

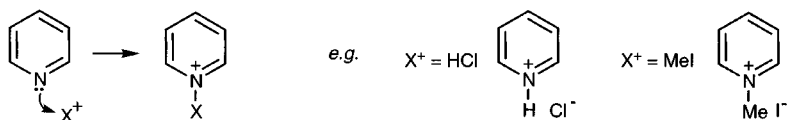
## 2 Reactivity of aromatic heterocycles

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This chapter describes in general terms the types of reactivity found in the typical six- and five-membered aromatic heterocycles. In addition to discussions of classical substitution chemistry, considerable space is devoted to radical substitution, metallation and palladium-catalysed reactions, since these areas have become very important in heterocyclic manipulations. In order to gain a proper appreciation of their importance in the heterocyclic context we provide an introduction to these topics, since they are only poorly covered in general organic text-books. Emphasis on the typical chemistry of individual heterocyclic systems is to be found in the summary/revision chapters (4, 7, 10, 12, 16, and 20) and a more detailed examination of typical heterocyclic reactivity, and many more examples for particular heterocyclic systems are to be found in the chapters – ‘Pyridines: reactions and synthesis’ etc. For the advanced student, it is recommended that this present chapter should be read in its entirety before moving on to the later chapters, and that the introductory summary/revision chapters, like ‘Typical reactivity of pyridines, quinolines and isoquinolines’ should be read before the more detailed discussions.

### 2.1 Electrophilic addition at nitrogen

Heterocycles which contain an imine unit ( $C=N$ ) as part of their ring structure – pyridines, quinolines, isoquinolines, 1,2- and 1,3-azoles, etc. – do not utilise the nitrogen lone pair in their aromatic  $\pi$ -system (cf. section 1.2) and therefore it is available for donation to electrophiles, just as in any simpler amine. In other words, such heterocycles are basic and will react with protons, or other electrophilic species, at nitrogen, by addition. In many instances the product salts, from such additions, are isolable.



For reversible additions, for example of a proton, the position of equilibrium depends on the  $pK_a$  of the heterocycle,<sup>1</sup> and this in turn is influenced by the substituents present on the ring: electron-releasing groups enhance the basicity and electron-withdrawing substituents reduce the basic strength. The  $pK_a$  of simple pyridines is of the order of 5, while those for 1,2- and 1,3-azoles depends on the character of the other heteroatom: pyrazole and imidazole, with two nitrogen atoms, have values of 2.5 and 7.1 respectively.

Related to basicity, but certainly not always mirroring it, is the *N*-nucleophilicity of imine-containing heterocycles. Here, the presence of substituents adjacent to the nitrogen can have a considerable effect on how easily reaction with alkyl halides takes place and indeed whether nitrogen attacks at carbon, forming  $N^+$ -alkyl salts,<sup>2</sup> or by deprotonation, bringing about a 1,2-dehydrohalogenation of the halide, the heterocycle then being converted into an *N*<sup>+</sup>-hydrogen salt. The classical study of the

slowing of *N*-alkylation by the introduction of steric interference at  $\alpha$ -positions of pyridines showed one methyl to slow the rate by about threefold, whereas 2,6-dimethyl substitution slowed the rate between 12 and 40 times.<sup>3</sup> Taking this to an extreme, 2,6-di-*t*-butylpyridine will not react at all with iodomethane, even under high pressure; the very reactive methyl fluorosulfonate will *N*-methylate it, but only under high pressure.<sup>4</sup> The quantitative assessment of reactivity at nitrogen must always take into account both steric (especially at the  $\alpha$ -positions) and electronic effects: 3-methylpyridine reacts faster ( $\times 1.6$ ) but 3-chloropyridine reacts slower ( $\times 0.14$ ) than pyridine. *Peri* substituents have a significant effect on the relative rates of reaction with iodomethane: for pyridine, isoquinoline (no *peri* hydrogen), quinoline, and 8-methylquinoline, rates are 50, 69, 8, and 0.008, respectively.

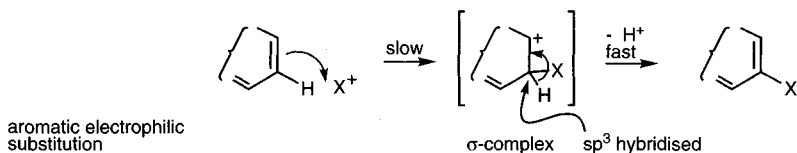
Other factors can influence the rate of quaternisation: all the diazines react with iodomethane more slowly than does pyridine. Pyridazine, much more weakly basic ( $\text{p}K_{\text{a}}$  2.3) than pyridine, reacts with iodomethane faster than the other diazines, a result which is ascribed to the ' $\alpha$  effect', i.e. the increased nucleophilicity is deemed to be due to electron repulsion between the two immediately adjacent lone pairs.<sup>5</sup> Reaction rates for iodomethane with pyridazine, pyrimidine and pyrazine are respectively 0.25, 0.044, and 0.036 relative to the rate with pyridine.

## 2.2 Electrophilic substitution at carbon<sup>6</sup>

The study of aromatic heterocyclic reactivity can be said to have begun with the results of electrophilic substitution processes – these were traditionally the means for the introduction of substituents onto heterocyclic rings. To a considerable extent that methodology has been superseded, especially for the introduction of carbon substituents, by methods relying on the formation of heteroaryllithium nucleophiles (section 2.6) and on palladium-catalysed processes (section 2.7). Nonetheless the reaction of heterocycles with electrophilic reagents is still extremely useful in many cases, particularly for electron-rich, five-membered heterocycles.

### 2.2.1 Aromatic electrophilic substitution – mechanism

Electrophilic substitution of aromatic (and heteroaromatic) molecules proceeds *via* a two-step sequence, initial addition (of  $\text{X}^+$ ) giving a positively charged intermediate (a  $\sigma$ -complex, or Wheland intermediate), then elimination (normally of  $\text{H}^+$ ), of which the former is usually the slower (rate-determining) step. Under most circumstances such substitutions are irreversible and the product ratio is determined by kinetic control.

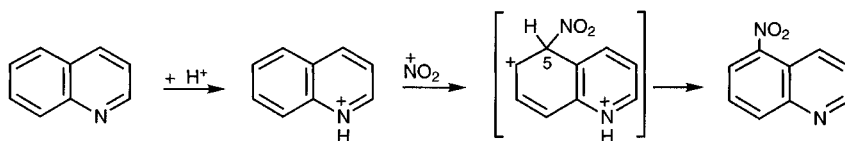


### 2.2.2 Six-membered heterocycles

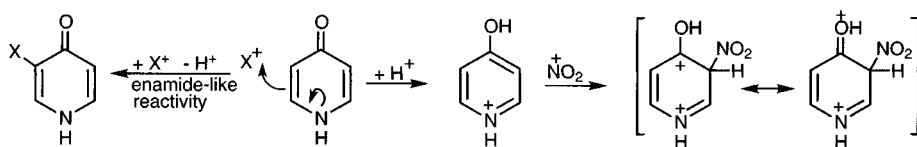
An initial broad division must be made in considering heteroaromatic electrophilic substitution, into those heterocycles which are basic and those which are not, for in the case of the former the interaction of nitrogen lone pair with the electrophile (cf. section 2.1), or indeed with any other electrophilic species in the proposed reaction

mixture (protons in a nitrating mixture, or aluminium chloride in a Friedel-Crafts combination) will take place far faster than any *C*-substitution, thus converting the substrate into a positively charged salt and therefore hugely reducing its susceptibility to attack by  $X^+$  at carbon. It is worth recalling the rate reduction attendant upon the change from benzene to *N,N,N*-trimethylanilinium cation ( $\text{PhN}^+\text{Me}_3$ ) where the electrophilic substitution rate goes down by a factor of  $10^8$  even though in this instance the charged atom is only attached to, and not a component of, the aromatic ring. Thus all heterocycles with a pyridine-type nitrogen (i.e. those containing  $\text{C}=\text{N}$ ) do not easily undergo *C*-electrophilic substitution, unless (a) there are other substituents on the ring which 'activate' it for attack, or (b) the molecule has another, fused benzene ring in which substitution can take place, or (c) there is a second hetero atom in a five-membered ring, which can release electrons to the attacking electrophile. For example, simple pyridines do not undergo many useful electrophilic substitutions, but quinolines and isoquinolines undergo substitution in the benzene ring. It has been estimated that the intrinsic reactivity of a pyridine (i.e. not protonated) to electrophilic substitution is around  $10^7$  times less than that of benzene, that is to say, about the same as that of nitrobenzene.

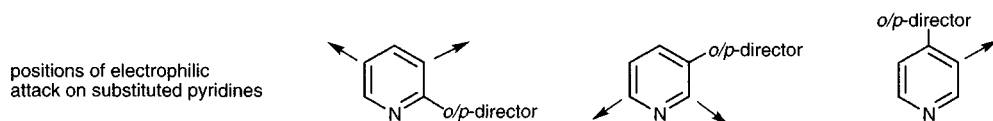
When quinoline or isoquinoline undergo nitration in the benzene ring the actual species attacked is the *N*-protonated heterocycle, and even though substitution is taking place in the benzene ring, it must necessarily proceed through a doubly charged intermediate: this results in a much slower rate of substitution than for the obvious comparison, naphthalene – the 5- and 8-positions of quinolinium are attacked at about a  $10^{10}$  slower rate than the 1-position of naphthalene, and it was estimated that the nitration of pyridinium cation is at least  $10^5$  slower still.<sup>7</sup> A study of the bromination of methylpyridines in acidic solution allowed an estimate of  $10^{-13}$  for the partial rate factor for bromination of a pyridinium cation.<sup>8</sup>



'Activating' substituents,<sup>9</sup> i.e. groups which can release electrons either inductively or mesomerically, make the electrophilic substitution of pyridine rings to which they are attached faster, for example 4-pyridone nitrates at the 3-position *via* the *O*-protonated salt.<sup>10</sup> In order to understand the activation, it is helpful to view the species attacked as a (protonated) phenol-like substrate. Electrophilic attack on neutral pyridones is best visualised as attack on an enamide. Dimethoxypyridines also undergo nitration *via* their cations, but the balance is often delicate, for example 2-aminopyridine brominates at C-5, in acidic solution, *via* the free base.<sup>11</sup>



Pyridines carrying activating substituents at C-2 are attacked at C-3/C-5, those with such groups at C-3 are attacked at C-2, and not at C-4, whilst those with substituents at C-4 undergo attack at C-3.

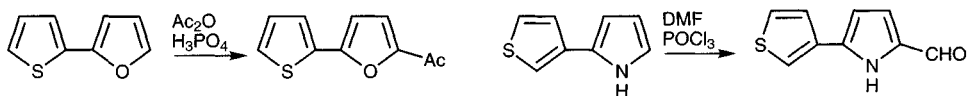


Substituents which reduce the basicity of a pyridine nitrogen can also influence the susceptibility of the heterocycle to electrophilic substitution, in these cases by increasing the proportion of neutral (more reactive) pyridine present at equilibrium: 2,6-dichloropyridine nitrates at C-3, as the free base, and only  $10^3$  times more slowly than 1,3-dichlorobenzene. As a rule-of-thumb it has been suggested that (i) pyridines with a  $pK_a > 1$  will nitrate as cations, slowly unless strongly activated, and at an  $\alpha$  or  $\beta$  position depending on the position of the substituent, (ii) weakly basic pyridines,  $pK_a < -2.5$ , nitrate as free bases, and at an  $\alpha$  or  $\beta$  position depending on the position of the substituent.<sup>11</sup>

Pyridines carrying strongly electron-withdrawing substituents, or heterocycles with additional heteroatoms, diazines for example, are so deactivated that electrophilic substitutions do not take place.

### 2.2.3 Five-membered heterocycles

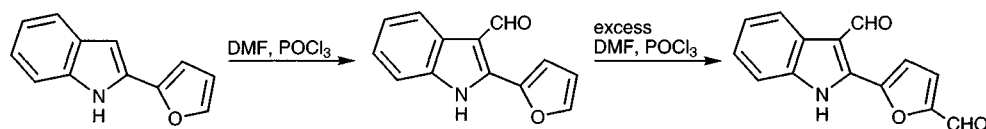
For five-membered, electron-rich heterocycles the utility of electrophilic substitutions is much greater.<sup>12</sup> Heterocycles such as pyrrole, thiophene and furan undergo a range of electrophilic substitutions with great ease, at either type of ring position, but with a preference for attack adjacent to the hetero atom – at their  $\alpha$ -positions. These substitutions are facilitated by electron-release from the hetero atom and, as a consequence, pyrroles are more reactive than furans which are in turn more reactive than thiophenes. Quantitative comparisons<sup>13</sup> of the relative reactivities of the three heterocycles vary from electrophile to electrophile, but for trifluoroacetylation, for example, the pyrrole:furan:thiophene ratio is:  $5 \times 10^7:1.5 \times 10^2:1$ ;<sup>14</sup> in formylation, furan is 12 times more reactive than thiophene,<sup>15</sup> and for acetylation, the value is 9.3.<sup>16</sup> In hydrogen exchange (deuteriodeprotonation) the partial rate factors for the  $\alpha$  and  $\beta$  positions of *N*-methylpyrrole<sup>17</sup> are  $3.9 \times 10^{10}$  and  $2.0 \times 10^{10}$  respectively; for this same process, the values for furan are  $1.6 \times 10^8$  and  $3.2 \times 10^4$  and for thiophene,  $3.9 \times 10^8$  and  $1.0 \times 10^5$  respectively,<sup>18</sup> and in a study of thiophene,  $\alpha:\beta$  ratios ranging from 100:1 to 1000:1 were found for different electrophiles.<sup>19</sup> Relative substrate reactivity parallels positional selectivity i.e. the  $\alpha:\beta$  ratio decreases in the order furan > thiophene > pyrrole.<sup>20</sup> Nice illustrations of these relative reactivities are found in acylations of compounds containing two different systems linked together.<sup>21</sup>



The positional selectivity of attack on pyrroles can be completely altered by the presence of bulky groups on nitrogen: 1-(*t*-butyldimethylsilyl)pyrrole and 1-(tri-*i*-propylsilyl)pyrrole are attacked exclusively at their  $\beta$ -positions.<sup>22</sup> Extremely electrophilic reagents (hard electrophiles) such as trimethylsilyl triflate attack *N*-methylpyrroles exclusively at a  $\beta$ -position.<sup>23</sup>

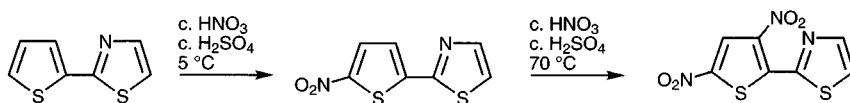
Indoles are only slightly less reactive than pyrroles, electrophilic substitution taking place in the heterocyclic ring, at a  $\beta$ -position: in acetylation using a Vilsmeier combination (*N,N*-dimethylacetamide/phosgene), the rate ratio compared with pyrrole is 1:3.<sup>24</sup> In contrast to pyrrole there is a very large difference in reactivity

between the two hetero-ring position in indoles: 2600:1,  $\beta$ : $\alpha$ , in Vilsmeier acetylation. With reference to benzene, indole reacts at its  $\beta$ -position around  $5 \times 10^{13}$  times as fast.<sup>25</sup> Again, these differences can be illustrated conveniently using an example<sup>26</sup> which contains two types of system linked together.



