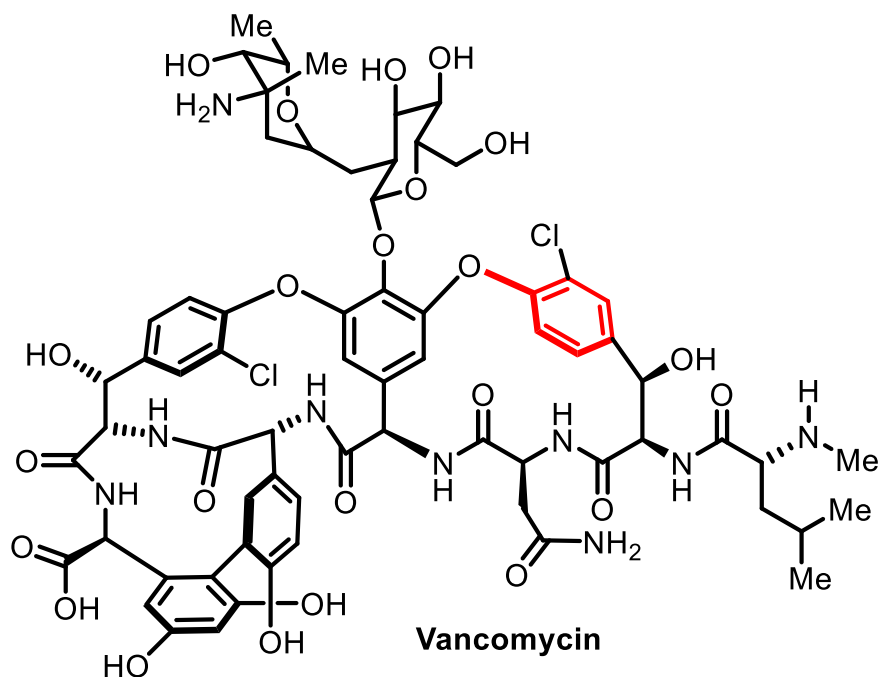
Draw a curly arrow reaction mechanism for the following reaction:



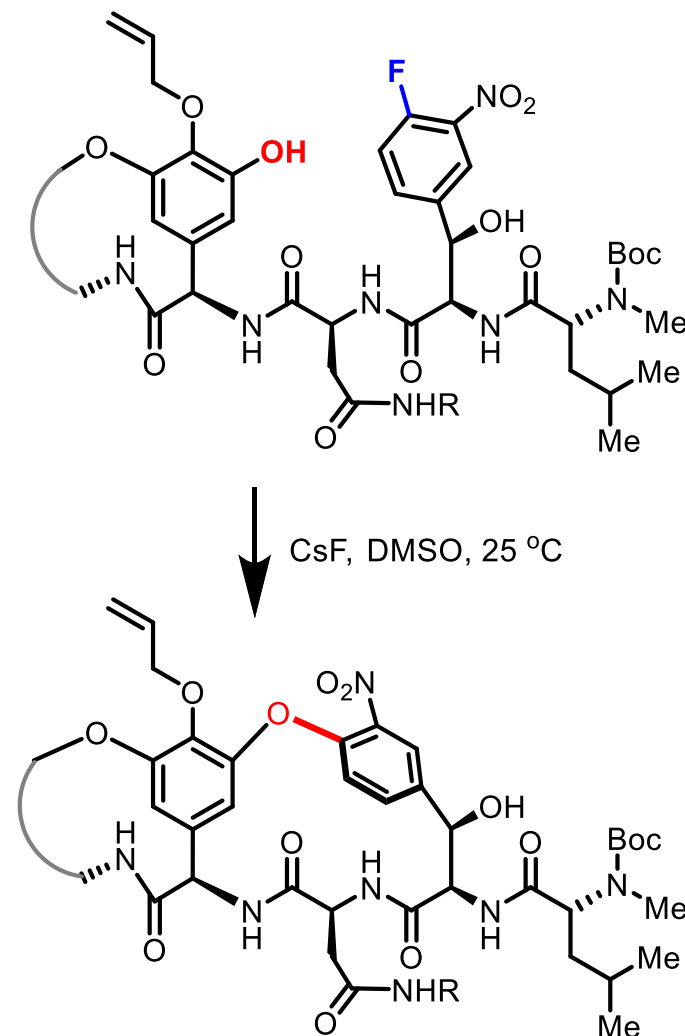


Nucleophilic aromatic substitution in action

Synthesis of **Vancomycin**: the antibiotic of last resort against Methicillin-resistant *Staphylococcus aureus* (MRSA) 'superbugs'



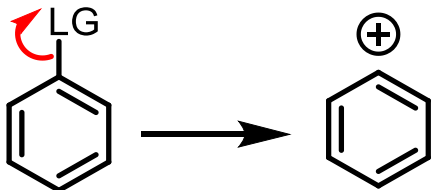
This slide is for general interest only. You do not need to remember the structure of Vancomycin for the exam.



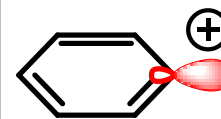


Nucleophilic aromatic substitution by S_N1

- Recap:

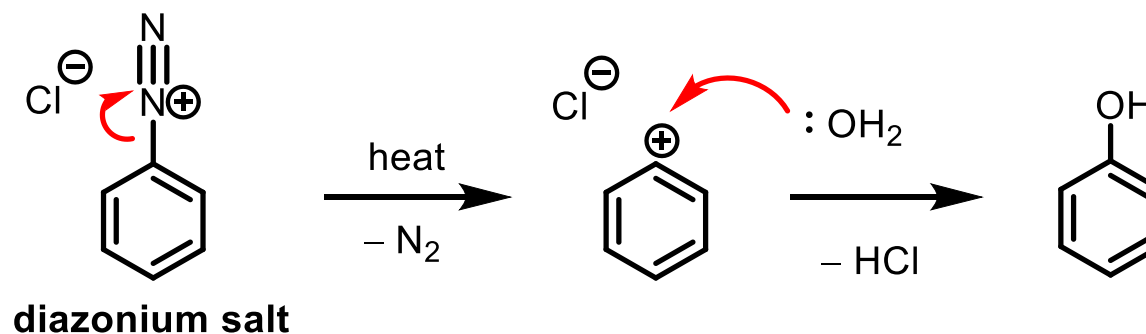


S_N1 **very unfavourable**
although it is possible with
very good leaving groups



empty sp^2
orbital orthogonal
to π -system

- Diazonium salts have an excellent leaving group:

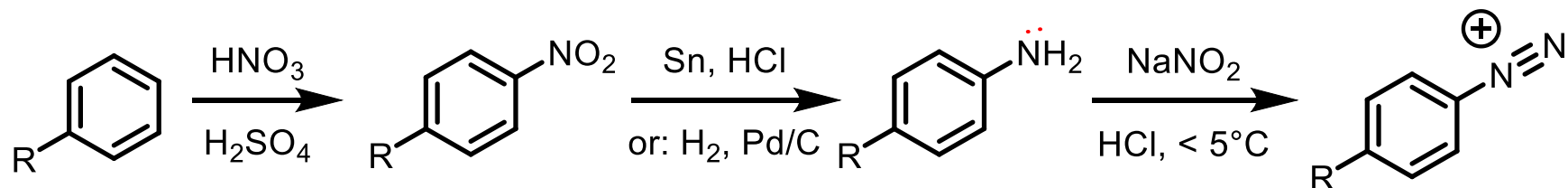


- N_2 (gas) is very stable due to the strong N–N triple bond; loss of N_2 is irreversible

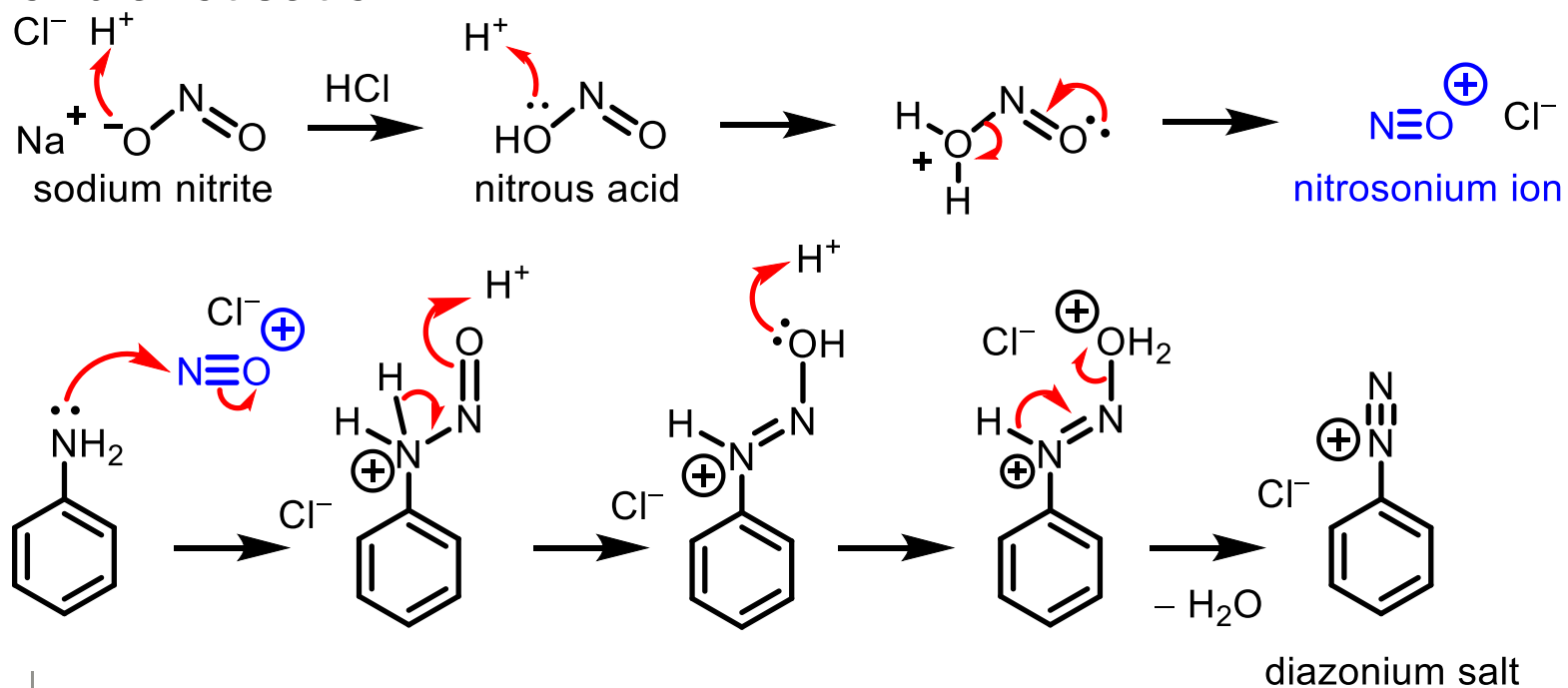


Diazonium salts

- Diazonium salts are readily available from anilines



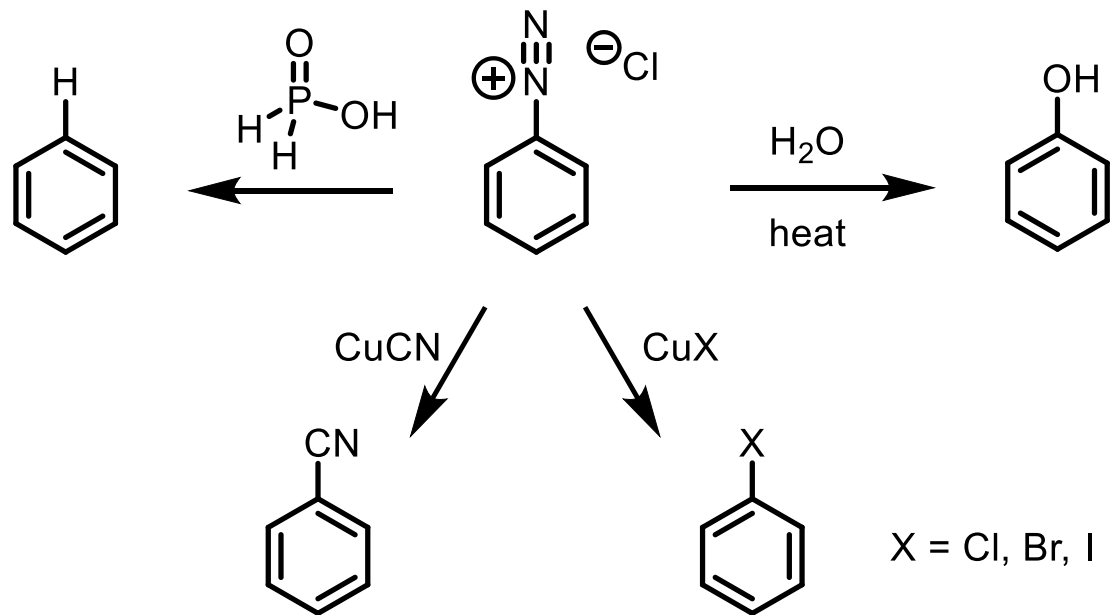
- Mechanism of diazotisation:





Diazonium salts

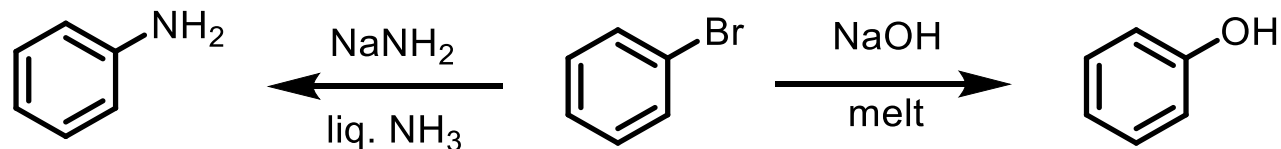
- Diazonium salts are very useful in synthesis as they can be converted into a wide range of products



