Chemistry II (Organic)

Heteroaromatic Chemistry
LECTURE 6
Pyridines: properties, syntheses & reactivity

Alan C. Spivey
a.c.spivey@imperial.ac.uk

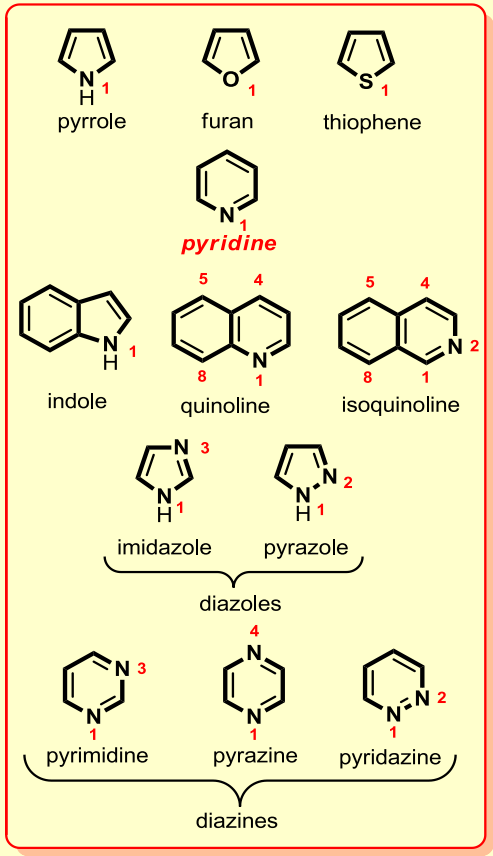
Imperial College London

Mar 2012

Format & scope of lecture 6

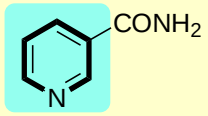
- ***Pyridines:***
  - structure, bonding & properties
  - syntheses
    - *via* cycloadditions
    - *via* cyclisations
  - reactivity
    - electrophilic addition at N (*N*-oxides *etc.*)
    - S_EAr
    - S_NAr
    - Metallation

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

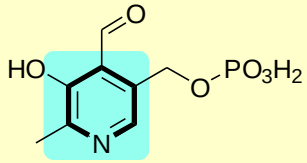


Pyridines *– Importance*

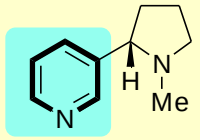
- ***Natural products*:**



niacin - vitamin B3
(skin growth promotor)

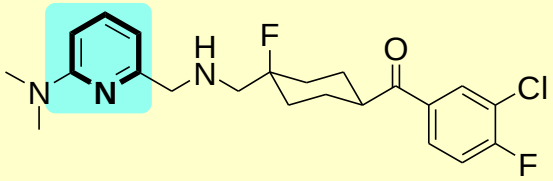


pyridoxal phosphate
(cofactor for transaminases)

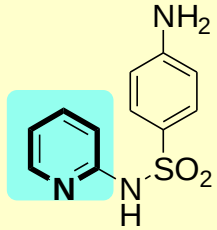


nicotine
(tobacco alkaloid
stimulant)

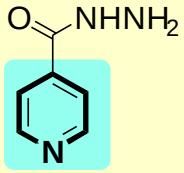
- ***Pharmaceuticals:***



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



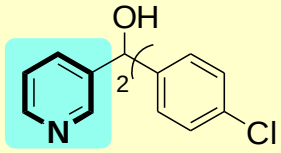
sulpharpyridine
(antibacterial)



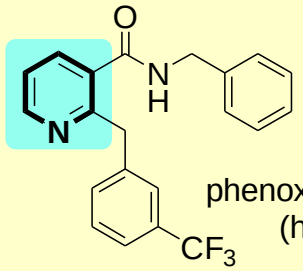
isoniazide
(antituberculosis)

- ***Agrochemicals:***

dowco 263
(fungicide)



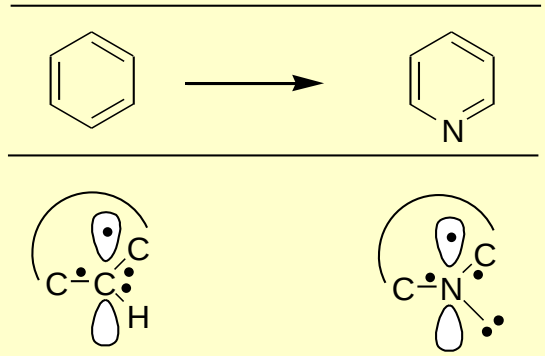
parinol
(fungicide)



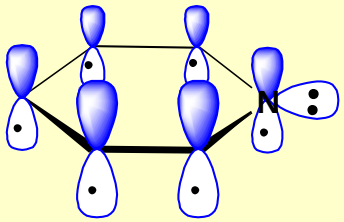
phenoxynicotinamide
(herbicide)

Benzene → 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 *C6*-symmetric but it retains 6p electrons and is still aromatic:



sp^2 hybrid **CH** sp^2 hybrid **N:**

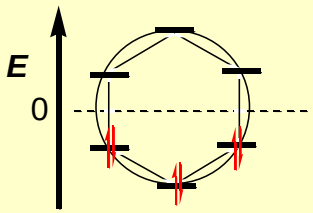


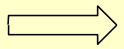
sp^2 lone pair in the plane of the ring
NOT involved in aromatic sextet