The reactivity of an indole is very comparable to that of a phenol: typical of phenols is their ability to be substituted even by weak electrophiles, like benzenediazonium cations, and indeed indoles (and pyrroles) also undergo such couplings; depending on pH, indoles can undergo such processes *via* a small equilibrium concentration of anion formed by loss of *N*-proton (cf. section 2.5); of course this is an even more rapid process, shown to be  $10^8$  faster than for the neutral heterocycle.<sup>27</sup> The Mannich substitution (electrophile:  $\text{CH}_2=\text{N}^+\text{Me}_2$ ) of 5- and 6-hydroxyindoles, takes place *ortho* to the phenolic activating group on the benzene ring, and not at the indole  $\beta$ -position.<sup>28</sup> Comparisons of the rates of substitution of the pairs furan/benzo[*b*]furan and thiophene/benzo[*b*]thiophene showed the bicyclic systems to be less reactive than the monocyclic heterocycles, the exact degree of difference varying from electrophile to electrophile.<sup>29</sup>

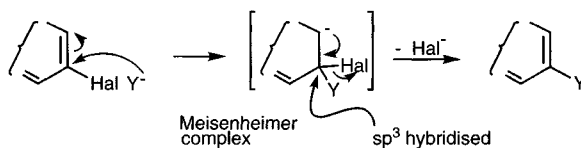
Finally, in the 1,2- and 1,3-azoles there is a fascinating interplay of the propensities of an electron-rich five-membered heterocycle with an imine, basic nitrogen. This latter reduces the reactivity of the heterocycle towards electrophilic attack at carbon, both by inductive and by mesomeric withdrawal, and also by conversion into salt in acidic media. For example, depending on acidity, the nitration of pyrazole can proceed by attack on the pyrazolium cation,<sup>30</sup> or *via* the free base.<sup>31</sup> A study of acid-catalysed exchange showed the order: pyrazole > isoxazole > isothiazole, paralleling pyrrole > furan > thiophene, but each is much less reactive than the corresponding heterocycle without the azomethine nitrogen, but equally, that each is still more reactive than benzene, the partial rate factors for exchange at their 4-positions being  $6.3 \times 10^9$ ,  $2.0 \times 10^4$  and  $4.0 \times 10^3$  respectively. Thiophene is  $3 \times 10^5$  times more rapidly nitrated than 4-methylthiazoles;<sup>32</sup> the nitration of a 2-(thien-2-yl)thiazole illustrates the relative reactivities.<sup>33</sup>



## 2.3 Nucleophilic substitution at carbon<sup>34</sup>

### 2.3.1 Aromatic nucleophilic substitution – mechanism

Nucleophilic substitution of aromatic compounds proceeds *via* an **addition** (of  $\text{Y}^-$ ) then **elimination** (of a negatively charged entity, most often  $\text{Hal}^-$ ) two-step sequence, of which the former is usually rate-determining. It is the stabilisation (delocalisation of charge) of the negatively charged intermediates (Meisenheimer complexes) which is the key to such processes, for example in reactions of *ortho* and *para* chloronitrobenzenes the nitro group is involved in the charge dispersal.

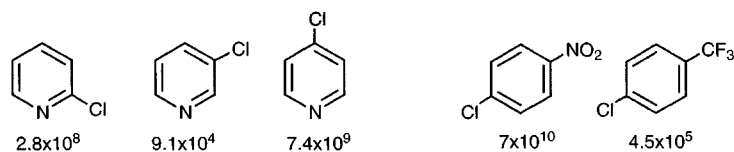


### 2.3.2 Six-membered heterocycles

In the heterocyclic field, the displacement of good leaving groups, often halide, by a nucleophile is a very important general process, especially for six-membered electron-poor systems. In the chemistry of five-membered aromatic heterocycles, such processes only come into play in special situations such as where, as in benzene chemistry, the leaving group is activated by an *ortho* or *para* nitro group, or in the azoles, where the leaving group is attached to an imine unit.

Positions  $\alpha$  and  $\gamma$  to an imine nitrogen are activated for the initial addition of a nucleophile by two factors: (i) inductive and mesomeric withdrawal of electrons by the nitrogen and (ii) inductive withdrawal of electrons by the halogen. The  $\sigma$ -adduct intermediate is also specially stabilised when attack is at  $\alpha$ - and  $\gamma$ -positions, since in these intermediates the negative charge resides largely on the nitrogen:  $\alpha$  and  $\gamma$  positions are much more reactive in nucleophilic displacements than  $\beta$  positions. A quantitative comparison for displacements of chloride with sodium methoxide in methanol showed the 2- and 4-chloropyridines to react at roughly the same rate as 4-chloronitrobenzene, with the  $\gamma$ -isomer somewhat more reactive than the  $\alpha$ -halide.<sup>35</sup> It is notable that even 3-chloropyridine, where only inductive activation can operate, is appreciably more reactive than chlorobenzene.

Rates of reaction with  $\text{MeO}^-$ , relative to chlorobenzene, at 50 °C

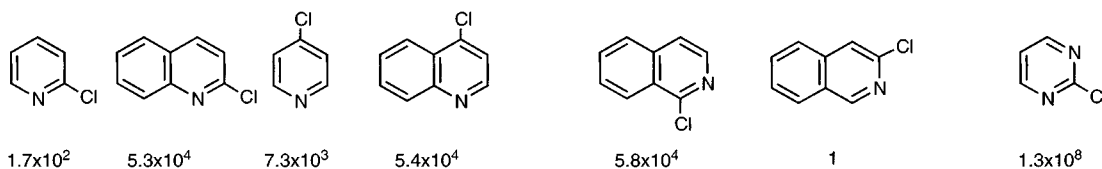


The presence of a formal positive charge on the nitrogen, as in *N*-oxides and *N*-alkylpyridinium salts, has a further very considerable enhancing effect on the rate of nucleophilic substitutions, *N*-oxidation having a smaller effect than quaternisation – in the latter there is a full formal positive charge on the molecule but *N*-oxides are overall electrically neutral. In reactions with methoxide, the 2-, 3- and 4-chloropyridine *N*-oxides are  $1.9 \times 10^4$ ,  $1.1 \times 10^5$ , and  $1.1 \times 10^3$  times more reactive than the corresponding chloropyridines, and displacements of halide in the 2-, 3- and 4-chloro-1-methylpyridinium salts are  $4.6 \times 10^{12}$ ,  $2.9 \times 10^8$ , and  $5.7 \times 10^9$  times more rapid. Another significant point to emerge from these rate studies concerns the relative rate enhancements, at the three ring positions: the effect of the charge is much greater at an  $\alpha$  than at a  $\gamma$  position such that in the salts the order is  $2 > 4 > 3$ , as opposed to both neutral pyridines, where the order of reactivity is  $4 > 2 > 3$ , and *N*-oxides, where the  $\alpha$ -positions end up at about the same reactivity as the  $\gamma$ -position.<sup>36</sup> The utility of nitrite as a leaving group in heterocyclic chemistry is emphasised by a comparison of its relative reactivity to nucleophilic displacement: 4-nitropyridine is about 1100 times more reactive than 4-bromopyridine. A comparison of the rates of displacement of 4-methylsulfonylpyridine with its *N*-methyl quaternary salt showed a

rise in rate by a factor of  $7 \times 10^8$ .<sup>37</sup> Although methoxide is not generally a good leaving group, when attached to a pyridinium salt it is only about 4 times less easily displaced than iodide, bromide and chloride; fluoride in the same situation is displaced about 250 times faster than the other halides.<sup>38</sup>

Turning to bicyclic systems, and a study of reaction with ethoxide, a small increase in the rate of reaction relative to pyridines was found for chloroquinolines at comparable positions.<sup>39</sup> In the bicyclic compounds, quaternisation again greatly increases the rate of nucleophilic substitution, having a larger effect ( $\sim 10^7$ ) at C-2 than at C-4 ( $\sim 10^5$ ).<sup>40</sup>

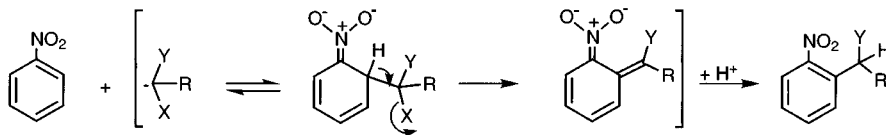
Relative rates for nucleophilic displacement with  $\text{EtO}^-$  at  $20^\circ\text{C}$



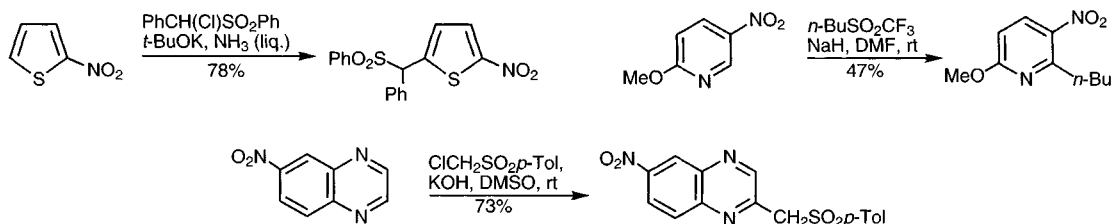
Diazines with halogen  $\alpha$  and  $\gamma$  to nitrogen are much more reactive than similar pyridines, for example 2-chloropyrimidine is  $\sim 10^6$  times more reactive than 2-chloropyridine.

### 2.3.3 Vicarious nucleophilic substitution (VNS substitution)<sup>41</sup>

A process known as 'Vicarious Nucleophilic Substitution' (VNS) of hydrogen has been widely applied to carboaromatic and to heteroaromatic compounds. In general form the process requires the presence of a nitro group on the substrate which permits the addition of a carbon nucleophile, of the form  $\text{C}(\text{X})(\text{Y})(\text{R})$ , where X is a potential leaving group and Y is an anion-stabilising group which permits the formation of the carbanion in the first place. Most often X is a halogen and Y is arylsulfonyl; with these, a typical sequence is shown below. Following addition, *ortho* or *para* to the nitro group, elimination of HX takes place to form a conjugated, non-aromatic nitronate which on reprotonation returns the molecule to aromaticity and produces the substituted product. Excess of the base used to generate the initial carbanion must be used in order to drive the process forward by bringing about the irreversible elimination of HX.



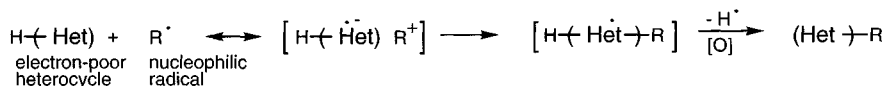
Examples of VNS processes will be found in several later chapters; given below are three typical sequences. The first example shows the operation of a VNS substitution in a five-membered heterocycle;<sup>42</sup> in the second example the anion-stabilising group (Y) (trifluoromethanesulfonyl) also serves as the leaving group (X).<sup>43</sup> The third example is somewhat unusual in that the attacking nucleophile does not enter *ortho* or *para* to the nitro group: addition at C-2 in 6-nitroquinoxaline produces an anion stabilised by delocalisation involving both N-1 and the nitro group.<sup>44</sup>



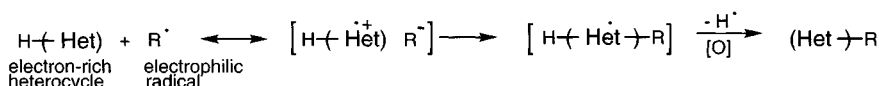
## 2.4 Radical substitution at carbon<sup>45</sup>

Both electron-rich and electron-poor heterocyclic rings are susceptible to substitution of hydrogen by free radicals. Although electrically neutral, radicals exhibit varying degrees of nucleophilic or electrophilic character and this has a very significant effect on their reactivity towards different heterocyclic types. These electronic properties are a consequence of the interaction between the SOMO (Singly Occupied Molecular Orbital) of the radical and either the HOMO, or the LUMO, of the substrate, depending on their relative energies; these interactions are usefully compared with charge transfer interactions.

