

# ***Chemistry II (Organic)***

## ***Heteroaromatic Chemistry***

### ***LECTURE 7***

#### ***Deprotonation &***

#### ***Benzo-heterocycles: Indoles & (Iso)quinolines***

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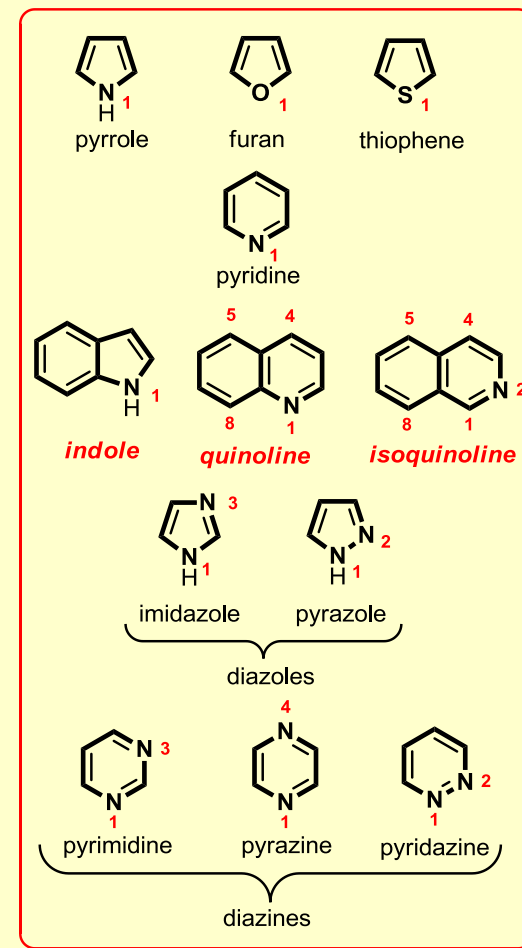
**Imperial College  
London**

***Mar 2012***

# Format & scope of lecture 7

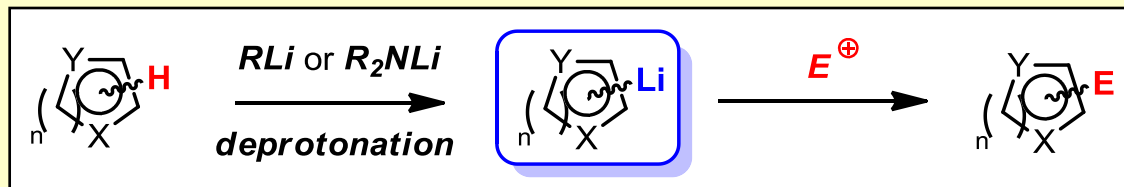
- **Deprotonation of heteroaromatics:**
  - Thermodynamic vs. kinetic deprotonation
  - azines
  - 5-membered heteroaromatics

- **Benzo-heterocycles – Indoles & (iso)quinolines:**
  - structure & properties
  - syntheses
  - reactivity



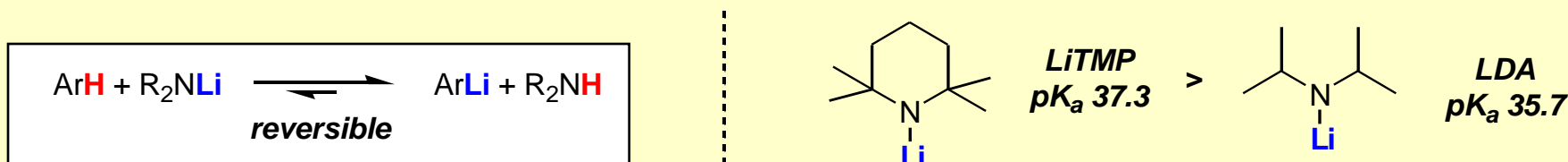
# Deprotonation - *thermodynamic vs kinetic*

- Overall process:



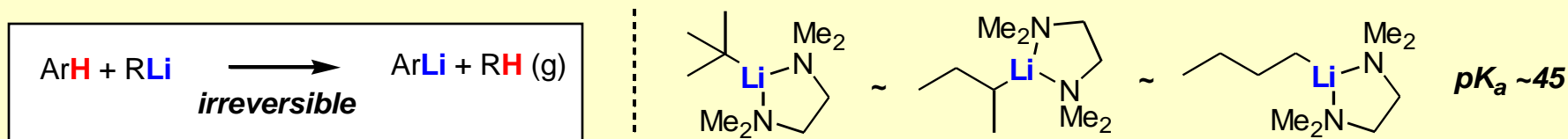
- thermodynamic deprotonation using hindered lithium amide bases:**

- 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:



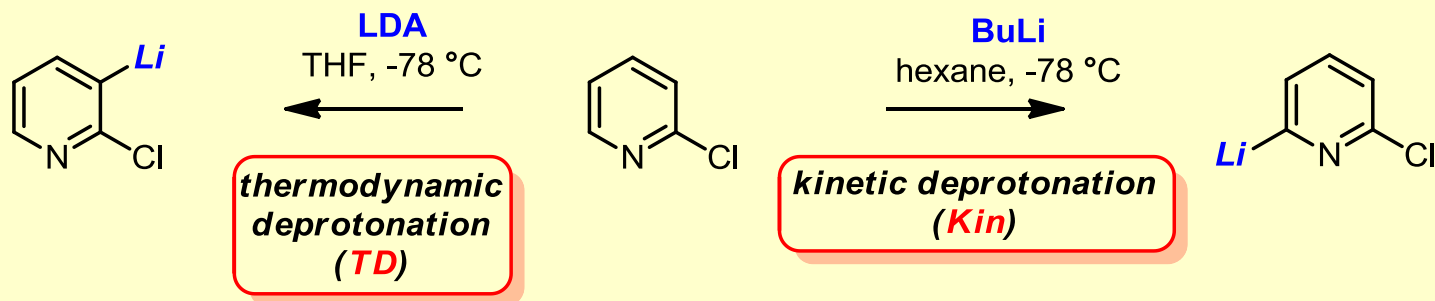
- kinetic deprotonation using alkyl lithium bases (RLi):**

- branched 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)



# Deprotonation - *regioselectivity*

- kinetically and thermodynamically most acidic protons may differ:



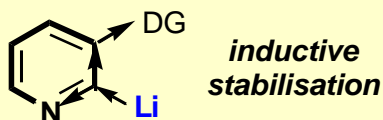
# Deprotonation – azines

- Deprotonation of **pyridines (and other azines)**:

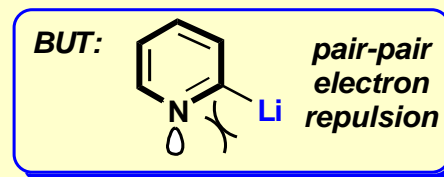
- **Thermodynamically more favourable** and **kinetically faster** than for **benzene** particularly for protons:

- *ortho* to ring N
- *ortho* to a “directing group (DG)” (see later)

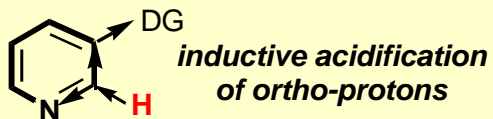
- **Thermodynamics:** ( $pK_a$  Ar<sub>C=N</sub>H ~35 cf. benzene ~40) due to:



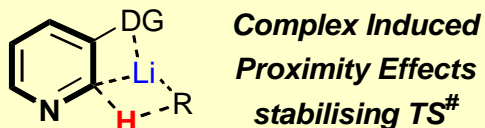
and



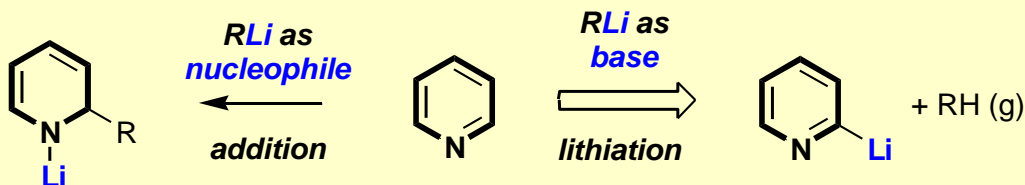
- **Kinetics:** due to:



and



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

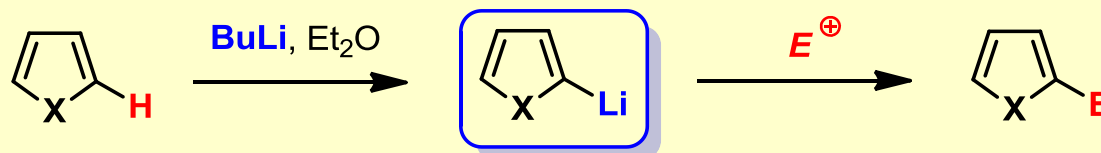


- **Reviews:** Snieckus & Beak *Angew. Chem. Int. Ed.* **2004**, 43, 2206 ([DOI](#)), Schlosser *Angew. Chem. Int. Ed.* **2005**, 44, 376 ([DOI](#)).

# Deprotonation - 5-ring heteroarenes

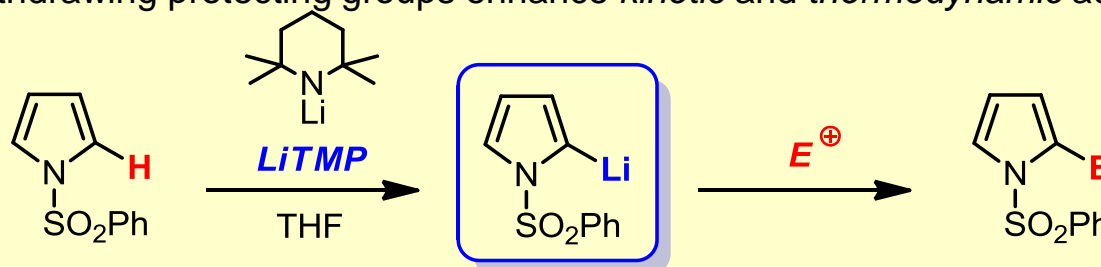
- **furans and thiophenes:**

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

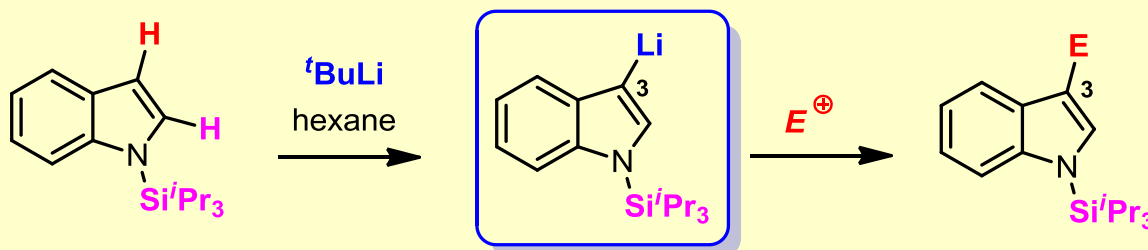


- **pyrroles: N-protection is required to avoid NH deprotonation (see lecture 2)**

- electron withdrawing protecting groups enhance *kinetic* and *thermodynamic* acidity of *ortho*-hydrogens



- **The concept of lateral protection can also be applied to deprotonation (cf.  $\text{S}_{\text{E}}\text{Ar}$ ):**