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

benzene

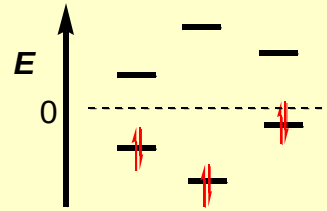
6 π e's





pyridine

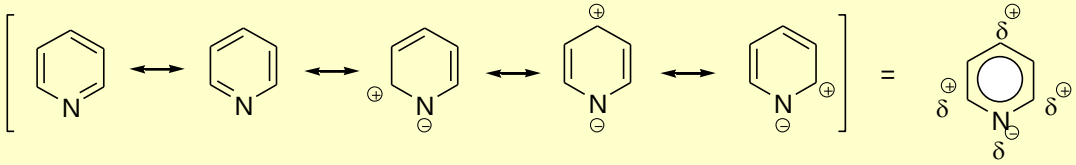
6 π e's



  - 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 ↔ Reactivity*

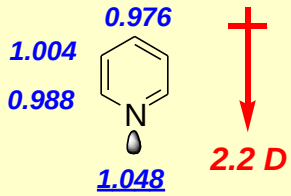
- Like benzene, pyridine has 6 π-electrons distributed over 6 atoms; However, both ***induction*** and ***resonance*** effects draw electron density towards the ***N*** atom so that the carbon framework is ***ELECTRON DEFICIENT***

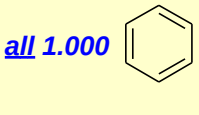


- The distribution of π-electron density is manifested in its ***calculated π-electron density*** and ***dipole moment*** (although this latter property is dominated by the sp^2 lone pair):

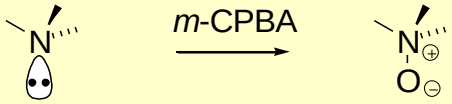
π-electron density:

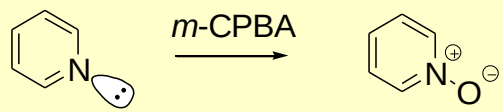
dipole moment:



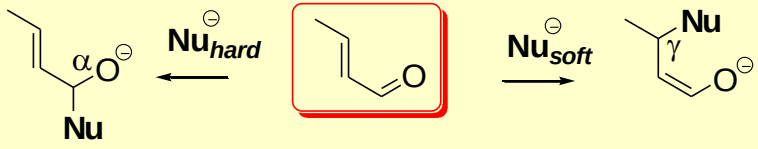


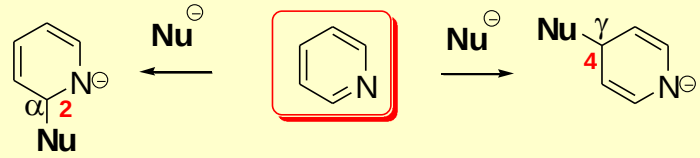
- The ***REACTIVITY*** of pyridine shows aspects which resemble the reactivity of:
  - ***benzene:*** substitution reactions; resistance to addition/ring-opening (to avoid loss of resonance energy)
  - ***tert-amines:*** protonation, alkylation, *N*-oxide formation & co-ordination to Lewis acids by the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

e.g. 

cf. 

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

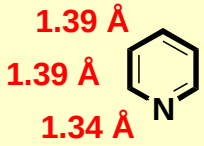
e.g. 

cf. 

Pyridine – *Structure and Properties*

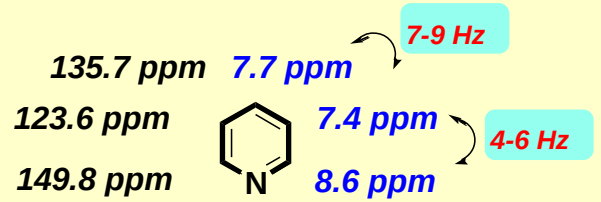
- A liquid bp 115 °C
- ***Bond lengths***, ***^{1}H*** and ***^{13}C NMR chemical shifts*** and ***coupling constants*** as expected for an aromatic system:

bond lengths:



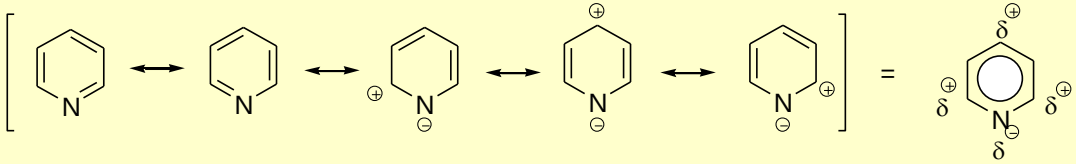
cf. **ave C-C 1.48 Å**
ave C=C 1.34 Å
ave C-N 1.45 Å

^{13}C and ^{1}H NMR:

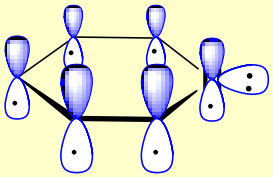


- ***Resonance energy:*** 117 kJmol^{-1} [*i.e.* lower than benzene (152)]
  - → can undergo ***nucleophilic addition*** reactions (particularly pyridinium salts)

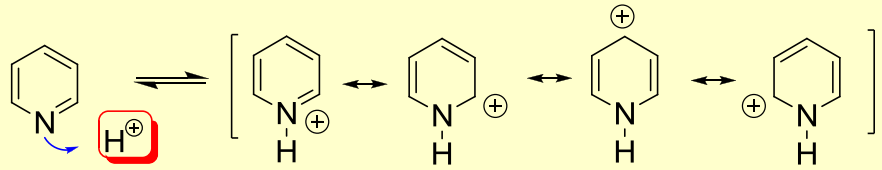
- ***Electron density:*** ***electron deficient*** *cf.* benzene
  - → ***reactive towards nucleophilic substitution (S$_N$Ar)***, poorly reactive towards electrophilic substitution (S$_E$Ar)