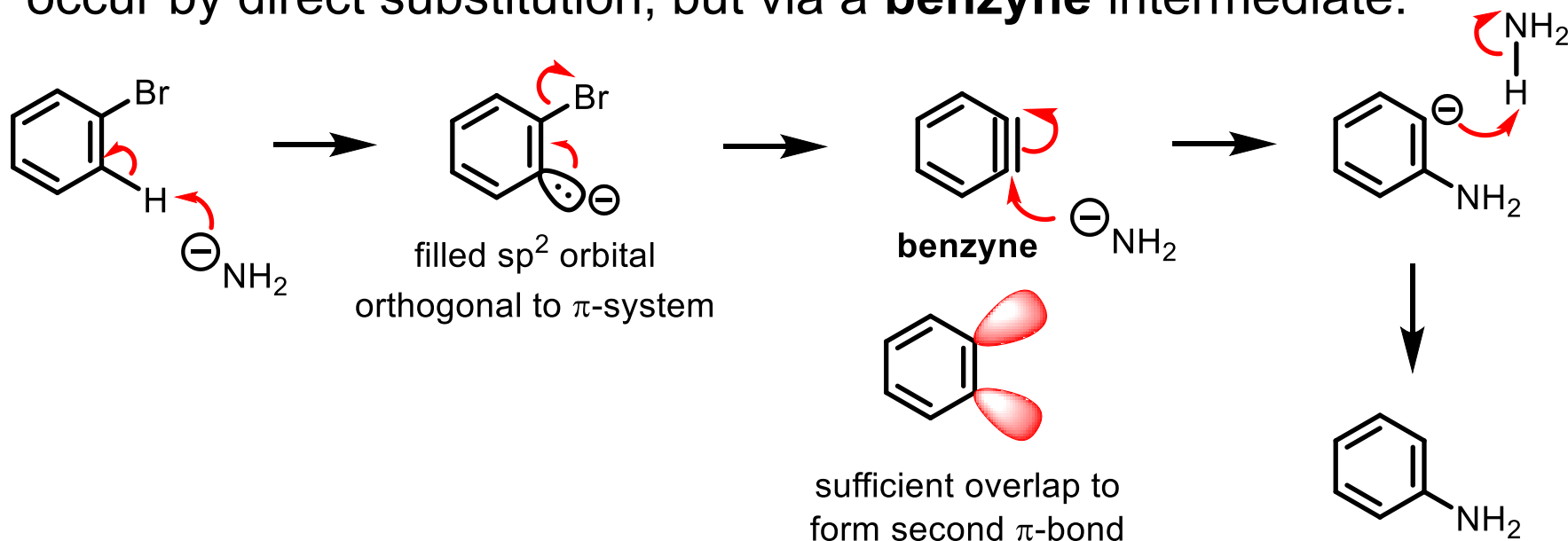
- The copper(I) catalysed conversion into halides is known as the Sandmeyer reaction. The mechanism for these reactions is more complicated than a simple $\text{S}_{\text{N}}1$ process.



Nucleophilic aromatic substitution by aryne mechanism



- It took a long time before anyone figured out the mechanism of these two reactions.
- They do NOT occur by direct substitution, but via a **benzyne** intermediate:

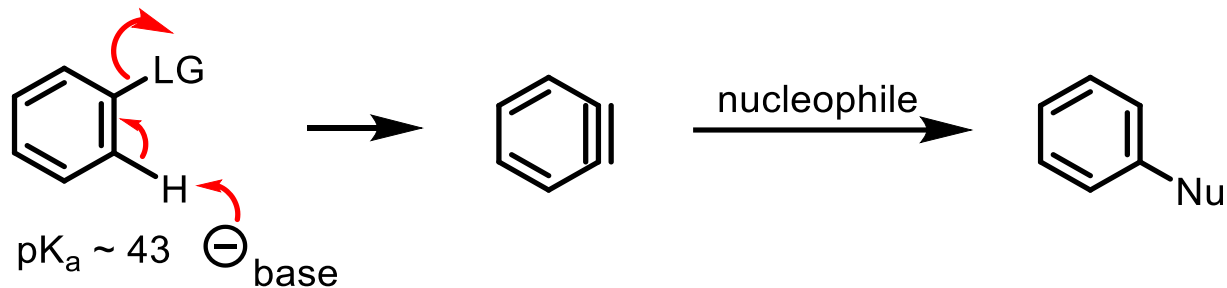


- Benzyne is electron-deficient and therefore **highly electrophilic**. It reacts readily with nucleophiles.

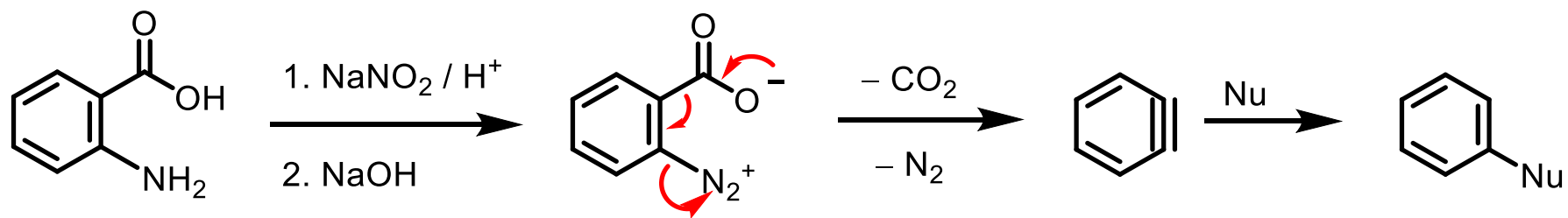


Benzyne formation

- Very strong base + benzene bearing good leaving group:



- Decarboxylation of diazonium salts:



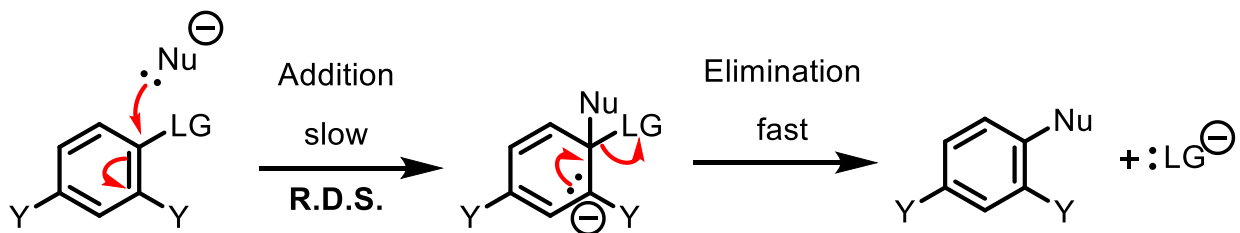


Summary

So far, you learned how to describe the reactivity of aromatics with nucleophiles.

- Nucleophilic aromatic substitution is much less common than electrophilic aromatic substitution.
- It can occur via three different mechanisms:

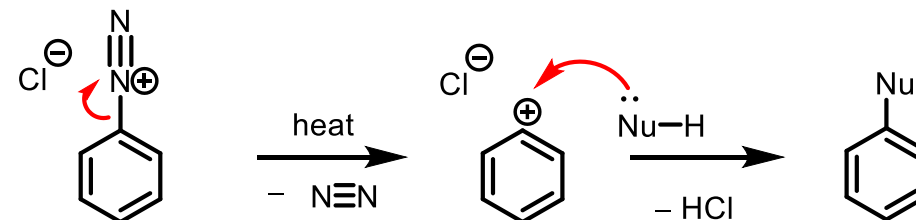
1. via addition-elimination mechanism



requires:

- leaving group: $\text{LG} = \text{F}$
- mesomerically EWG ($\text{Y} = \text{NO}_2, \text{CN}, \text{COR}, \text{CO}_2\text{R}$, etc.)

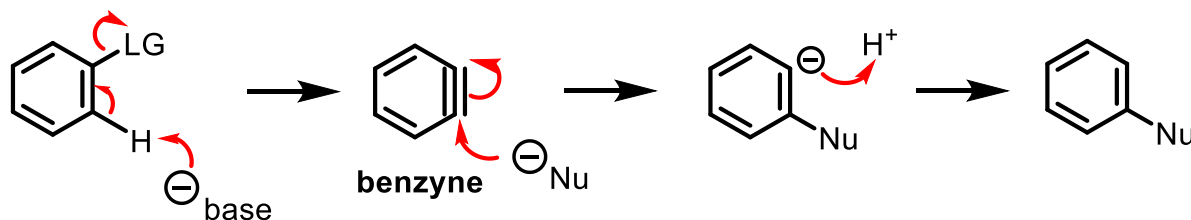
2. via $\text{S}_{\text{N}}1$ mechanism



requires:

- excellent leaving group (diazonium salt)

3. via a benzyne intermediate



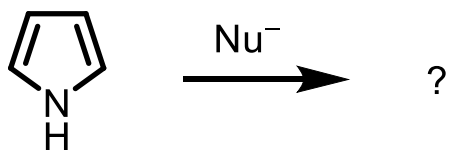
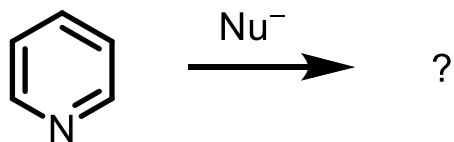
requires:

- strong base (e.g. NaNH_2)
- good LG



What about heteroaromatics?

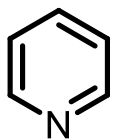
How do heteroaromatic molecules react with nucleophiles?



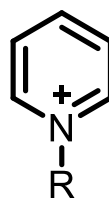


6-Membered Heteroaromatics: Pyridines

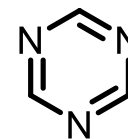
- The aromatic π -system is **electron-deficient** (because of the electronegative N) → **electrophilic** aromatic ring
- Nucleophilic attack, which is rare in benzene chemistry (unless $-M$ substituents are present), **occurs relatively easily in pyridines** (and other 6-membered ring heteroaromatics) because of their **imine-like properties**.
- Increasing the electron-deficiency in the ring (e.g. by *N*-alkylation or by increasing the number of N atoms in the ring), increases susceptibility to nucleophilic attack.



attacked at C-2 and C-4 by strong nucleophiles, e.g. LiAlH_4 , NaNH_2 , RLi , RMgX



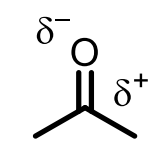
attacked by weaker nucleophiles, e.g. OH^- , CN^- , NaBH_4



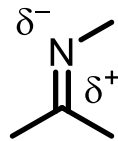
attacked by very weak nucleophiles, e.g. water at 25 °C



Revision: Reactivity of Imines

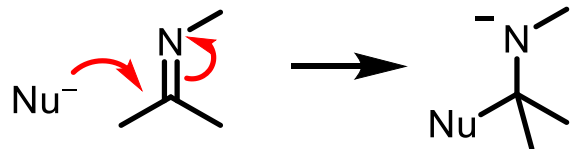


carbonyl

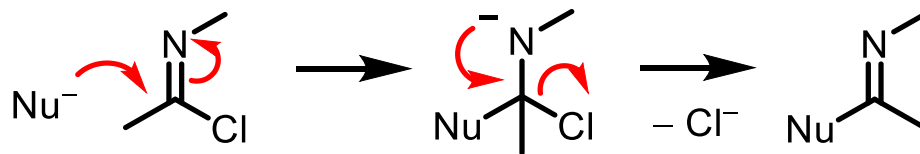


imine

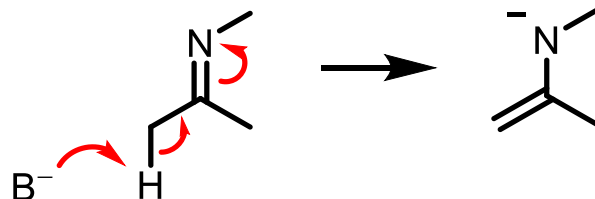
- Imines are susceptible to nucleophilic attack:



- Halogen derivatives are reactive, and the halide is readily displaced:



- α -protons are acidic:

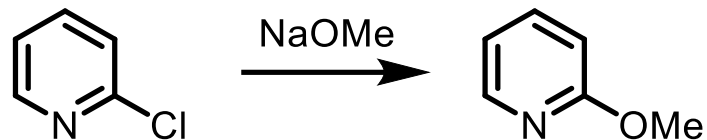




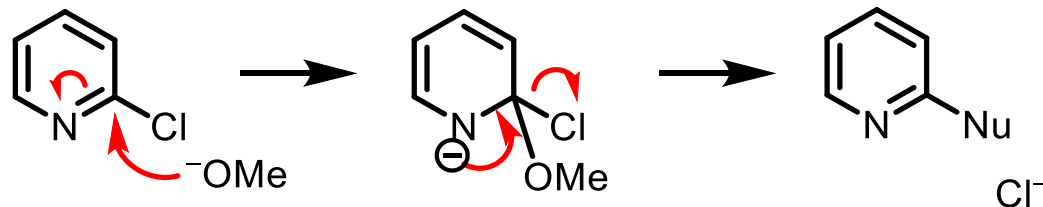
Nucleophilic Aromatic Substitution of Pyridines

2-Chloropyridines

- In contrast to halobenzene derivatives, 2-chloropyridine is very reactive towards nucleophilic attack (3×10^8 more reactive than PhCl for methoxide as nucleophile).