**Nucleophilic radicals** carry cation-stabilising groups on the radical carbon, allowing electron density to be transferred from the radical to an electron-deficient heterocycle; they react therefore only with electron-poor heterocycles and will not attack electron-rich systems: examples of such radicals are  $\cdot\text{CH}_2\text{OH}$ ,  $\text{alkyl}\cdot$ , and  $\text{acyl}\cdot$ . Substitution by such a radical can be represented in the following general way:



**Electrophilic radicals**, conversely, are those which would form stabilised anions on gaining an electron, and therefore react readily with electron-rich systems: examples are  $\cdot\text{CF}_3$  and  $\cdot\text{CH}(\text{CO}_2\text{Et})_2$ . Substitution by such a radical can be represented in the following general way:



Aryl radicals can show both types of reactivity. A considerable effort (mainly older work) was devoted to substitutions by aryl radicals; they react with electron-rich and electron-poor systems at about the same rate but often with poor regioselectivity.<sup>46</sup>

### 2.4.1 Reactions of heterocycles with nucleophilic radicals

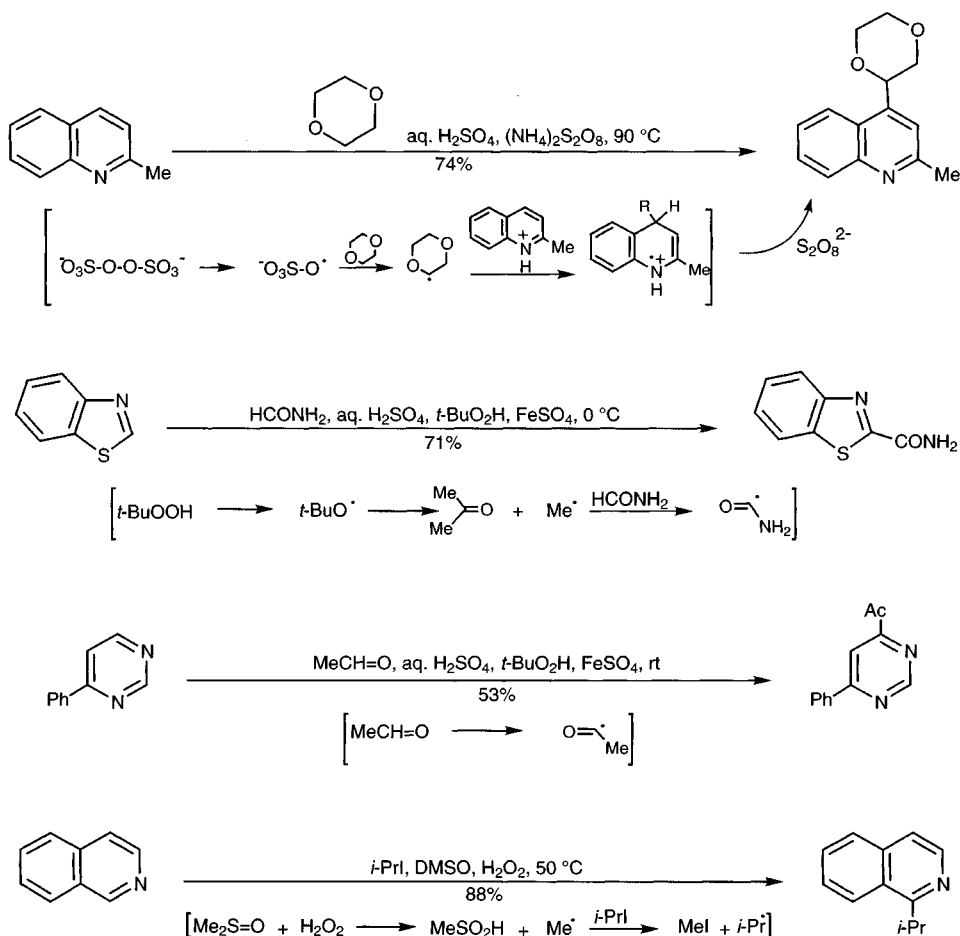
#### The Minisci reaction<sup>47</sup>

The reaction of nucleophilic radicals, under acidic conditions, with heterocycles containing an imine unit is by far the most important and synthetically useful radical substitution of heterocyclic compounds. Pyridines, quinolines, diazines, imidazoles, benzothiazoles, and purines are amongst the systems which have been shown to react with a wide range of nucleophilic radicals, selectively at positions  $\alpha$  and  $\gamma$  to the nitrogen, with replacement of hydrogen. Acidic conditions are essential because *N*-protonation of the heterocycle both greatly increases its reactivity and promotes regioselectivity towards a nucleophilic radical, most of which hardly react at all with

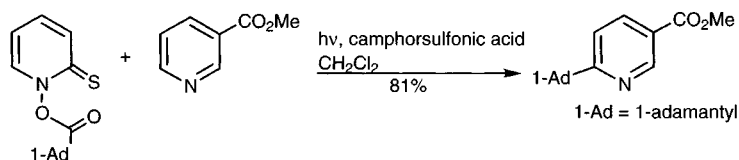


the neutral base. A particularly useful feature of the process is that it can be used to introduce acyl groups, directly, i.e. to effect the equivalent of a Friedel-Crafts substitution – impossible under normal conditions for such systems (cf. section 2.2.2). Tertiary radicals are more stable, but also more nucleophilic and therefore more reactive than methyl radicals in Minisci reactions. The majority of Minisci substitutions have been carried out in aqueous, or at least partially aqueous, media, making isolation of organic products particularly convenient.

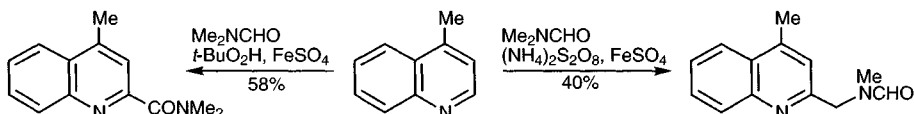
Several methods have been employed to generate the required radical, many depending on the initial formation of oxy- or methyl radicals which then abstract hydrogen or iodine from suitable substrates; both these are illustrated by the typical examples shown below.<sup>48</sup> The re-aromatisation of the intermediate radical-cation is usually brought about by its reaction with excess of the oxidant used to form the initial radical.



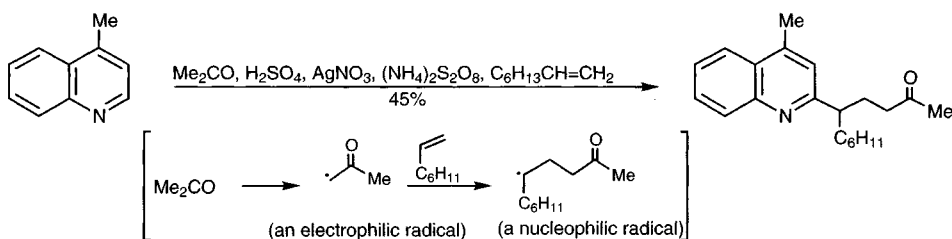
In contrast to the oxidative generation of radicals described above, reductions of alkyl iodides using tris(trimethylsilyl)silane also produces alkyl radicals under conditions suitable for Minisci-type substitution.<sup>49</sup> Carboxylic acids ( $\alpha$ -keto acids) are also useful precursors for alkyl<sup>50</sup> (acyl<sup>51</sup>) radicals *via* silver-catalysed peroxide oxidation, or from their 1-hydroxypyridine-2-thione derivatives using Barton's method,<sup>52</sup> the latter in non-aqueous conditions.



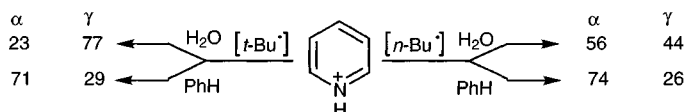
*N,N*-Dialkylformamides can be converted into either alkyl or acyl radicals, depending on the conditions.<sup>53</sup>



An instructive and useful process is the two-component coupling of an alkene with an electrophilic radical: the latter will of course not react with the protonated heterocycle, but after addition to the alkene a nucleophilic radical is generated which will react.<sup>54</sup>

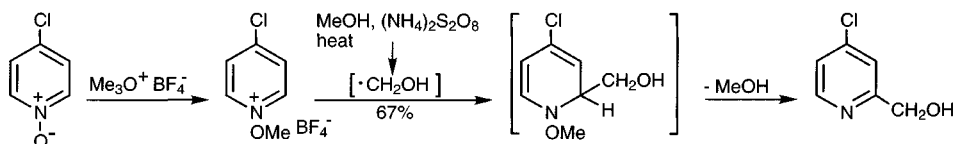


When more than one reactive position is available in a heterocyclic substrate, as is often the case for pyridines for example, there are potential problems with regioselectivity or/and disubstitution (since the product of the first substitution is often as reactive as the starting material). Regioselectivity is dependent to a certain extent on the nature of the attacking radical and the solvent, but may be difficult to control satisfactorily.<sup>55</sup>



A point to note is that for optimum yields, radical substitutions are often not taken to full conversion (of starting heterocycle), but as product and starting material are often easily separated this is usually not a problem. Ways of avoiding disubstitution include control of pH (when the product is less basic than the starting material), or the use of a two-phase medium to allow extraction (removal) of a more lipophilic product out of the aqueous acidic reaction phase.

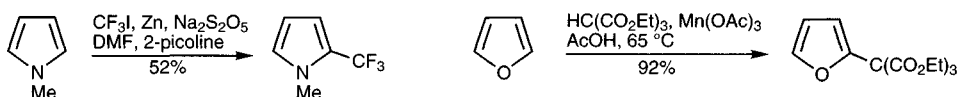
Very selective monosubstitution can also be achieved by the ingenious use of an  $N^+$ -methoxy-quaternary salt, in place of the usual protonic salt. Here, rearomatisation is the result of loss of methanol, leaving as a product a much less reactive, neutral pyridine.<sup>56</sup>



In addition to substitution of hydrogen, *ipso* replacement of nitro, sulfonyl, and acyl substituents can occur, and may compete with normal substitution.<sup>57</sup>

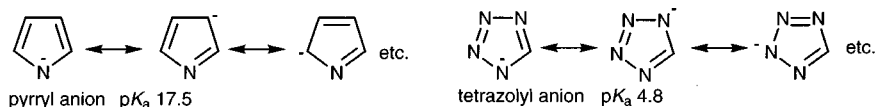
## 2.4.2 Reactions with electrophilic radicals

Although much less well developed than the Minisci reaction, substitution with electrophilic radicals can be used in some cases to achieve selective reaction in electron-rich heterocycles.<sup>58</sup>



## 2.5 Deprotonation of *N*-hydrogen<sup>59</sup>

Pyrroles, imidazoles, pyrazoles and benzo-fused derivatives which have a free *N*-hydrogen have  $pK_a$  values for the loss of the *N*-hydrogen as a proton in the region of 14–18. This is to say that they can be completely converted into anions by reaction with strong bases like sodium hydride or *n*-butyllithium. Even in the simplest of these examples, pyrrole itself, the acidity ( $pK_a$  17.5) is very considerably greater than that of its saturated counterpart, pyrrolidine ( $pK_a \sim 44$ ); similarly the acidity of indole ( $pK_a$  16.2) is much greater than that of aniline ( $pK_a$  30.7). One may rationalise this relatively increased acidity on the grounds that the charge is not localised, and this is illustrated by resonance forms which show the delocalisation of charge around the heterocycle. With the addition of electron-withdrawing substituents, or with the inclusion of extra heteroatoms, especially imine groups, the acidity is enhanced. A nice, though extreme, example is tetrazole for which the  $pK_a$  is 4.8, of the same order as a carboxylic acid.

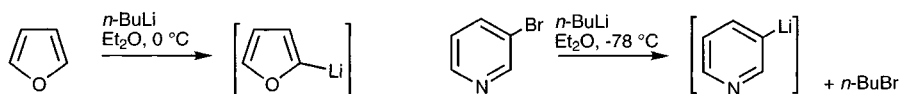


## 2.6 Organometallic derivatives

The most important developments in heterocyclic chemistry in the last twenty or so years are probably in the area of organometallic chemistry, particularly transition-metal-catalysed reactions and the reactions of lithio-derivatives, reflecting development in these areas in organic chemistry as a whole. Even since the 3rd Edition of this book, significant further advances have been made, with improved preparations of boron, magnesium, and zinc compounds and with new ligands for palladium-catalysed reactions which considerably broaden their scope.

## 2.6.1 Lithium derivatives<sup>60</sup>

Lithio-heterocycles have proved to be the most useful organometallic derivatives: they react with the whole range of electrophiles in a manner exactly comparable to that of aryllithiums and can often be prepared by direct metallation (*C*-hydrogen deprotonation), as well as by halogen exchange between halo-heterocycle and alkyllithium. As well as reaction with carbon electrophiles, lithiated species are often the most convenient source of heterocyclic derivatives of less electropositive metals, such as zinc, boron, silicon, and tin (sections 2.6.2 and 2.6.3), which are now widely used in coupling reactions (section 2.7.2.2).