- ***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$_3$N, pK$_a$ 11) because of difference in hybridisation (sp^2 *vs.* sp^3; see supplementary slide 1):



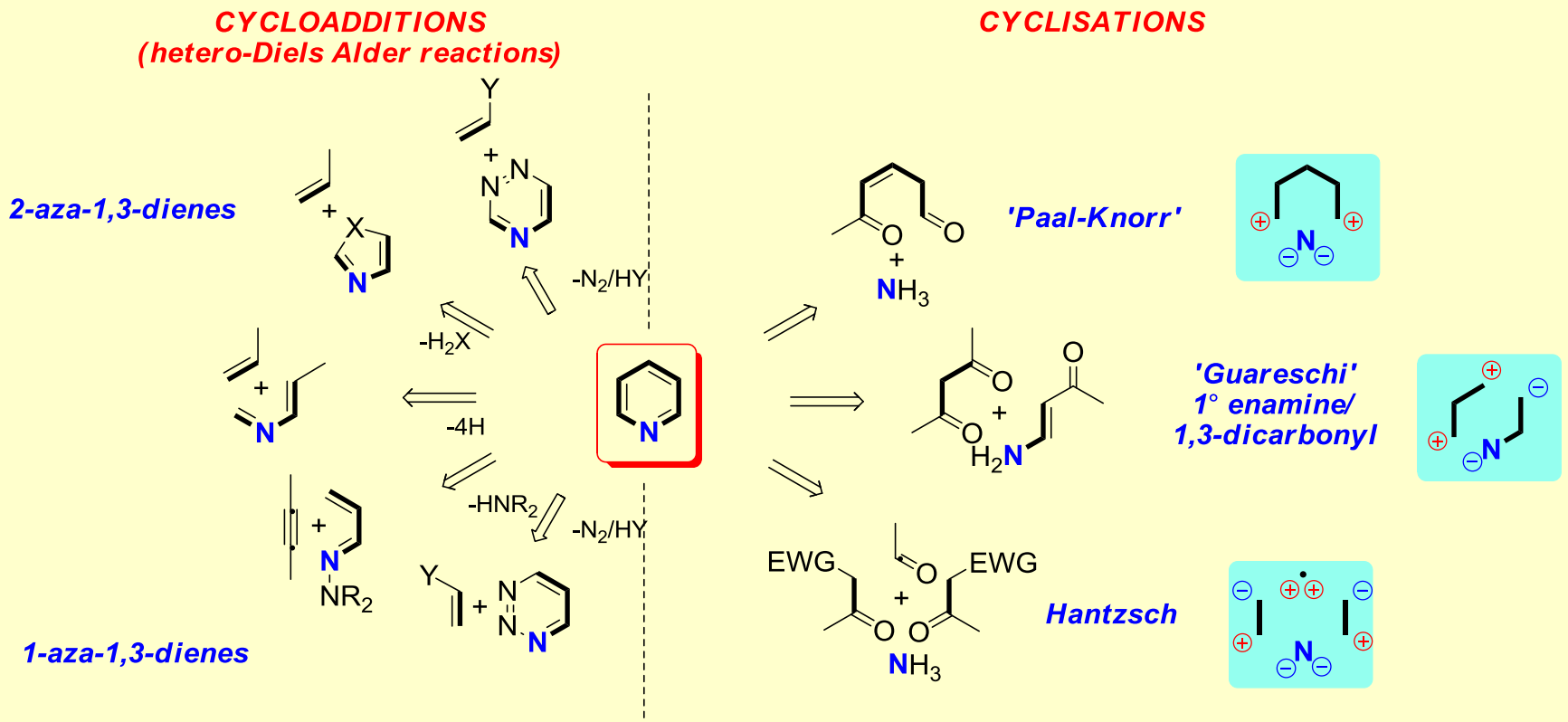
sp^2 lone-pair is NOT part of aromatic sextet 'π-deficient'



pK$_a$ 5.2

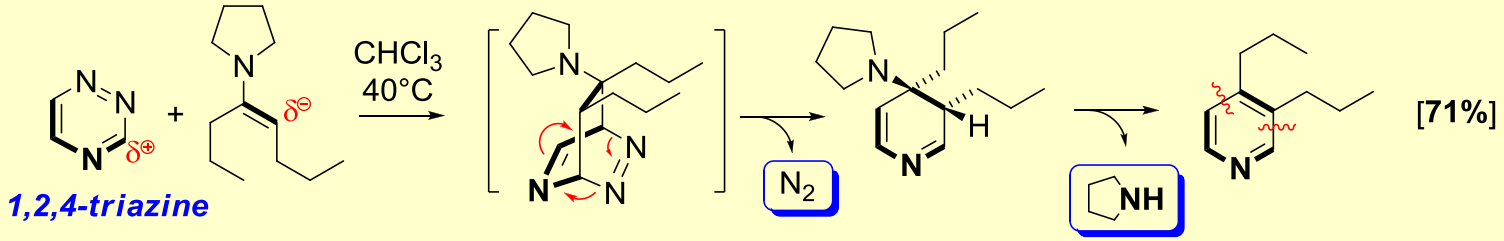
Pyridines – *Syntheses*

- ***Pyridines*** can be prepared by ***cycloaddition*** or ***cyclisations/cyclocondensation:***
  - some common approaches are:

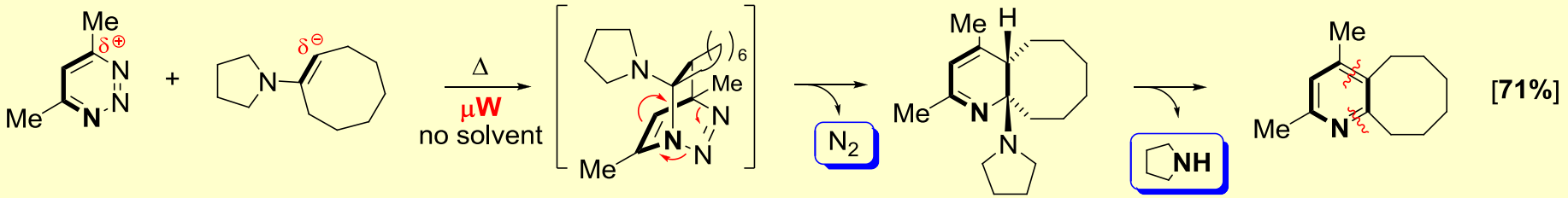


- ***CYCLOADDITION REACTIONS:***
  - ***aza-Diels-Alder*** between aza-1,3-dienes and alkenes/alkynes (usually ***inverse electron demand***)
  - generally give non-aromatic heterocycles → extrusion of small molecule(s) → aromatic species

- ***2-Aza-1,3-dienes:***
  - *e.g.* inverse electron demand hetero-Diels-Alder cycloaddition of 1,2,4-trazine with an enamine:

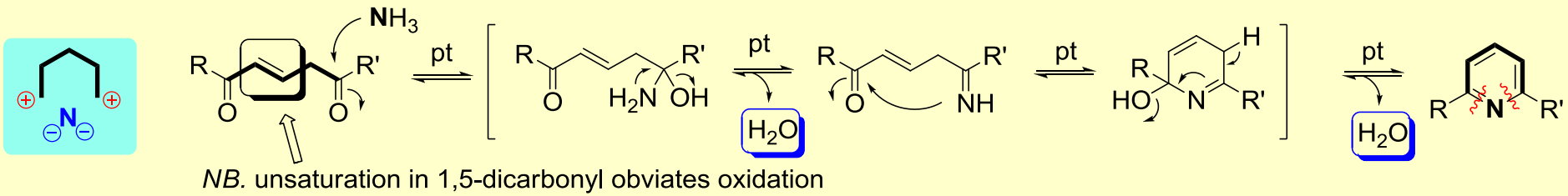


- ***1-Aza-1,3-dienes:***
  - *e.g.* inverse electron demand hetero-Diels-Alder cycloaddition of a 1,2,3-trazine with an enamine:

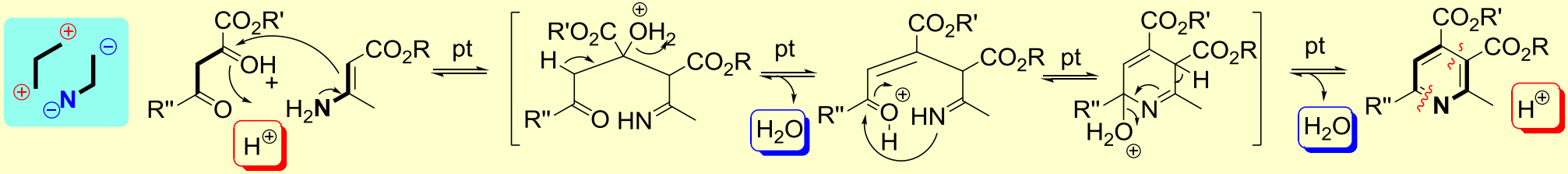


Pyridines – *Synthesis by cyclisation/cyclocondensation*

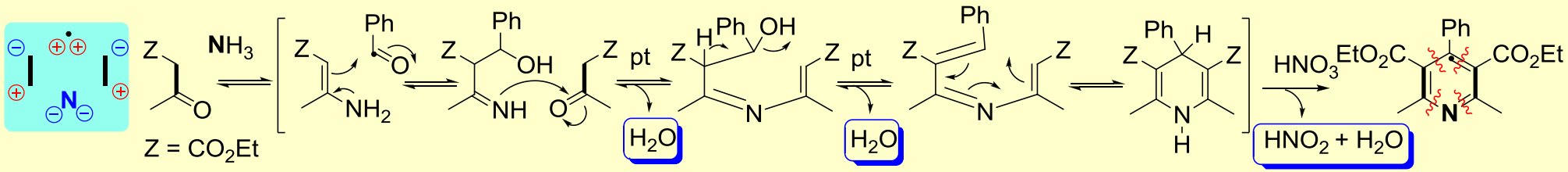
- ***Paal-Knorr (Type I):*** 1,5-dicarbonyl with NH_3



