Chemistry II (Organic)

Heteroaromatic Chemistry
LECTURE 7
Deprotonation &
Benzo-heterocyces: Indoles & (Iso)quinolines

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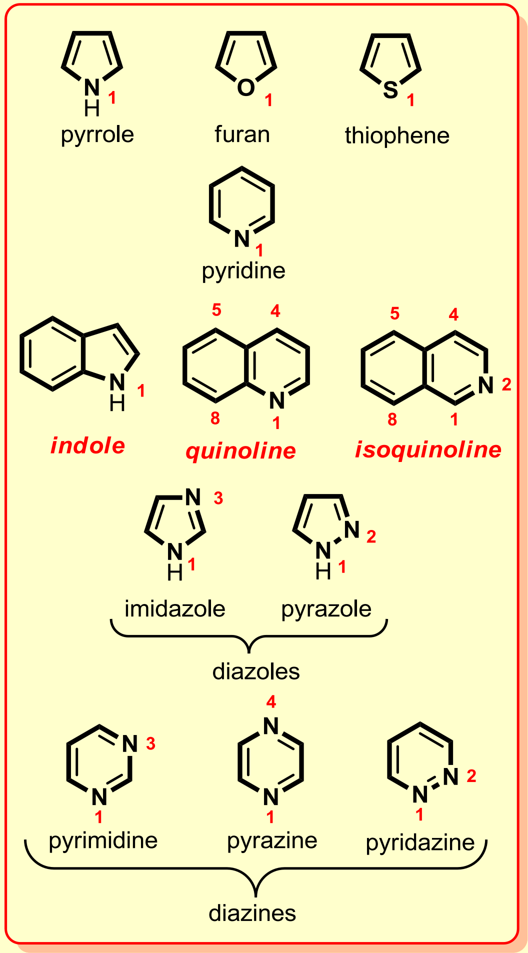
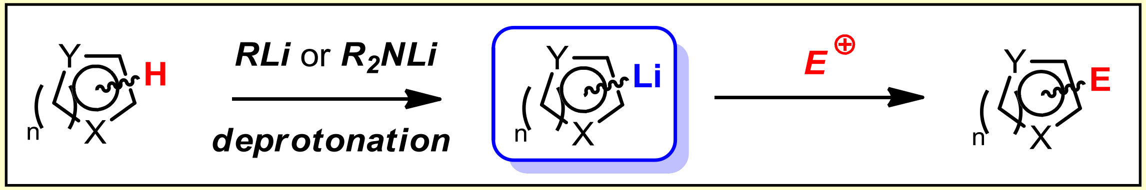
Format & scope of lecture 7

- ***Deprotonation of heteroaromatics:***
  - Thermodynamic *vs*. kinetic deprotonation
  - azines
  - 5-membered heteroaromatics
- ***Benzo-heterocycles – Indoles & (iso)quinolines:***
  - structure & properties
  - syntheses
  - reactivity



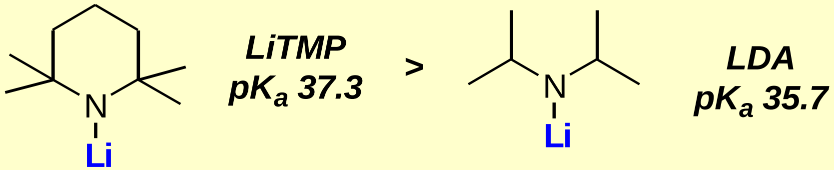
Deprotonation - *thermodynamic vs kinetic*

- ***Overall process:***



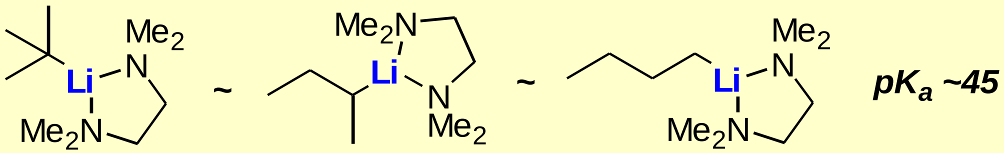
- ***thermodynamic deprotonation using <u>hindered</u> lithium amide bases:***
  - amine anions are poorly nucleophilic and undergo slow competitive addition reactions
  - ***reversible equilibration***, success depends on the pK_a of the heteroaryl proton being lower than that of the amine:

$$\boxed{\mathrm{Ar\textbf{H} + R_2N\textbf{Li} \underset{\textit{reversible}}{\rightleftharpoons} Ar\textbf{Li} + R_2N\textbf{H}}}$$



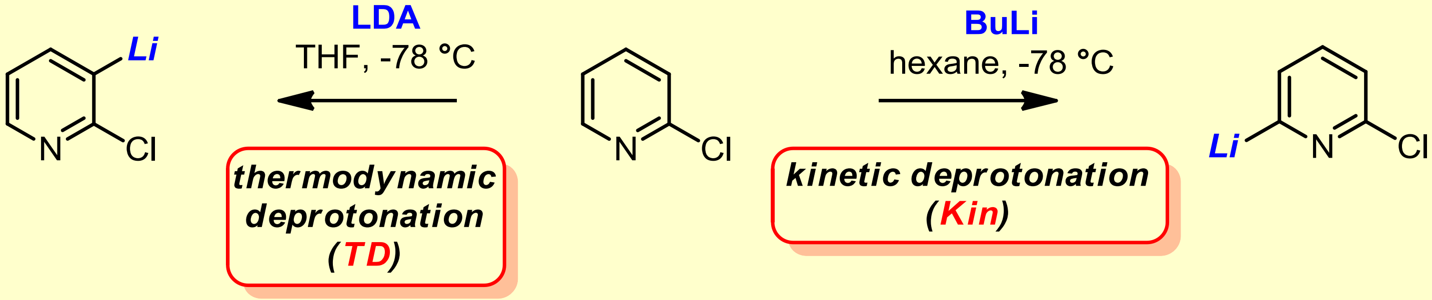
- ***kinetic deprotonation using alkyl lithium bases (RLi):***
  - <u>branched</u> alkyl lithiums undergo slow competitive nucleophilic addition reactions
  - ***irreversible loss of RH***, maximum basicity of alkyl lithiums is in non-co-ordinating solvents *e.g.* hexane (with TMEDA co-solvent to break up aggregates – *i.e*. form monomeric species)

$$\boxed{\mathrm{Ar\textbf{H} + R\textbf{Li} \xrightarrow[\textit{irreversible}]{} Ar\textbf{Li} + R\textbf{H}\ (g)}}$$



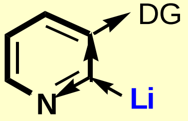
Deprotonation - *regioselectivity*

- ***kinetically and thermodynamically most acidic protons may differ:***



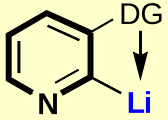
Deprotonation – *azines*

- Deprotonation of ***pyridines (and other azines):***
  - ***Thermodynamically more favourable*** and ***kinetically faster*** than for ***benzene*** particularly for protons:
    - *ortho* to ring N
    - *ortho* to a "directing group (DG)" (see later)
  - ***Thermodynamics:*** (pK_a $Ar_{C=N}H$ ~35 *cf.* benzene ~40) due to:



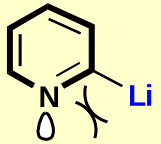
inductive stabilisation

and



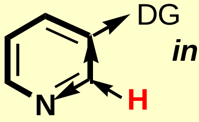
chelative stabilisation

BUT:



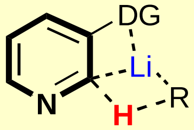
pair-pair electron repulsion

  - ***Kinetics:*** due to:



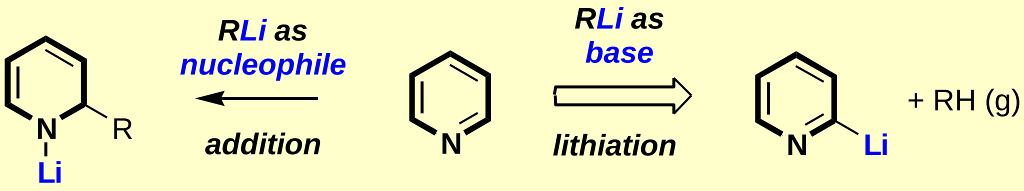
inductive acidification of ortho-protons

and



Complex Induced Proximity Effects stabilising TS$^{\#}$

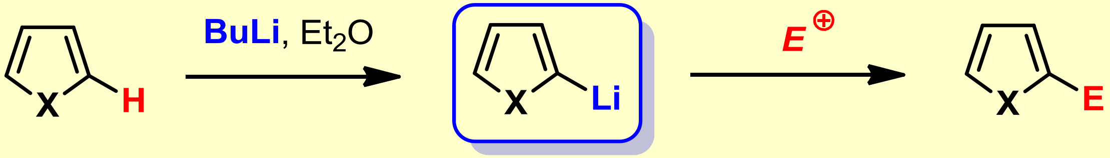
  - ***Low temperatures*** & ***bulky bases*** required to supress ***addition reactions*** to ***C=N function:***



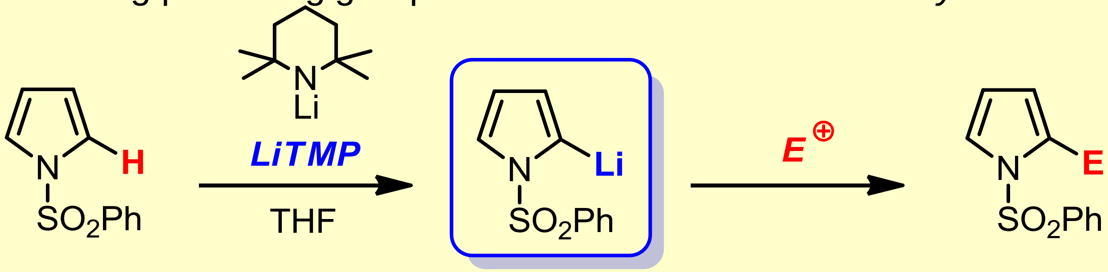
  - ***Reviews:*** Snieckus & Beak *Angew. Chem. Int. Ed.* **2004**, *43*, 2206 (DOI), Schlosser *Angew. Chem. Int. Ed.* **2005**, *44*, 376 (DOI).

Deprotonation - *5-ring heteroarenes*

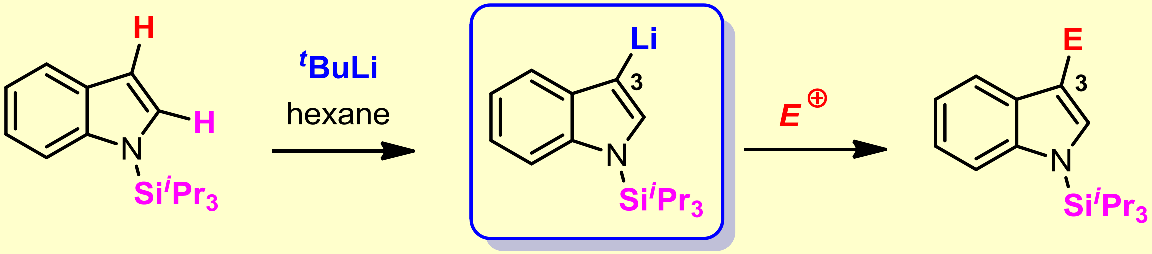
- ***furans and thiophenes:***
  - facile *kinetic* and *thermodynamic* deprotonation of hydrogens *ortho* to ring heteroatom



- ***pyrroles: N-protection is required to avoid NH deprotonation (see lecture 2)***
  - electron withdrawing protecting groups enhance *kinetic* and *thermodynamic* acidity of *ortho*-hydrogens



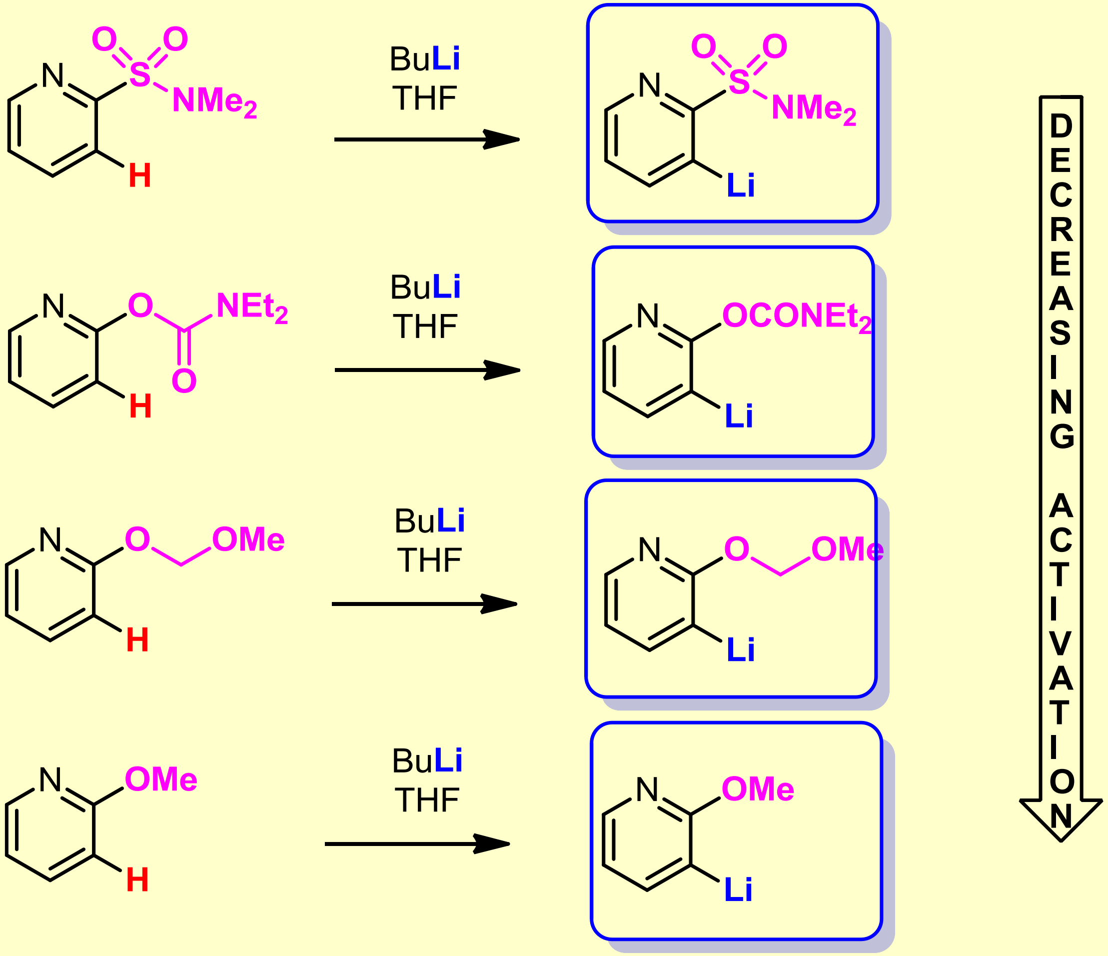
- ***The concept of lateral protection can also be applied to deprotonation (cf. S_EAr):***