### 2.6.1.1 Direct lithiation (*C*-hydrogen deprotonation)

Many heterocyclic systems react directly with alkyllithiums or with lithium amides to give the lithio-heterocycle *via* abstraction of a proton. Although a 'free' anion is never formed, the ease of lithiation correlates well with *C*-hydrogen acidity and of course this, with the stability of the corresponding conjugate base (carbanion).<sup>61</sup> Lithiations by deprotonation are therefore directly related to base-catalysed proton exchange<sup>62</sup> using reagents such as sodium methoxide, at much higher temperatures, which historically provided the first indication that preparative deprotonations might be regioselective and thus of synthetic value. It must be remembered that kinetic and equilibrium acidities may be different; thermodynamic products are favoured by higher temperatures and by more polar solvents.

The detail of the mechanism of metallation is still under discussion; it may involve a four-centre transition state.



The main factor giving increased acidity of heterocyclic *C*-hydrogen relative to benzenoid *C*-hydrogen is the inductive effect of the heteroatom(s) thus metallation occurs at the carbon  $\alpha$  to the heteroatom, where the inductive effect is felt most strongly, unless other factors, with varying degrees of importance, intervene. These include the following:

#### Mesomerism

Except in the case of side-chain anions (section 2.6.4), the 'anion' orbital is orthogonal to the  $\pi$ -system and so it is not mesomerically delocalised. However, electron density and therefore *C*-hydrogen acidity at ring carbons, is affected by resonance effects.

#### Coordination of the metal counterion to the heteroatom

Stronger coordination between the metal of the base and a heteroatom leads to enhanced acidity of the adjacent *C*-hydrogen due to increased inductive withdrawal of electron density – it is proportionately stronger, for example, for oxygen than for sulfur.

### Lone pair interactions

Repulsion between the electrons in the orbital of the ‘anion’ and an adjacent heteroatom lone pair has a destabilising influence. This effect is thought to be important in pyridines and other azines.<sup>63</sup>

### Polarisability of the heteroatom

More polarisable atoms such as sulfur are able to disperse charge more effectively.

### Substituent effects

Directed metallation (DoM)<sup>64</sup> is extremely useful in heterocyclic chemistry, just as in carbocyclic chemistry. Metallation *ortho* to the directing group is promoted by either inductive effects (e.g. Cl, F), or chelation (e.g.  $\text{CH}_2\text{OH} \rightarrow \text{CH}_2\text{OLi}$ ), or a combination of these, and may overcome the intrinsic regioselectivity of metallation of a particular heterocycle. When available, this is by far the most important additional factor influencing the regioselectivity of lithiation.

### Lithiating agents

Lithiations are normally carried out with alkyllithiums or lithium amides. *n*-Butyllithium is the most widely used alkyllithium but *t*-butyllithium and occasionally *s*-butyllithium are used when more powerful reagents are required. Phenyllithium was used in older work but is uncommon now although it can be of value when a less reactive, more selective base is required.<sup>65</sup> A very powerful metallating reagent is formed from a mixture of *n*-butyllithium and potassium *t*-butoxide: this produces the potassium derivative of the heterocycle.

Lithium diisopropylamide ( $\text{LiN}(i\text{-Pr})_2$ ; LDA) is the most widely used lithium amide but lithium 2,2,6,6-tetramethylpiperidide (LiTMP) is rather more basic and less nucleophilic – it has found particular use in the metallation of diazines. Alkyllithiums are stronger bases than the lithium amides, but usually react at slower rates. Metallations with the lithium amides are reversible so for efficient conversion, the heterocyclic substrate must be more acidic ( $> 4 \text{ p}K_{\text{a}}$  units) than the corresponding amine.

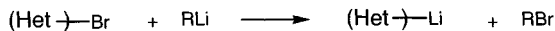
### Solvents

Ether solvents –  $\text{Et}_2\text{O}$  and THF – are normally used. The more strongly coordinating THF increases the reactivity of the lithiating agent by increasing its dissociation. A mixture of ether, THF and pentane (Trapp’s solvent) can be employed for very low temperature reactions ( $< 100^\circ\text{C}$ ) (THF alone freezes at this temperature). To increase the reactivity of the reagents even further, ligands such as TMEDA (*N,N,N,N*’-tetramethylethylenediamine;  $\text{Me}_2\text{N}(\text{CH}_2)_2\text{NMe}_2$ ) or HMPA ( $(\text{Me}_2\text{N})_3\text{PO}$ ) (CAUTION: carcinogen) are sometimes added – these strongly and specifically coordinate the metal cation. While these additives are undoubtedly beneficial in some cases, the efficacy of TMEDA has been questioned.<sup>66</sup>

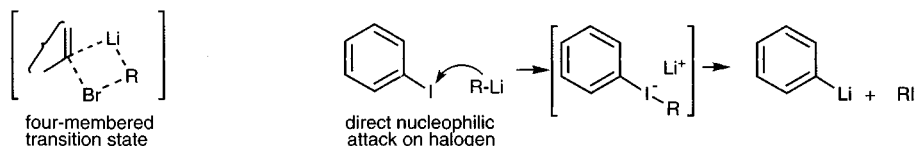
#### 2.6.1.2 Halogen exchange

Bromo- and iodo-heterocycles react rapidly with alkyllithiums, even at temperatures as low as  $-100^\circ\text{C}$ , to give the lithio-heterocycle. Where alternative exchanges are possible, the site of reaction is governed by the stability of the ‘anion’ formed, just as

for direct lithiation by deprotonation. Exchange of fluorine is unknown and of chlorine, rare enough to assume that it is inert.

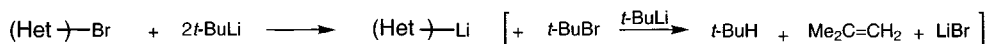


Mechanistically, the exchange process may involve a four-membered transition state, or may possibly proceed *via* an electron-transfer sequence, however direct nucleophilic attack, at least on iodine, has been demonstrated in the case of iodobenzene,<sup>67</sup> and cannot therefore be dismissed as a mechanism.

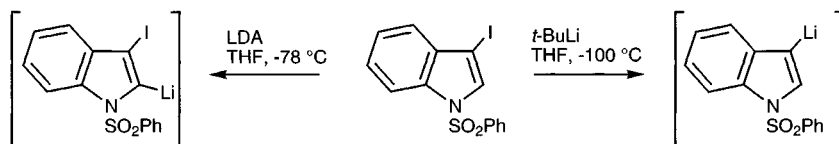


### Halogen exchange reagents

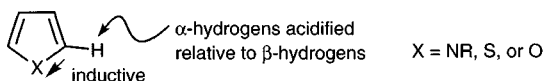
*n*-Butyllithium is the usual exchange reagent; the *n*-butyl bromide byproduct does not usually interfere with subsequent steps. When the presence of an alkyl bromide is undesirable, two equivalents of *t*-butyllithium can be employed – the initially formed *t*-butyl bromide is consumed by reaction with the second equivalent of alkyllithium, producing isobutene.



It is very important to differentiate between pure bases, such as lithium diisopropylamide, which act only by deprotonation, and alkyllithiums which can act as bases or take part in halogen exchange. When using alkyllithiums, exchange is favoured over deprotonation by the use of lower temperatures. The reaction of 3-iodo-1-phenylsulfonylindole with the two types is illustrative.<sup>68</sup>

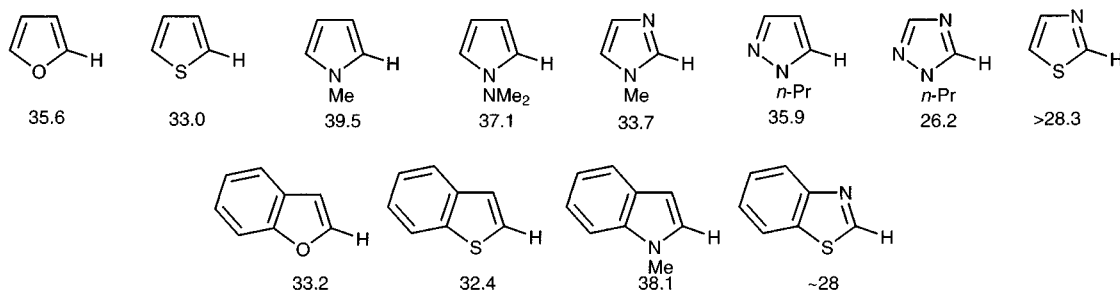


#### 2.6.1.3 Ring lithiation of five-membered heterocycles



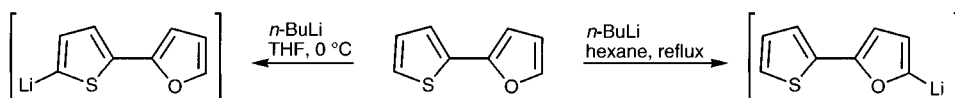
The inductive effect of the heteroatom, which withdraws electrons to a greater extent from an adjacent carbon atom ( $\alpha$ -positions), allows direct  $\alpha$ -lithiation of practically all five-membered heterocycles. The relative 'acidities' of  $\alpha$ -hydrogens in some different classes are illustrated in the table below.

# Equilibrium $pK_a$ values<sup>#</sup> for deprotonation of some five-membered heterocycles in THF<sup>69</sup>

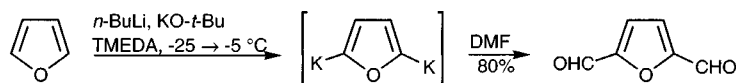


<sup>#</sup>Measured  $pK_a$  values vary according to solvent etc.

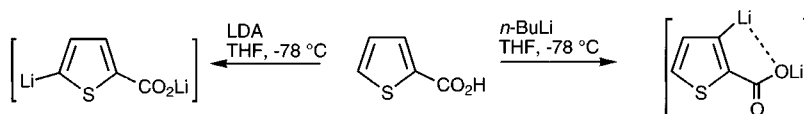
Despite the lower electronegativity of sulfur, and hence a weaker inductive effect, thiophene metallates about as readily as furan, probably in part because the higher polarisability of sulfur allows more efficient charge distribution;<sup>70</sup> d-orbital participation is thought to be relatively unimportant in the stabilisation of carbanionic centres adjacent to sulfur. The lithiation of 2-(2-furyl)thiophene, in either ring depending on conditions, is instructive;<sup>71</sup> preferential lithiation of the furan ring in the non-polar solvent is probably due to stronger coordination of lithium to the oxygen, thus increasing the inductive effect on the  $\alpha$ -hydrogen in the furan ring.



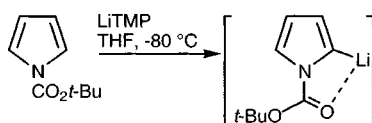
The use of stronger bases can result in dimetallation.<sup>72</sup>



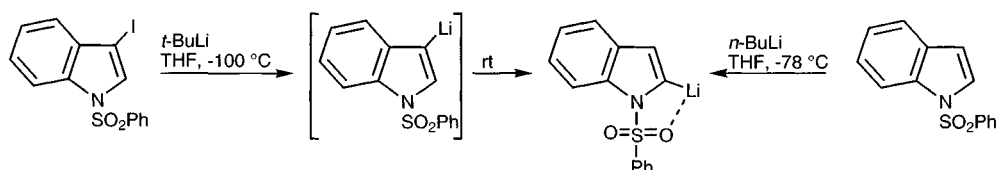
Directing groups can overcome the normal tendency for  $\alpha$ -lithiation in five-membered heterocycles, as shown in the thiophene example below, however the use of lithium diisopropylamide does allow 'normal'  $\alpha$ -lithiation.<sup>73</sup>



Lithiation of pyrroles is complicated by the presence of a much more acidic hydrogen on nitrogen, however 1-methylpyrrole lithiates, at C-2, albeit under slightly more vigorous conditions than for furan.<sup>74</sup> Removable protecting groups on the pyrrole nitrogen allow  $\alpha$ -lithiation, *t*-butoxycarbonyl (Boc), is an example; it has additional advantages: not only is it easily hydrolytically removed, but it also withdraws electrons thus acidifying the  $\alpha$ -hydrogen further, and finally, provides chelation assistance.<sup>75</sup>

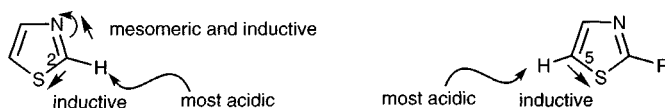


Benzo[*b*]thiophenes and benzo[*b*]furans, and *N*-blocked indoles lithiate on the heterocyclic ring,  $\alpha$  to the heteroatom.<sup>76</sup> Lithiation at the other hetero-ring position can be achieved *via* halogen exchange, but low temperatures must be maintained to prevent equilibration to the more stable 2-lithiated heterocycle.<sup>68</sup>

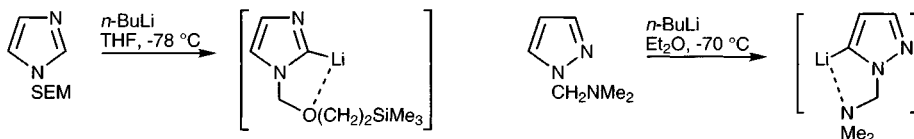


Benzene ring lithiated intermediates can be prepared by metal-halogen exchange, even, in the case of indoles, without protection of the NH, i.e. it is possible to produce an *N,C*-dilithiated species.<sup>77</sup>

The 1,3-azoles lithiate very readily, at C-2. One may understand this in terms of a combination of the acidifying effects seen at an  $\alpha$ -position of pyridine (both inductive and mesomeric electron withdrawal, see section 2.6.1.4) with that at the  $\alpha$ -positions of thiophene, furan, and pyrrole (inductive only). 2-Substituted-1,3-azoles generally lithiate at C-5.<sup>78</sup>