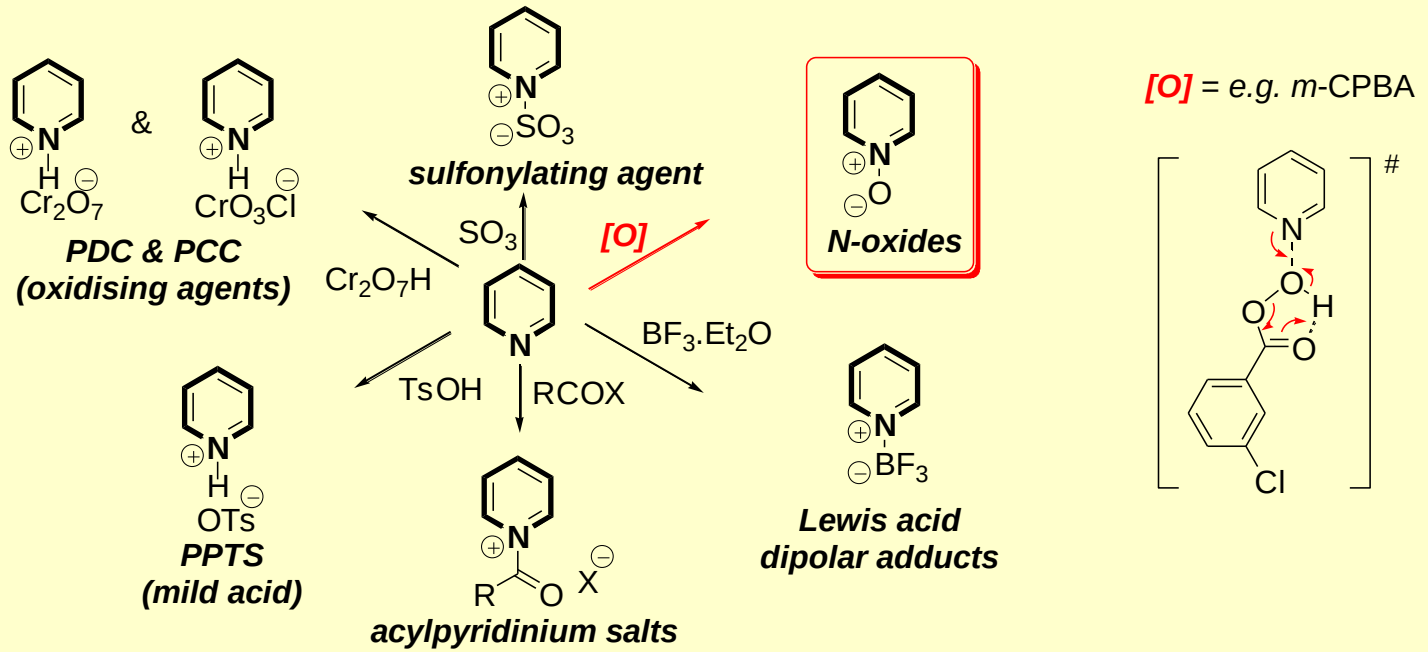
- ***'Guareschi' (Type II):*** 1,3-dicarbonyl with 1° enamine



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



- ***Electrophilic <u>addition</u> to the pyridyl N:***

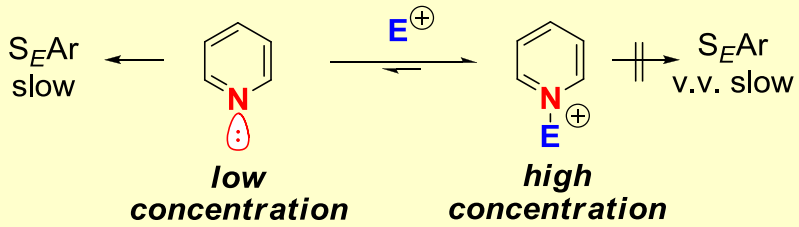


  - *N*-oxides are particularly valuable because they:
    - are more susceptible to S_EAr than pyridines: but react at ***C4*** *cf.* ***C3*** for pyridines (see later)
    - are more susceptible to S_NAr than pyridines: same selectivity: *i.e.* **C4** > ***C2*** >> ***C3*** (see later)
    - promote *ortho*-metallation (*i.e.* deprotonation)
    - allow some synthetically useful rearrangements

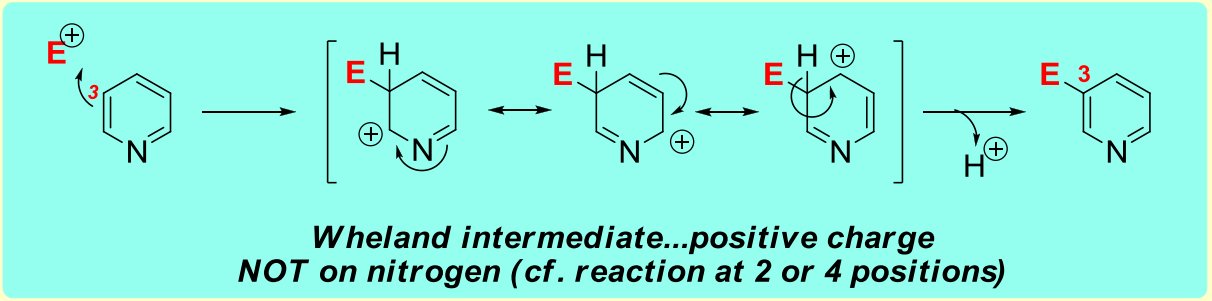
    - for details see supplementary slides 2-3