- ***NOT generally susceptible to addition reactions***

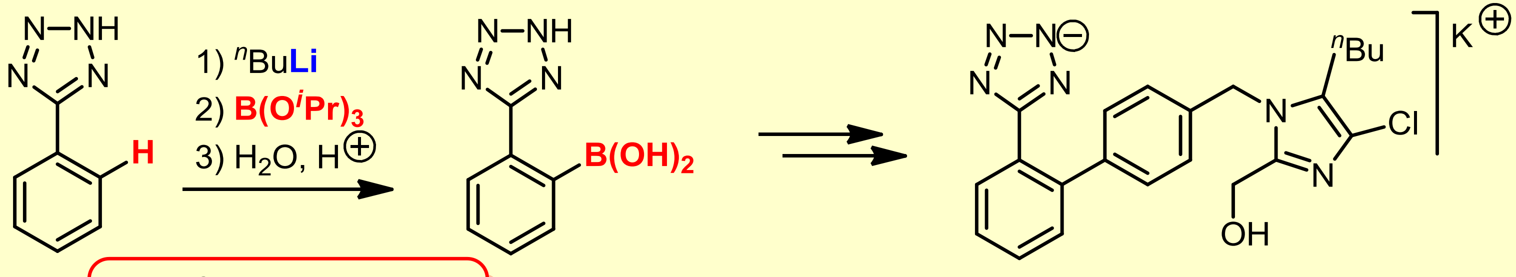
Directing Groups - *directed ortho-metalation (DoM)*

- ***Many substituents kinetically and thermodynamically acidify hydrogens ortho to themselves:***
  - *e.g.*



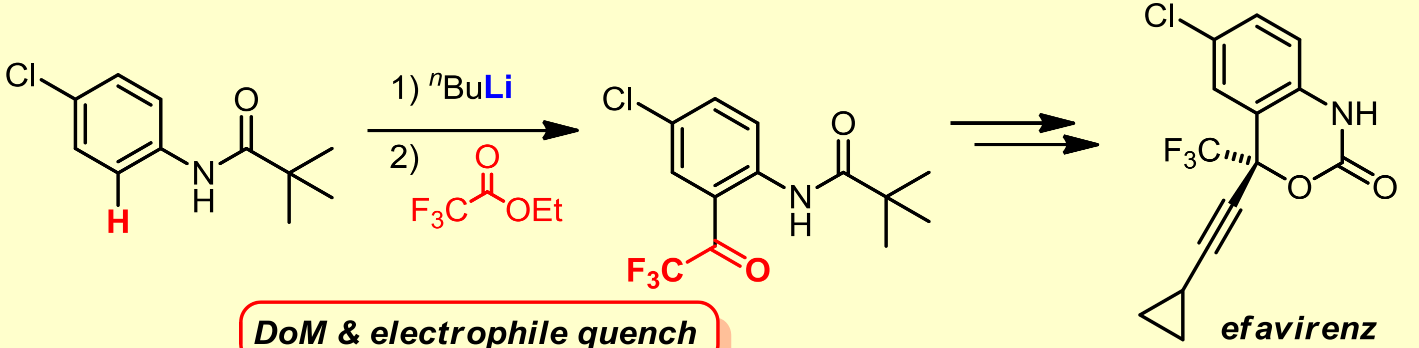
Pharmaceutical preparation by DoM

- ***losartan potassium: antihypertensive***
  - Process route for Merck (Rouhi *Chem. Eng. News* **2002**, *July 22*, 46) (**DOI**)



losartan potassium
angiotensin II receptor (type AT 1) antagonist

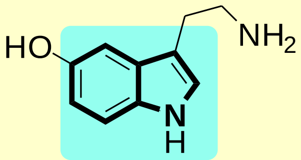
- ***efavirenz: anti-viral, anti-AIDS***
  - Process route for Bristol-Myers Squibb (Rouhi *Chem. Eng. News* **2002**, *July 22*, 46) (**DOI**)



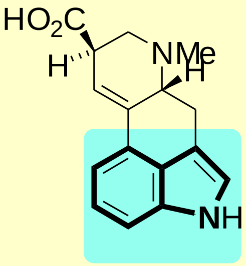
efavirenz
non-nucleoside reverse transcriptase inhibitor

Indoles – *Importance*

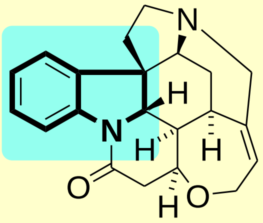
- ***Natural products*:**



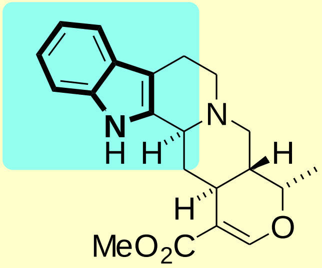
5-hydroxytryptamine
(seratonin)



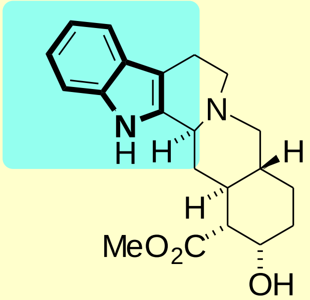
lysergic acid
(ergot alkaloid psychadelic)



strychnine
(strychnos alkaloid poison)

