

Chemistry II (Organic)

Heteroaromatic Chemistry

LECTURE 6

Pyridines: properties, syntheses & reactivity

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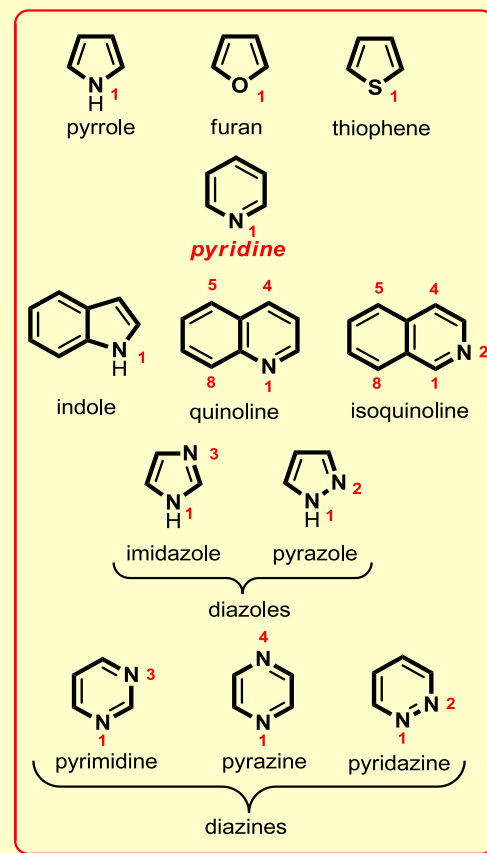
**Imperial College
London**

Mar 2012

Format & scope of lecture 6

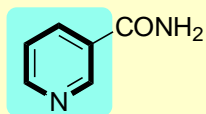
- **Pyridines:**
 - structure, bonding & properties
 - syntheses
 - *via* cycloadditions
 - *via* cyclisations
 - reactivity
 - electrophilic addition at N (*N*-oxides *etc.*)
 - S_EAr
 - S_NAr
 - Metallation

- **Supplementary slides 1-4**
 - Hybridisation and pKa
 - *N*-oxides reactivity
 - revision of S_NAr mechanism

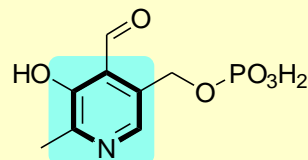


Pyridines – Importance

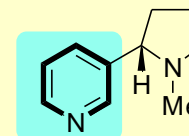
■ Natural products:



niacin - vitamin B3
(skin growth promotor)

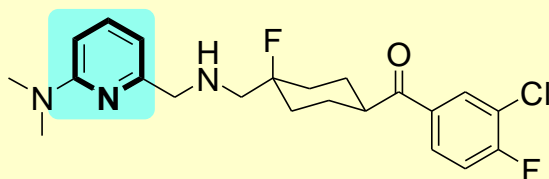


pyridoxal phosphate
(cofactor for transaminases)

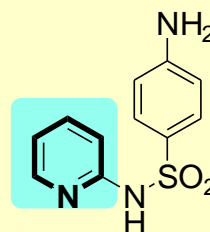


nicotine
(tobacco alkaloid
stimulant)

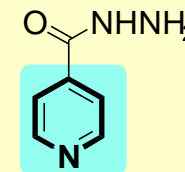
■ Pharmaceuticals:



5-HT_{1A} receptor antagonist
(antidepressant)



sulphapyridine
(antibacterial)

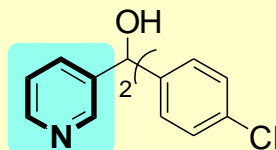


isoniazide
(antituberculosis)

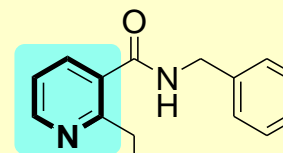
■ Agrochemicals:



dowco 263
(fungicide)



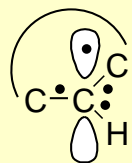
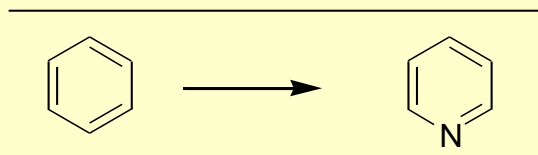
parinol
(fungicide)



phoxynicotinamide
(herbicide)

Benzene \rightarrow Pyridine

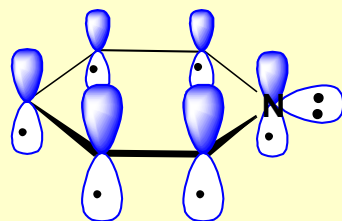
- **Pyridine** can be considered as benzene in which one **CH** unit has been replaced by an iso-electronic **N** unit
 - it is no longer C_6 -symmetric but it retains 6p electrons and is still aromatic:



sp^2 hybrid **CH**

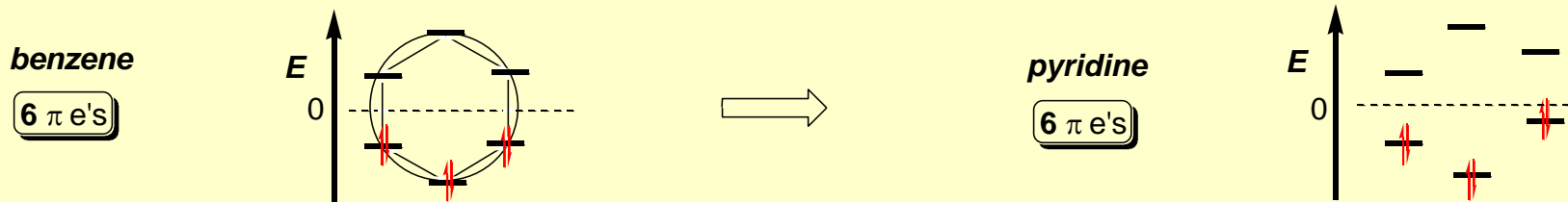


sp^2 hybrid **N**:



sp^2 lone pair in the plane of the ring
NOT involved in aromatic sextet

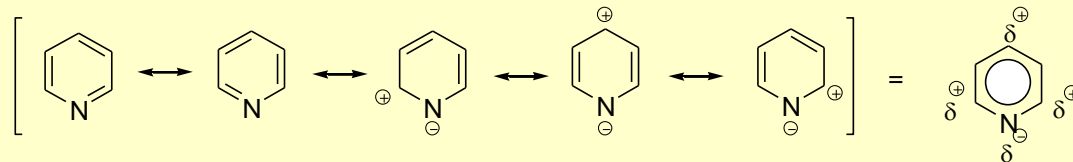
- The MO diagram for pyridine resembles that for benzene (lecture 1) but loss of symmetry \rightarrow loss of degeneracy:



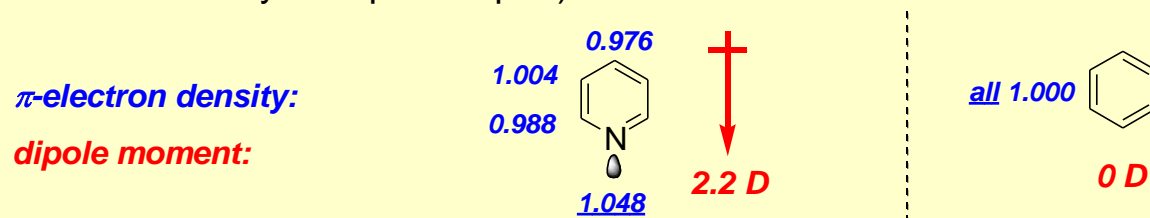
- As for **pyrrole** the energy match and orbital overlap between the **N**-centred p-orbital and the adjacent **C**-centred p-orbitals is relatively poor so the **resonance energy is lower** than for **benzene**: 117 kJmol^{-1} cf. 152 kJmol^{-1}

Pyridine: Calculated Electron Density \leftrightarrow Reactivity

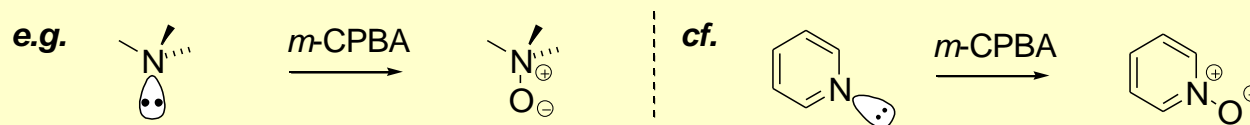
- Like benzene, pyridine has 6 π -electrons distributed over 6 atoms; However, both **induction** and **resonance** effects draw electron density towards the **N** atom so that the carbon framework is **ELECTRON DEFICIENT**



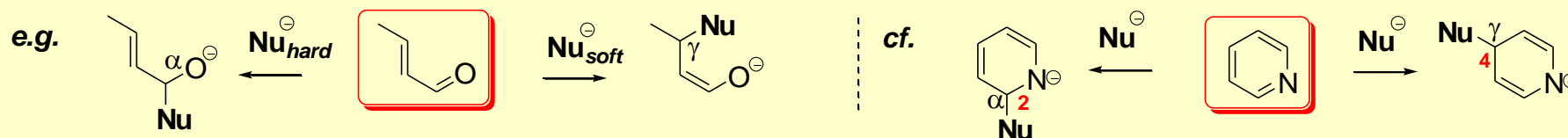
- The distribution of π -electron density is manifested in its **calculated π -electron density** and **dipole moment** (although this latter property is dominated by the sp^2 lone pair):



- The **REACTIVITY** of pyridine shows aspects which resemble the reactivity of:
 - benzene**: substitution reactions; resistance to addition/ring-opening (to avoid loss of resonance energy)
 - tert-amines**: protonation, alkylation, *N*-oxide formation & co-ordination to Lewis acids by the **N** lone pair:



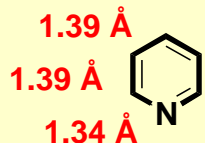
- conjugated imines/carbonyl compounds**: susceptibility to attack by nucleophiles at α /**C2** and γ /**C4** positions:



Pyridine – Structure and Properties

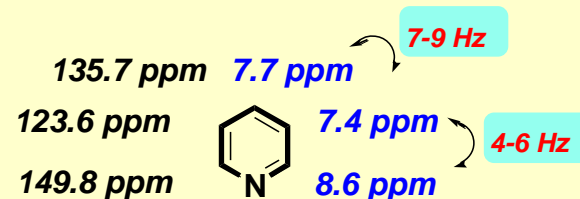
- A liquid bp 115 °C
- **Bond lengths**, ^1H and ^{13}C NMR **chemical shifts** and **coupling constants** as expected for an aromatic system:

bond lengths:

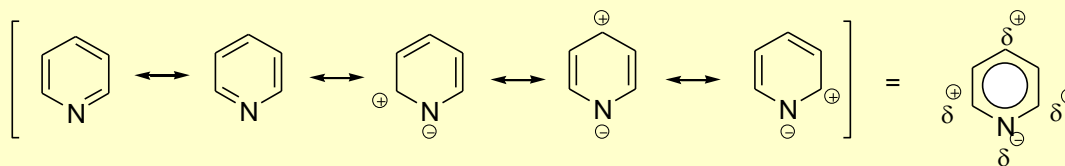


cf. ave C-C 1.48 Å
ave C=C 1.34 Å
ave C-N 1.45 Å

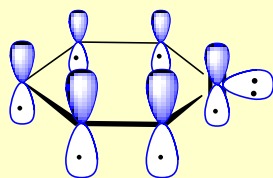
^{13}C and ^1H NMR:



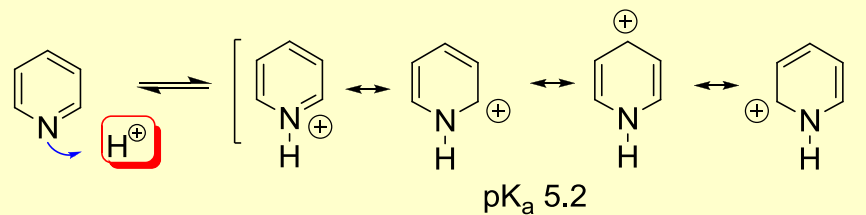
- **Resonance energy:** 117 kJmol $^{-1}$ [*i.e.* lower than benzene (152)]
 - → can undergo **nucleophilic addition** reactions (particularly pyridinium salts)
- **Electron density:** **electron deficient** cf. benzene
 - → **reactive towards nucleophilic substitution ($\text{S}_{\text{N}}\text{Ar}$)**, poorly reactive towards electrophilic substitution ($\text{S}_{\text{E}}\text{Ar}$)