Pyridines *– Reactivity cont.*

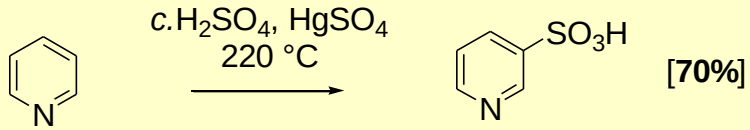
- ***Electrophilic <u>substitution</u>:*** *via* addition-elimination (S_EAr)
  - **<u>reactivity:</u>** unreactive towards most electrophiles (**E**$^+$); <<benzene (relative rate $\times 10^{-12}$); similar to nitrobenzene
    - ***Two factors:*** 1) 'π-deficient'; 2) salt formation *via* ***N*** lone pair:



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

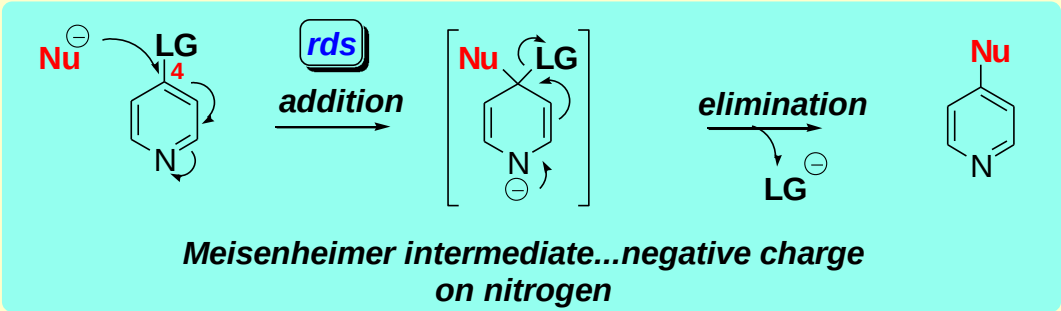


  - ***e.g.*** **<u>sulfonylation:</u>** (**E**$^+$ = SO_3H^+)



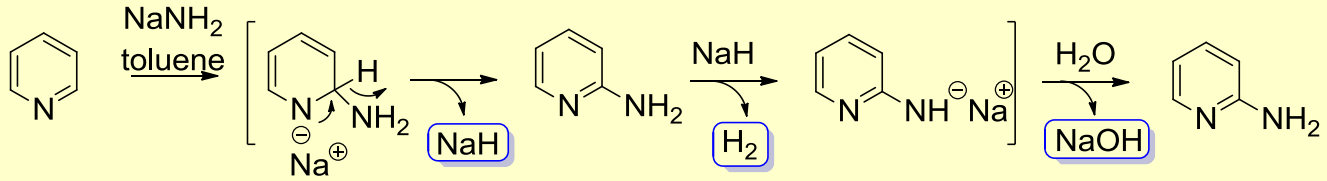
Pyridines *– Reactivity cont.*

- ***Nucleophilic <u>substitution</u>:*** *via* addition-elimination (S_NAr)
  - **<u>reactivity:</u>** reactive towards strong nucleophilies (**Nu**$^-$)
  - **<u>regioselectivity:</u>** 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



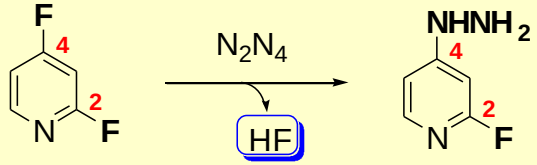
Meisenheimer intermediate...negative charge on nitrogen

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



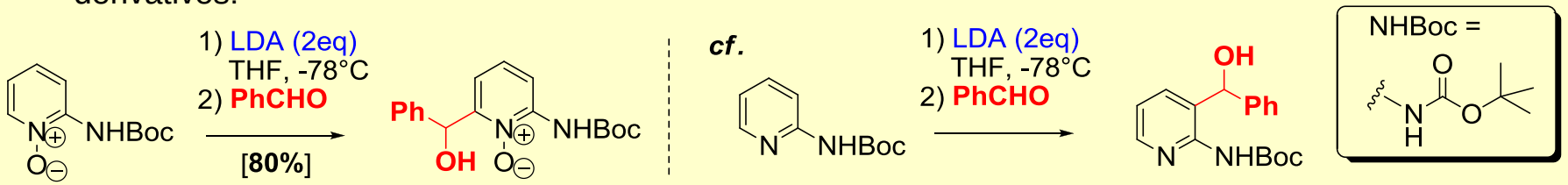
NB. anomalous selectivity for C2
KNH_2 reacts at C4