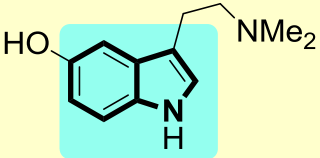


ajmalicine
(vinca alkaloid)

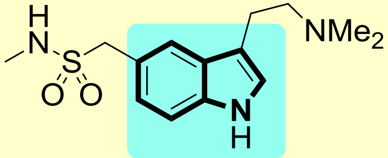


yohimbine

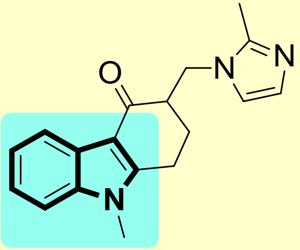
- ***Pharmaceuticals:***



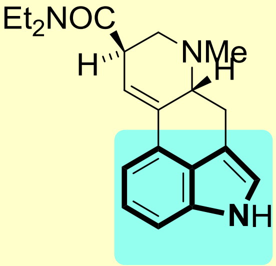
bufotenine
(jet-lag medication)



sumatriptan
(Imitrex$^{\mathrm{TM}}$, migrane relief)

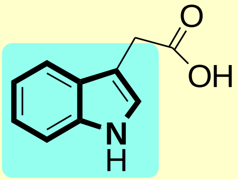


ondansetron
(Zofran$^{\mathrm{TM}}$, anti-nausea in cancer chemotherapy)

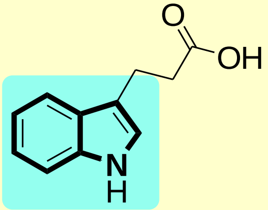


lysergic acid diethylamide
(LSD, psychadelic)

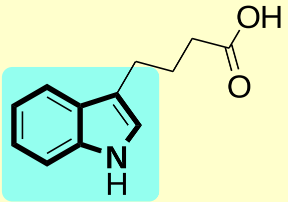
- ***Agrochemicals:***



heteroauxin
(plant growth regulator)



indole-3-propanoic acid
(plant growth regulator)

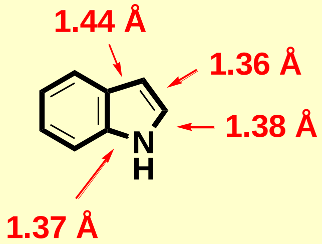


seradix
(plant growth regulator)

Indole *– Structure and Properties*

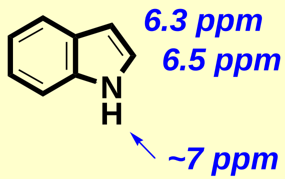
- A colourless, crystalline solid, mp 52 °C
- ***Bond lengths*** and ***^{1}H NMR chemical shifts*** as expected for an aromatic system:

bond lengths:



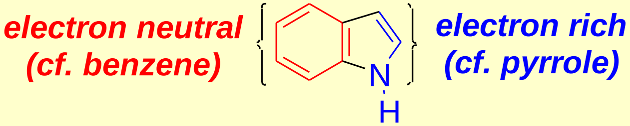
cf. ave C-C 1.48 Å
ave C=C 1.34 Å
ave C-N 1.45 Å

^{1}H NMR:

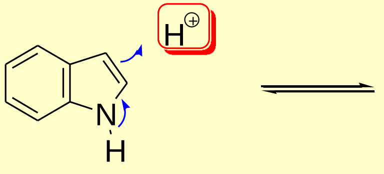


- ***Resonance energy:*** 196 kJmol^{-1} [most of which is acounted for by the benzenoid ring (*cf.* benzene, 152 kJmol^{-1}, naphthalene, 252 kJmol^{-1} & pyrrole, 90 kJmol^{-1})]:
  - ❑ → resonance energy associated with pyrrolic ring is significantly less than for pyrrole itself – hence enamine character of N1-C2-C3 unit is pronounced

- ***Electron density:*** pyrrolic ring is ***electron rich***, just a little less electron rich than pyrrole; benzenoid ring has similar electron density to benzene:
  - ❑ → ***very reactive towards electrophilic substitution (S_EAr)*** at ***C3***
  - ❑ → unreactive towards nucleophilic substitution (S_NAr)

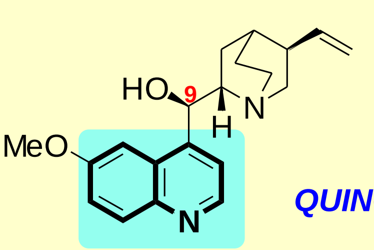


- ***NH-acidic*** (pK$_a$ 16.2; *cf.* ***pyrrole*** 17.5). ***Non-basic***; as for pyrrole, the ***N*** lone pair is involved in aromatic system; protonation occurs at ***C3*** (as for an enamine):

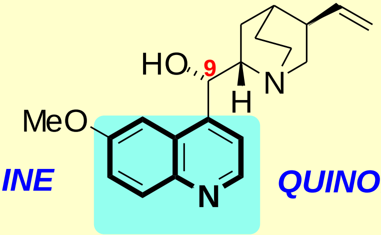


Quinolines & Isoquinolines *– Importance*

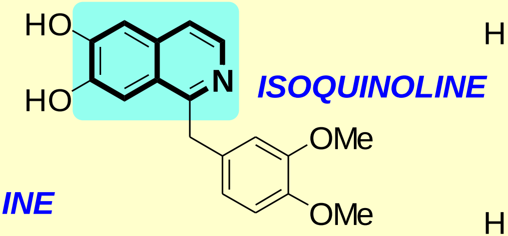
- ***Natural products*:**



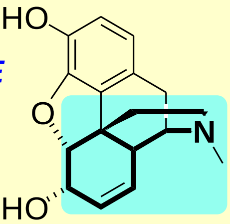
quinine
(antimalarial)



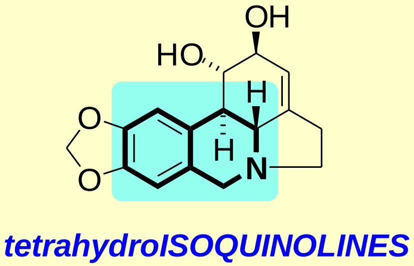
quinidine



papaverine
(opium alkaloid
vasodilator)

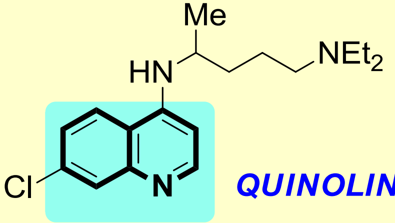


morphine
(analgesic)

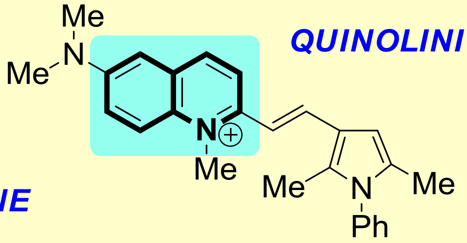


lycorine
(anti-tumour)