- **Basic** (pK_{a} 5.2) because the **N** lone pair is **NOT** part of the aromatic sextet of electrons. Less basic than a *tert*-amine (e.g. Et_3N , pK_{a} 11) because of difference in hybridisation (sp^2 vs. sp^3 ; see supplementary slide 1):



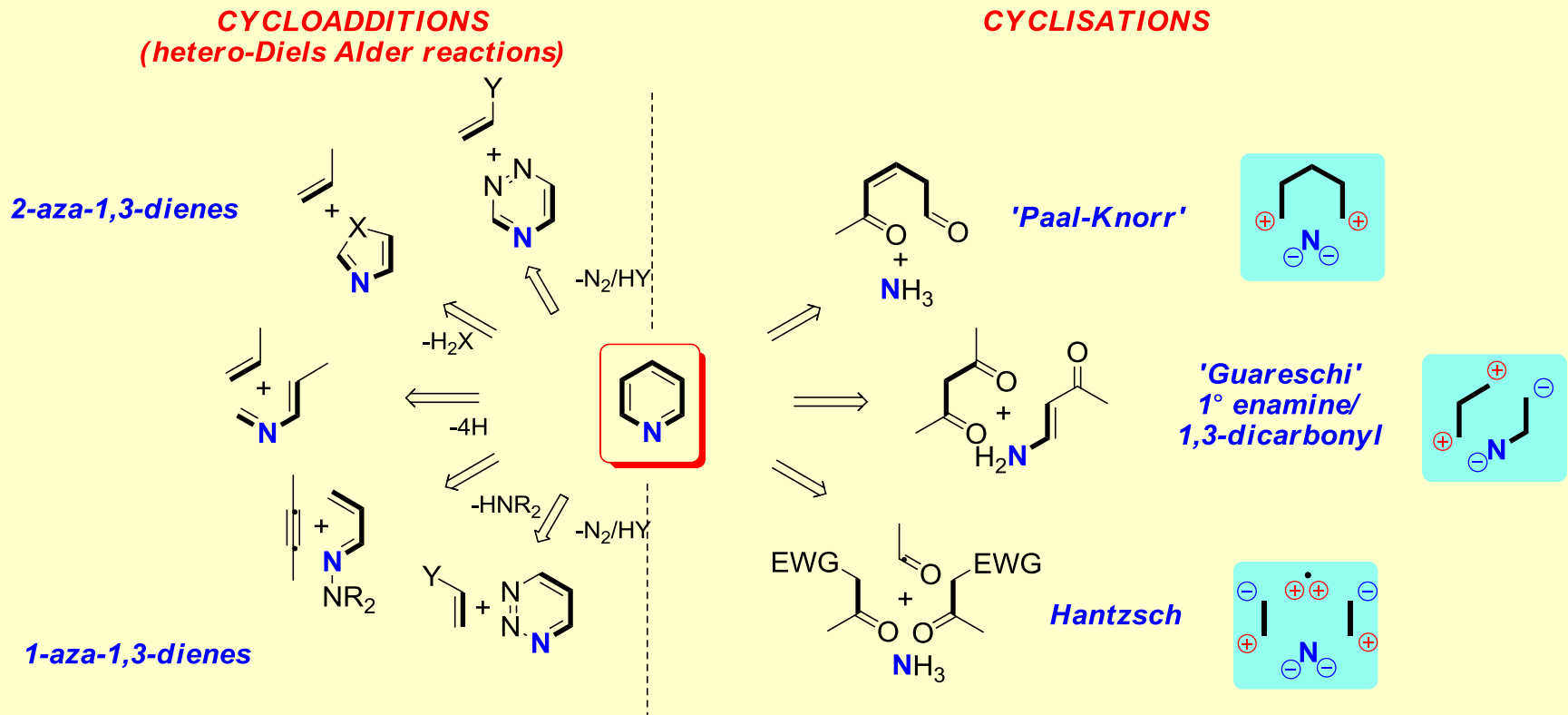
sp^2 lone-pair is NOT part of aromatic sextet 'π-deficient'



Pyridines – Syntheses

■ **Pyridines** can be prepared by **cycloaddition** or **cyclisations/cyclocondensation**:

□ some common approaches are:



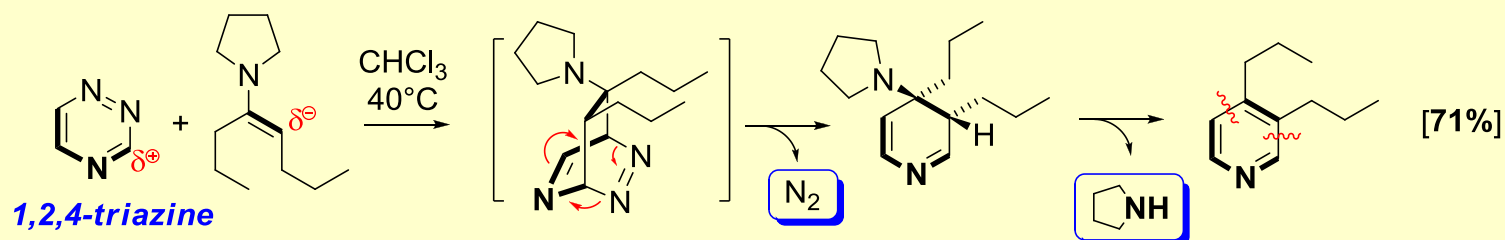
Pyridines – Synthesis by cycloaddition

■ CYCLOADDITION REACTIONS:

- **aza-Diels-Alder** between aza-1,3-dienes and alkenes/alkynes (usually **inverse electron demand**)
- generally give non-aromatic heterocycles → extrusion of small molecule(s) → aromatic species