- Mechanism:

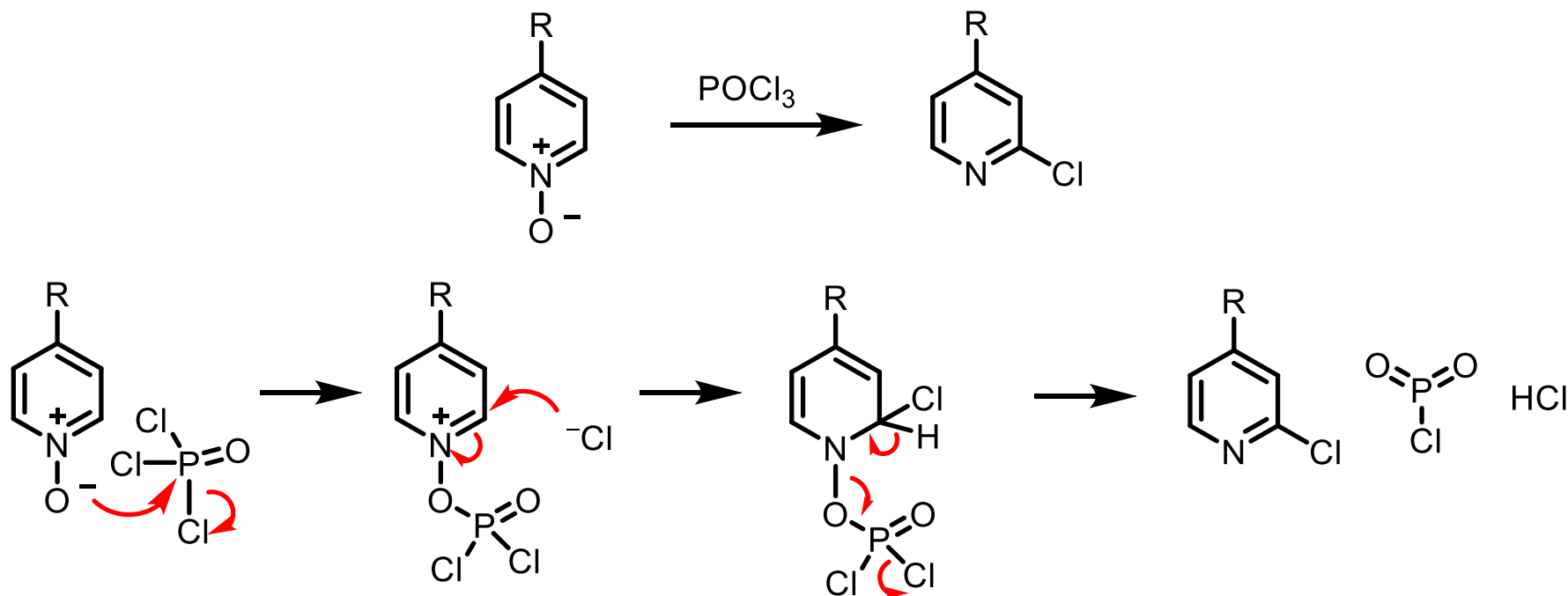




Nucleophilic Aromatic Substitution of Pyridines

Pyridine N-oxide

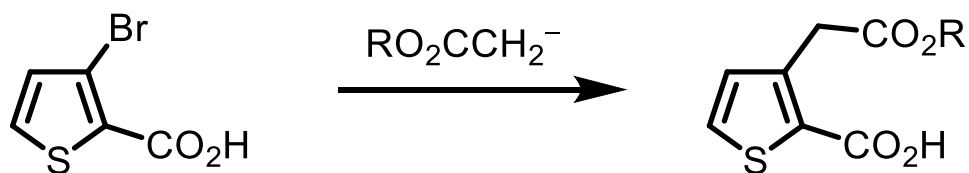
- We have already seen that pyridine-N-oxide is more susceptible to electrophilic attack than pyridine itself.
- It is also more susceptible to nucleophilic attack.





5-Membered Heteroaromatics

- Recap: **5-membered heterocycles** are “pi-excessive” (higher π -electron density) and therefore more nucleophilic than benzene
- **Nucleophilic attack is difficult** on electron rich rings: rare for simple pyrroles etc.
- Nucleophilic attack becomes more favourable when electron-withdrawing groups are present:

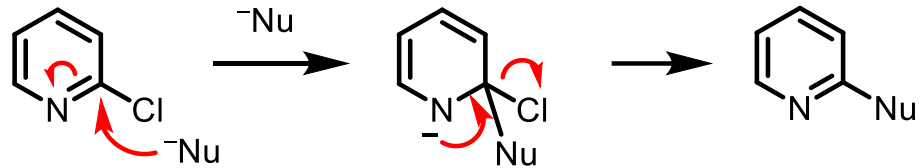




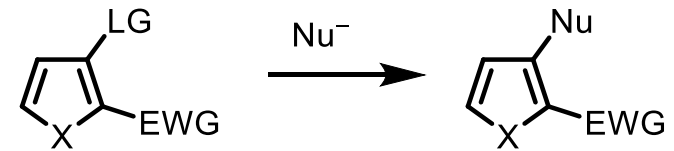
Summary

In this part of the lecture, you learned how to describe the reactivity of 6- and 5-membered heteroaromatics with nucleophiles:

nucleophilic aromatic substitution: easy



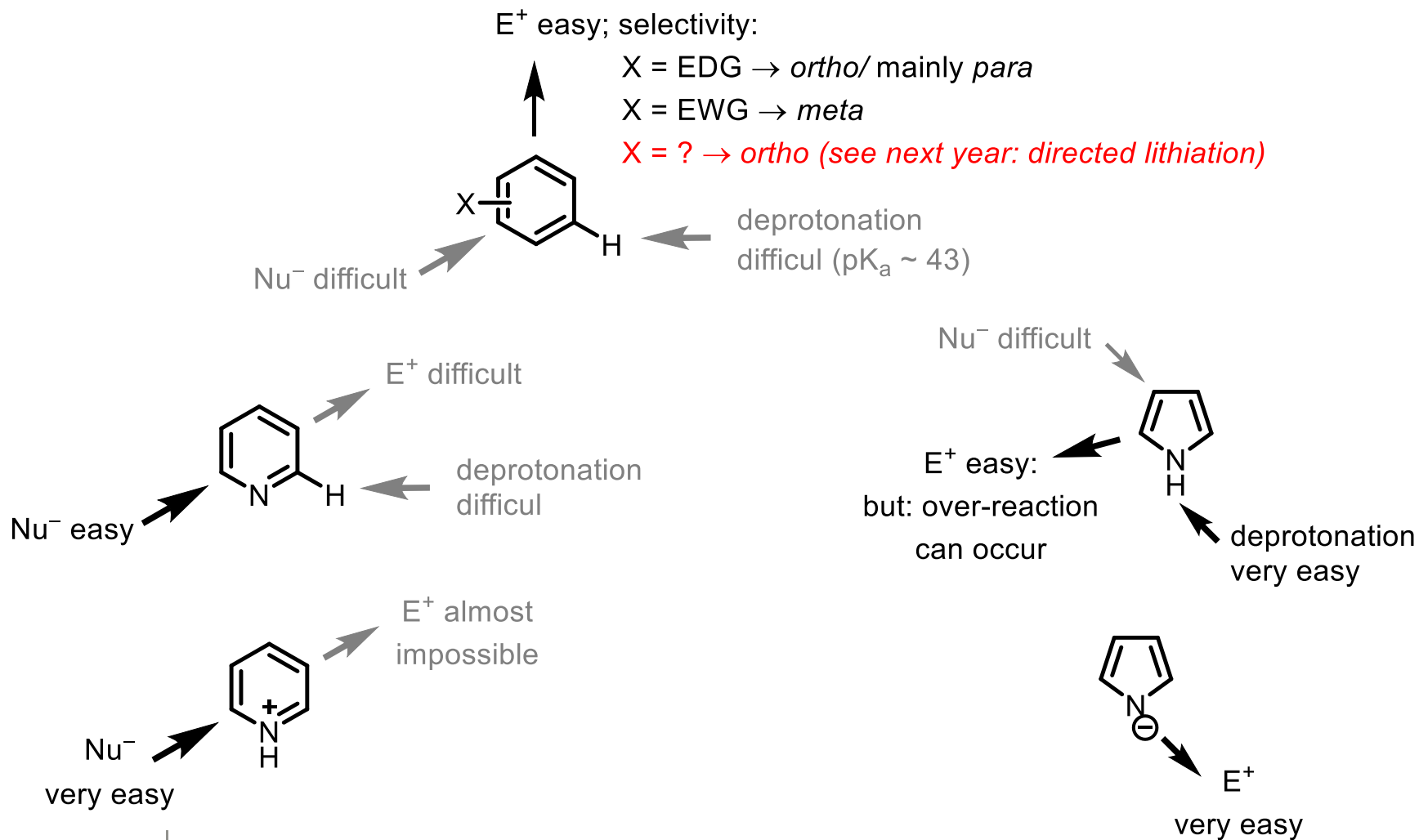
nucleophilic aromatic substitution: rare, requires EWG





Summary of reactivity

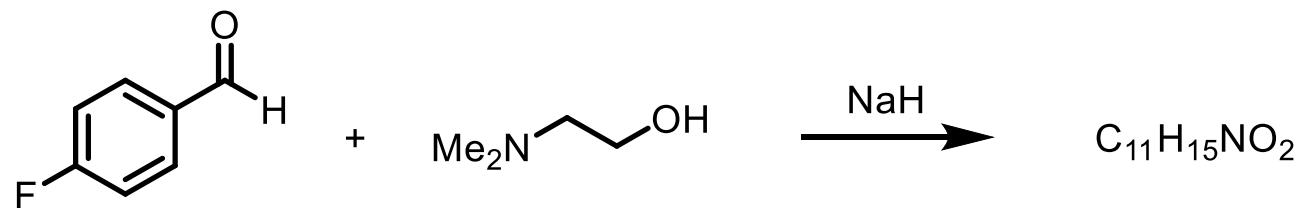
Reactivity of (hetero)aromatics with electrophiles and nucleophiles



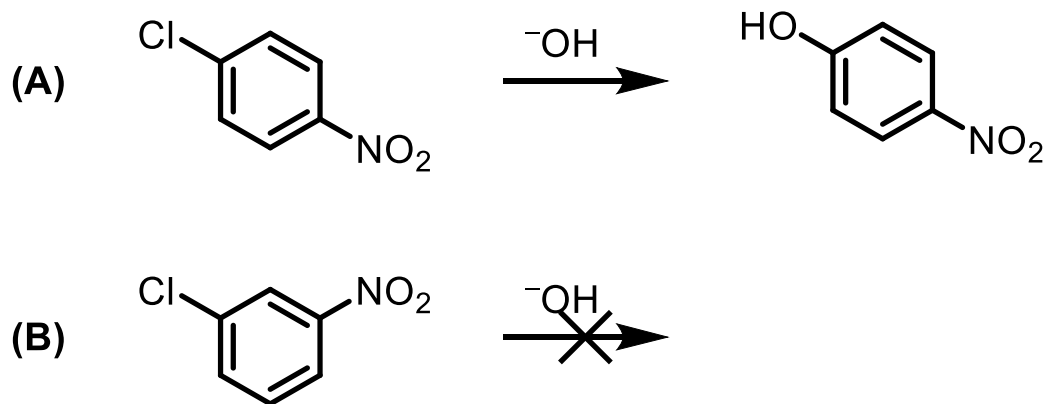


Topic 6 – Practice questions

1. What is the product of the following reaction? Provide a reaction mechanism.



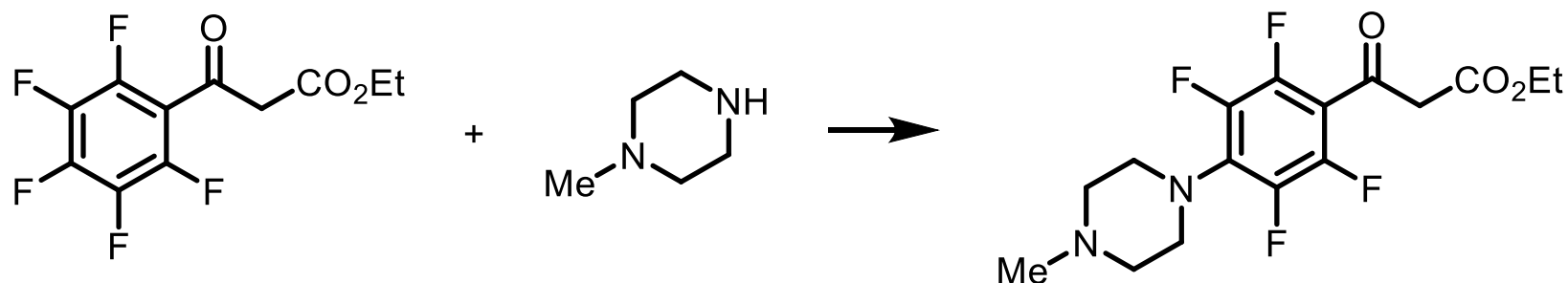
2. Provide a reaction mechanism for reaction A. Why does the reaction not work when the nitro group is *meta* to the chloro-substituent (B)?



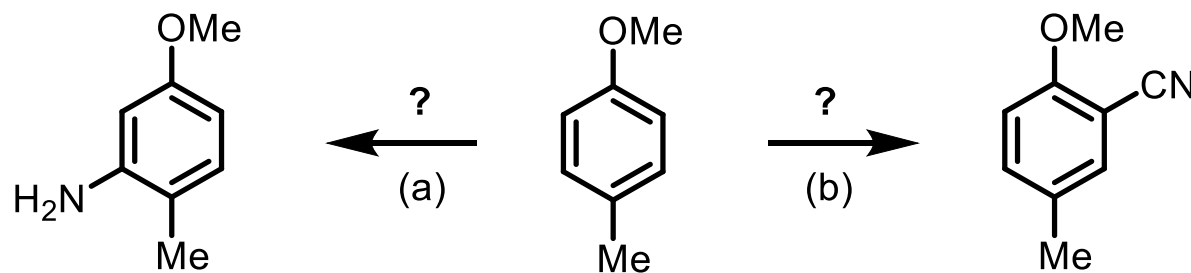


Topic 6 – Practice questions

3. Suggest a mechanism for the following reaction and explain the selectivity.



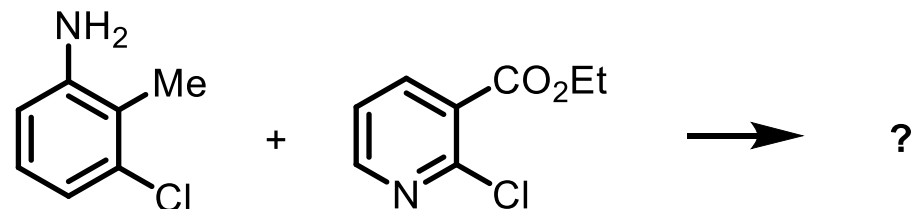
4. How would you carry out these two transformations?