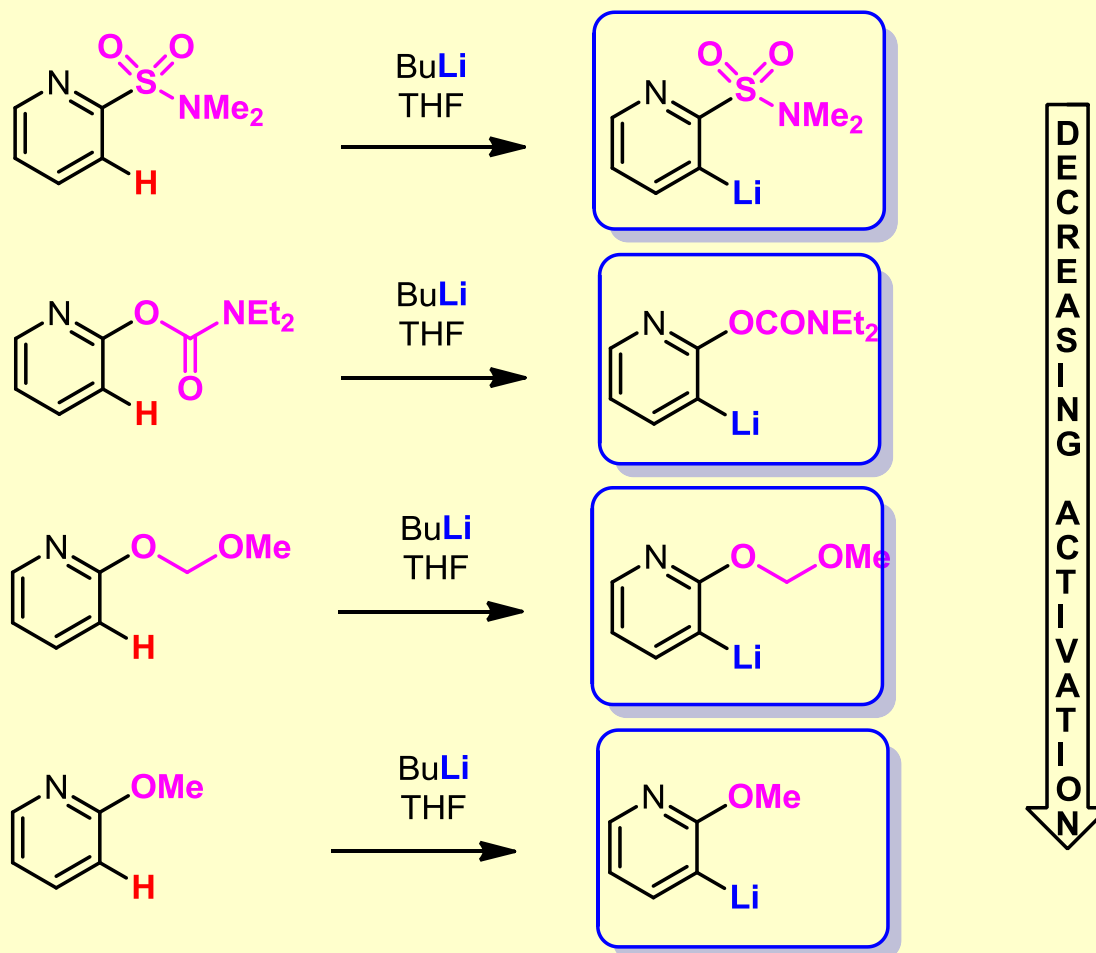


- **NOT generally susceptible to addition reactions**

# Directing Groups - *directed ortho-metalation (DoM)* <sup>7</sup>

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

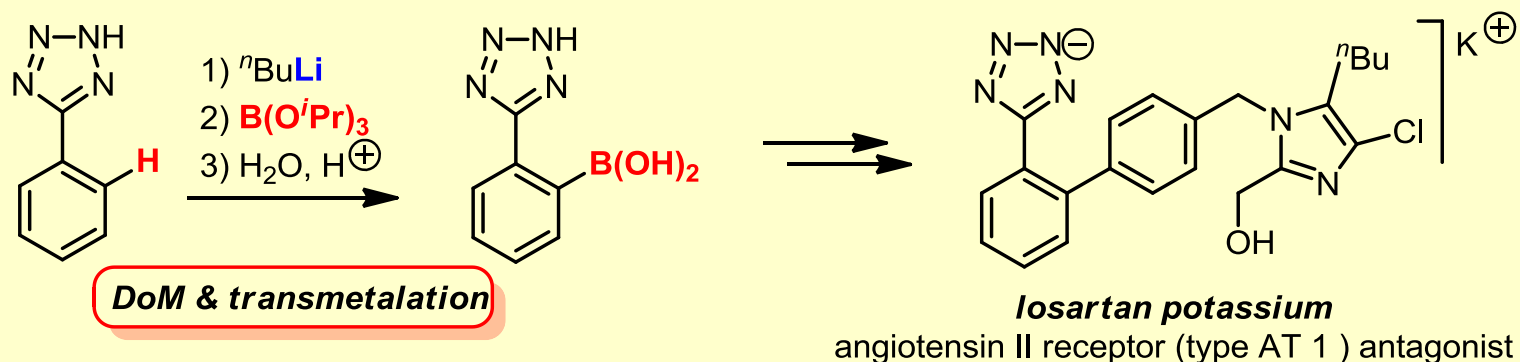
– e.g.



# Pharmaceutical preparation by DoM

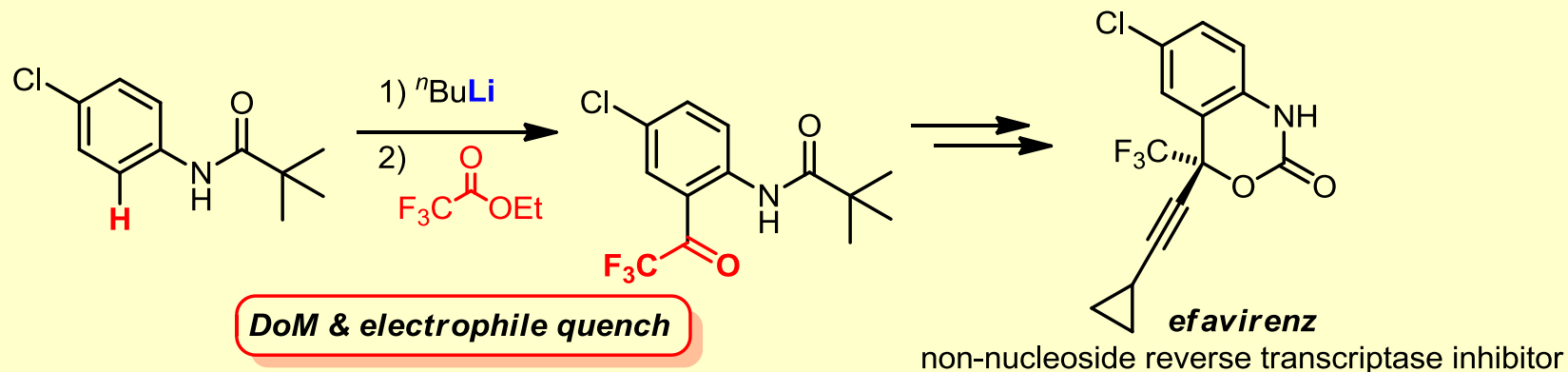
- **losartan potassium: antihypertensive**

- Process route for Merck (Rouhi *Chem. Eng. News* **2002**, July 22, 46) ([DOI](#))



- **efavirenz: anti-viral, anti-AIDS**

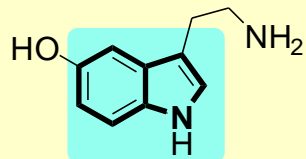
- Process route for Bristol-Myers Squibb (Rouhi *Chem. Eng. News* **2002**, July 22, 46) ([DOI](#))



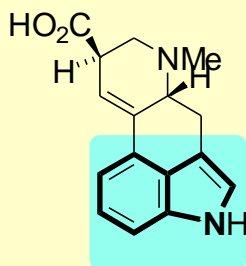


# Indoles – Importance

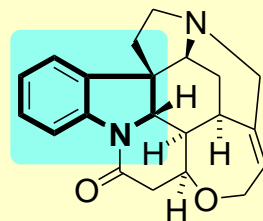
## ■ Natural products:



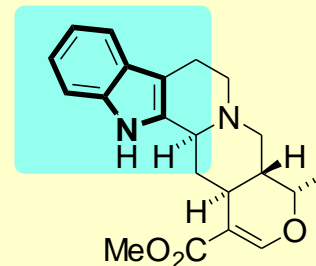
5-hydroxytryptamine  
(serotonin)