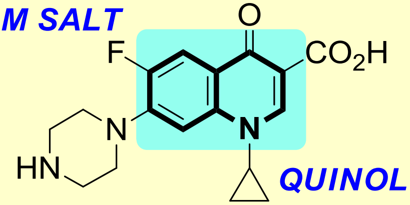
- ***Pharmaceuticals:***



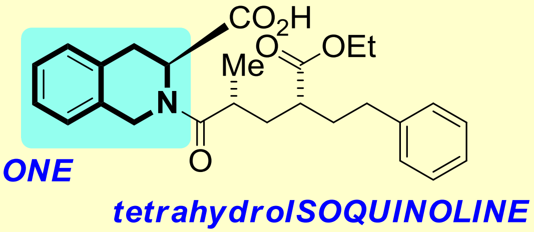
chloroquine
(anitmalarial)



cyanine dye
(control of pinworm infection)



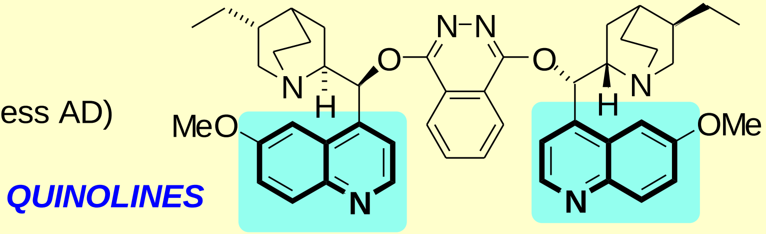
ciprofloxacin
(Cipro^{TM}, antibiotic)



quinapril
(Accupril^{TM}, ACE
inhibitor for high blood
pressure)

- ***Chiral catalysts:***
  - Sharpless *Angew. Chem. Int. Ed.* **2002**, *41*, 2024 (DOI):

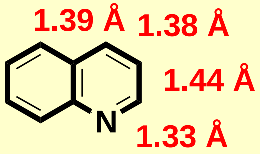
(DHQD)$_2$PHAL
(in AD-mix β for Sharpless AD)



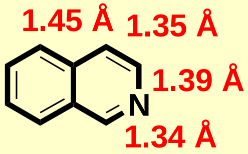
Quinolines & Isoquinolines – *Structure and Properties*

- ***Quinoline:*** colourless liquid, bp 237 °C; ***isoquinoline:*** colourless plates, mp 26 °C
- ***Bond lengths*** and ***^{1}H NMR chemical shifts*** as expected for aromatic systems:

bond lengths:



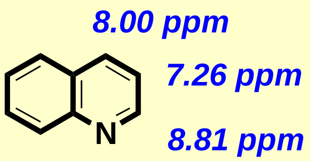
quinoline



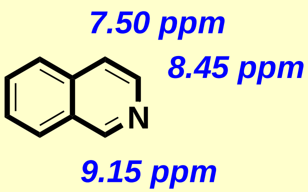
isoquinoline

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

^{1}H NMR:



quinoline

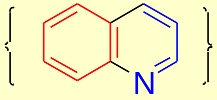


isoquinoline

- ***Resonance energies: quinoline*** = 222 kJmol^{-1} (*cf.* 252 kJmol^{-1} naphthalene)

- ***Electron density:*** for both systems the ***pyridinyl ring*** is ***electron deficient*** (*cf.* ~pyridine); the ***benzenoid ring*** is slightly electron deficient relative to ***benzene*** itself:

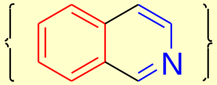
electron neutral (cf. benzene)



electron deficient (cf. pyridine)

quinoline

electron neutral (cf. benzene)

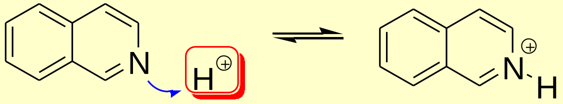


electron deficient (cf. pyridine)

isoquinoline

  - ❑ → both ***quinoline*** and ***isoquinoline*** are:
    - reactive towards electrophiic substitution (S_EAr) in the benzenoid ring
    - reactive towards nucleophilic subnstitution (S_NAr) in the pyridinyl ring

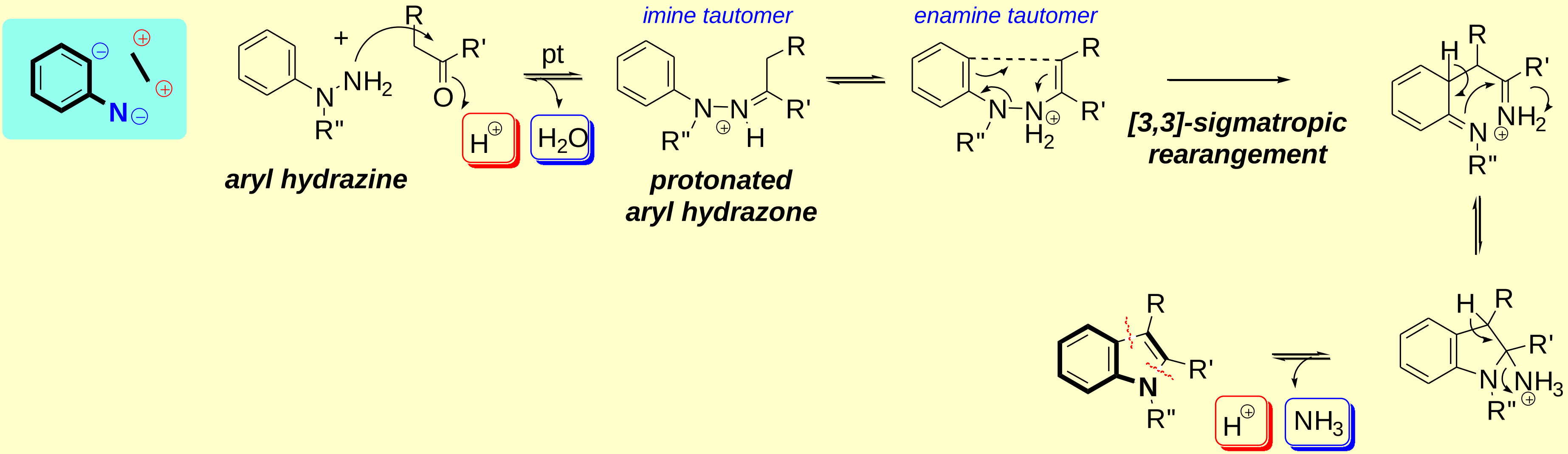
- ***Basic:*** both systems have pK_as similar to pyridine (5.2):
  - ❑ ***quinoline:*** pK_a = 4.9
  - ❑ ***isoquinoline:*** pK_a = 5.1



isoquinoline (pK_a 5.1)