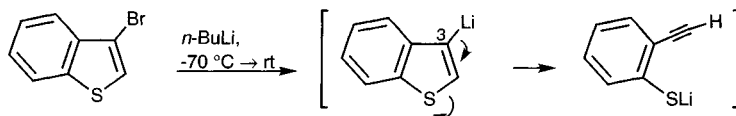


For imidazoles, it is usual for the *N*-hydrogen first to be masked,<sup>79</sup> and a variety of protecting groups have been used for that purpose, many of which provide additional stabilisation and an additional reason for regioselective  $\alpha$ -lithiation by coordinating the lithium: trimethylsilylethoxymethyl ( $\text{Me}_3\text{Si}(\text{CH}_2)_2\text{OCH}_2$ ; SEM) is one such group.<sup>80</sup>



It is a significant comment on the relative ease of  $\alpha$ -lithiation in six- and five-membered systems that (*N*-protected) pyrazoles lithiate at C-5, i.e. in the pyrrole-like  $\alpha$ -position, though, again chelation assistance from the *N*-protecting group also directs to C-5.<sup>81</sup>

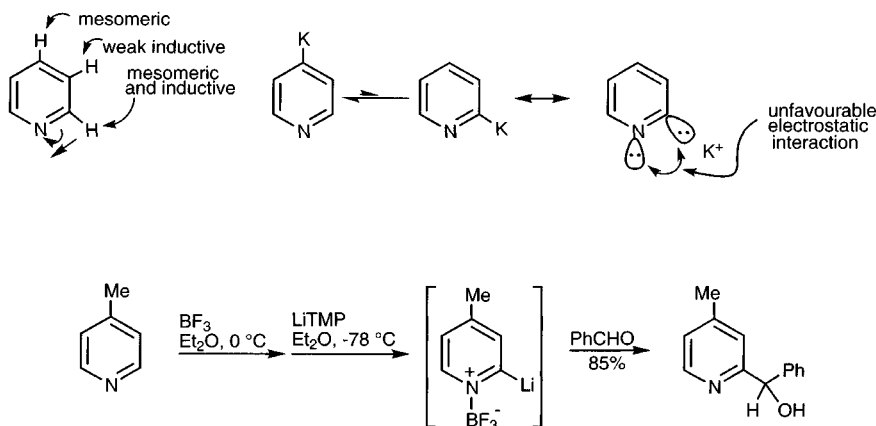
One must be aware that hetero-ring cleavage<sup>82</sup> can occur in  $\beta$ -lithiated five-membered systems, because the heteroatom can act as a leaving group, if the temperature is allowed to rise.<sup>83</sup>





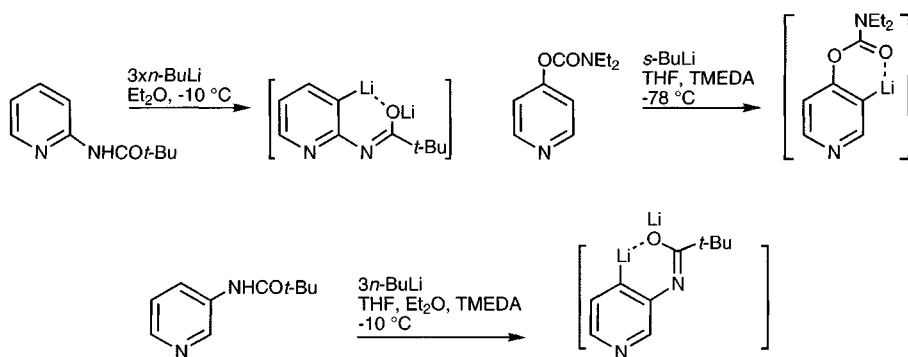
### 2.6.1.4 Ring lithiation of six-membered heterocycles

The preparation of lithiated derivatives of six-membered heterocycles like pyridines, quinolines and diazines must overcome the problem that they are susceptible to nucleophilic addition/substitution (section 2.3.2) by the lithium reagents. In contrast to the selective lithiation of five-membered rings, the direct metallation of pyridine is quite difficult and complex, but it can be achieved using the very strong base combination *n*-butyllithium/potassium *t*-butoxide. In relatively non-polar solvents (ether/hexane) kinetic 2-metallation predominates but in a polar solvent (THF/HMPA/hexane), or under equilibrating conditions, the 4-isomer is the major product. The pyridine  $\alpha$ - and  $\gamma$ -positions, being more electron-deficient than a  $\beta$ -position, have the kinetically most acidic protons, and of the two former anions, location of negative charge at the  $\gamma$ -position is the more stable situation, perhaps due to unfavourable repulsion between the coplanar nitrogen lone pair and the  $\alpha$ -‘anion’ only in the former. In non-polar solvents stronger coordination of the metal cation with the nitrogen lone pair will reduce this repulsive interaction and thus increase the relative stability of the  $\alpha$  ‘anion’.<sup>84</sup> As a corollary of this, pyridine can be selectively lithiated at C-2 when the lone pair is tied up as a complex with boron trifluoride.<sup>85</sup> This is consistent with much earlier studies of base-catalysed exchange when it was demonstrated that *N*-oxides and  $N^+$ -alkyl quaternary salts exchange more rapidly at an  $\alpha$  position.<sup>86</sup>

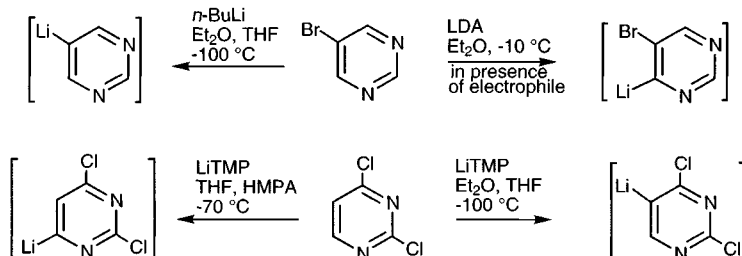


All the isomerically pure lithio-pyridines can be prepared by halogen exchange, though 3-bromopyridine requires a lower temperature to discourage nucleophilic addition; bromopicolines can be similarly converted, without deprotonation at the methyl groups (cf. section 2.6.3.1).

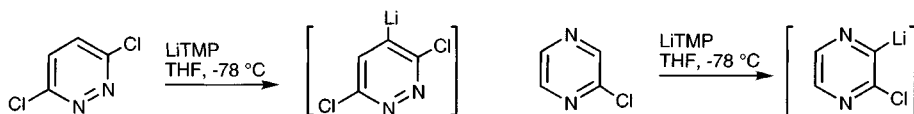
Pyridines carrying groups which direct metallation *ortho*, using chelation and/or inductive influences, can be directly lithiated without risk of nucleophilic addition. When the group is at a 2-<sup>87</sup> or 4-position<sup>88</sup>, lithiation must occur at a  $\beta$ -carbon; pyridines with *ortho*-directing groups located at a  $\beta$  position usually lithiate at C-4: this is true for example of chloro- and fluoropyridines;<sup>89</sup> 3-methoxymethoxy-,<sup>90</sup> 3-pivaloylamino-,<sup>91</sup> 3-trimethylsilylethoxymethoxy-<sup>92</sup>, 3-*t*-butylaminosulfonyl-,<sup>93</sup> pyridines; pyridines carrying a 3-diethylaminocarbonyloxy or 3-diethylaminothiocarbonyloxy group;<sup>94</sup> and the adduct from 3-formylpyridine and Me<sub>2</sub>N(CH<sub>2</sub>)<sub>2</sub>NMeLi,<sup>95</sup> however 3-ethoxypyridine metallates at C-2.<sup>96</sup>



Quinolines react like pyridines but are more susceptible to nucleophilic addition;<sup>97</sup> this is also an increased problem with pyrimidines, relative to pyridines, but nevertheless they can be lithiated by deprotonation or by halogen exchange at low temperatures, around  $-100^\circ C$ . The presence of 2- and/or 4-substituents adds some stability to lithiated pyrimidines.<sup>98</sup>

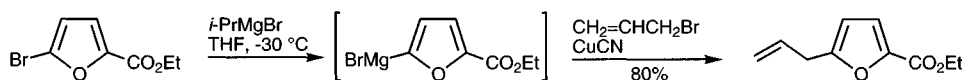


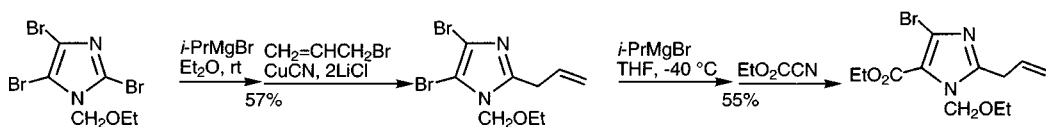
Pyrazines and pyridazines react in accord with the principles discussed above.<sup>99</sup>



## 2.6.2 Magnesium derivatives<sup>100</sup>

While Grignard reagents have been widely used in carboaromatic chemistry, the direct preparation of heterocyclic Grignard reagents by the standard method – halo-compound with magnesium – is often difficult, particularly for heterocycles containing a basic nitrogen. However, exchange of bromo- or iodo-heterocycles with alkyl Grignard reagents, preferably *i*-propylmagnesium halides or di-*i*-propylmagnesium, allows access to the magnesium derivatives of a wide range of heterocycles, from pyrroles to thiazoles and pyridines. The preparation of heteroaryl Grignards in this way has even been used in solid phase synthesis. Pyridyl sulfoxides will also undergo exchange to give pyridyl Grignard species.<sup>101</sup> While possibly not quite as reactive as their carboaromatic counterparts, heteroaryl Grignard reagents will react with a good range of electrophiles, sometimes requiring the assistance of a copper salt as catalyst.



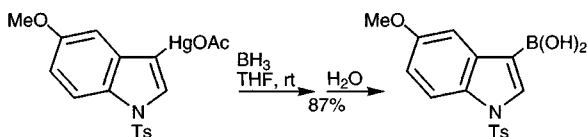
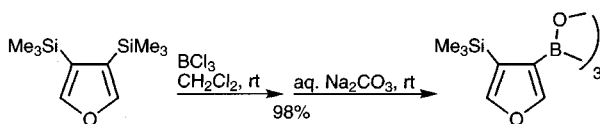
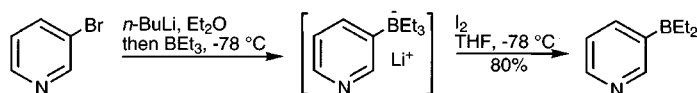
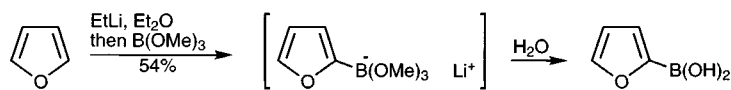


### 2.6.3 Boron, silicon, and tin reagents

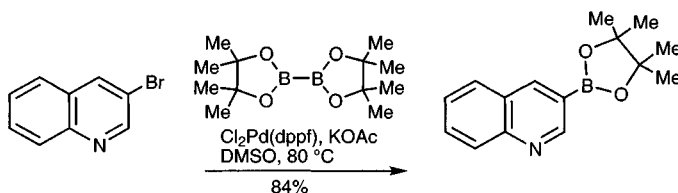
**Caution:** while very useful, many organotin compounds are toxic and should be handled with care. Trimethyltin derivatives in particular are highly toxic and whenever possible should be replaced by the slightly less reactive but much less toxic, tri-*n*-butyl analogues.

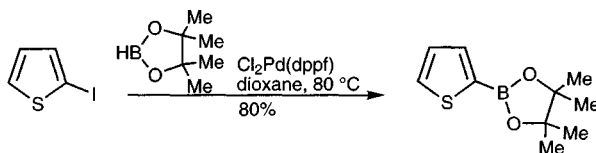
#### 2.6.3.1 Synthesis

The most general preparative method for silanes,<sup>102</sup> stannanes, and boronic acids is the reaction of a heteroarylolithium with a chlorosilane, a chlorostannane, or with a borate ester,<sup>103</sup> respectively. 3-Diethylborylpyridine can be similarly prepared by reaction of the lithiopyridine with triethylborane, followed by cleavage of an ethyl group with iodine; this method does not work for electron-rich systems such as furan due to preferential cleavage of the heterocyclic group.<sup>104</sup> Transmetalation reactions can also be of use in specific cases.<sup>105</sup>

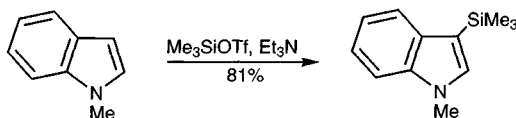


Boronic esters are also available via the palladium-catalysed boronation of halides.<sup>106</sup>