Topic 6 – Practice questions

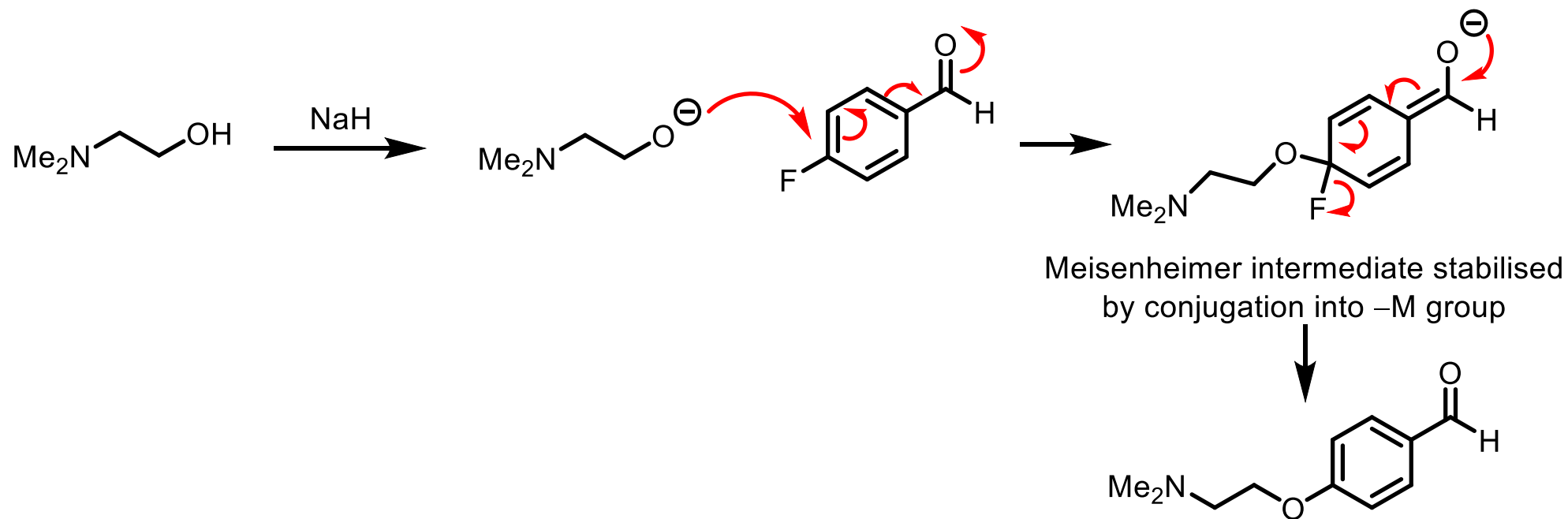
5. Draw a mechanism and suggest a product for this nucleophilic substitution.





Topic 6 practice questions: Solution

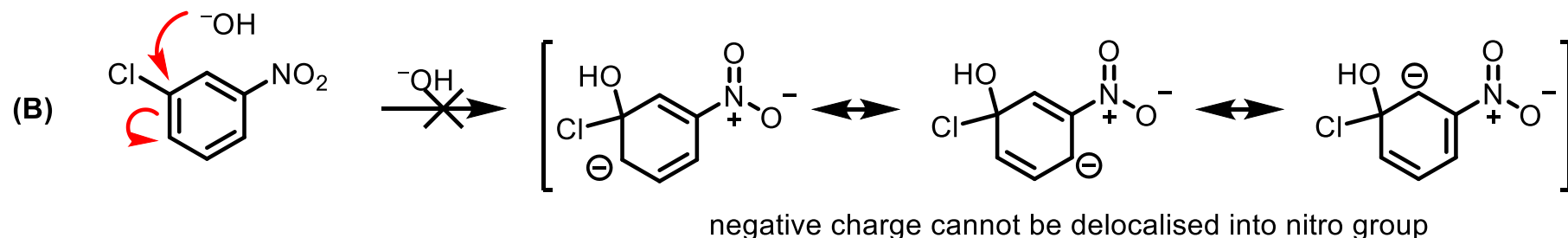
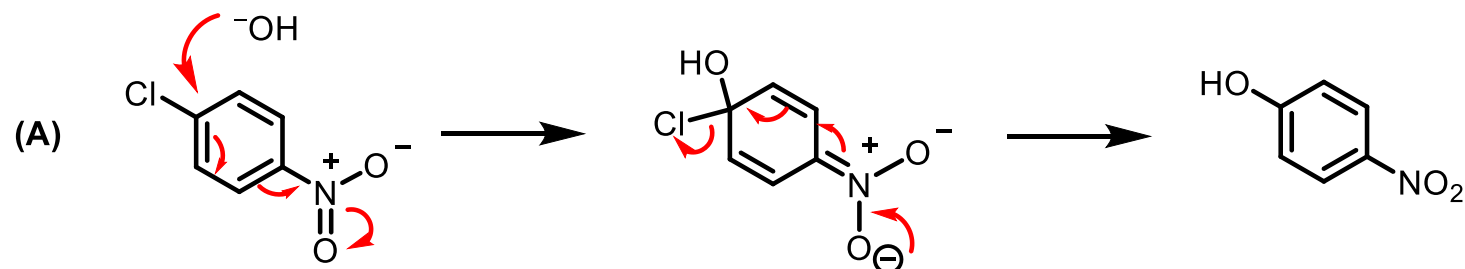
1. What is the product of the following reaction? Provide a reaction mechanism.





Topic 6 practice questions: Solution

2. Provide a reaction mechanism for reaction A. Why does the reaction not work when the nitro group is *meta* to the chloro-substituent (B)?

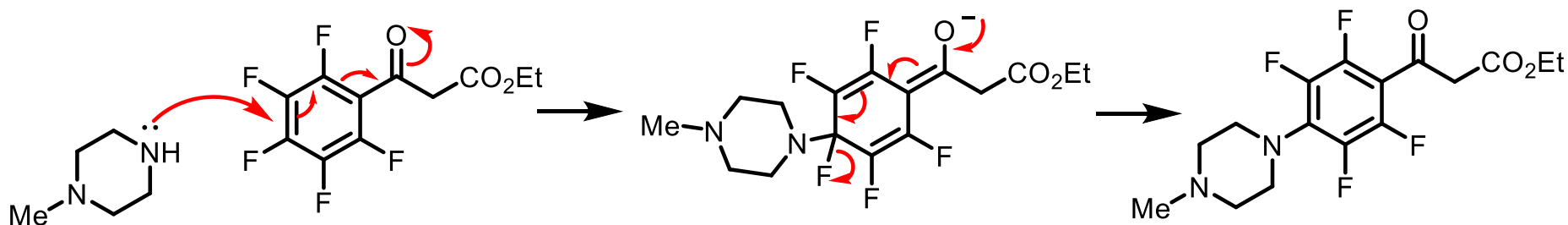




Topic 6 practice questions: Solution

3. Suggest a mechanism for the following reaction and explain the selectivity.

Both *ortho*- and *para*-positions are activated towards nucleophilic attack by the electron-withdrawing ketone. *Para* is preferred due to steric hindrance between the large nucleophile and the ketone.

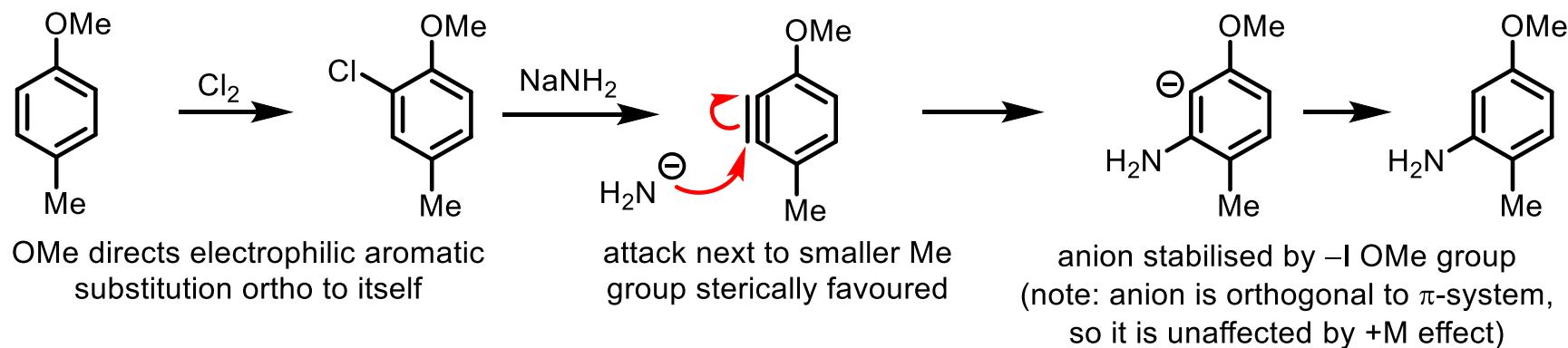




Topic 6 practice questions: Solution

4. How would you carry out these two transformations?

- a. NH_2 groups are usually introduced by nitration and reduction, but the methoxy group directs nitration *ortho* to itself, giving the wrong regioisomer (keep this in mind for part b). An alternative is chlorination followed by benzyne formation:

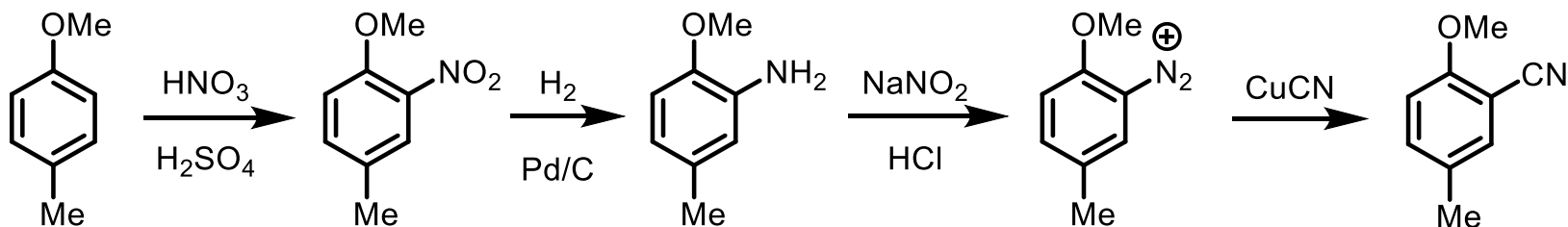




Topic 6 practice questions: Solution

4. How would you carry out these two transformations?

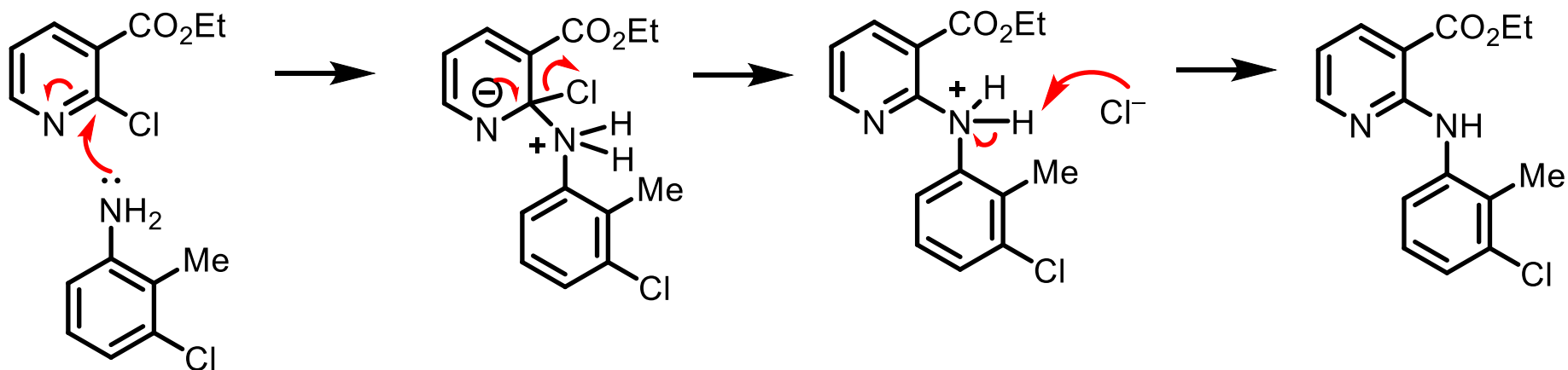
b. Nitration ortho to the methoxy group and functional group modification affords the correct product:





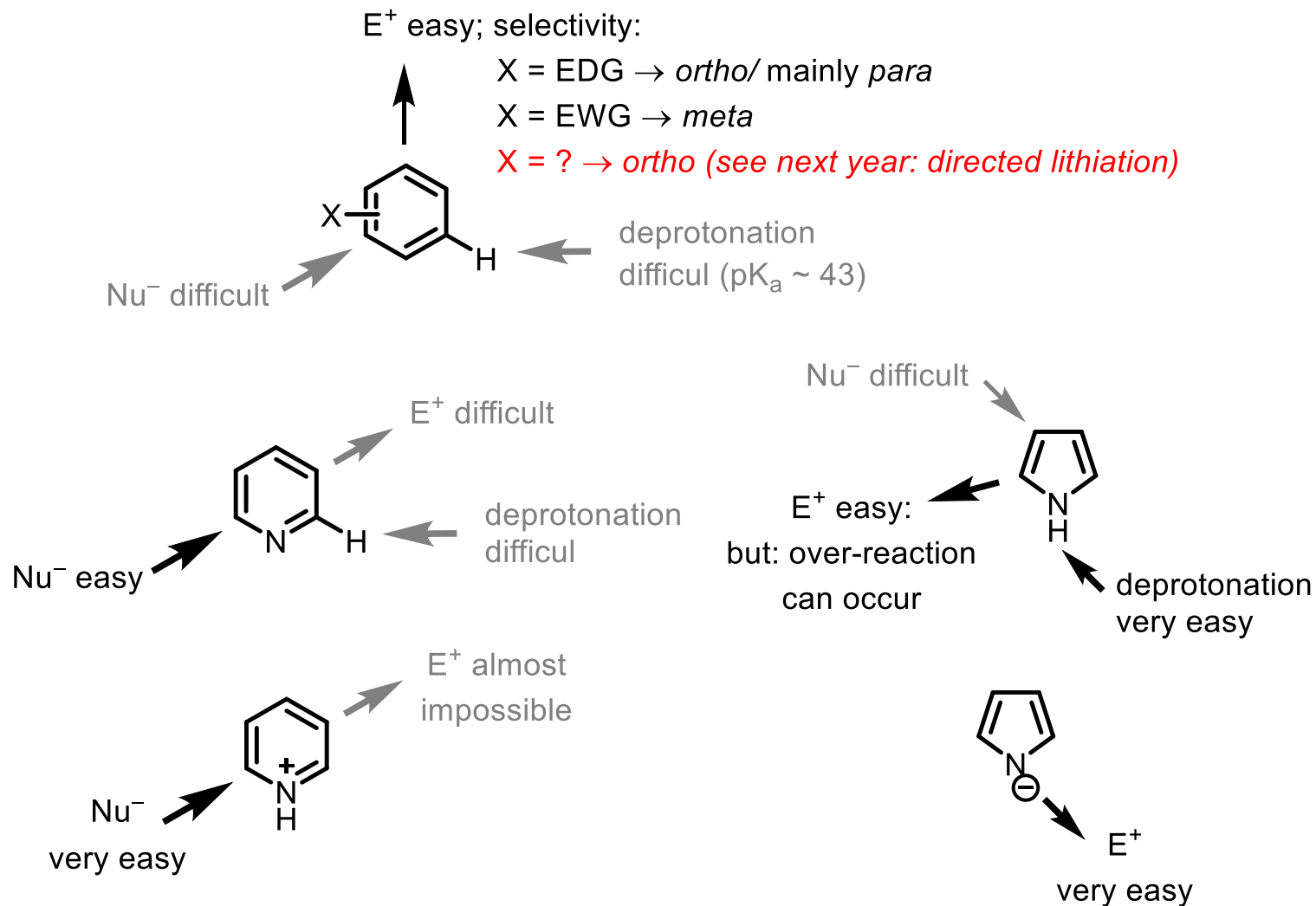
Topic 6 practice questions: Solution

5. Draw a mechanism and suggest a product for this nucleophilic substitution.





Summary: Reactivity of (hetero)aromatics





Topic 7: Synthesis of Heteroaromatics

Topic 7: Synthesis of Heteroaromatics

7.1 Synthesis of Heteroaromatics: Carbonyl Chemistry

7.2 Synthesis of Heteroaromatics: Electrophilic Aromatic Substitution

Learning outcomes

In this lecture, you will learn how to synthesis heteroaromatic compounds

- from dicarbonyl compounds;
- using electrophilic aromatic substitution reactions.