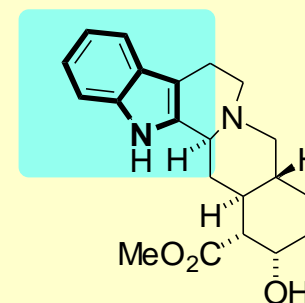
lysergic acid  
(ergot alkaloid psychadelic)



strychnine  
(strychnos alkaloid poison)

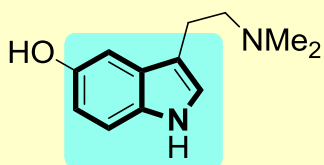


ajmalicine  
(vinca alkaloid)

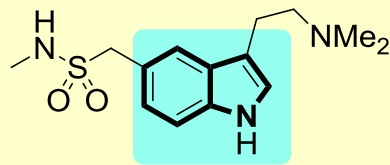


yohimbine

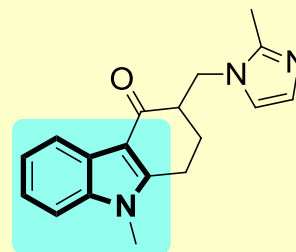
## ■ Pharmaceuticals:



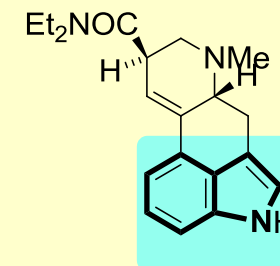
bufotenine  
(jet-lag medication)



sumatriptan  
(Imitrex<sup>TM</sup>, migraine relief)

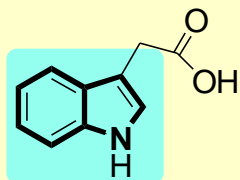


ondansetron  
(Zofran<sup>TM</sup>, anti-nausea in cancer chemotherapy)

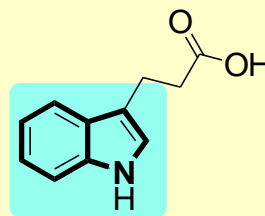


lysergic acid diethylamide  
(LSD, psychadelic)

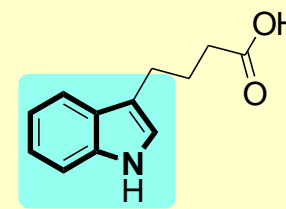
## ■ Agrochemicals:



heteroauxin  
(plant growth regulator)



indole-3-propanoic acid  
(plant growth regulator)

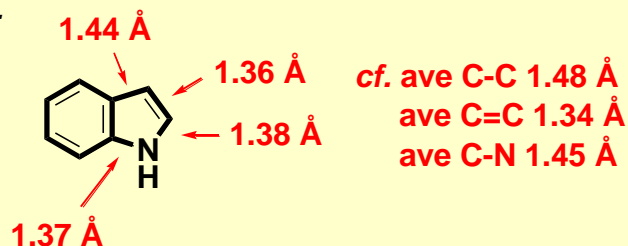


seradix  
(plant growth regulator)

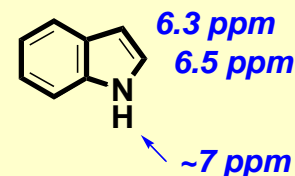
# Indole – Structure and Properties

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

bond lengths:



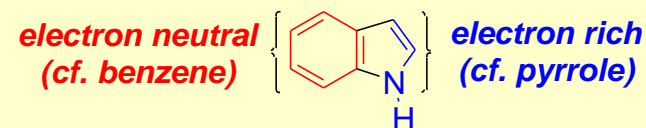
$^1\text{H NMR}$ :



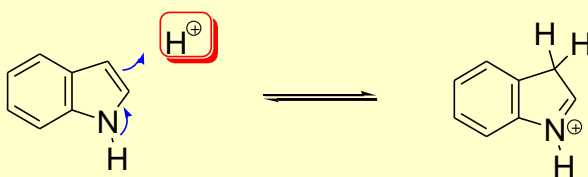
- **Resonance energy:** 196 kJmol<sup>-1</sup> [most of which is accounted for by the benzenoid ring (cf. benzene, 152 kJmol<sup>-1</sup>, naphthalene, 252 kJmol<sup>-1</sup> & pyrrole, 90 kJmol<sup>-1</sup>):
  - → resonance energy associated with pyrrolic ring is significantly less than for pyrrole 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 ( $\text{S}_{\text{E}}\text{Ar}$ ) at C3**
- → unreactive towards nucleophilic substitution ( $\text{S}_{\text{N}}\text{Ar}$ )

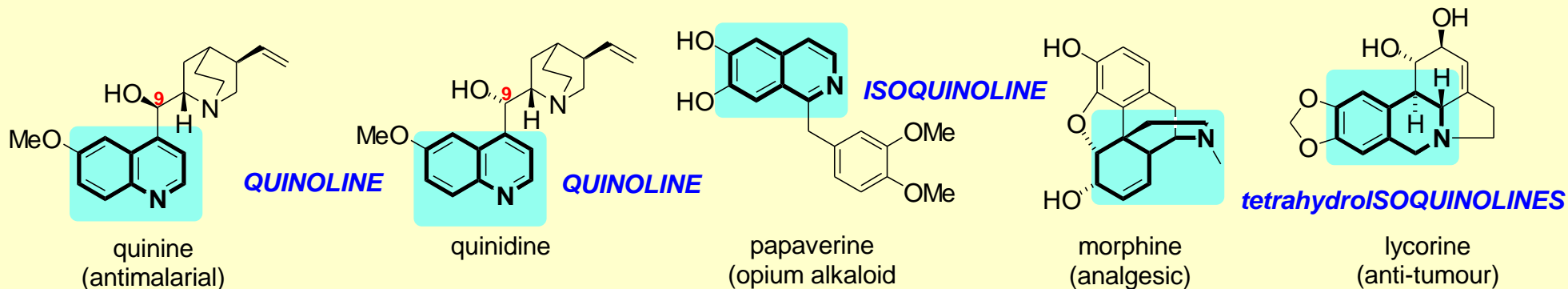


- **NH-acidic** ( $\text{pK}_{\text{a}}$  16.2; cf. **pyrrole** 17.5). **Non-basic**; as for pyrrole, the **N** lone pair is involved in aromatic system; protonation occurs at **C3** (as for an enamine):