Indoles *– Syntheses*

- ***Fischer:*** aryl hydrazine with enolisable ketone

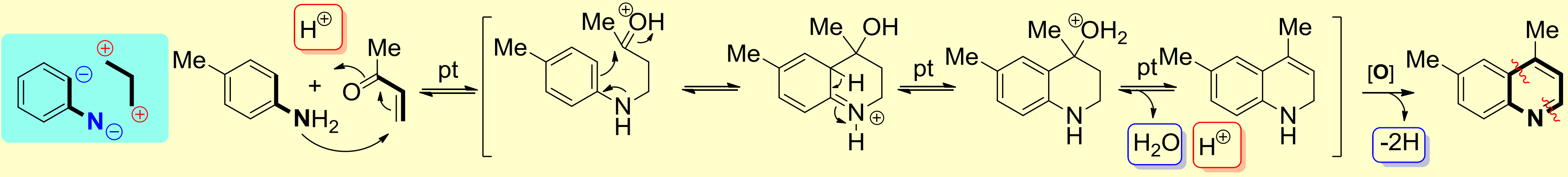


- ***NOTES:***
  - aryl hydrazone cyclisation under acidic or Lewis acidic conditions
  - high temperature (≥150 °C) but varies with catalyst & solvent *etc.*
  - ketones that are able to form regioisomeric enamines can give mixtures of products but cyclisation is preferred *via* ***more substituted enamine*** (*i.e.* the more thermodynamically stable one)
  - driving forces:
    - 1) loss of H_2O & NH_3 [*i.e.* ΔS° +ive, entropically favourable]
    - 2) N-N (weak bond) broken & C-C (strong bond) formed [*i.e.* ΔH° -ive, enthalpically favourable]
    - 3) aromaticity of product indole [*i.e.* ΔH° -ive, enthalpically favourable]

Quinolines & Isoquinolines – *Syntheses*

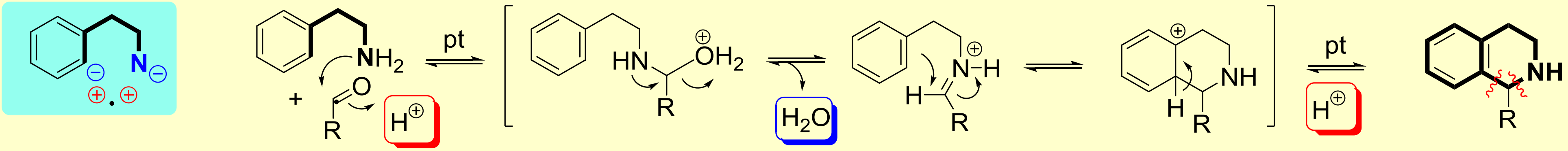
Quinolines:

- ***Doebner-von Miller:*** enone with aniline then *in situ* oxidation:
  - *via apparent* 1,4-addition of aniline NH_2 group to enone then cyclodehydration then dehydrogenation (oxidation) by the ***imine*** formed between the enone and aniline in a side reaction



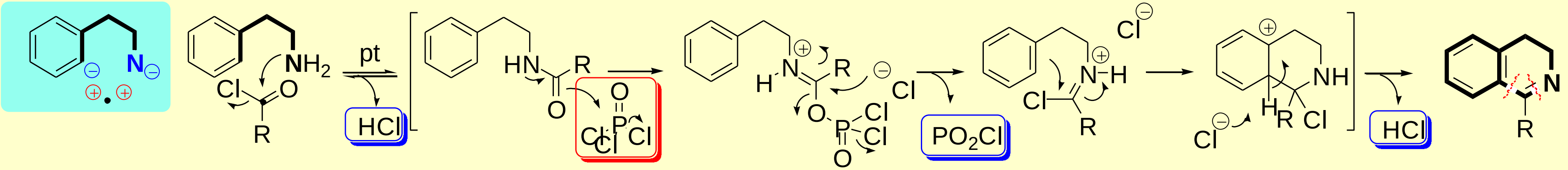
*(Tetrahydro)**isoquinolines**:*

- ***Pictet-Spengler:*** β-phenethylamine with aldehyde (intramolecular Mannich)



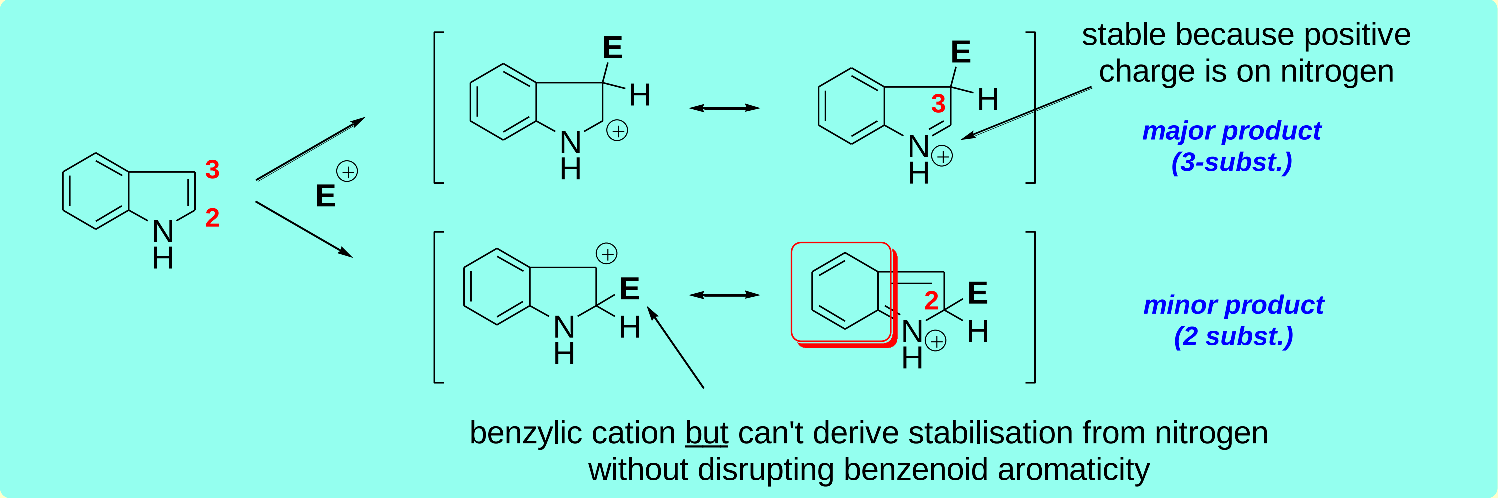
*(Dihydro)**isoquinolines**:*

- ***Bischler-Napieralski:*** β-phenethylamine with acid chloride



Indoles *– Reactivity*

- ***Electrophilic substitution:*** *via* addition-elimination (S_EAr) in the pyrrolic ring
  - **reactivity:** reactive towards many electrophiles (**E$^+$**); ~pyrrole
  - **regioselectivity:** the kinetic 3-substituted product predominates (*cf.* 2-position for pyrrole); predict by estimating the energy of the respective Wheland intermediates → 3-substitution is favoured:



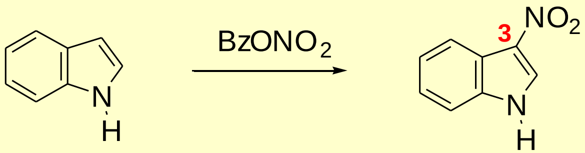
stable because positive charge is on nitrogen

major product (3-subst.)

minor product (2 subst.)

benzylic cation but can't derive stabilisation from nitrogen without disrupting benzenoid aromaticity

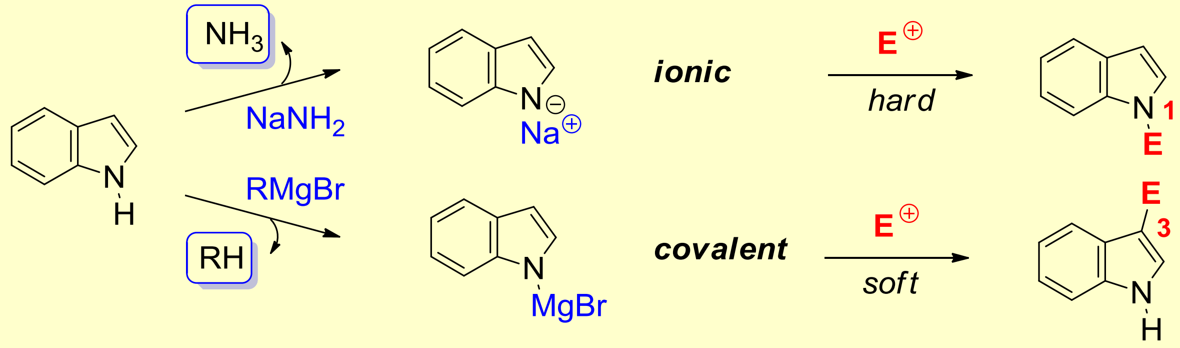
  - ***e.g.*** **nitration:** (**E**$^+$ = NO_2^+)



Indoles *– Reactivity cont.*

- ***Metallation:*** (NH pK_a = 16.2) *NB*. For an overview & mechanistic discussion see Joule & Smith (5th Ed) chapter 4.

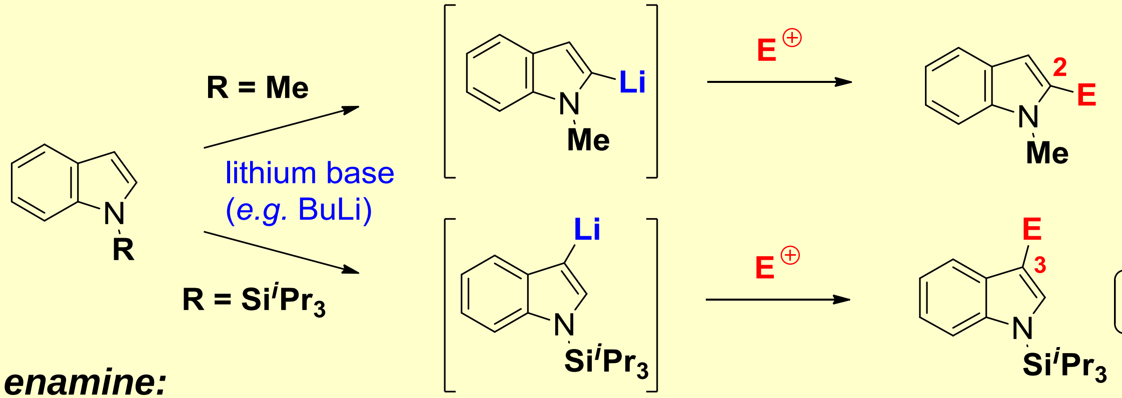
NH-indoles:
(N-metallation)



metallated indole is an ambident nucleophile

$E^{\oplus}X^{\ominus}$ = MeI, RCOCl *etc.*

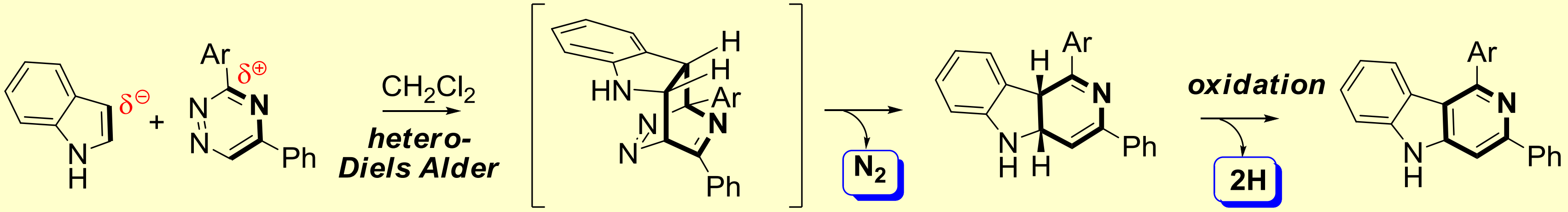
NR indoles:
(C-metallation)



$E^{\oplus}X^{\ominus}$ = MeI, RCOCl *etc.*

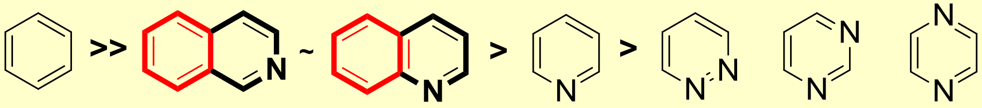
lateral protectcion

- ***Reaction as an enamine:***
  - *e.g.* as hetero-Diels-Alder dienophile



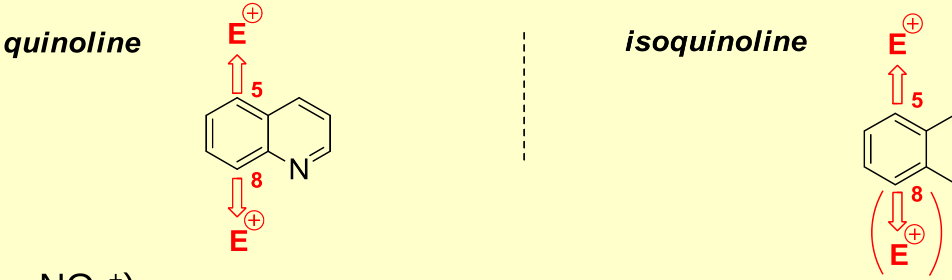
Quinolines & Isoquinolines – *Reactivity*

- ***Electrophilic substitution:*** *via* addition-elimination (S_EAr) in the benzenoid ring (*i.e.* more electron rich ring)
  - **reactivity:** reactive towards many electrophiles (**E^+**); <benzene but >pyridine