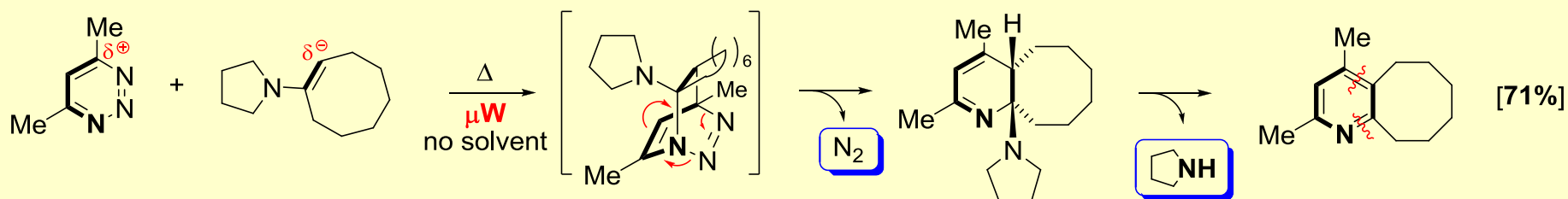
■ 2-Aza-1,3-dienes:

- e.g. inverse electron demand hetero-Diels-Alder cycloaddition of 1,2,4-triazine with an enamine:



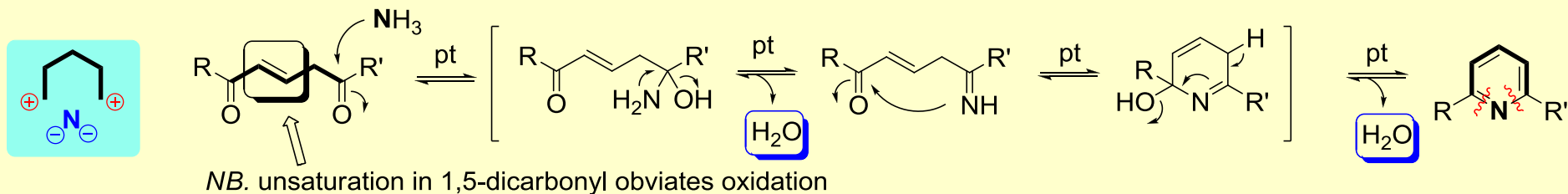
■ 1-Aza-1,3-dienes:

- e.g. inverse electron demand hetero-Diels-Alder cycloaddition of a 1,2,3-triazine with an enamine:

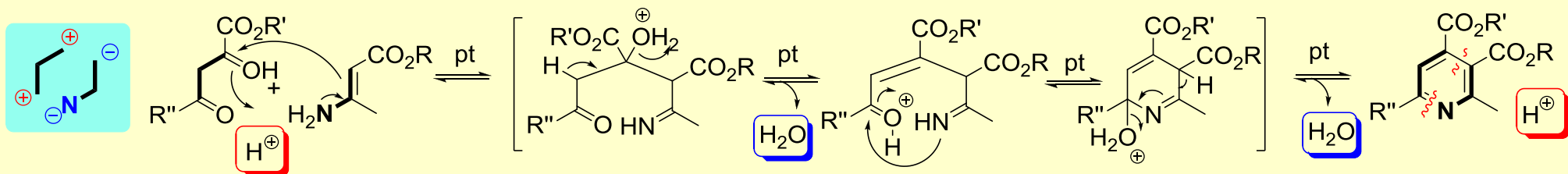


Pyridines – Synthesis by cyclisation/cyclocondensation

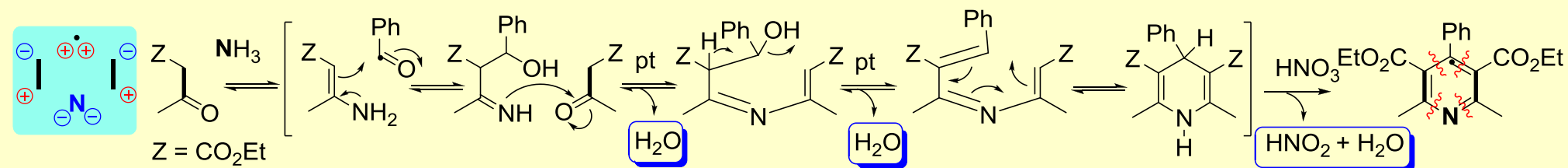
- **Paal-Knorr (Type I):** 1,5-dicarbonyl with NH_3