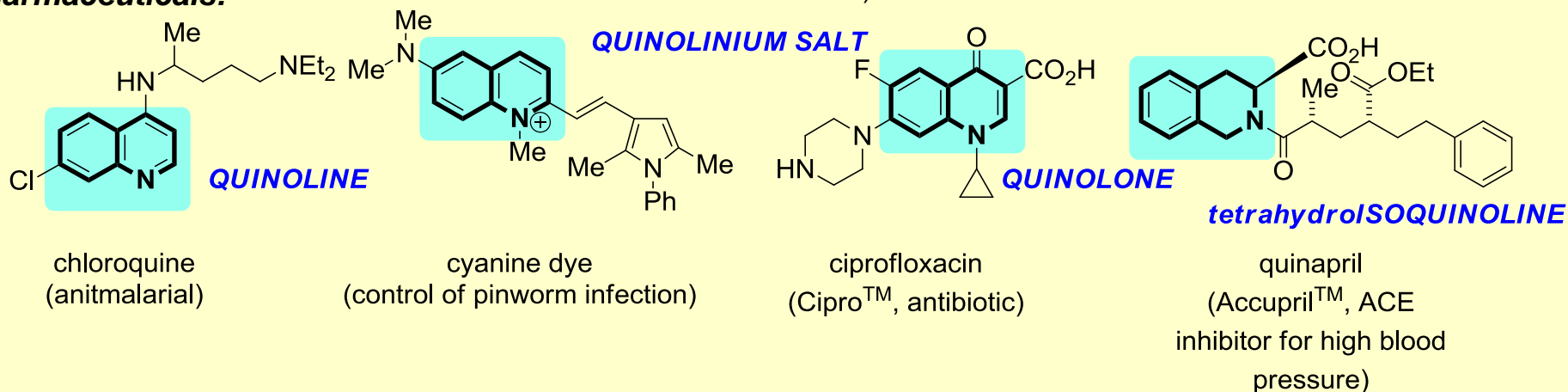


# Quinolines & Isoquinolines – Importance

## ■ Natural products:



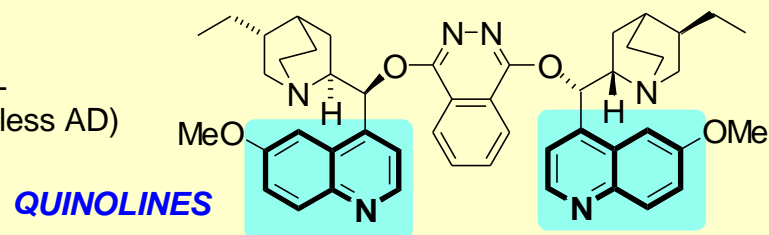
## ■ Pharmaceuticals:



## ■ Chiral catalysts:

□ Sharpless *Angew. Chem. Int. Ed.* **2002**, *41*, 2024 ([DOI](#)):

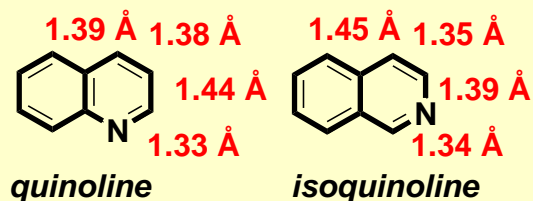
(DHQD)<sub>2</sub>PHAL  
(in AD-mix β for Sharpless AD)



# Quinolines & Isoquinolines – Structure and Properties

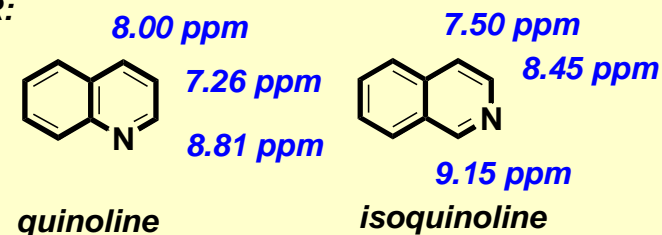
- **Quinoline:** colourless liquid, bp 237 °C; **isoquinoline:** colourless plates, mp 26 °C
- **Bond lengths** and  **$^1\text{H NMR}$  chemical shifts** as expected for aromatic systems:

bond lengths:

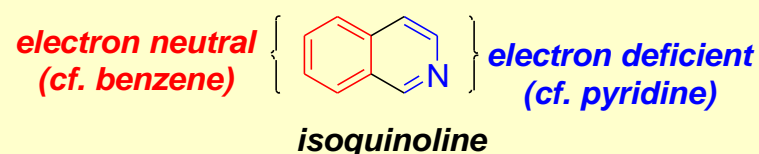
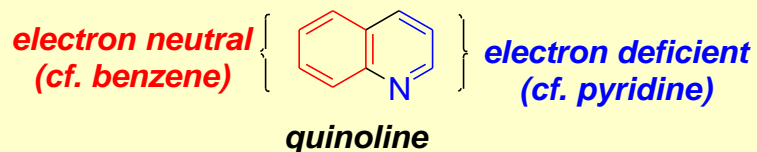


cf. ave C-C 1.48 Å  
ave C=C 1.34 Å  
ave C-N 1.45 Å

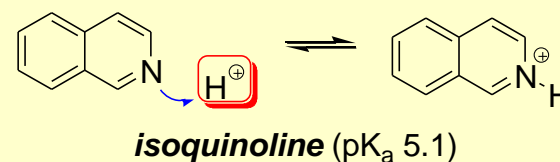
$^1\text{H NMR}$ :



- **Resonance energies:** **quinoline** = 222 kJmol<sup>-1</sup> (cf. 252 kJmol<sup>-1</sup> 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:

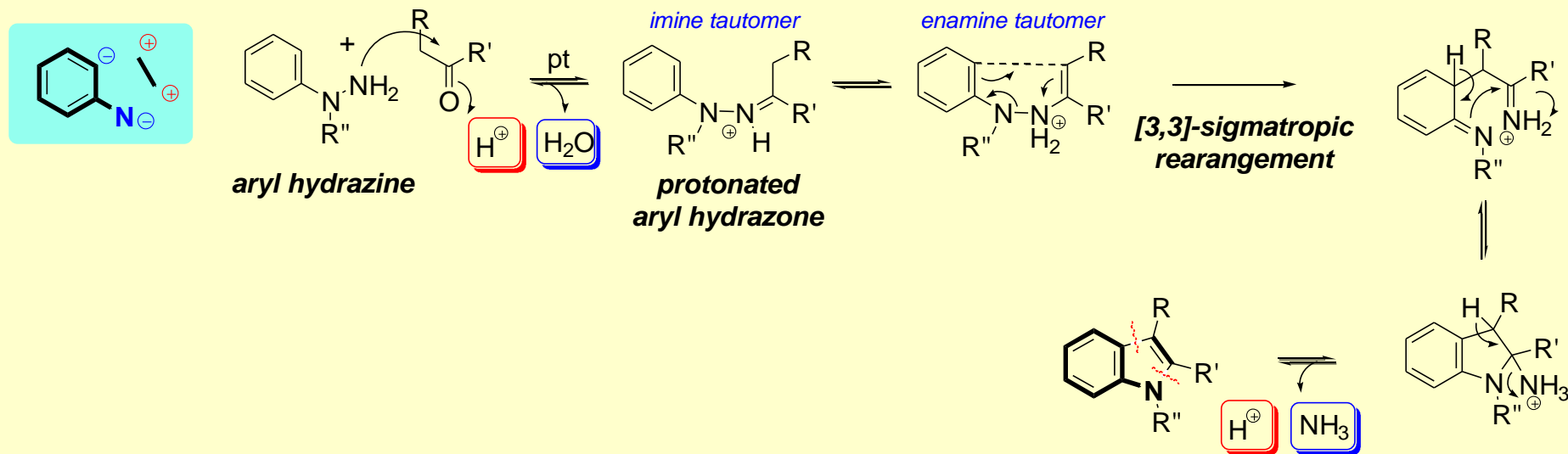


- → both **quinoline** and **isoquinoline** are:
  - reactive towards electrophilic substitution ( $\text{S}_{\text{E}}\text{Ar}$ ) in the benzenoid ring
  - reactive towards nucleophilic substitution ( $\text{S}_{\text{N}}\text{Ar}$ ) in the pyridinyl ring
- **Basic:** both systems have  $\text{pK}_{\text{a}}$ s similar to pyridine (5.2):
  - **quinoline:**  $\text{pK}_{\text{a}} = 4.9$
  - **isoquinoline:**  $\text{pK}_{\text{a}} = 5.1$



# Indoles – Syntheses

## ■ **Fischer:** aryl hydrazine with enolisable ketone



## ■ **NOTES:**

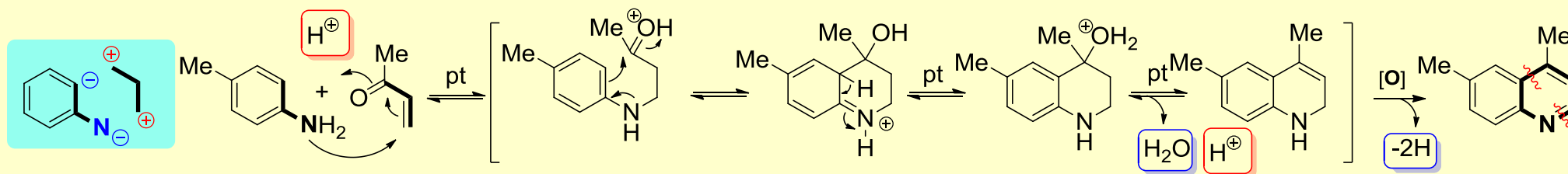
- aryl hydrazone cyclisation under acidic or Lewis acidic conditions
- high temperature ( $\geq 150$  °C) but varies with catalyst & solvent *etc.*
- ketones that are able to form regioisomeric enamines can give mixtures of products but cyclisation is preferred *via more substituted enamine* (*i.e.*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

# Quinolines & Isoquinolines – Syntheses

## ■ Quinolines:

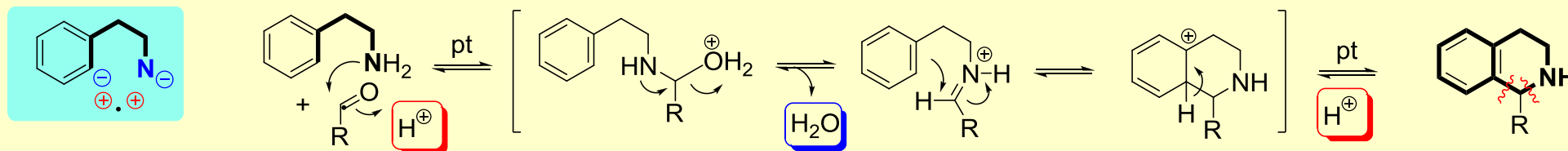
□ **Doebner-von Miller:** enone with aniline then *in situ* oxidation:

- *via apparent 1,4-addition of aniline NH<sub>2</sub> group to enone then cyclodehydration then dehydrogenation (oxidation) by the **imine** formed between the enone and aniline in a side reaction*



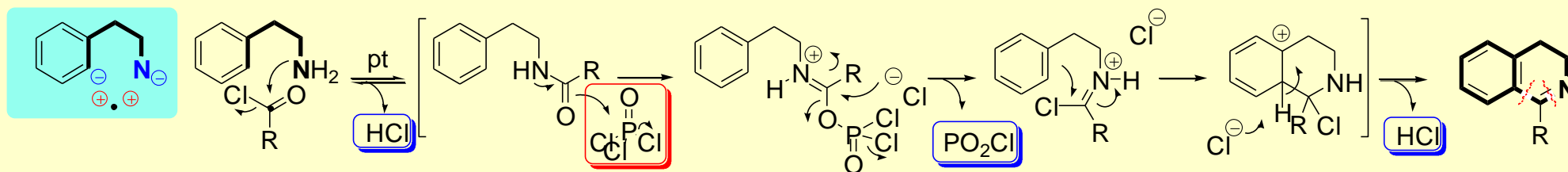
## ■ (Tetrahydro)isoquinolines:

□ **Pictet-Spengler:**  $\beta$ -phenethylamine with aldehyde (intramolecular Mannich)