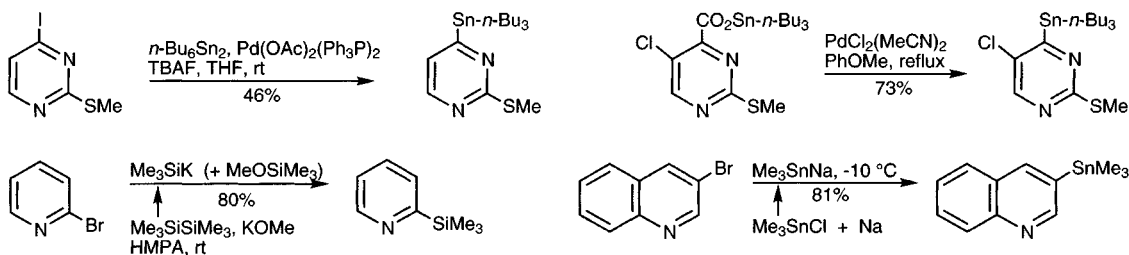




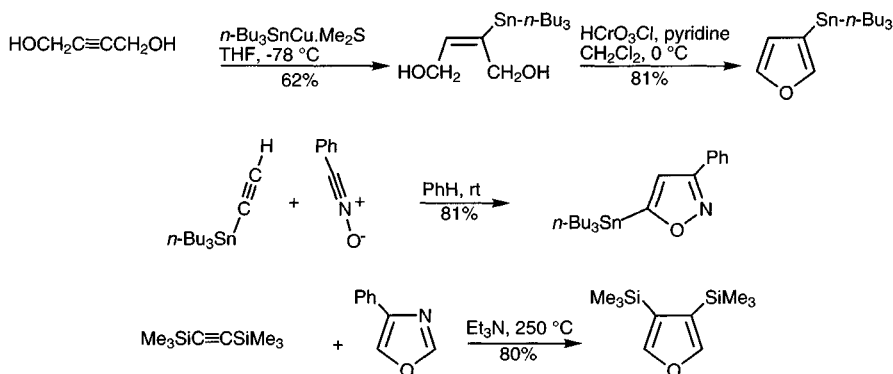
It is possible to directly silylate indoles and pyrroles *via* electrophilic substitution.<sup>107</sup>



Useful alternative preparations of stannanes include palladium-catalysed decarboxylation of stannyl esters or coupling of halo compounds with hexaalkyldistannanes;<sup>108</sup> coupling with hexaalkyldisilanes requires rather more vigorous conditions.<sup>109</sup> Trialkylstannyl and trialkylsilyl anions are highly reactive and will displace halogen without the use of a catalyst.<sup>110</sup>



The relatively high stability of carbon-silicon/boron/tin bonds allows the 'metal' to be carried through many heterocyclic syntheses as an inert substituent: some examples are shown below.<sup>111</sup>

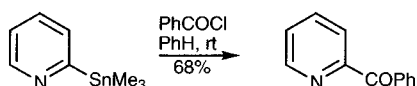
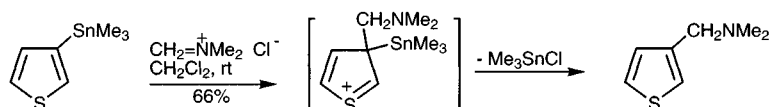


### 2.6.3.2 Reactions

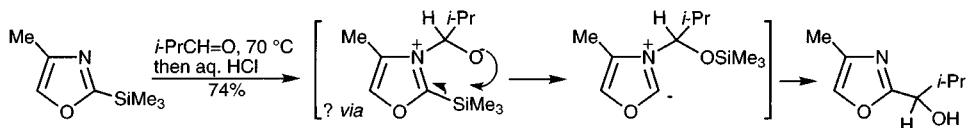
The heteroaryl derivatives of boron, silicon, and tin, which show related patterns of reactivity, have found considerable application in synthesis. Unlike lithium compounds, they are generally fairly stable to air and water but will undergo a range of selective reactions under relatively mild conditions. Heteroaryl boronic acids and stannanes are particularly useful as the organometallic component in palladium-catalysed coupling reactions (section 2.7.2.2); heteroaromatic silanes such as 2-

(ethyldifluorosilyl)thiophene,<sup>112</sup> 2-(fluorodimethylsilyl)thiophene,<sup>113</sup> 2-trimethylsilylthiazole and 1-methyl-2-(trimethyl(methoxy)silyl)pyrrole<sup>114</sup> also participate in cross coupling reactions.

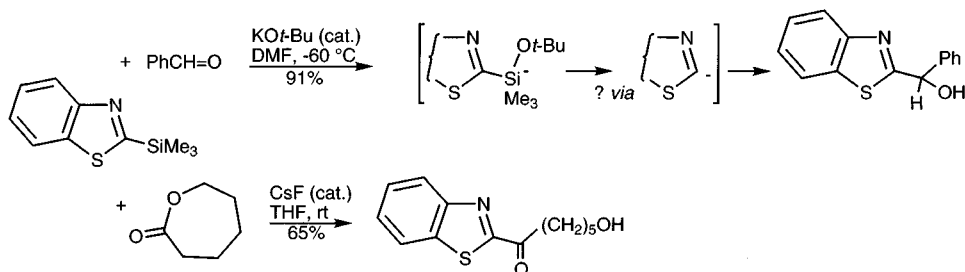
All three elements are susceptible to *ipso* replacement by electrophiles – such reactions have been studied extensively for arylsilanes and arylstannanes, where they occur *via* an electrophilic addition/silicon elimination mechanism analogous to other aromatic substitutions, but at a much faster rate than the corresponding replacement of hydrogen.<sup>115</sup> *Ipso* substitutions also take place on heterocycles and, in the case of electron-rich systems, probably *via* the same type of mechanism.

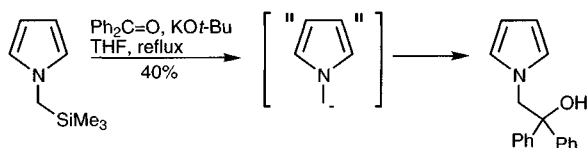


Most applications, however, have been in heterocycles containing an imine unit with the silicon (tin) directly attached;<sup>116</sup> such heterocycles undergo electrophilic attack reluctantly (section 2.2.2) so a mechanism involving coordination to nitrogen may be involved;<sup>117</sup> for example a 2-trimethylstannylpyridine will react readily with an acid chloride but its 3-isomer is inert under the same conditions, though palladium-catalysed coupling can be achieved with the 3- and 4-isomers under different conditions and *via* a different mechanism.<sup>118</sup> The oxazole example shown below illustrates prior interaction with the ring nitrogen.

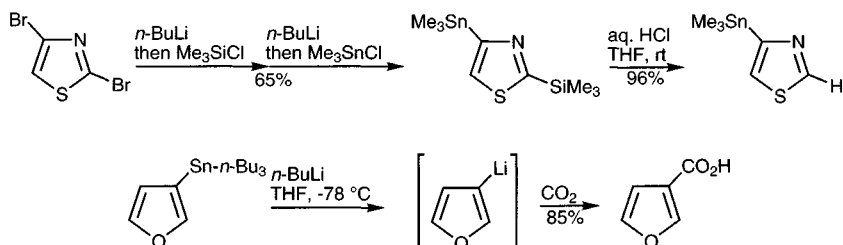


Silanes will also react with electrophiles with catalysis by fluoride or methoxide.<sup>119</sup> Here, an intermediate complex is formed *in situ* which reacts like a carbanion but under much milder conditions than would a lithio-derivative. This reaction can even be used to generate the equivalent of a  $\text{CH}_2$ -carbanion on a five-membered heterocyclic nitrogen.<sup>120</sup>

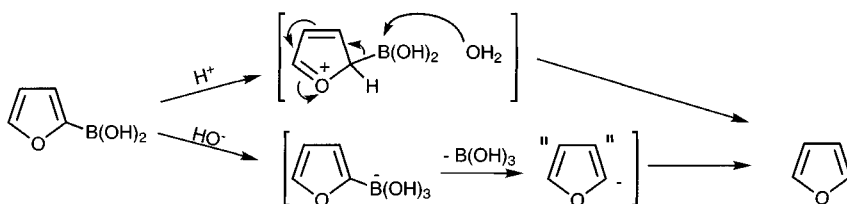




In addition to acting as a functional group, silanes can also be used as protecting groups for 'acidic' C-hydrogen, being removable at a later stage using fluoride or acid.<sup>121</sup> Stannanes are also valuable precursors for regiospecific formation of heteroarylolithiums *via* reaction with alkylolithiums.<sup>111</sup>

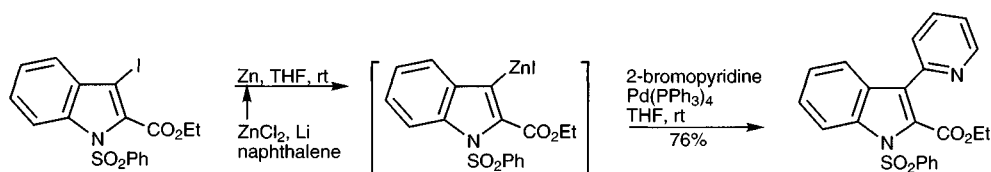


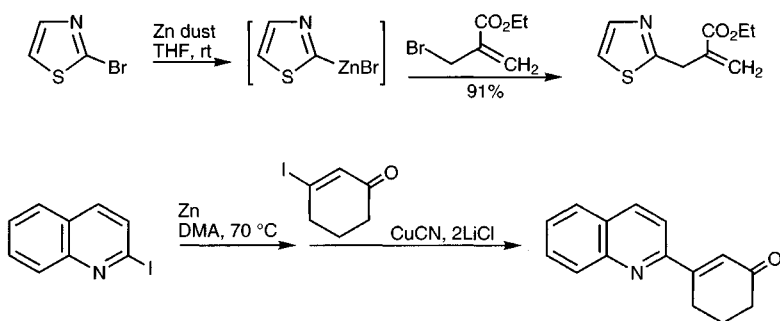
Although boronic acids are very reactive to *ipso* displacement by some electrophiles such as halonium ions, these reactions have found only occasional synthetic use. The C-boron bond can be cleaved by base, or acid, at rates depending on the corresponding carbanion stability or ease of protonation of the ring, respectively. When a relatively stable carbanion can be formed, such as in furan boronic acids containing electron-withdrawing groups, base-catalysed deboronation can become an important unwanted side-reaction during palladium-catalysed boronic acid couplings.<sup>122</sup> Indeed, imidazole and oxazole 2-boronic acids have not yet been isolated, possibly due to their very ready deboronation.



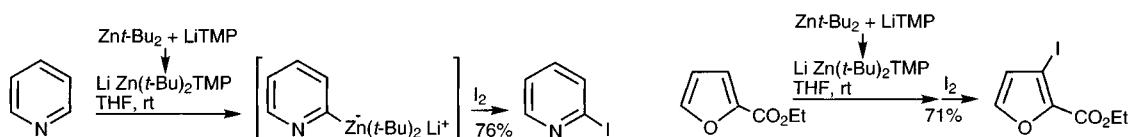
## 2.6.4 Zinc reagents

Heteroarylzinc compounds are of particular use in palladium-catalysed couplings, being compatible with many functional groups. They have usually been prepared by exchange reactions<sup>123</sup> (*in situ*) of zinc halides with heteroarylolithiums but this method limits their usefulness. Efficient methods are now available for their direct preparation from either Rieke zinc<sup>124</sup> or commercial zinc dust<sup>125</sup> and the heteroaryl halide, in both electron-rich and electron-poor systems.



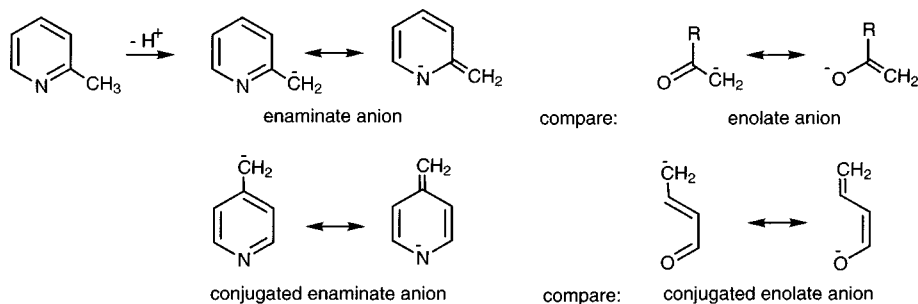


Directed *ortho* metallation can be carried out with a tetramethylpiperidyl zincate, but the only reported reactions of the resulting heteroarylzincates have been with iodine and benzaldehyde.<sup>126</sup>

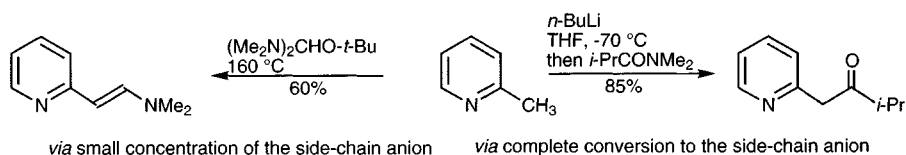


### 2.6.5 Side-chain metallation of 6-membered heterocycles ('lateral metallation')<sup>127</sup>

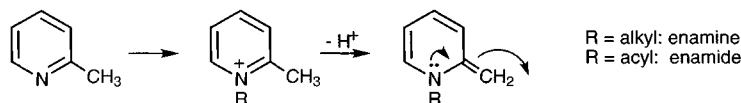
Anions on alkyl side-chains and immediately adjacent to a heterocyclic ring are subject to varying degrees of stabilisation by interaction with the ring. The most favourable situation is where the side-chain is on an  $\alpha$  or a  $\gamma$  carbon with respect to a C=N, as in the 2-, 6-, and 4-positions of a pyridine. Such anions are stabilised in much the same way as an enolate (conjugated enolate). We use the word 'enamine' to describe this nitrogen-containing, enolate-like anion.