- **'Guareschi' (Type II):** 1,3-dicarbonyl with 1° enamine

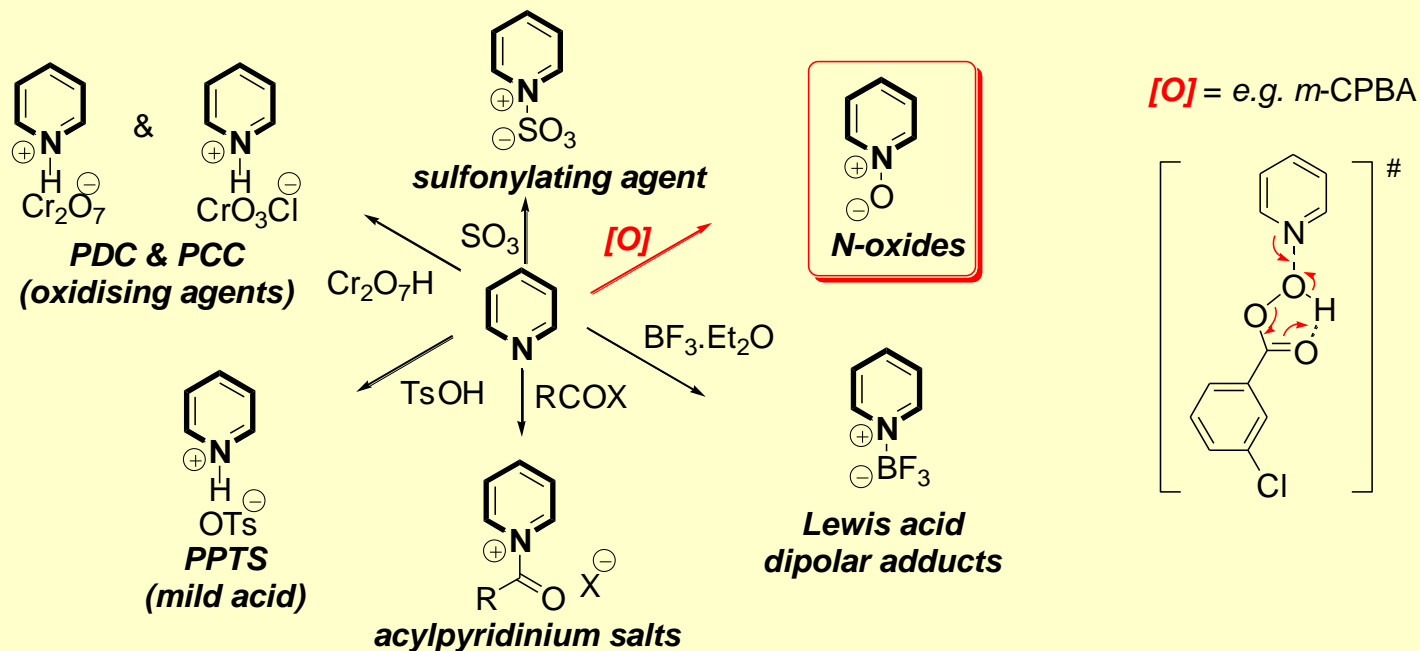


- **Hantzsch:** 1,3-dicarbonyl($\times 2$) & aldehyde with NH_3 then oxidation (typically with HNO_3 , lecture 2)



Pyridines – Reactivity

■ Electrophilic addition to the pyridyl N:



□ N-oxides are particularly valuable because they:

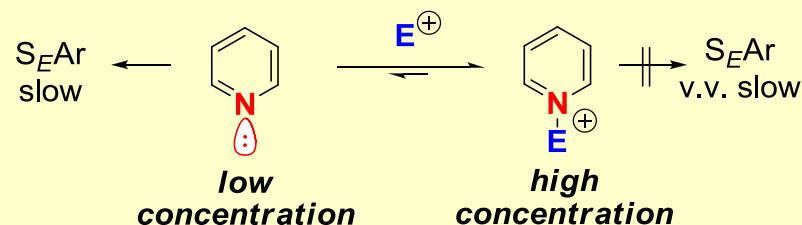
- are more susceptible to S_EAr than pyridines: but react at **C4** cf. **C3** for pyridines (see later)
- are more susceptible to S_NAr than pyridines: same selectivity: *i.e.* **C4** > **C2** >> **C3** (see later)
- promote *ortho*-metallation (*i.e.* deprotonation)
- allow some synthetically useful rearrangements
- for details see supplementary slides 2-3

Pyridines – Reactivity cont.

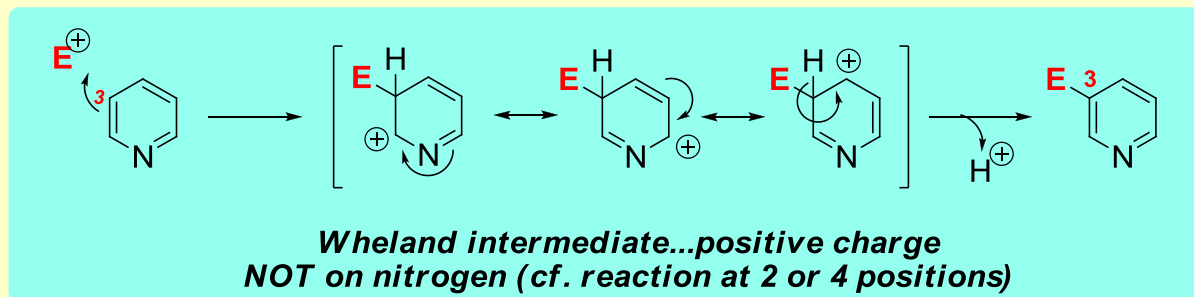
■ **Electrophilic substitution:** via addition-elimination (S_EAr)

□ **reactivity:** unreactive towards most electrophiles (E^+); \ll benzene (relative rate $\times 10^{-12}$); similar to nitrobenzene

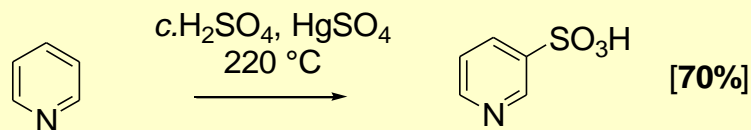
■ **Two factors:** 1) ' π -deficient'; 2) salt formation via **N** lone pair:



□ **regioselectivity:** the kinetic 3- & 5-products predominate; reaction at these positions avoid unfavourable positive charge build-up on nitrogen in the Wheland-type intermediate:

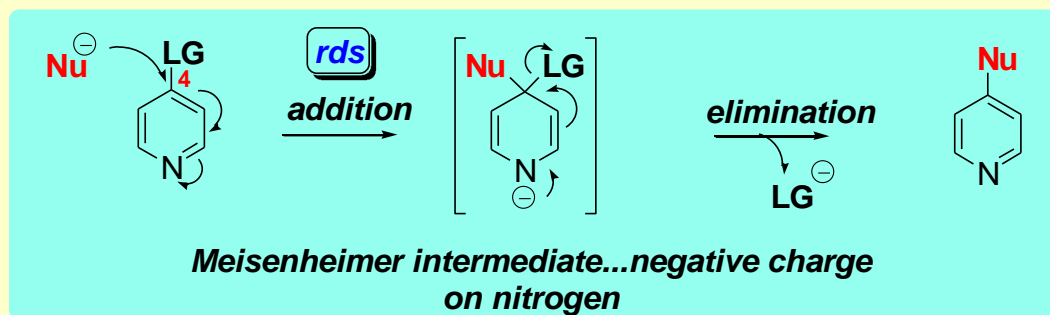


□ e.g. **sulfonylation:** ($E^+ = SO_3H^+$)

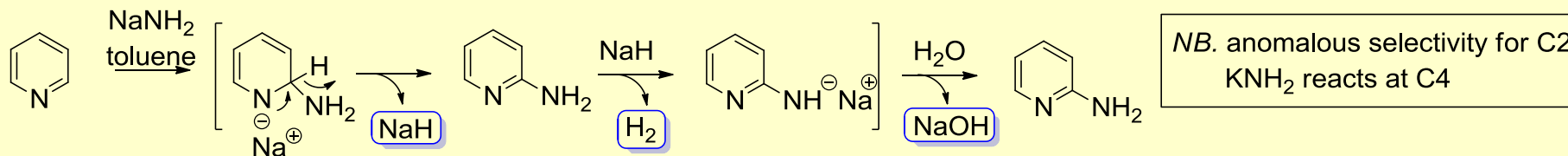


Pyridines – Reactivity cont.