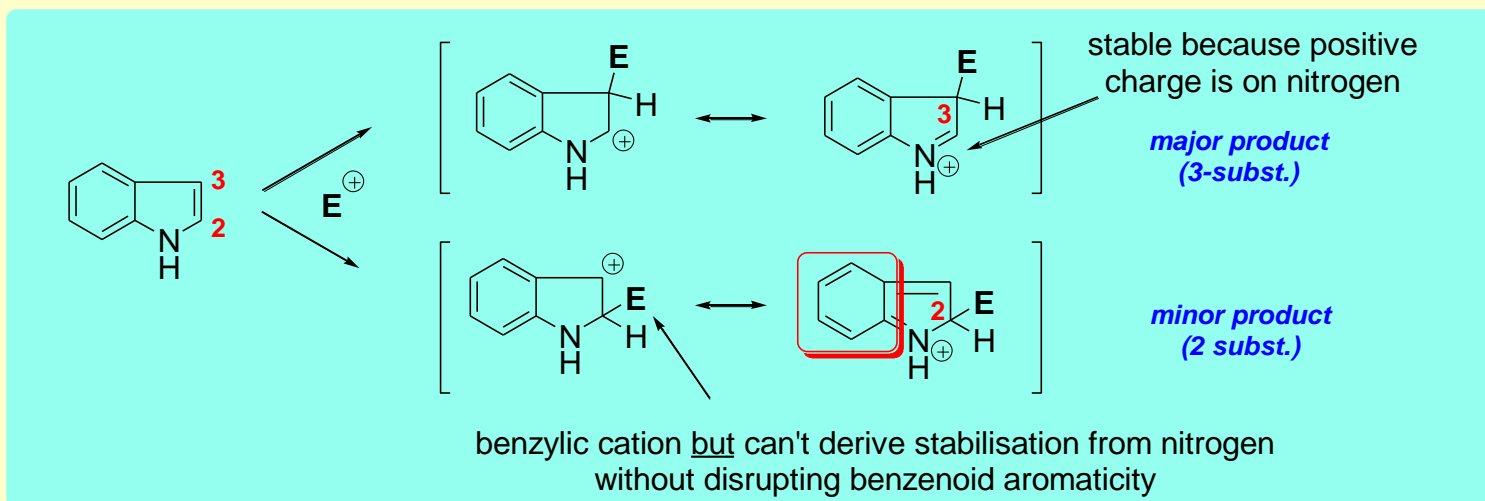
## ■ (Dihydro)isoquinolines:

□ **Bischler-Napieralski:**  $\beta$ -phenethylamine with acid chloride

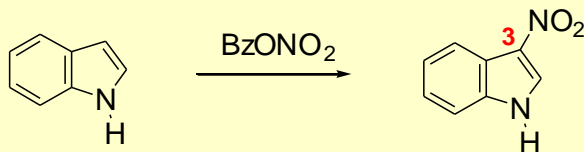


# Indoles – Reactivity

- **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:

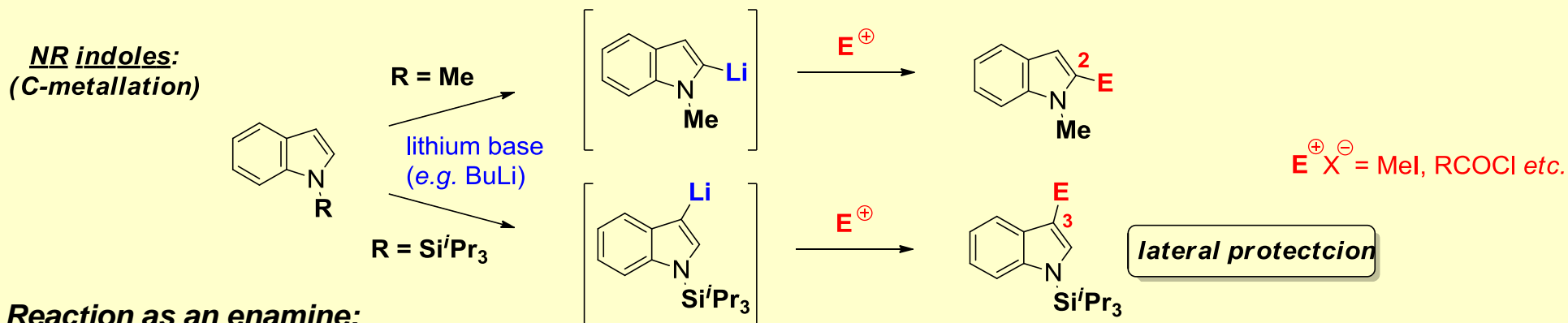
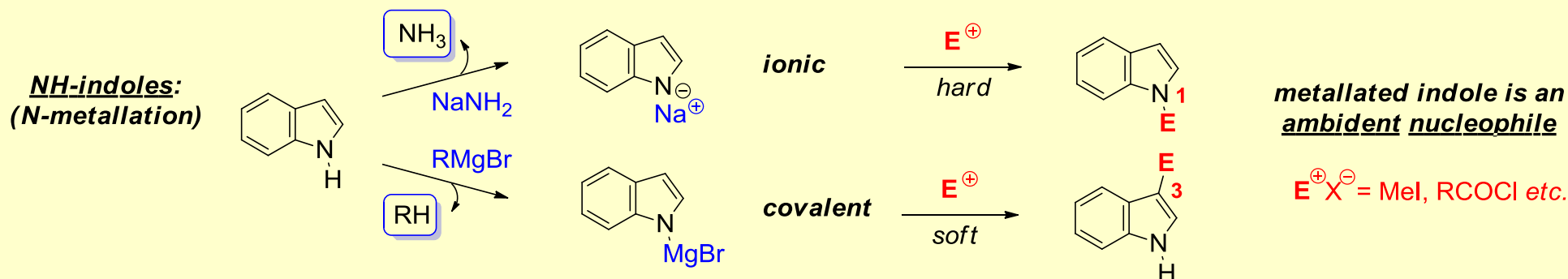


- **e.g. nitration:** ( $E^+ = NO_2^+$ )



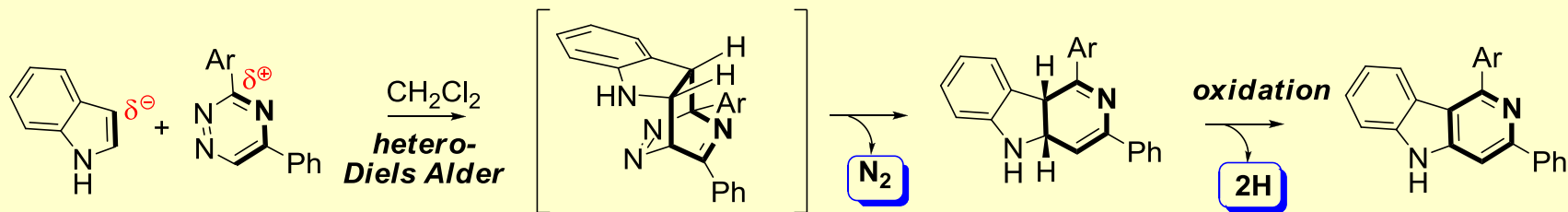
# Indoles – Reactivity cont.

- **Metallation:** (NH pK<sub>a</sub> = 16.2) NB. For an overview & mechanistic discussion see Joule & Smith (5<sup>th</sup> Ed) chapter 4.