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



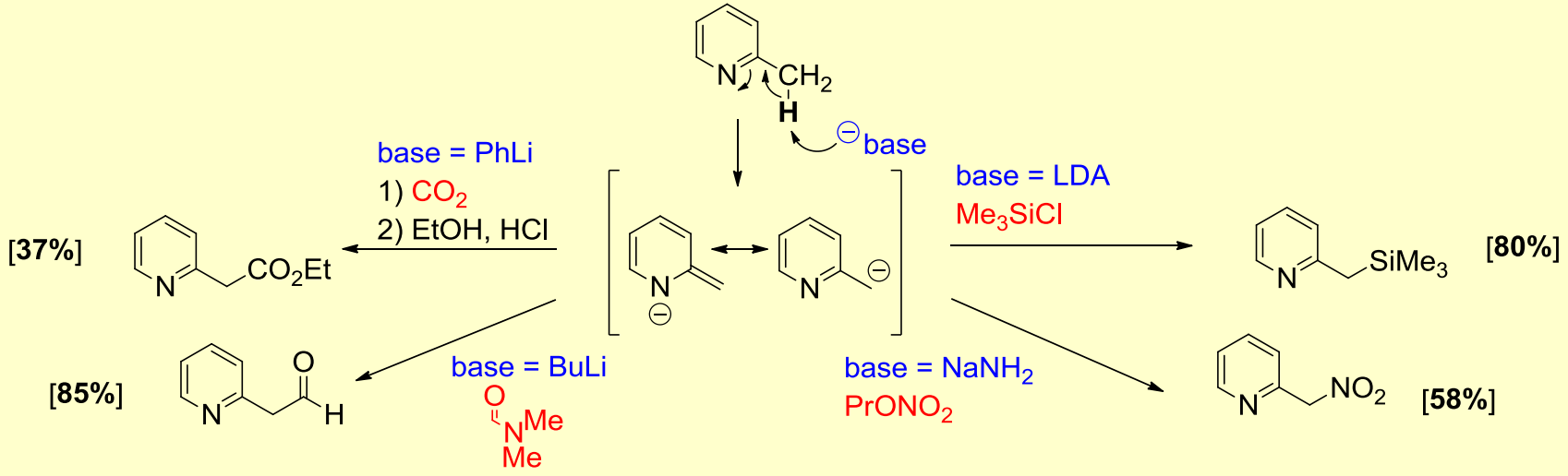
Pyridines *– Reactivity cont.*

- ***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).

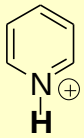
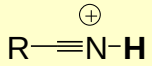
- ***Metallation at benzylic C2 & C4 positions:***
  - have similar acidity to protons ***α-to a carbonyl*** (pK_a ~25) and can be readily deprotonated (even with alkoxides) to give ***enaminate anion:***



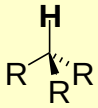
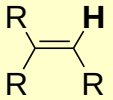
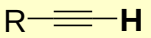
Supplementary Slide 1 – *Nitrogen Basicity ↔ Hybridisation of Lone Pair*

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

e.g.

sp^3	sp^2	sp
(25% s character)	***(33% s character)***	***(50% s character)***
		
pK_a **= +11**	pK_a **= +5.2**	pK_a **= -10**

cf.

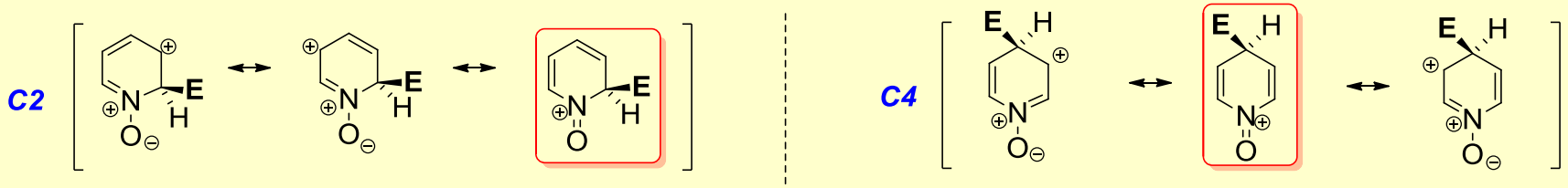
		
pK_a **= +50**	pK_a **= +40**	pK_a **= +25**

rationale

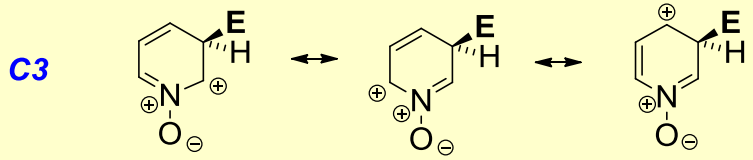
- greater s-character:
- → lower energy orbital (= ‘more electronegative’)
- → less able to carry +ive charge
- → more able to carry -ive charge

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

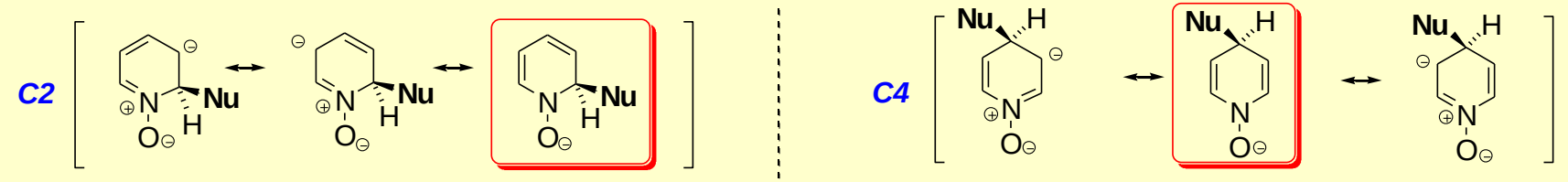
- Pyridine-*N*-oxides are ***more reactive towards S_EAr*** than pyridines & react at ***C4*** (*cf.* ***C3***) because:
  - 1) the N lone pair is no longer available to form unreactive salts (→ faster reactions)
  - 2) a resonance form in which an oxygen lone pair can help stabilise the positive charge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