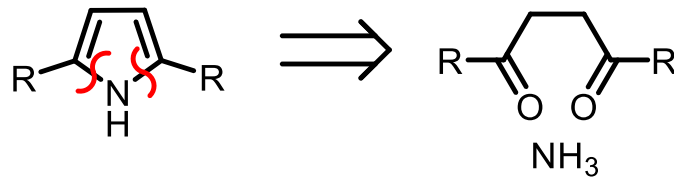
Synthesis of Heteroaromatics

- Thermodynamics and entropy are on our side in the synthesis of heteroaromatics:
 - Formation of strong C–O, C–N and C–S bonds
 - Formation of very stable (aromatic) 5- and 6-membered rings
 - Intramolecular reactions favoured over intermolecular reactions.

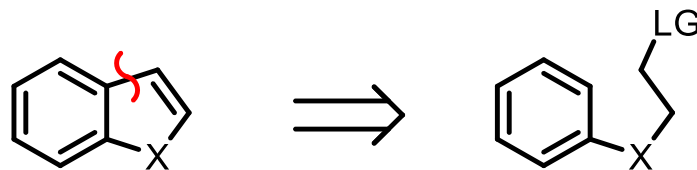


Synthesis of Heteroaromatics

- We will discuss two main strategies:
 1. Synthesis of heteroaromatics exploiting **carbonyl chemistry**:
revise 1st year carbonyl chemistry (imine and oxime formation, Aldol, etc.)



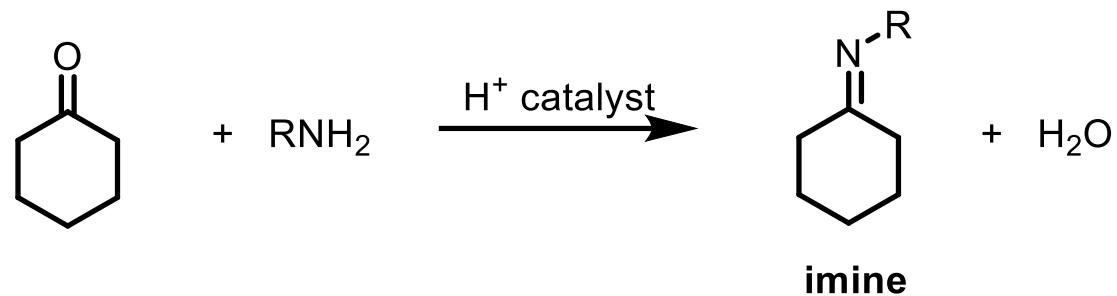
2. Synthesis of fused heteroaromatics using **electrophilic aromatic substitution** approach:



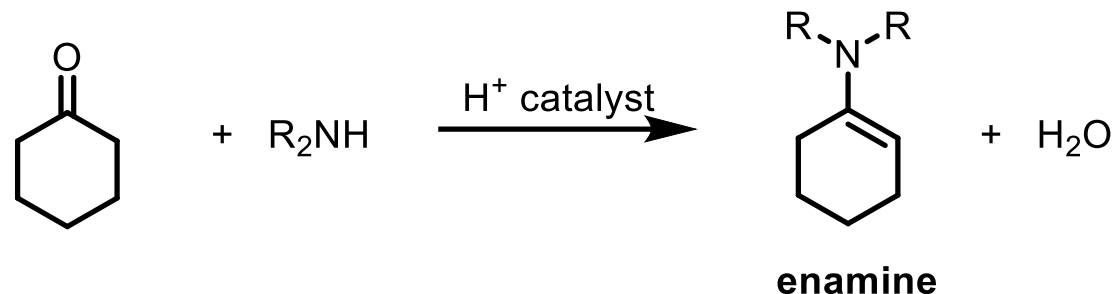


Revision: Reaction of ketones with amines

Primary amines react to give imines:



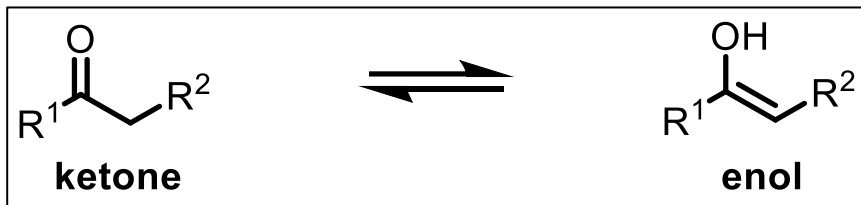
Secondary amines react to give enamines:





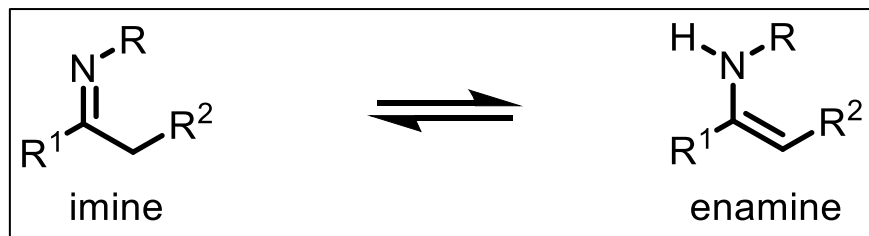
Revision: Keto-enol tautomerism

Keto-enol tautomerism can be catalysed by acid or base:



Tautomerism = a reaction that (only) involves the intramolecular transfer of a proton.

Imines undergo similar tautomerism reactions:

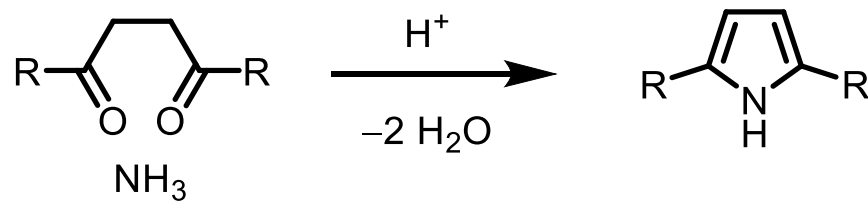


Tip: Practise drawing both acid- and base-catalysed curly arrow mechanisms for this.



Paal Knorr Synthesis

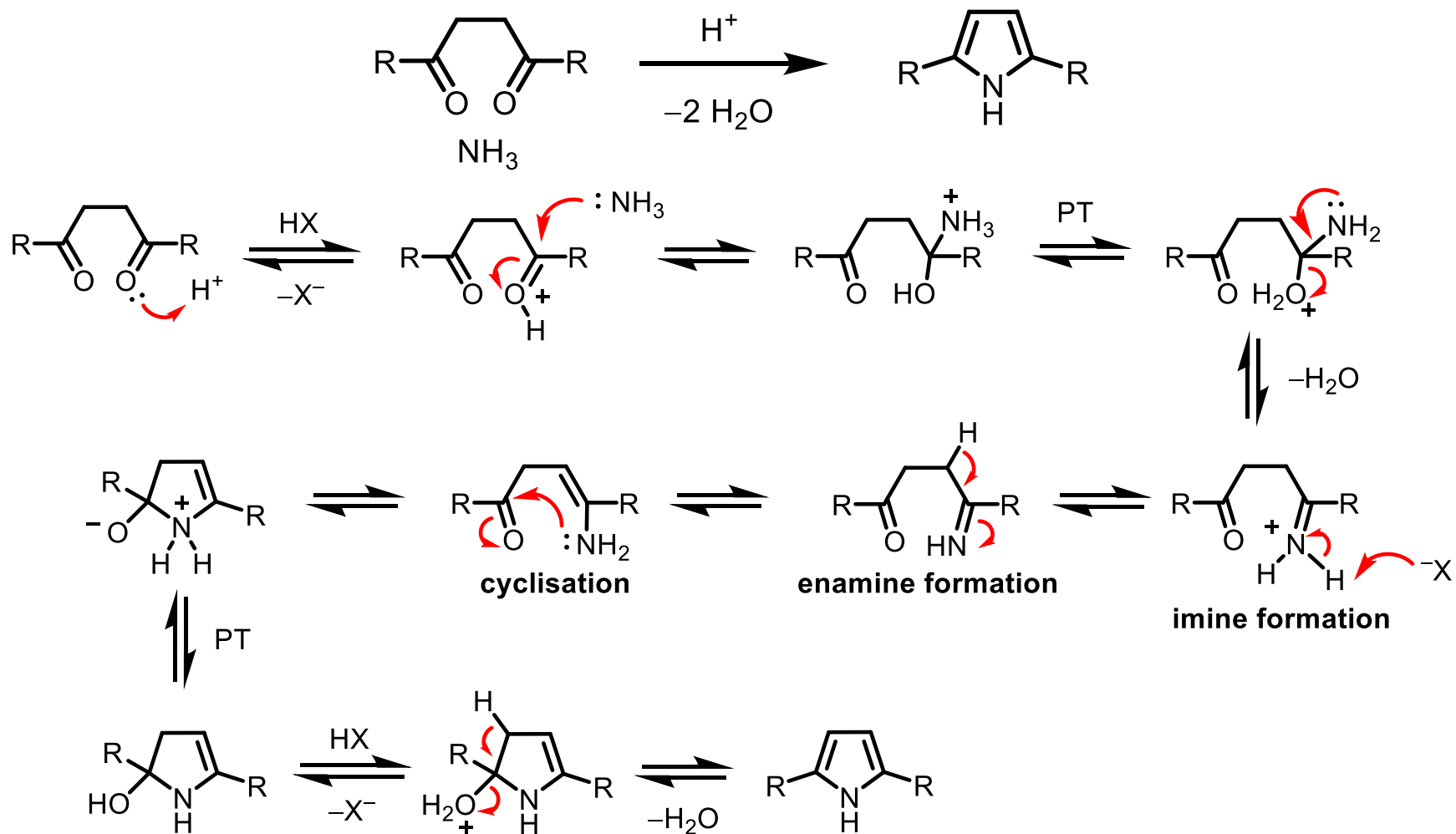
- 5-membered heterocycles are easiest to make from 1,4-dicarbonyls.
- *e.g.* pyrroles:



- Mechanism:



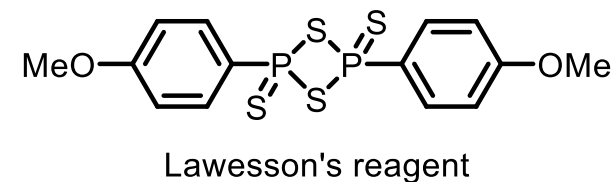
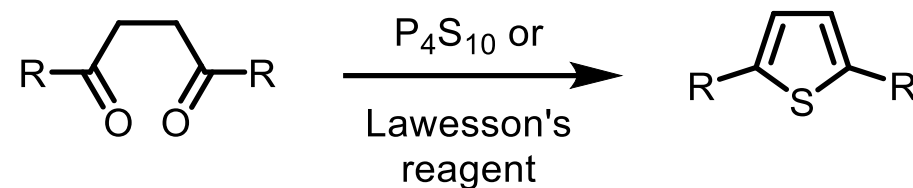
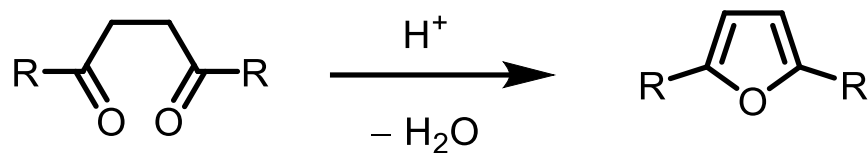
Synthesis of heteroaromatics from dicarbonyls: Paal Knorr Synthesis





Paal Knorr Synthesis

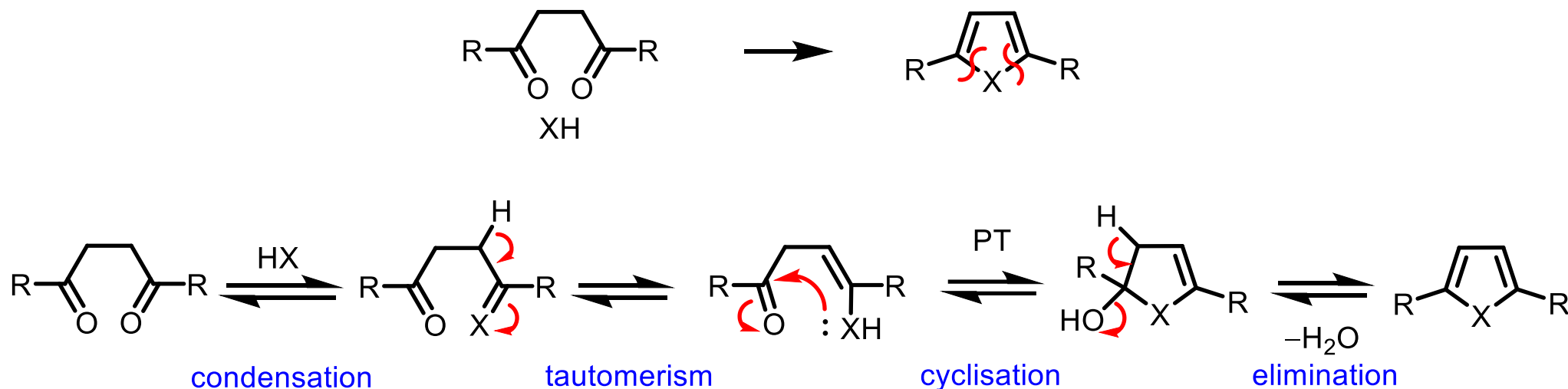
- Similar strategies are possible for furans and thiophenes:





Summary

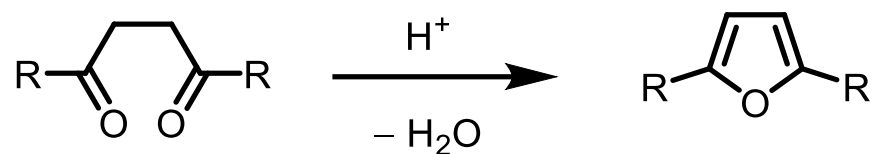
5-membered heteroaromatics can be synthesised from dicarbonyls. It may look like we have covered three different reactions on the previous slides, but the mechanism follows the same general steps:





Paal Knorr Synthesis

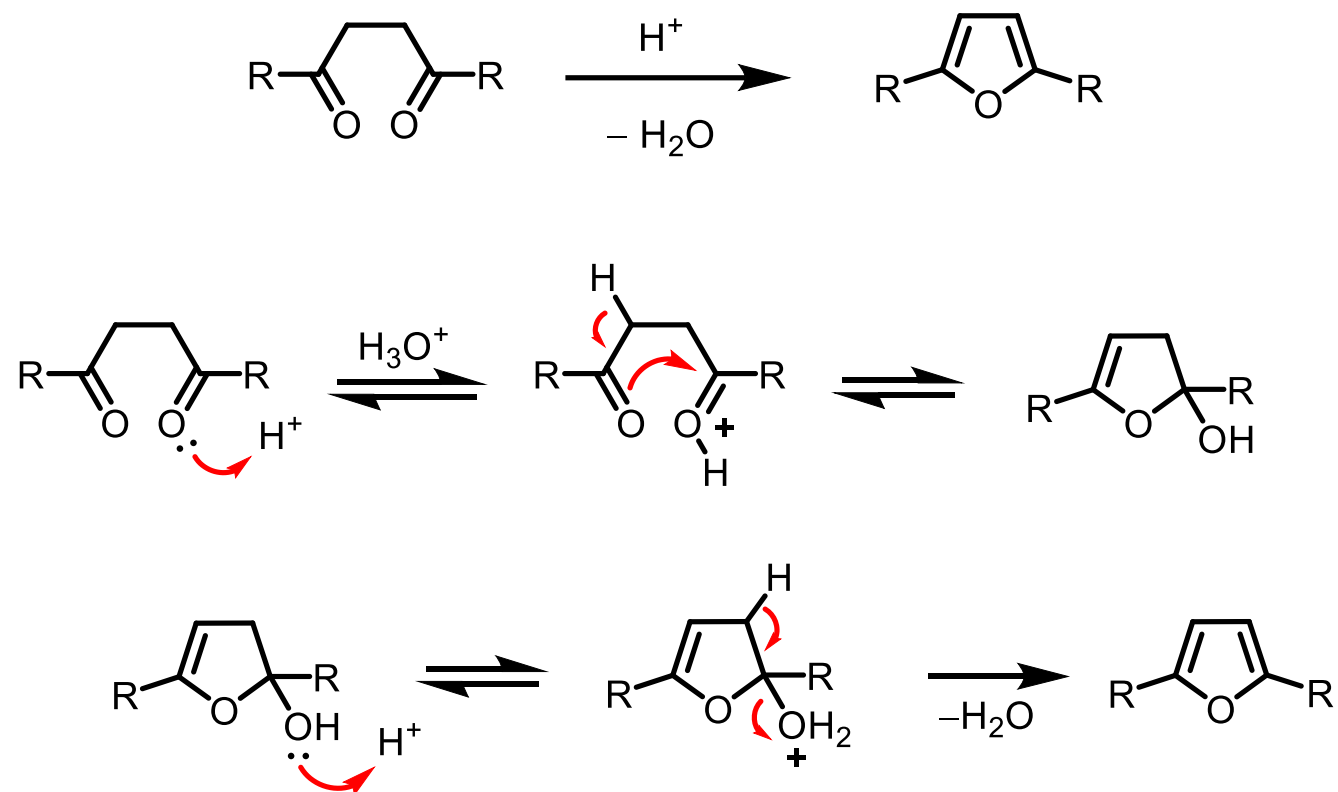
- **Question:** Draw a Paal-Knorr reaction mechanism for the formation of furan:





Paal Knorr Synthesis

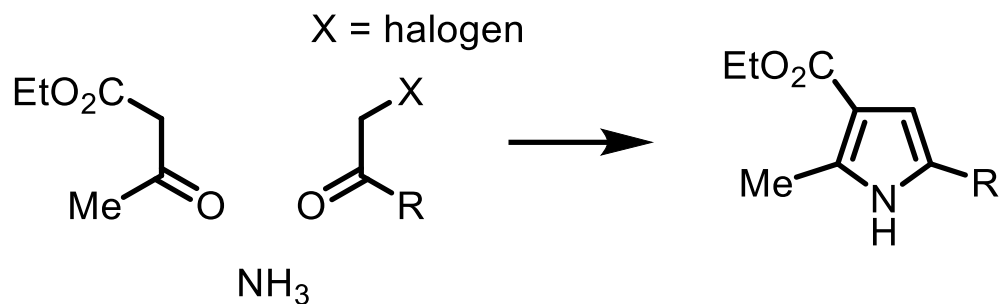
- Question:** Draw a Paal-Knorr reaction mechanism for the formation of furan:



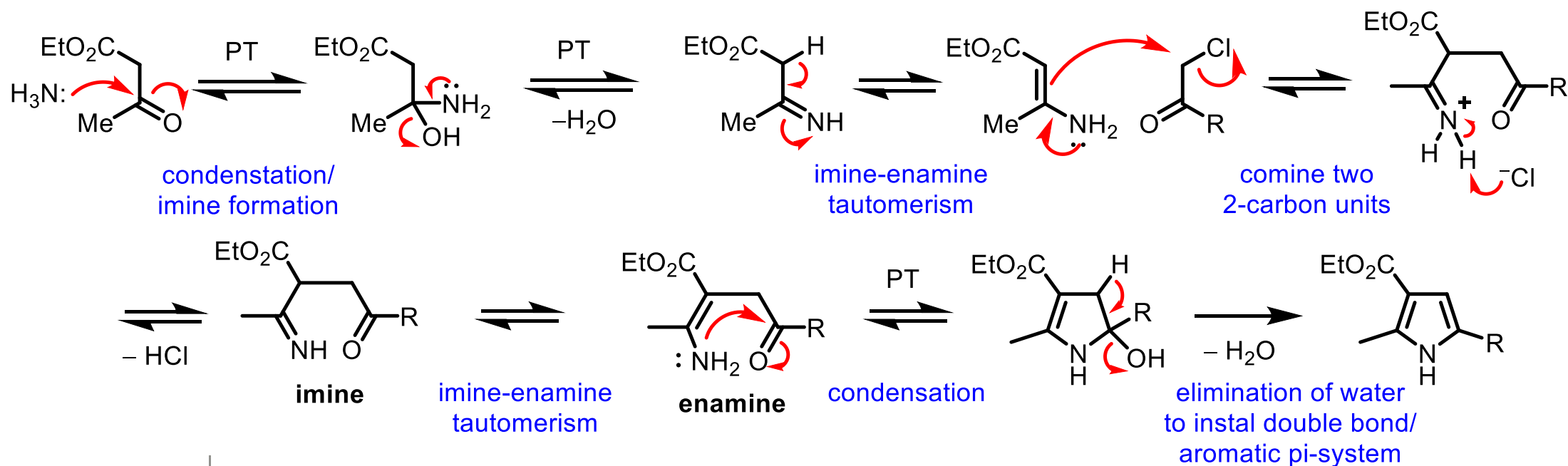


Pyrrole Synthesis

- If 1,4-dicarbonyls are not readily available, we can combine two 2-carbon units.



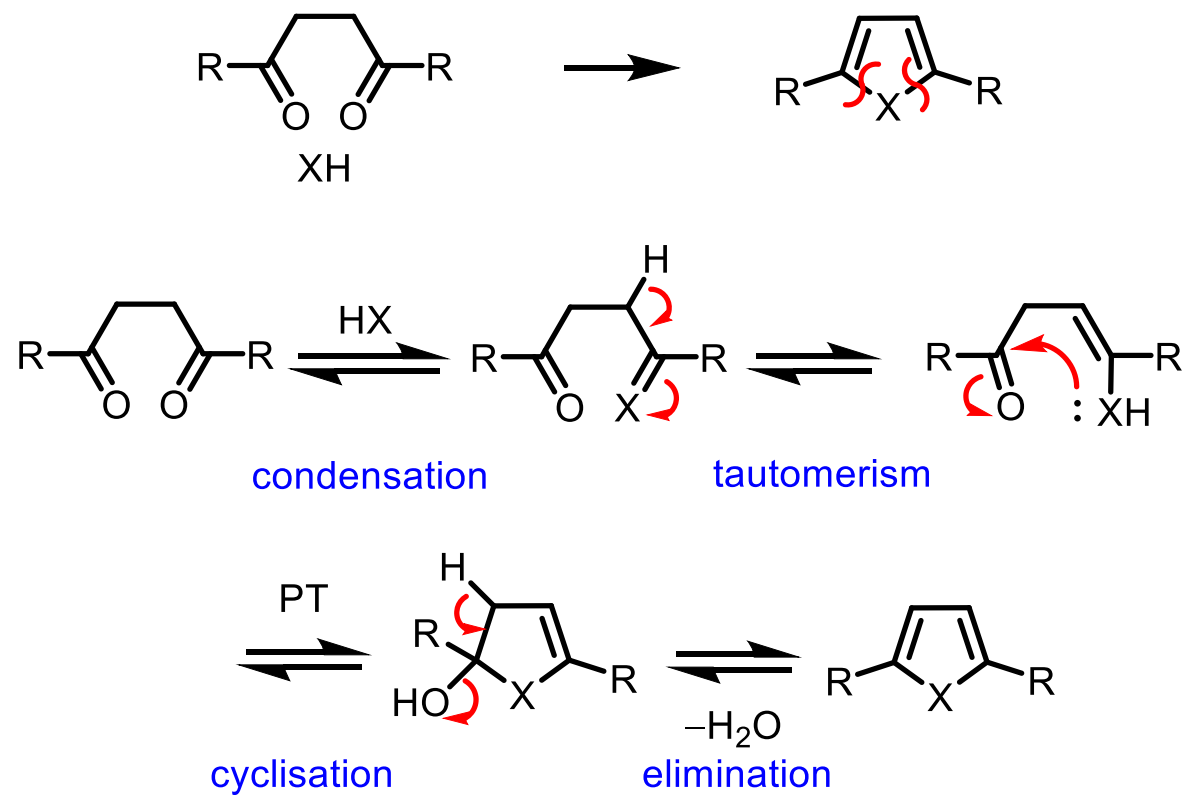
- Mechanism:





Summary

In the last lecture, you learned that 5-membered heteroaromatics can be synthesised from dicarbonyls:

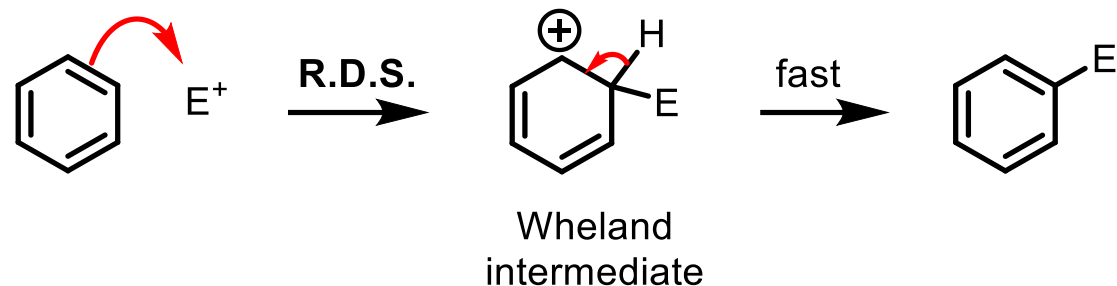




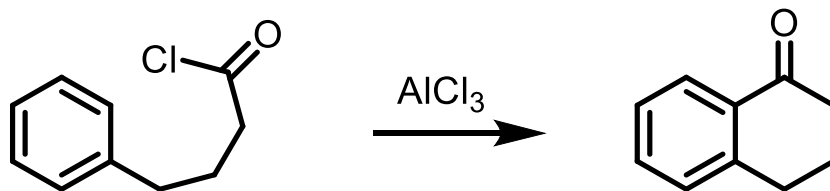
Synthesis of heteroaromatics via electrophilic aromatic substitution

Electrophilic aromatic substitution

- Recap:



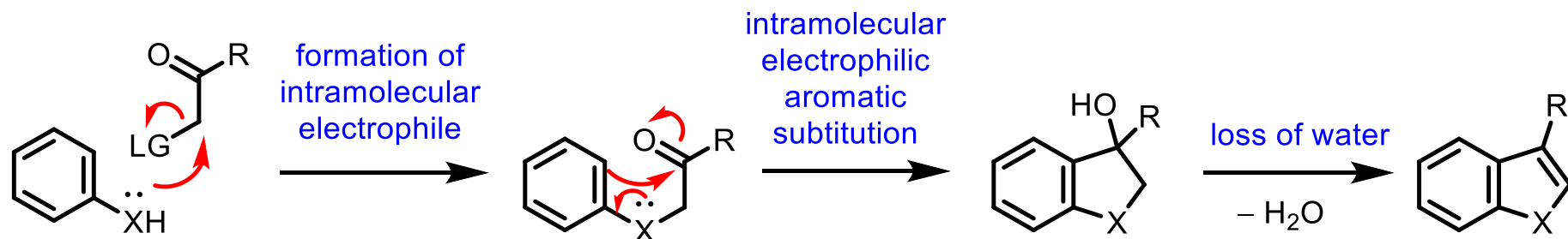
- Electrophilic substitution reactions on benzene derivatives can also occur in an **intramolecular** manner leading to the **formation of another ring** (*i.e.* a fused ring system).