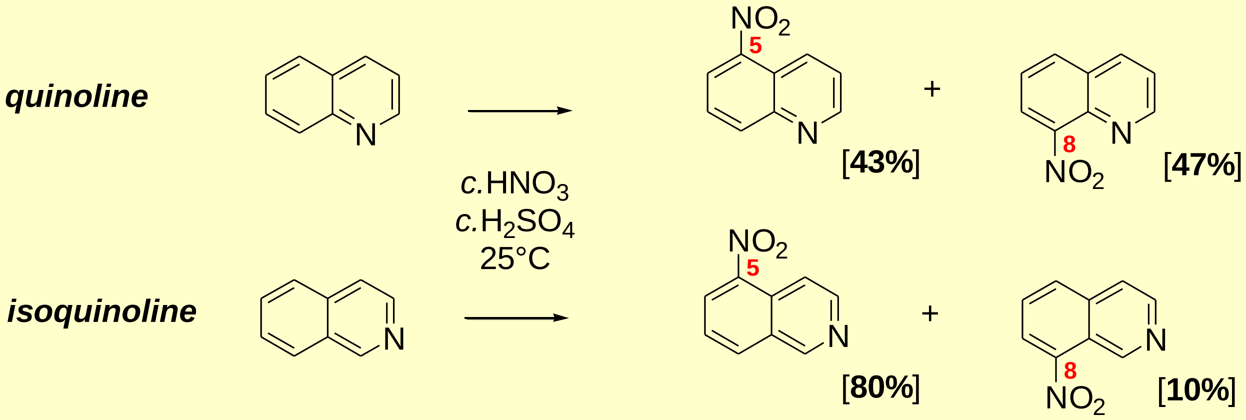


relative rates **1** **~10^{-5}** **~10^{-6}** **~10^{-12}**

  - **regioselectivity:** substitution at ***C5*** (& ***C8*** for quinolines) predominate – *via* most stable Wheland intermediates:

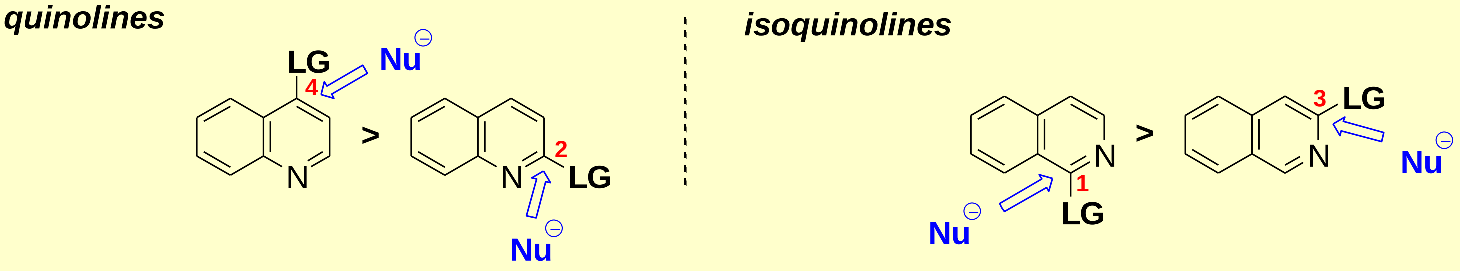


  - ***e.g.*** **nitration**: (**E^+** = NO_2^+)

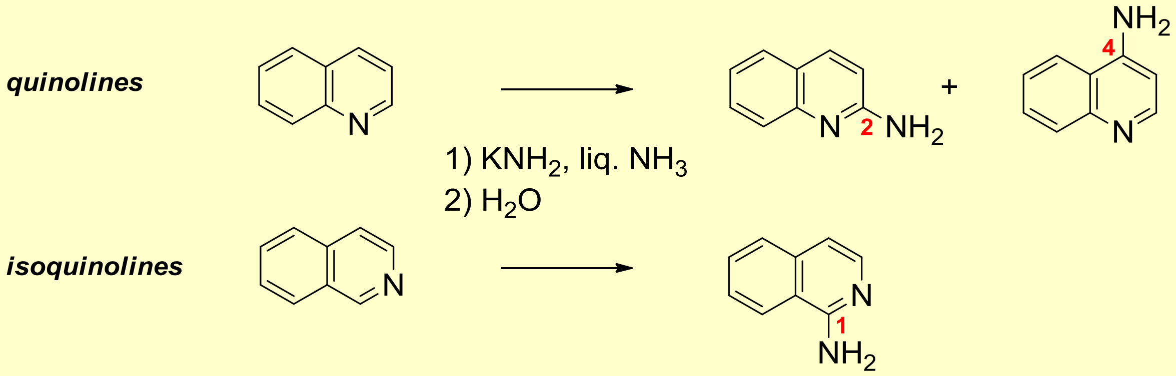


Quinolines & Isoquinolines *– Reactivity cont.*

- ***Nucleophilic substitution:*** *via* addition-elimination (S_NAr)
  - **reactivity:** reactive towards nucleophilies (**Nu**$^-$) provided leaving group is situated at appropriate carbon
  - **regioselectivity:** reactive at positions for which the Meisenheimer type intermediates have negative charge stabilised on the electronegative nitrogen [‘leaving group’ (LG) can be H but Cl, Br, NO_2 *etc.* more facile]:
    - ***quinoline: C4*** > ***C2*** – *i.e.* as for pyridine
    - ***isoquinoline: C1*** > ***C3***

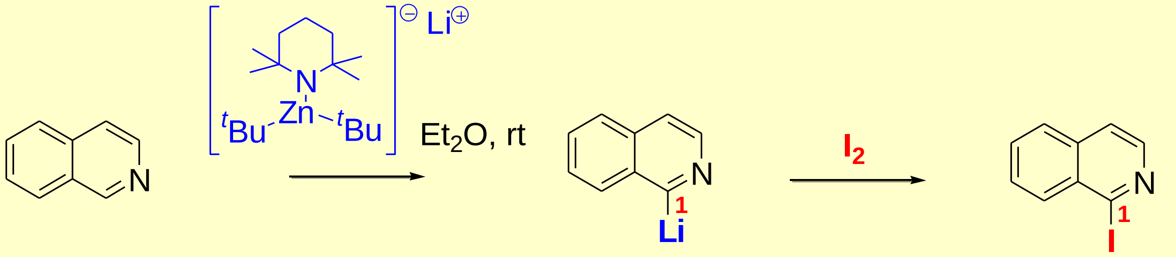


- *e.g.* **the Chichibabin reaction:** (**Nu**$^-$ = NH_2^-, LG = H)



Quinolines & Isoquinolines – *Reactivity cont.*

- ***Metallation:***
  - deprotonation by strong bases *ortho* to the ***N*** is difficult due to competing addition reactions but can be achieved using *e.g.* highly basic and non-nucleophilic zincates:



[93%]

- ***Metallation at benzylic positions:***
  - deprotonation at benzylic positions that give ***enaminate anions*** (*i.e.* ***C4*** > ***C2*** for ***quinoline***; ***C1*** > ***C3*** for ***isoquinoline***) are facile (*i.e.* as for pyridine):