- **Reaction as an enamine:**

- e.g. as hetero-Diels-Alder dienophile

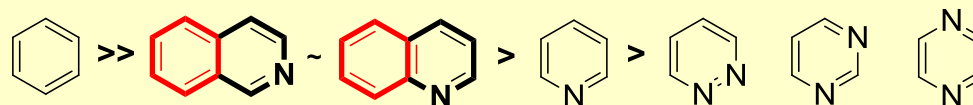




# Quinolines & Isoquinolines – Reactivity

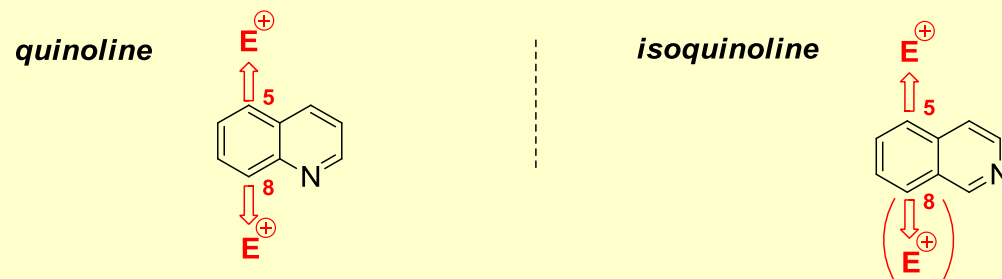
- **Electrophilic substitution:** via addition-elimination ( $S_EAr$ ) in the benzenoid ring (*i.e.* more electron rich ring)

- **reactivity:** reactive towards many electrophiles ( $E^+$ ); <benzene but >pyridine

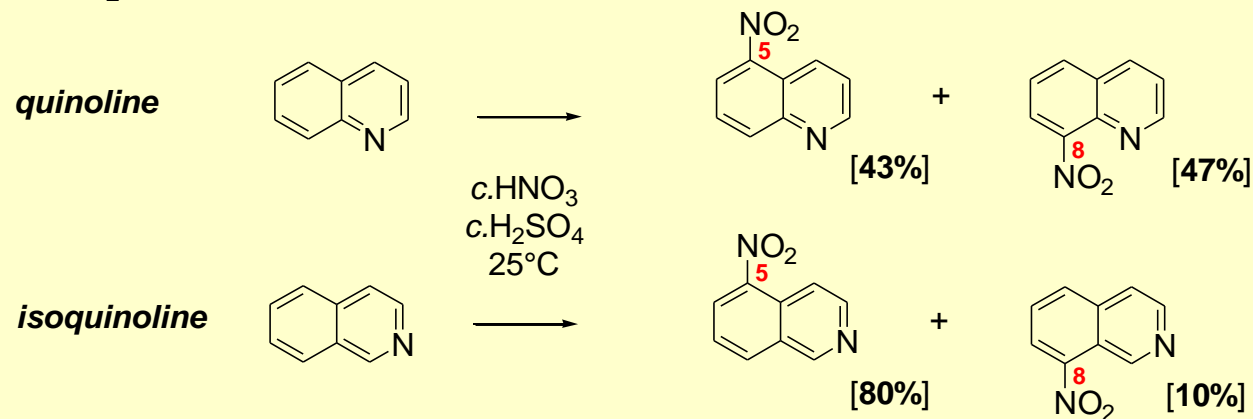


relative rates    1                     $\sim 10^{-5}$                      $\sim 10^{-6}$                      $\sim 10^{-12}$

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



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

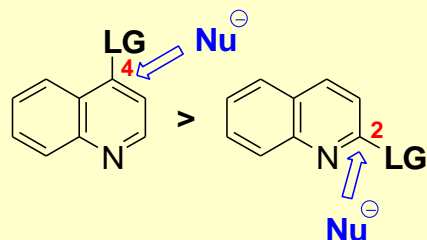


# Quinolines & Isoquinolines – Reactivity cont.

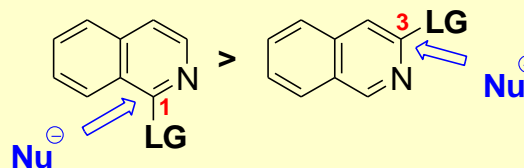
## ■ **Nucleophilic substitution:** via addition-elimination ( $S_NAr$ )

- **reactivity:** reactive towards nucleophiles ( $Nu^-$ ) 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

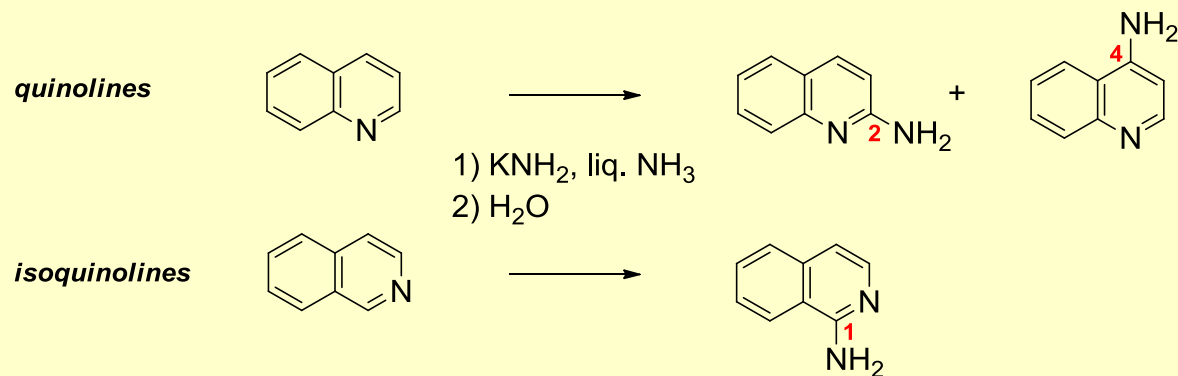
quinolines



isoquinolines



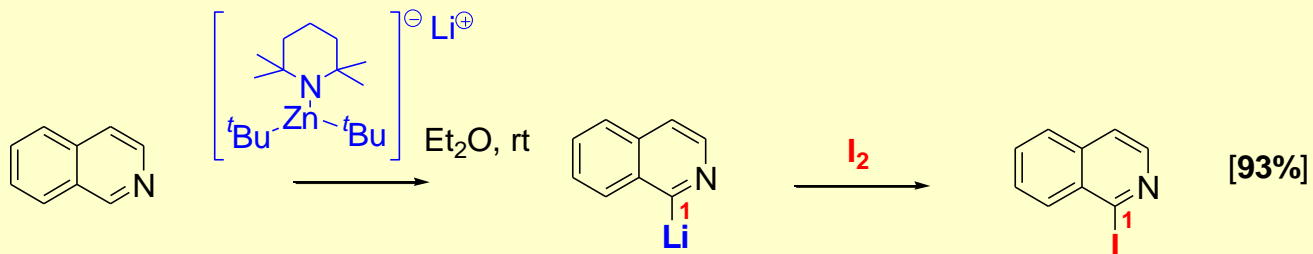
- **e.g. the Chichibabin reaction:** ( $Nu^- = NH_2^-$ , LG = H)



# 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:



## Metallation at benzylic positions:

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