Synthesis of fused heteroaromatics

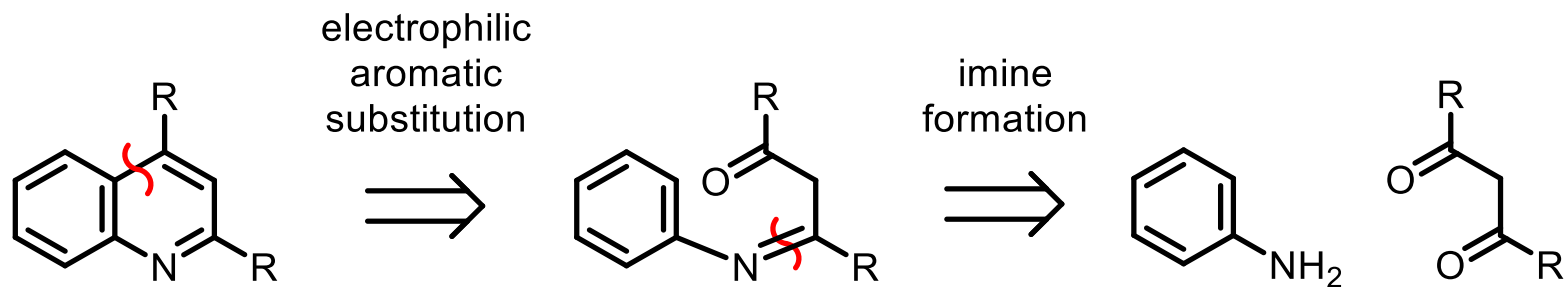
If the side chain contains a **heteroatom**, the new ring formed is heterocyclic. This is the best way to make important **heteroaromatic compounds** such as quinolines, isoquinolines and indoles:





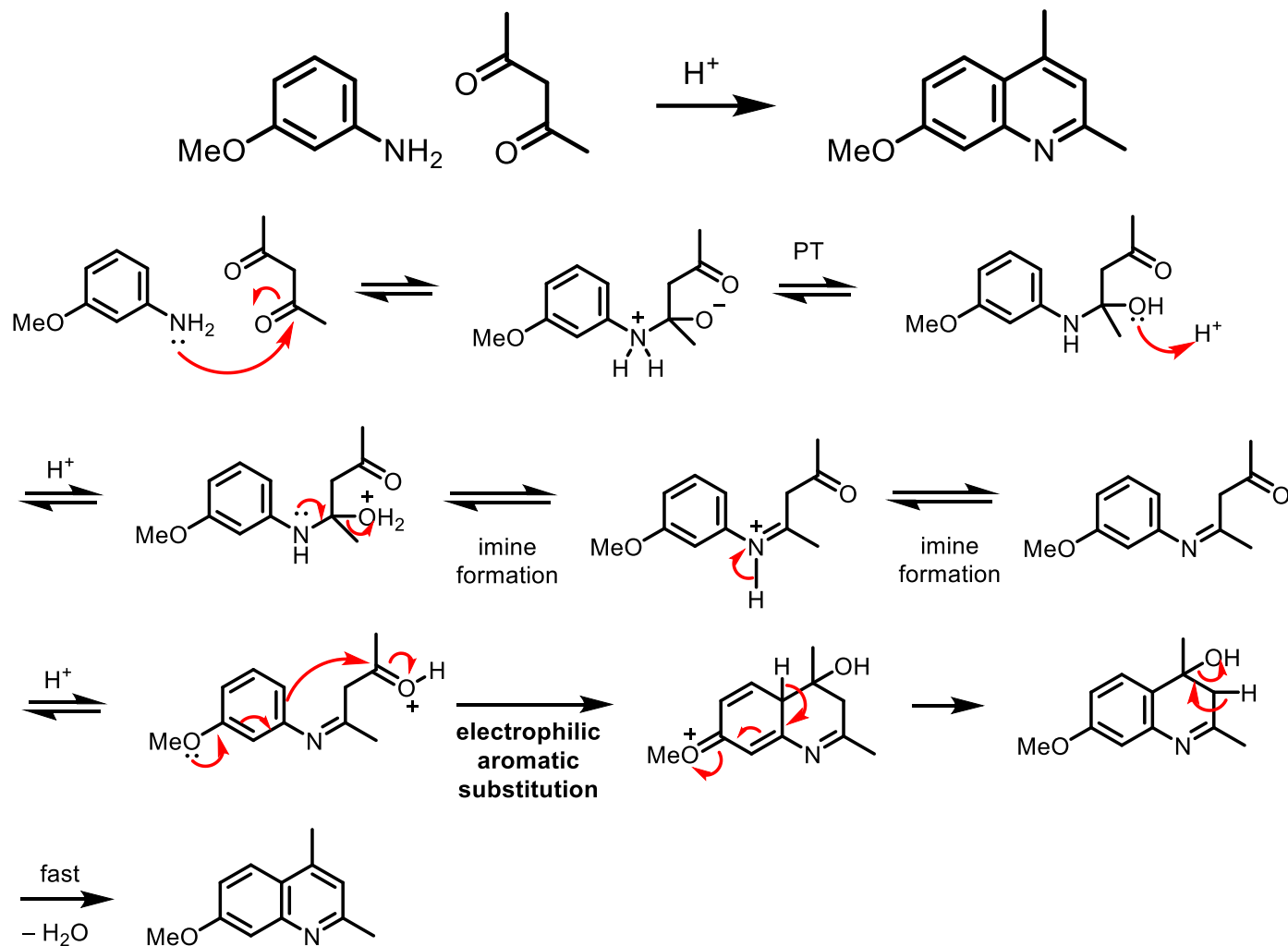
Coombes quinoline synthesis

Quinolines are best synthesised from an appropriate aniline derivative by building the heterocyclic pyridine ring:





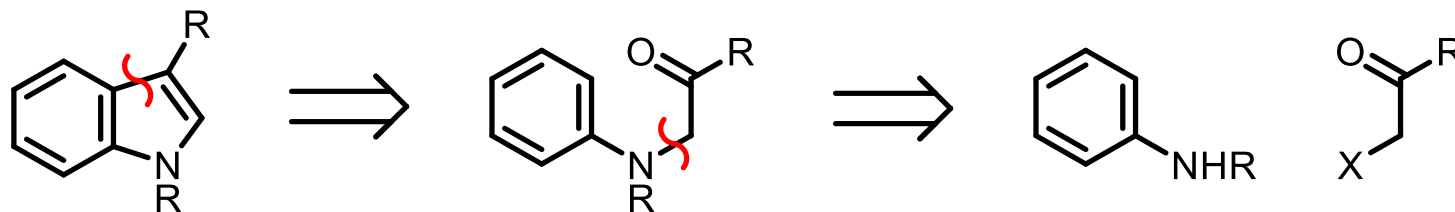
Coombes quinoline synthesis



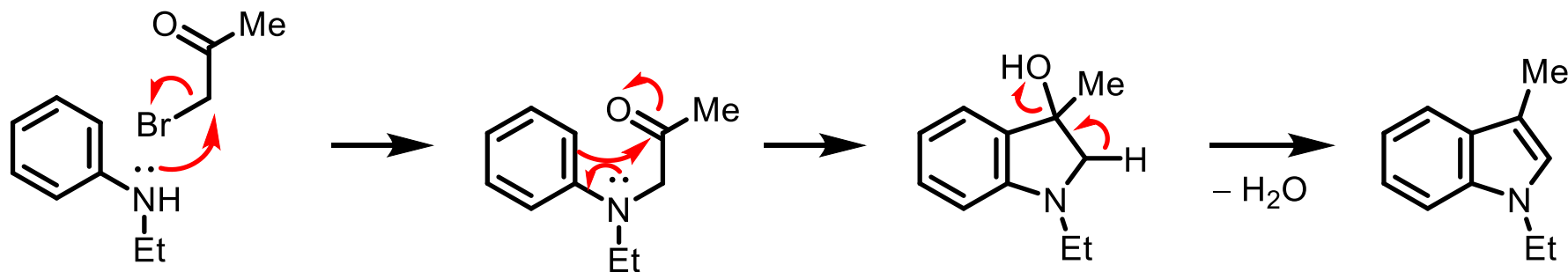


Bischler indole synthesis

- A similar strategy may be employed for the synthesis of **indoles**:



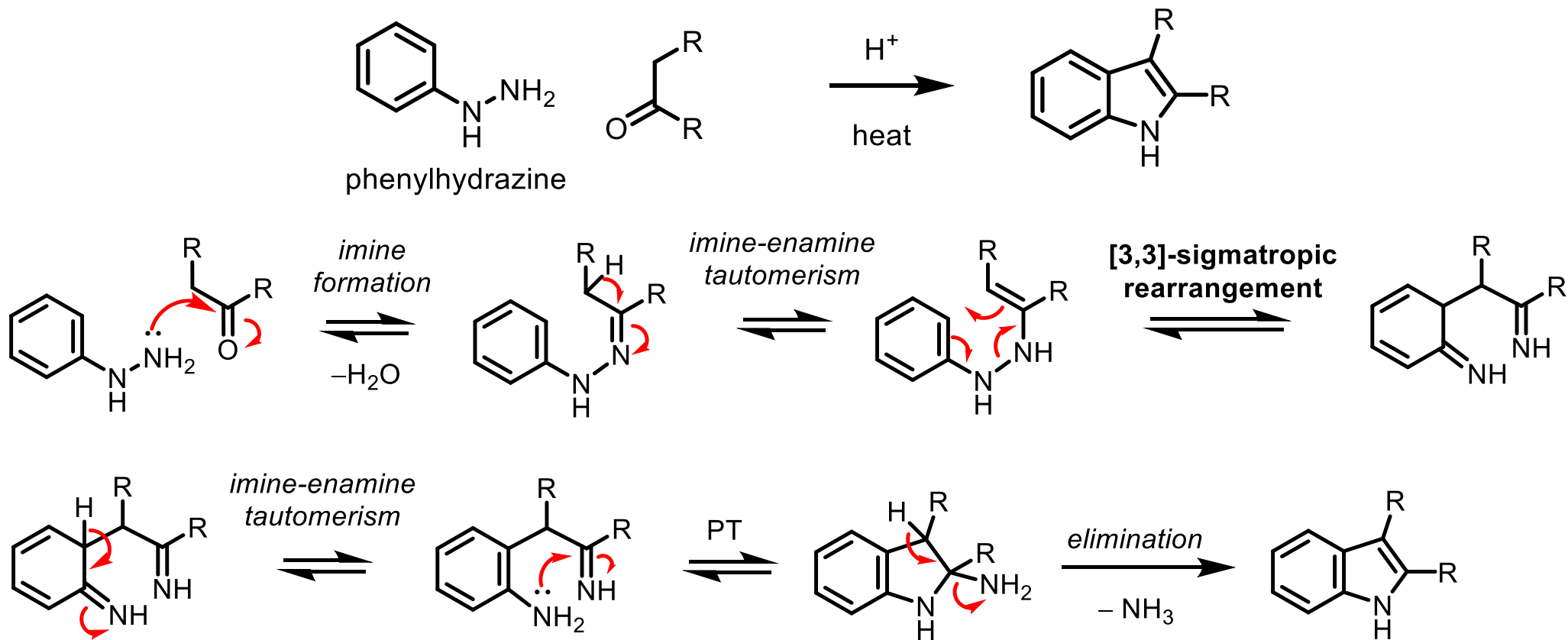
- Mechanism:





Fischer indole synthesis

- The most famous indole synthesis is the Fischer indole synthesis:

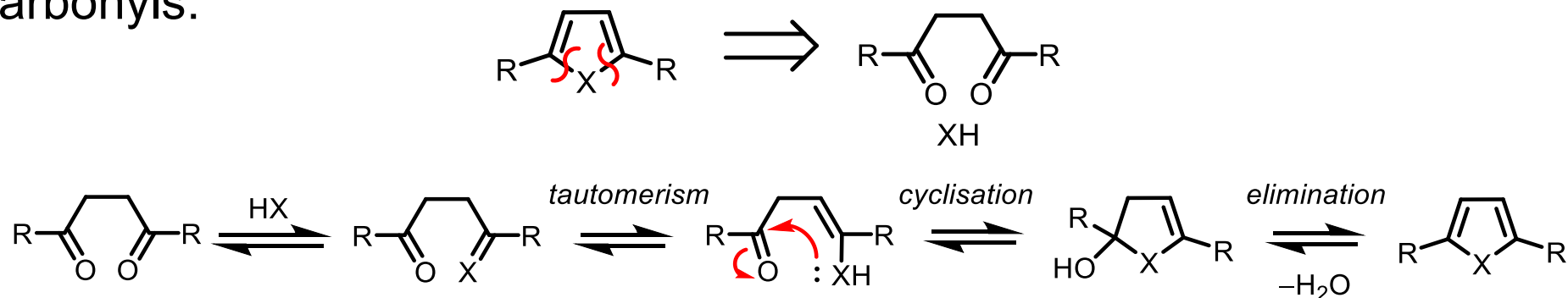




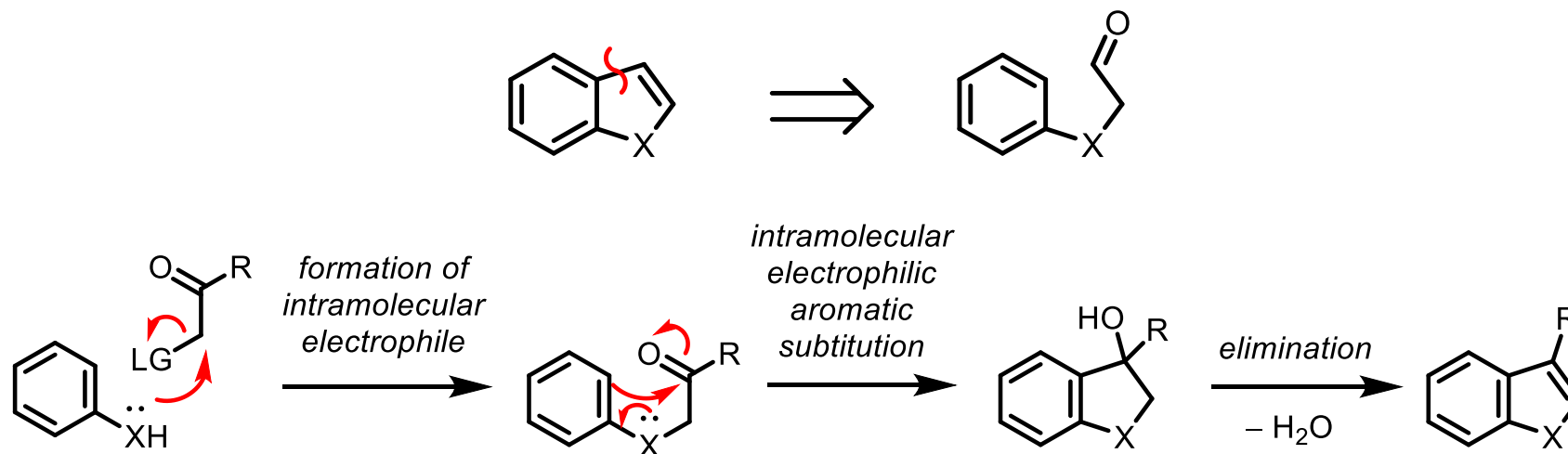
Summary

In the last two lectures, you learned how to synthesise heteroaromatic compounds

- from dicarbonyls:



- using intramolecular electrophilic aromatic substitution reactions:



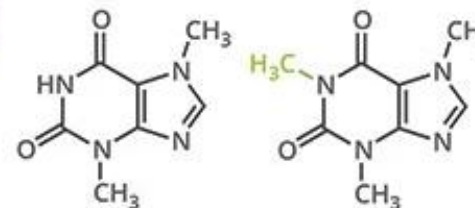


Merry Christmas!