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

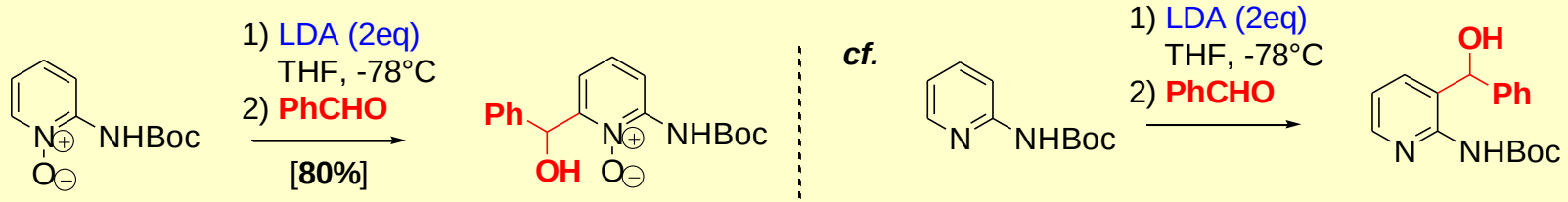


- Pyridine-*N*-oxides are also ***more reactive towards S_NAr*** than pyridines because a resonance form in which the negative charge in the Meisenheimer intermediate is localised on the electronegative oxygen is possible for reaction at ***C4*** & **C2** (*i.e.* same regioselectivity as for pyridine):

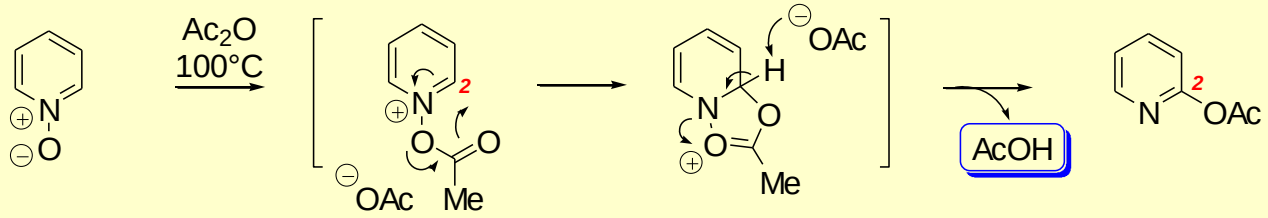


Supplementary Slide 3 – *Pyridine-N-oxide reactivity – metallation & rearrangements*

- 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:

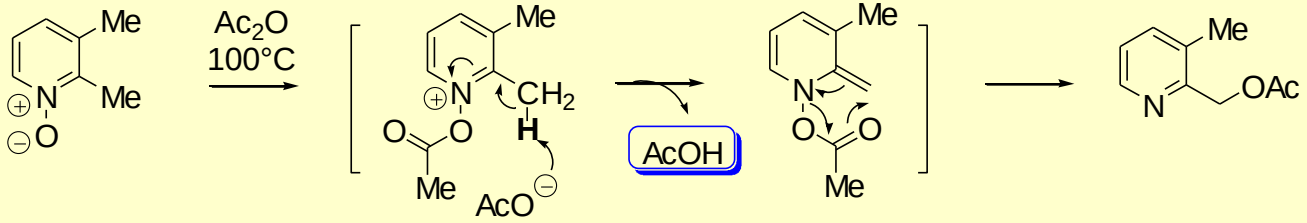


- Pyridine-*N*-oxides also undergo some useful rearrangements to give oxygenated pyridines:
  - ***2-acetoxylation:***



nucleophilic attack at C-2

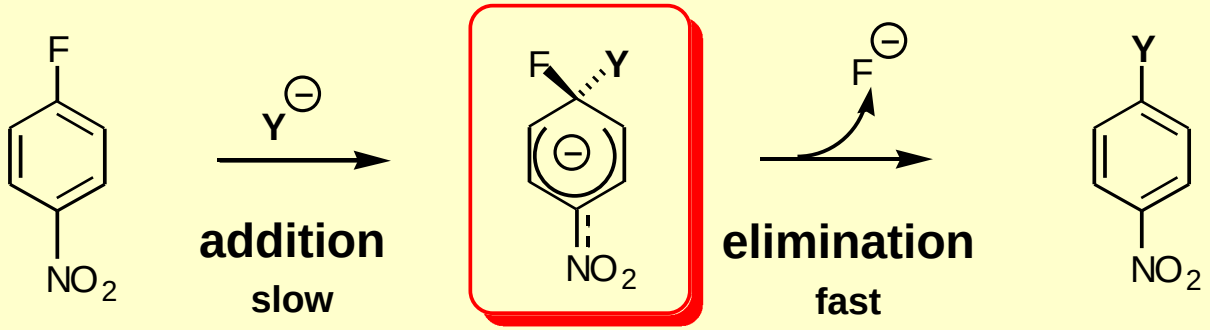
  - ***benzylic acetoxylation:***

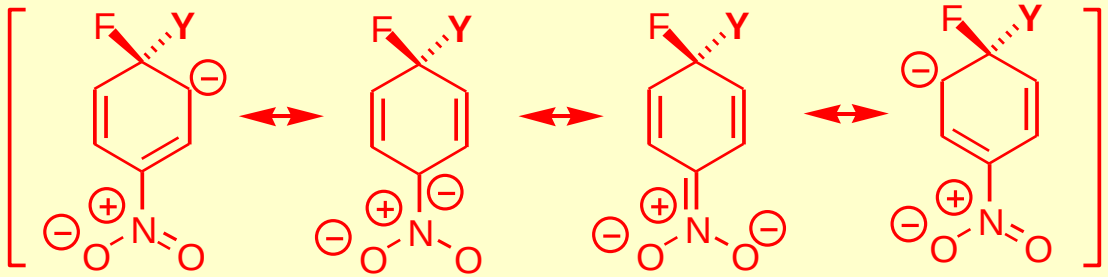


benzylic deprotonation

Supplementary Slide 4 – *Nucleophilic Aromatic Substitution: S_NAr*

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





<u>notes</u>

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