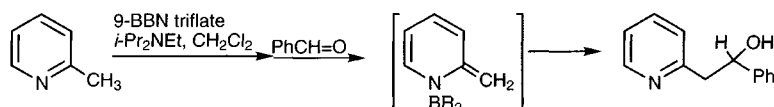
Quantitative measures for some methyl deprotonations are: 2-methylpyridine ( $pK_a$  34), 3-methylpyridine ( $pK_a$  37.7), 4-methylpyridine ( $pK_a$  32.2), 4-methylquinoline ( $pK_a$  27.5).<sup>128</sup> These values can be usefully compared with those typical for ketone  $\alpha$ -deprotonation (19–20) and toluene side-chain deprotonation ( $\sim 41$ ). Thus strong bases can be used to convert methylpyridines quantitatively into side-chain anions, however the enolate-like stabilisation of the anion is sufficient that reactions can often be carried out using weaker bases under equilibrating conditions, i.e. under conditions where there is only a small percentage of anion present at any one time. It may be that under such conditions, side-chain deprotonation involves *N*-hydrogen-bonded or *N*-coordinated pyridines.



An alternative means for effecting reaction at a side-chain depends on a prior electrophilic addition to the nitrogen: this acidifies further the side-chain hydrogens, then deprotonation generates an enamine or an enamide, each being nucleophilic at the side-chain carbon.

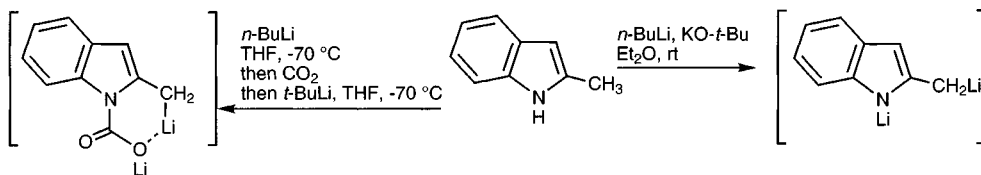


One of the most elegant examples of this principle is the generation and use of *N*-dialkylboryl derivatives.<sup>129</sup>

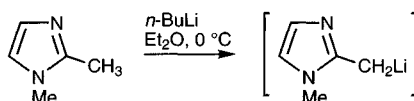


## 2.6.6 Side-chain metallation of five-membered heterocycles

The metallation of a side-chain on a simple five-membered heterocycle is much more difficult than in the six-membered series, because no enamine stabilising resonance is available. Nonetheless it also is selective for an alkyl adjacent to the heteroatom, because the heteroatom acidifies by induction. Relatively more forcing conditions need to be applied, especially if an *N*-hydrogen is present,<sup>130</sup> but an elegant method has been developed for indoles, in which the first-formed *N*-anion is blocked with carbon dioxide, the lithium carboxylate thus formed then neatly also facilitating 2-methyl-lithiation by intramolecular chelation; this device has the further advantage that, following reaction of the side-chain anion with an electrophile, the *N*-protecting group is removed simply, during aqueous processing.<sup>131</sup>



Side-chains at C-2 on 1,3-azoles are activated in a manner analogous to pyridine  $\alpha$ -alkyl groups, and can be metallated, but more care is needed to avoid ring metallation.<sup>132</sup>





## 2.7 Palladium-catalysed reactions<sup>133</sup>

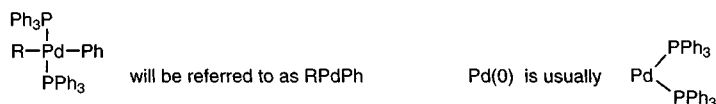
Transition metal-catalysed reactions are probably the most rapidly expanding area in organic chemistry at present and they have been used extensively in both the ring synthesis and the functionalisation of heterocycles. As well as completely new modes of reactivity, variants of older synthetic methods have been developed using the milder and more selective processes which attach to the use of transition metal catalysts. Palladium is by far the most important and widely used catalyst due to the very wide range of reaction types in which it can function. Nickel catalysts (mechanistically similar to palladium) have also been used, but for a narrower range of reactions.

In general, heterocyclic compounds undergo palladium-catalysed reactions in a way analogous to carbocycles; heterocyclic sulfur and nitrogen atoms seldom interfere with these (homogeneous) palladium catalysts, which must be contrasted with the well-known poisoning of hydrogenation catalysts such as palladium metal on carbon by sulfur- and nitrogen-containing molecules.

Palladium-catalysed processes typically utilise only 1–5 mol% of the catalyst and proceed through small concentrations of transient palladium species: there is a sequence of steps, each with an organopalladium intermediate, and it is important to become familiar with these basic organopalladium processes in order to rationalise the overall conversion. Concerted, rather than ionic, mechanisms are the rule so it is misleading to compare them too closely with apparently similar ‘classical’ organic mechanisms, however ‘curly arrows’ can be used as a memory aid (in the same way as one may use them for cycloaddition reactions), and this is the way in which palladium-catalysed reactions are ‘explained’ in the following discussion.

### 2.7.1 Basic organopalladium processes<sup>134</sup>

**Note:** For clarity, ligands which are not involved in the transformation under consideration are omitted from the following schemes, however it is important to understand that most organopalladium compounds normally exist as 4-coordinate, square-planar complexes:



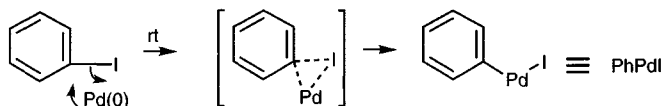
Despite an apparent similarity between  $\text{RPdX}$  and  $\text{RMgX}$ , their chemical properties are very different. The former are usually stable to air and water and unreactive to the usual electrophilic centres such as carbonyl, whereas  $\text{RMgX}$  do react with oxygen, water, and carbonyl compounds.

#### 2.7.1.1 Concerted reactions

##### Oxidative addition

Aromatic and vinylic halides react with  $\text{Pd(0)}$  to give an organopalladium halide: aryl(or alkenyl) $\text{PdHal}$ . This is formally similar to the formation of a Grignard reagent from magnesium metal,  $\text{Mg(0)}$ , and a halide, but mechanistically, a concerted, direct ‘insertion’ of palladium into the carbon–halogen bond is believed to be involved. The ease of reaction:  $\text{X} = \text{I} > \text{Br} \sim \text{OTf} > > \text{Cl} > > \text{F}$ , explains why chloro and fluoro substituents can normally be tolerated, not interfering in palladium-catalysed processes. As a simple illustration,  $\text{Pd(PPh}_3)_4$  reacts with

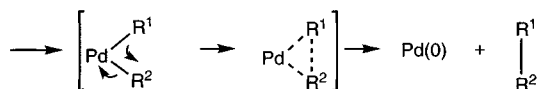
iodobenzene at room temperature, but requires heating to 80 °C for a comparable insertion into bromobenzene. Although alkyl halides will undergo oxidative addition to Pd(0), the products are generally much less stable.



Palladium(0) exhibits a degree of nucleophilic character, thus electron-withdrawing substituents increase the reactivity of aryl halides in oxidative additions. This is exemplified in the heterocyclic context: the inductive effect of imine units allows 2-chloropyrimidine (it is slightly less reactive than bromobenzene), and even 3-chloropyridine<sup>135</sup> to react (even the moderate inductive effect at the  $\beta$ -position gives rise to a significantly higher rate of reaction relative to chlorobenzene) although a more reactive catalyst is required for the latter case (cf. section 2.7.2.2). However, the parallel with reactivity towards nucleophiles is not always exact. For example, 4-chloropyridine is more reactive than the 2-chloro isomer towards nucleophilic substitution, but the reverse is true in the palladium-catalysed couplings of these isomers.<sup>136</sup>

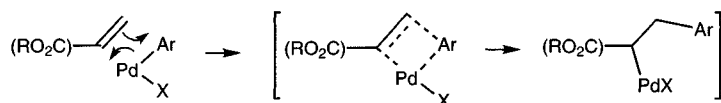
### Reductive elimination

Organopalladium species with two organic units attached to the metal,  $\text{R}^1\text{PdR}^2$ , are generally unstable: extrusion of the metal, in a zero oxidation state, takes place, with the consequent linking of the two organic units. Because this is again a concerted process, stereochemistry in the organic moiety(ies) is conserved.



### 1,2-Insertion

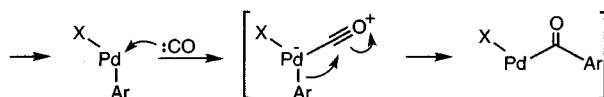
Organopalladium halides add readily to double and triple bonds in a concerted, and therefore *syn*, manner (*via* a  $\pi$ -complex, not shown for clarity).



This process works best with electron-deficient alkenes such as ethyl acrylate, but will also take place with isolated, or even with electron-rich, alkenes. In reactions with acrylates, the palladium becomes attached to the carbon adjacent to the ester, i.e. the aromatic moiety becomes attached to the carbon  $\beta$  to the ester.

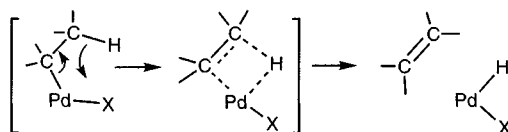
### 1,1-Insertion

Carbon monoxide, and isonitriles, will insert into a carbon-palladium bond.



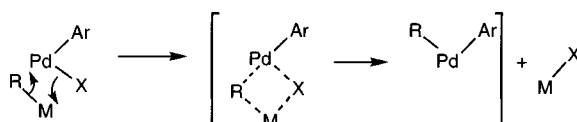
### $\beta$ -Hydride elimination

When a *syn*  $\beta$ -hydrogen is present in an alkylpalladium species a rapid elimination of a palladium hydride occurs, generating an alkene. This reaction is much faster in  $\text{RPdX}$  than in  $\text{R}_2\text{Pd}$  and is the reason that attempted palladium-catalysed reactions of alkyl halides often fail.



### Transmetallation

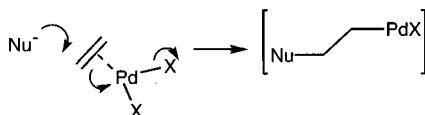
Palladium(II) compounds such as  $\text{ArPdX}$  and  $\text{PdX}_2$  generally react readily with a wide variety of organometallic reagents, of varying nucleophilicity, such as  $\text{R}_4\text{Sn}$ ,  $\text{RB(OH)}_2$ ,  $\text{RMgX}$ , and  $\text{RZnX}$ , transferring the R group to palladium with overall displacement of X. The details of the reactions are not fully understood and probably vary from metal to metal, but a concerted transfer is probably the best means for their interpretation.



#### 2.7.1.2 Ionic reactions

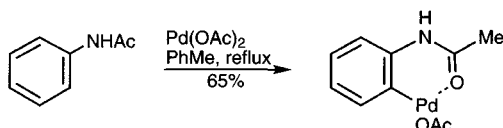
##### Addition to palladium-alkene $\pi$ -complexes

Like those of  $\text{Hg}^{2+}$  and  $\text{Br}^+$ ,  $\text{Pd}^{2+}$ -alkene complexes are very susceptible to attack by nucleophiles. In contrast to the reactions described in section 2.7.1.1 (1,2-insertion), this process exhibits *anti* stereospecificity.

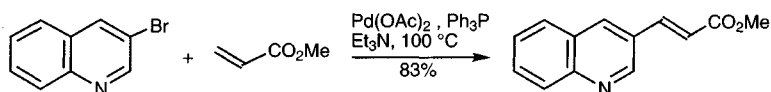


### Aromatic palladation

In reactions like aromatic mercuriation, palladium(II) compounds will metallate aromatic rings *via* an electrophilic substitution, hence electron-rich systems are the most reactive.<sup>137</sup> *ortho*-Palladation assisted by electron-releasing chelating groups has been used frequently.<sup>138</sup>

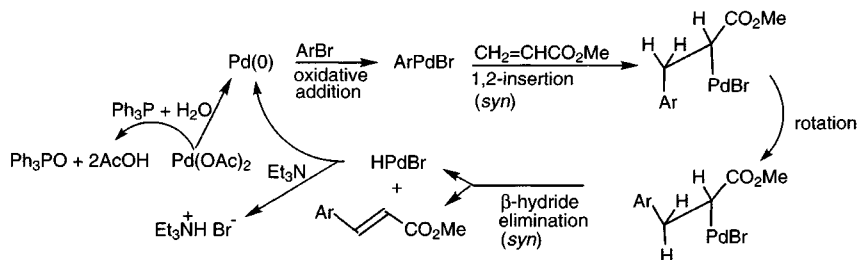


## 2.7.2 Palladium-catalysed reactions in heterocyclic chemistry

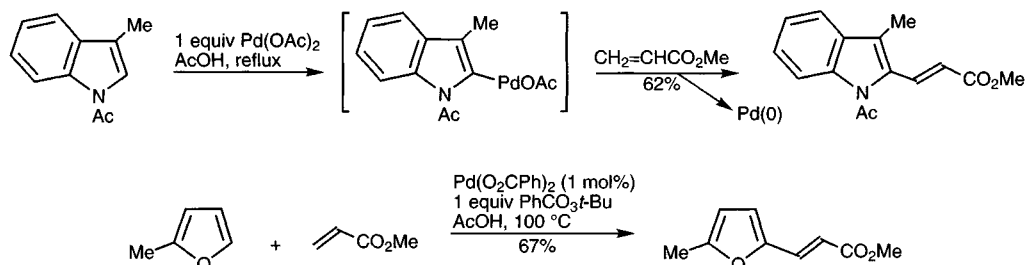
2.7.2.1 Heck reactions<sup>139</sup>

The standard Heck conditions shown in the example above<sup>140</sup> illustrate a common cause of confusion in understanding palladium-catalysed reactions, for while  $\text{Pd}(0)$  is actually involved in the catalytic cycle, palladium(II) acetate is generally used as an ingredient. This is just a matter of convenience because palladium acetate is stable and easily stored; it is reduced to  $\text{Pd}(0)$  by the phosphine (with a trace of water) or triethylamine *in situ* in a preliminary, initiating step.