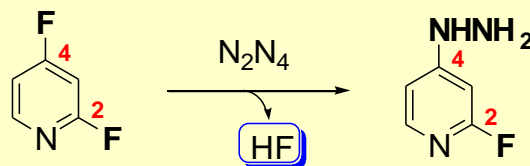
- **Nucleophilic substitution:** via addition-elimination (S_NAr)
 - **reactivity:** reactive towards strong nucleophiles (Nu^-)
 - **regioselectivity:** substitution at 4 & 2 positions ($C4 > C2$) → Meisenheimer intermediates have negative charge stabilised on the electronegative nitrogen
 - 'leaving group' (LG) can be H but Cl, Br, NO_2 etc. more facile
 - nucleophiles include alkoxides, amines, thiolates, organolithiums and Grignard reagents



- e.g. **the Chichibabin reaction:** ($Nu^- = NH_2^-$, LG = H)



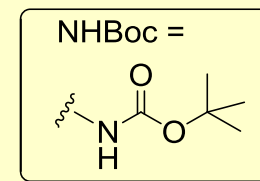
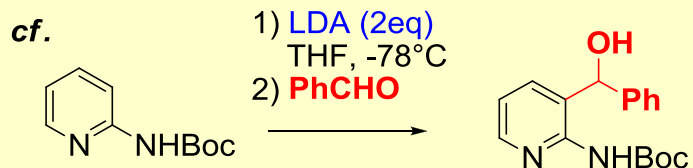
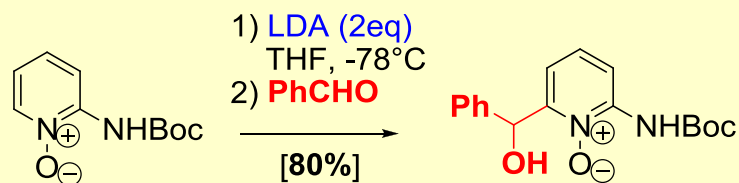
- e.g. **hydrazination:** ($Nu^- = N_2H_4$, LG = F)



Pyridines – Reactivity cont.

■ Metallation *ortho* to N:

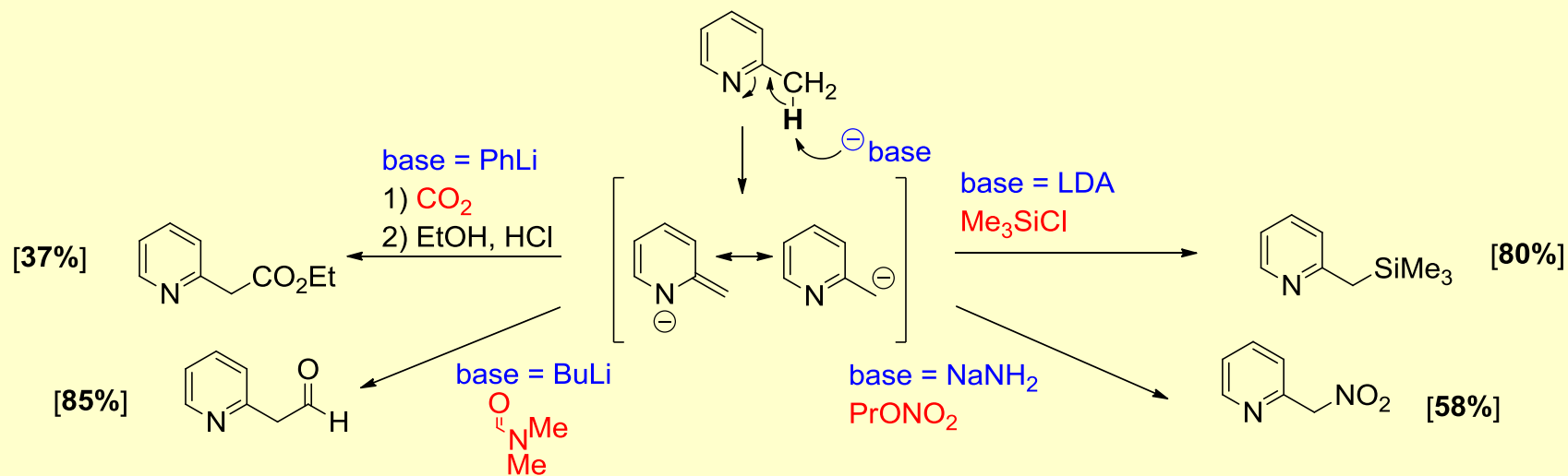
- deprotonation by strong bases *ortho* to the N with lithium amide bases possible but more facile on N-oxide derivatives:



- *i.e.* the *ortho* directing effect of the 'NLiBoc' group overrides that of the ring N but not that of the N-oxide
- NB. For an overview & mechanistic discussion see **LECTURE 7** (also: Joule & Smith (5th Ed) chapter 4).