Next semester:

- In-class test: Friday, week 20 (Feb 6th) 4–6 pm
- Revision workshops (check your timetables)

HOLLY BERRIES

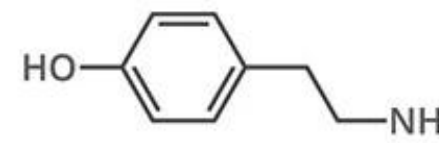


THEOBROMINE

CAFFEINE

Holly berries contain bitter compounds, such as saponins and alkaloids, which make them mildly toxic if eaten. One alkaloid culprit is theobromine, also found in small amounts in chocolate. The leaves of some species contain caffeine too.

MISTLETOE BERRIES

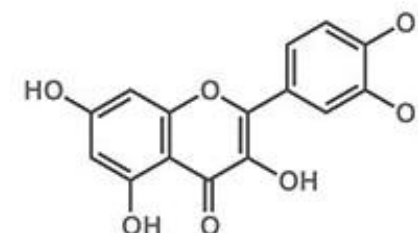


TYRAMINE

Berries also contain viscotoxins and phoratoxin

Mistletoe berries are mildly toxic if ingested. The berries contain toxic peptides as well as the alkaloid tyramine, which can interfere with monoamine oxidase inhibitors (MAOIs), drugs used to treat depression. This interference can lead to severely elevated blood pressure.

CRANBERRIES



QUERCETIN

Cranberries have a reputation as a health food. Scientists have shown that polyphenols in the berries, such as quercetin, can slow the growth of or kill cancer cells. Similar findings in human studies, though, have been limited. Evidence that cranberry juice can treat urinary tract infections is similarly limited.

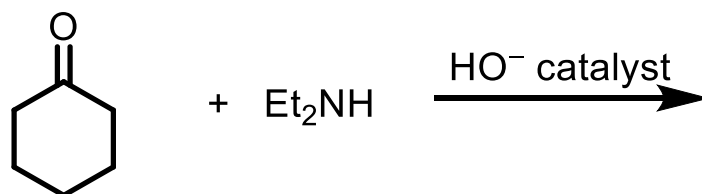


© C&EN 2015 Created by Andy Brunning for Chemical & Engineering News

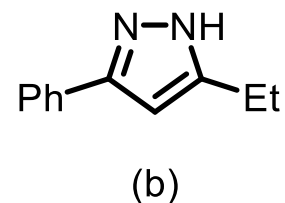
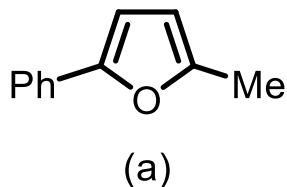


Topic 7: Practice questions

1. Draw a curly arrow reaction mechanism and product for the following base-catalysed reaction:



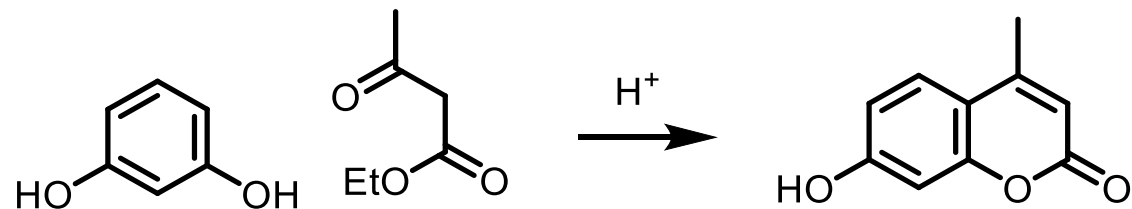
2. How would you synthesise these heteroaromatics? Provide starting materials and mechanisms. (Hint: Disconnect the carbon–heteroatom bonds to determine which nucleophiles and electrophiles are needed.)





Practise questions

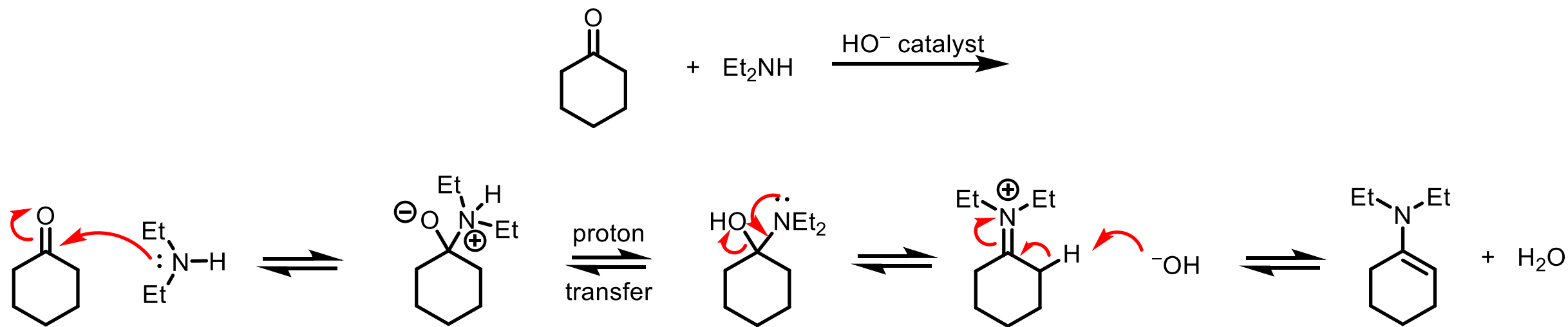
3. Propose a mechanism for the following reaction. Is the heterocyclic ring created in this reaction aromatic? (Does it fulfil the 4 rules of aromaticity?)





Topic 8 practice questions: Answers

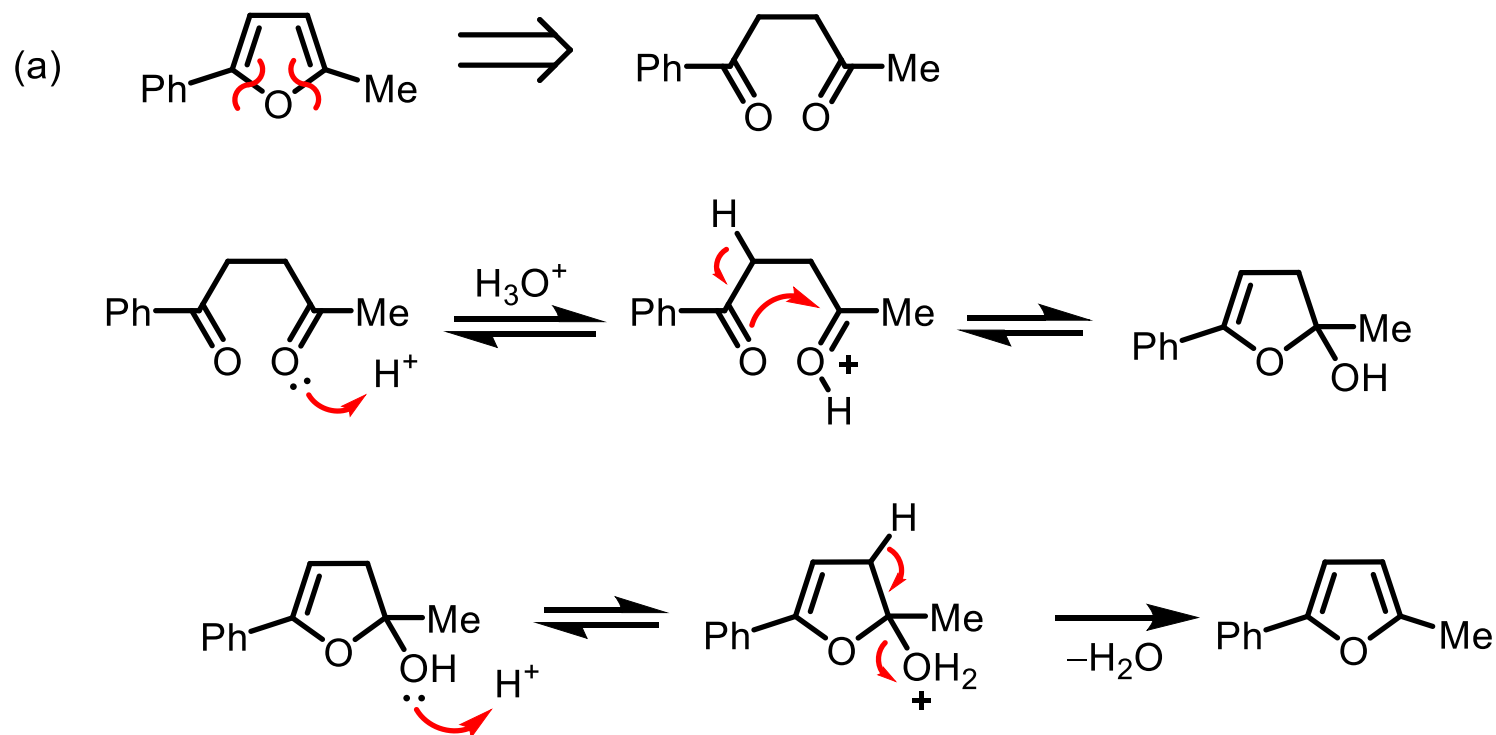
1. Draw a curly arrow reaction mechanism and product for the following base-catalysed reaction:





Topic 7 practice questions: Answers

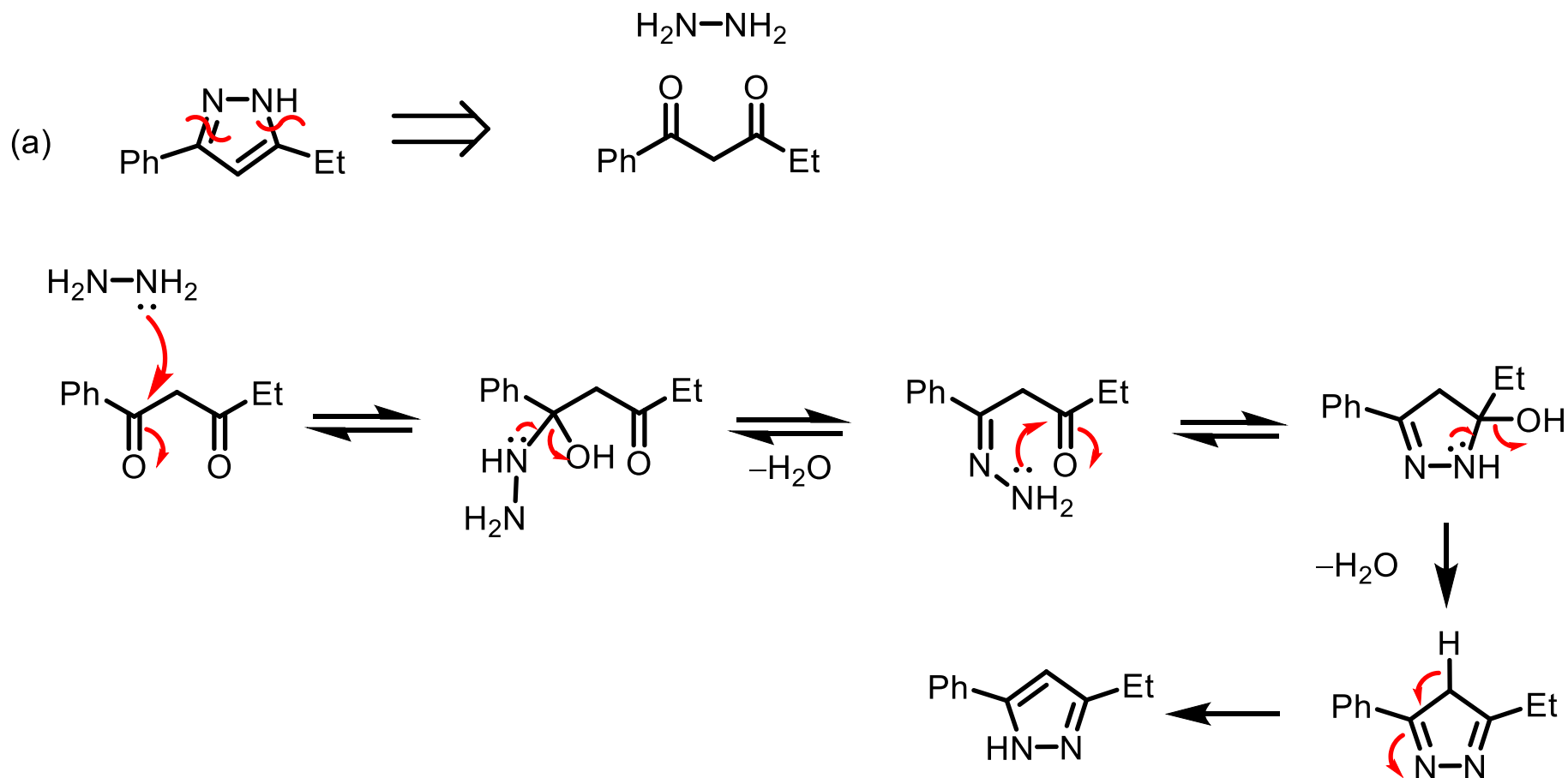
2. How would you synthesise these heteroaromatics? Provide starting materials and mechanisms.





Topic 7 practice questions: Answers

2. How would you synthesise these heteroaromatics? Provide starting materials and mechanisms.





Practise questions

3. Propose a mechanism for the following reaction. Is the heterocyclic ring created in this reaction aromatic? (Does it fulfil the 4 rules of aromaticity?)