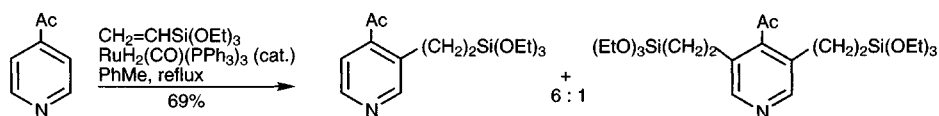
The standard Heck reaction involves the reaction of an aryl halide with an alkene, commonly acrylate, to give a styrene (cinnamate) in the presence of a catalytic amount of palladium (often less than 1 mol %). The sequence involves (i) oxidative addition of the halide to  $\text{Pd}(0)$  followed by (ii) 1,2-insertion into the alkene; rotation then occurs to produce a species with hydrogen *syn* to palladium, then (iii)  $\beta$ -hydride elimination gives the styrene and regenerates  $\text{Pd}(0)$ , which rejoins the catalytic cycle and can take part in a second oxidative addition, and so on.



The electron-rich nature of heterocycles such as indoles, furans, and thiophenes allows a different type of Heck reaction to be carried out.<sup>141</sup> In this 'oxidative' modification the aryl palladium derivative is generated by electrophilic palladation with a palladium(II) reagent. This process is not catalytic in the standard way, but can be made so by the addition of a reoxidant selective for  $\text{Pd}(0)$ ; note, that the catalytic  $\text{Pd}(0)$  could not effect the first (electrophilic) ring palladation.<sup>142</sup>

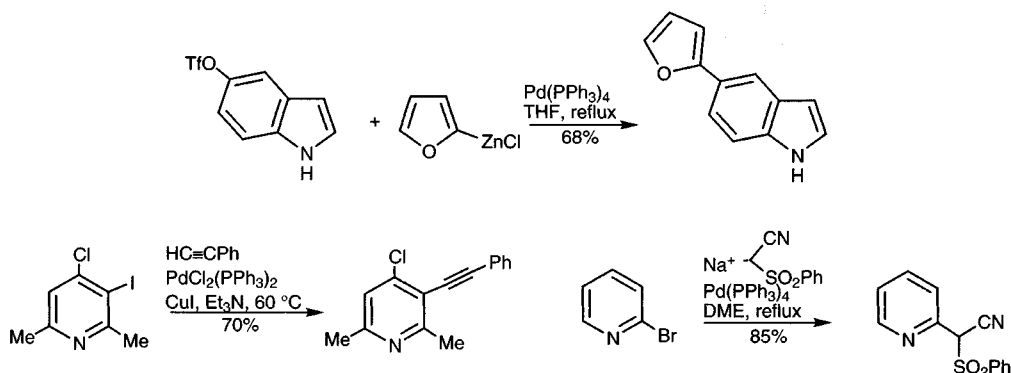


A different type of metallation, directed by acyl groups at either the pyridine 3- or 4-position, uses a catalytic ruthenium complex in the presence of an alkene and results in a reductive Heck-type substitution, as illustrated below. The mechanism involves insertion of the metal into a C–H bond. The process is non-polar and works equally well with electron-rich heterocycles, for example indole.<sup>143</sup>

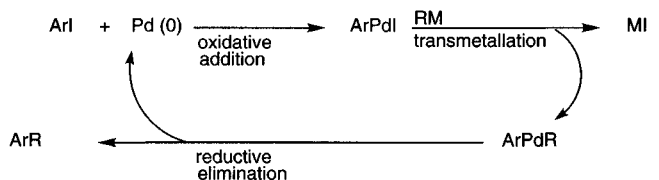


### 2.7.2.2 Coupling reactions

Heteroaryl halides (or phenolic triflates) take part in palladium-catalysed couplings with a wide range of organometallic and anionic reagents; in contrast to the Heck reaction, the catalyst is often provided as preformed  $\text{Pd}(0)$ , in a complex such as tetrakis(triphenylphosphine)palladium(0),  $\text{Pd}(\text{PPh}_3)_4$ .<sup>144</sup>

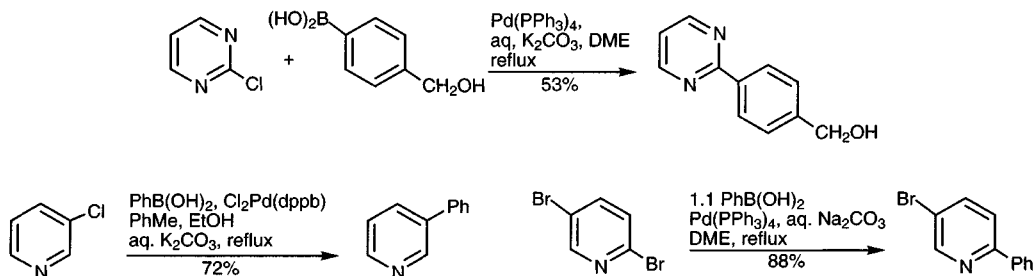


These conversions also involve catalytic cycles: (i) oxidative addition is again the first step, but then (ii) transmetalation, and (iii) reductive elimination give product and regenerate  $\text{Pd}(0)$ .

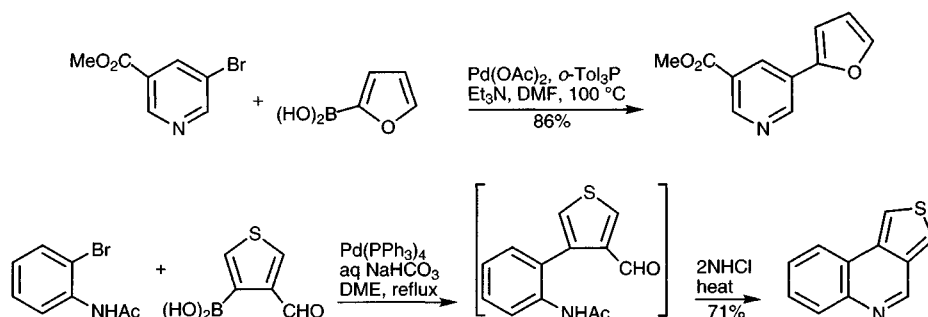


In the heterocyclic context there are examples in which RM is  $\text{HetSnR}_3$ ,  $\text{HetB}(\text{OH})_2$ ,  $\text{HetBEt}_2$ ,  $\text{HetMgX}$ ,  $\text{HetZnX}$ ,  $\text{HetTiX}_3$ ,  $\text{HetZrXL}_2$ ,  $\text{M}=\text{Het}$

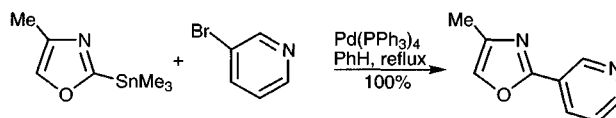
The electron-withdrawing effect of typical azines makes chlorine substituents sufficiently reactive that they can participate in palladium-catalysed reactions, even at a pyridine  $\beta$ -position.<sup>145</sup>  $\alpha$ -Activation can serve to allow regioselective reaction in the presence of a  $\beta$ -halogen (cf. section 2.7.1.1, oxidative addition) and this should be contrasted with lithiation by exchange which shows the opposite regioselectivity.



Where a heterocyclic organometallic reagent is required, Grignard and zinc derivatives are often satisfactory; complications sometimes attend the use of lithio derivatives. The use of boronic acids has become very popular on account of their clean reactions, general stability to air and water, and their compatibility with practically any functional group: furan, thiophene, indole and pyridine boronic acids have all been used.<sup>146</sup>

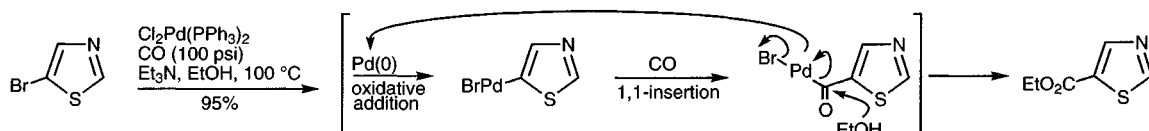


Some boronic acids may not be so stable, particularly diazole boronic acids, and in these cases tin derivatives can be used,<sup>147</sup> though they must be treated with caution as some are highly toxic.



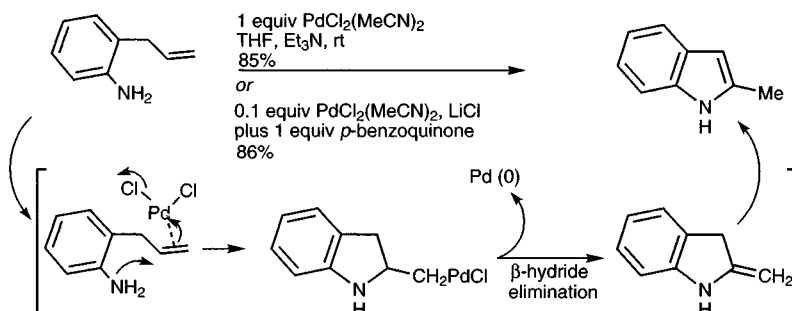
### 2.7.2.3 Carbonylation reactions

Acyl palladium species, formed by insertion of carbon monoxide into the usual aryl palladium halides, react readily with nucleophiles such as amines and alcohols to give amides and esters respectively; interception with hydride produces aldehydes.<sup>148</sup>



### 2.7.2.4 Synthesis of benzo-fused heterocycles

Nucleophilic cyclisations onto palladium-complexed alkenes have been used to prepare indoles, benzofurans and other fused systems. The process can be made catalytic in some cases by the use of reoxidants such as benzoquinone or copper(II) salts.



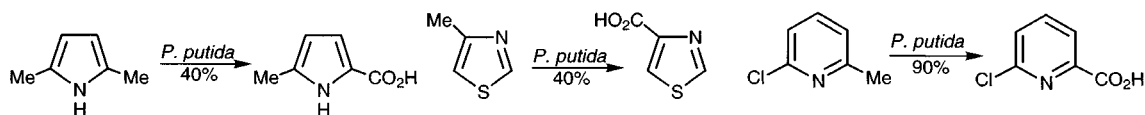
## 2.8 Oxidation and reduction<sup>149</sup> of heterocyclic rings

Generally speaking the electron-poor heterocycles are more resistant to oxidative degradation than are electron-rich systems – it is usually possible to oxidise alkyl side-chains attached to electron-poor heterocycles whilst leaving the ring intact; this is not generally true of electron-rich, five-membered systems.

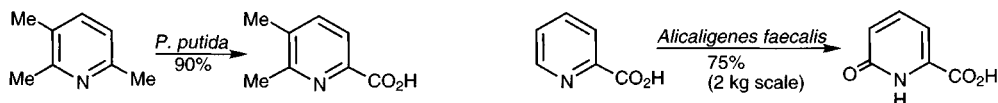
The conversion of monocyclic heteroaromatic systems into reduced, or partially reduced derivatives is generally possible, especially in acidic solutions where it is a cation which is the actual species reduced. It follows that the six-membered types, which always have a basic nitrogen, are more easily reduced than the electron-rich, five-membered counterparts; heteroaromatic quaternary salts are likewise easily reduced.

## 2.9 Bioprocesses in heterocyclic chemistry<sup>150</sup>

The use of biological methods has a small but significant niche in synthetic heterocyclic chemistry, being used both on a research scale and for fine chemicals production. The processes may use isolated enzymes or whole microorganisms, the main reactions being oxidations of a heterocyclic nucleus or of side-chains. Some other reaction types are referred to later in the book, for example enzyme-catalysed base exchange in nucleosides and the deamination of adenosine.

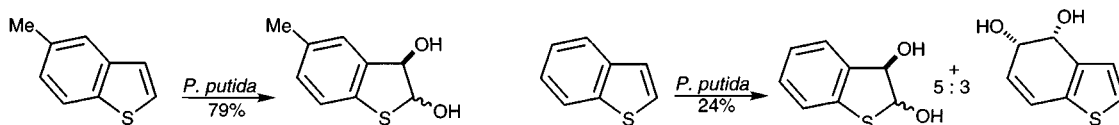


A particular advantage of biological methods is their potential regio-, stereo- and enantioselectivity, which may not be attainable using chemical reagents. On the other hand, non-selective reactions have their uses: for example, the subjection of natural products to non-selective oxidations will generate a series of starting materials for the preparation of a wider range of analogues for biological evaluation.

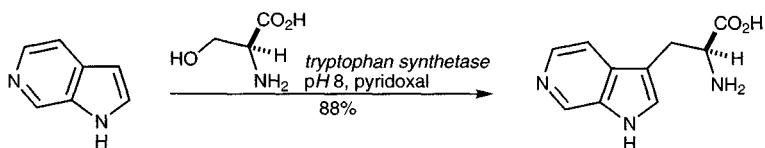


The oxidation of pyridines to pyridones<sup>151</sup> and the selective oxidation of a side-chain in alkylpyridines and other azines, have been well studied.<sup>152</sup>

The enantioselective *cis* dihydroxylation<sup>153</sup> of benzothiophenes and benzofurans by *Pseudomonas putida* is analogous to well known conversions of simple benzenoid compounds,<sup>154</sup> but in the heterocyclic context, hydroxyl groups introduced at an  $\alpha$ -carbon easily epimerise. Indole gives indoxyl probably via dehydration of an intermediate 2,3-diol.



The introduction of an amino acid side-chain onto 4-, 5-, 6-, and 7-azaindoles by an enzyme-catalysed alkylation with serine is an impressive demonstration of the power of biological methods.<sup>155</sup>



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