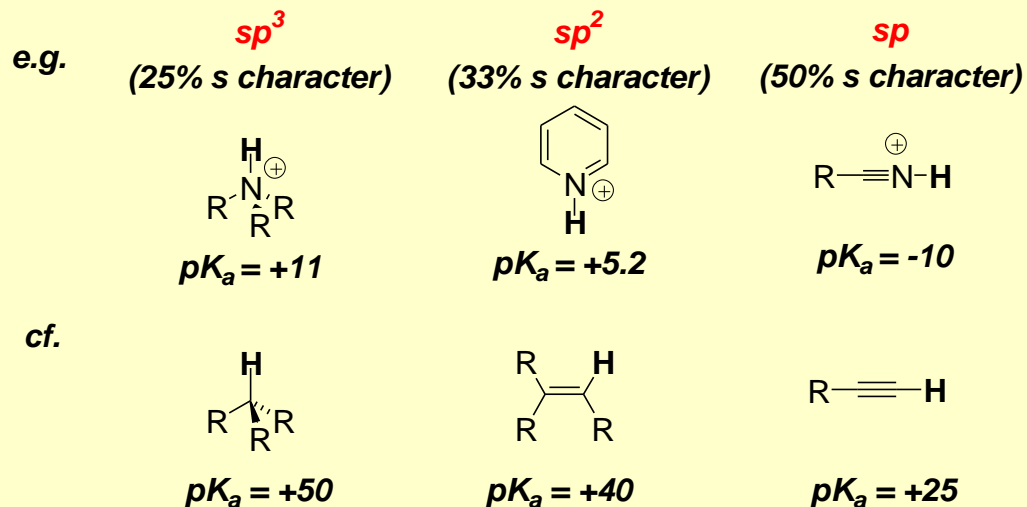
■ Metallation at benzylic C2 & C4 positions:

- have similar acidity to protons α -to a carbonyl ($pK_a \sim 25$) and can be readily deprotonated (even with alkoxides) to give **enamine anion**:



Supplementary Slide 1 – Nitrogen Basicity ↔ Hybridisation of Lone Pair

- The **basicity** of a **N lone pair** depends critically on its **hybridisation state**:

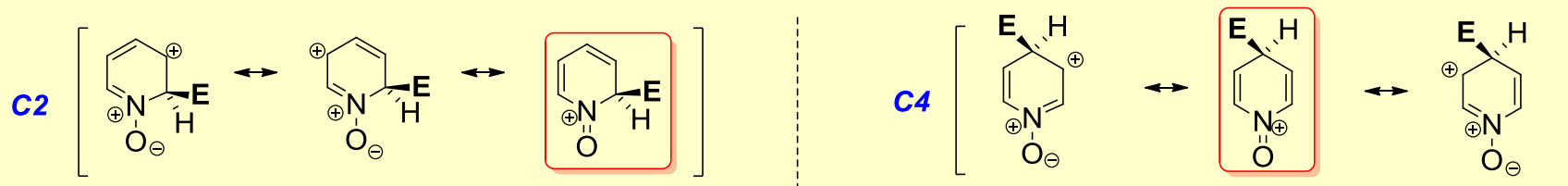


rationale

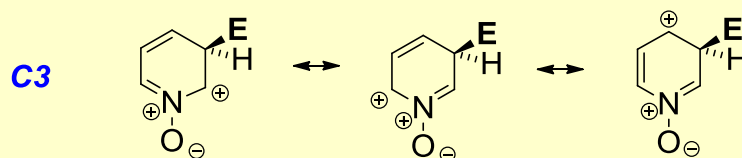
- greater s-character:
- → lower energy orbital (= 'more electronegative')
- → less able to carry +ive charge
- → more able to carry -ive charge

Supplementary Slide 2 – Pyridine-*N*-oxide reactivity – S_EAr & S_NAr

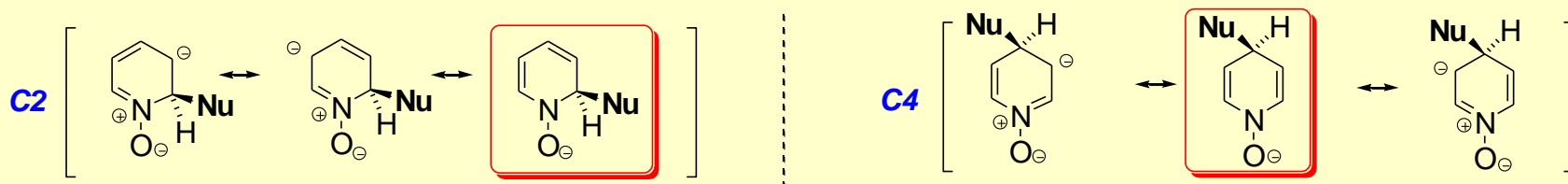
- Pyridine-*N*-oxides are **more reactive towards S_EAr** than pyridines & react at **C4** (cf. **C3**) because:
 - 1) the N lone pair is no longer available to form unreactive salts (\rightarrow faster reactions)
 - 2) a resonance form in which an oxygen lone pair can help stabilise the positive charge in the Wheland intermediate is possible for reaction at **C4** (& **C2**) (\rightarrow different regioselectivity):



*reaction at C2 & C4 allows resonance forms involving oxygen -
reaction at C4 favoured in practice, mainly for steric reasons*

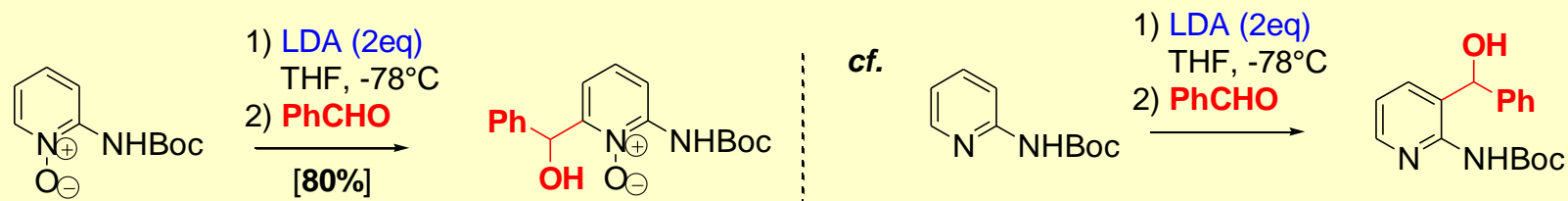


- Pyridine-*N*-oxides are also **more reactive towards S_NAr** than pyridines because a resonance form in which the negative charge in the Meisenheimer intermediate is localised on the electronegative oxygen is possible for reaction at **C4** & **C2** (i.e. same regioselectivity as for pyridine):



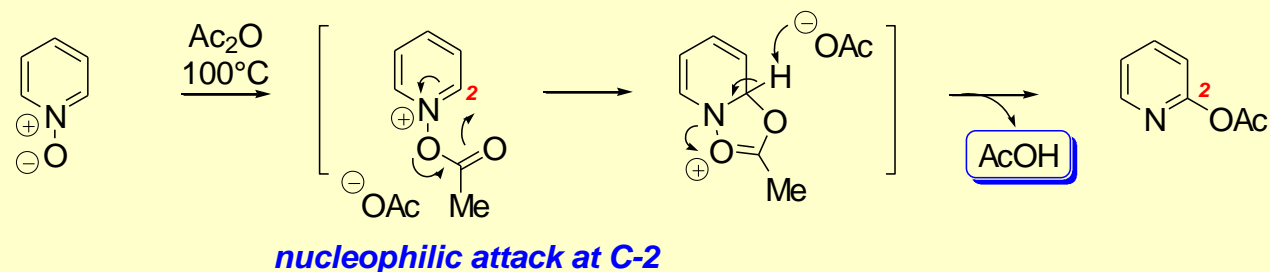
Supplementary Slide 3 – Pyridine-*N*-oxide reactivity – metallation & rearrangements

- Pyridine-*N*-oxides are **more readily metallated** (i.e. **deprotonated**) at the *ortho* positions than pyridines
 - this is because the *N*-oxide decreases pair-pair electron repulsions and increases chelation:

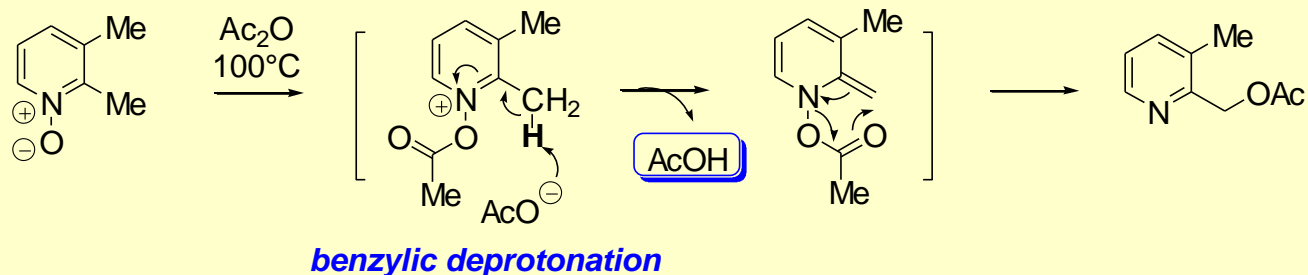


- Pyridine-*N*-oxides also undergo some useful rearrangements to give oxygenated pyridines:

- 2-acetoxylation:**



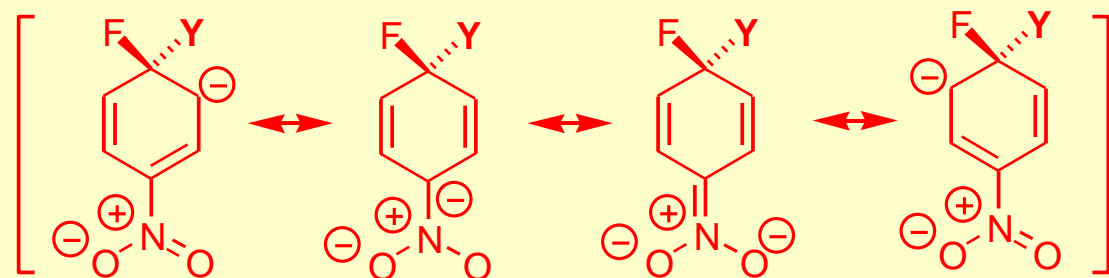
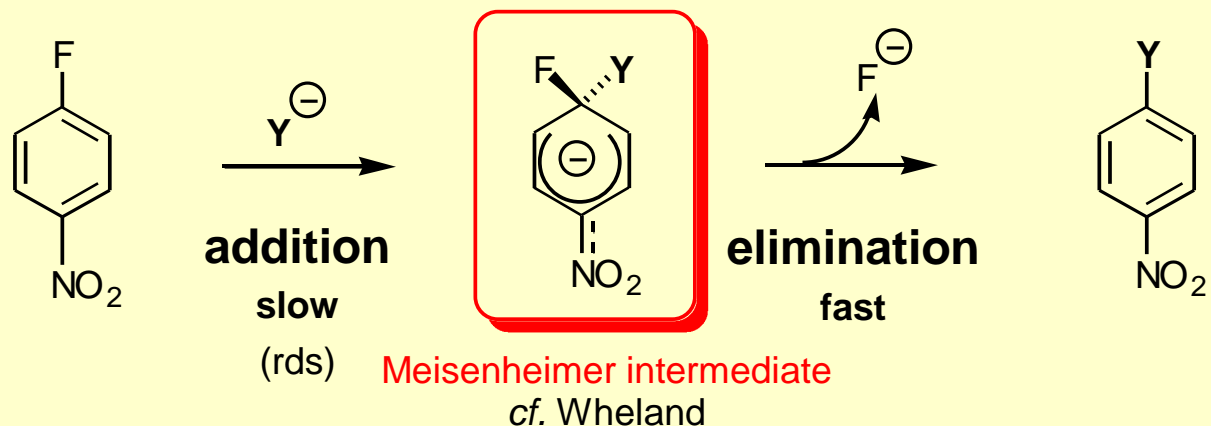
- benzylic acetoxylation:**



Supplementary Slide 4 – Nucleophilic Aromatic Substitution: S_NAr

■ **Mechanism:** addition-elimination

- Rate = $k[ArX][Y^-]$ (bimolecular but rate determining step does *NOT* involve departure of LG (cf. S_N2))
- e.g. 4-fluoro nitrobenzene:



notes

- *Intermediates:* energy minima
- *Transition states:* energy maxima
- Meisenheimer intermediate is NOT aromatic but stabilised by delocalisation
- Generally under kinetic control

