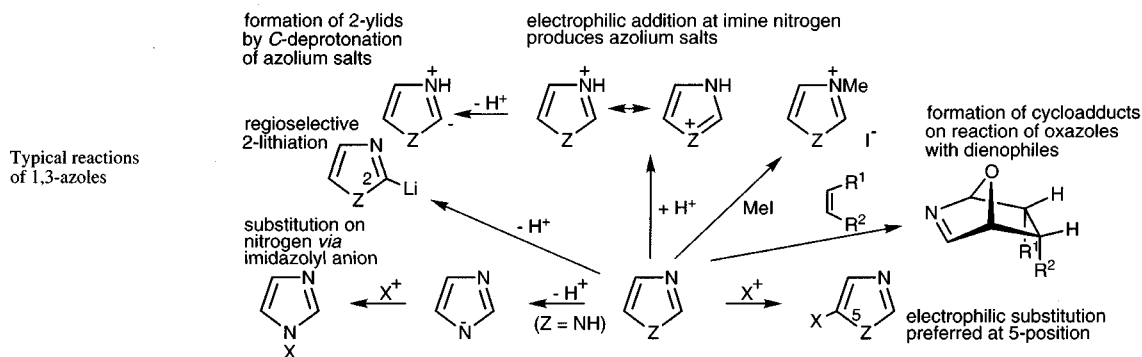
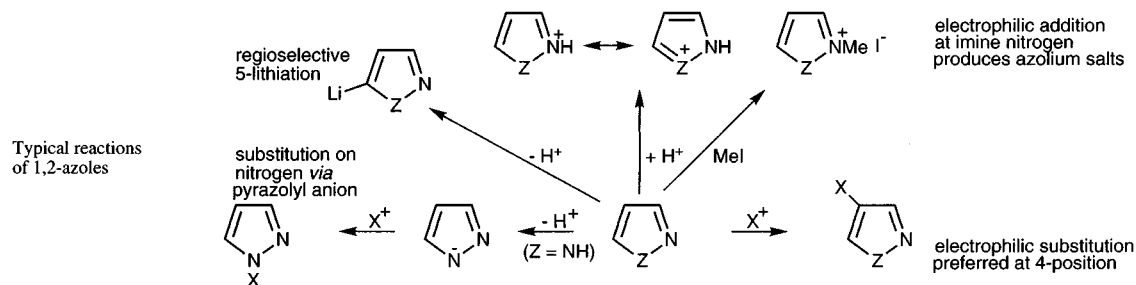


## 20 Typical reactivity of 1,3- and 1,2-azoles

The 1,3- and 1,2-azoles each contain one heteroatom in an environment analogous to that of the nitrogen in pyridine – an imine nitrogen – and one heteroatom in the environment of the nitrogen in pyrrole, the sulfur in thiophene, or the oxygen in furan, respectively. Consequently, their chemical reactions present a fascinating combination and mutual interaction of the types of reactivity which have been described earlier in this book for pyridines on the one hand and for pyrrole, thiophene and furan on the other, with the variation in electronegativity of the five-membered-type heteroatom having a substantial differentiating effect.

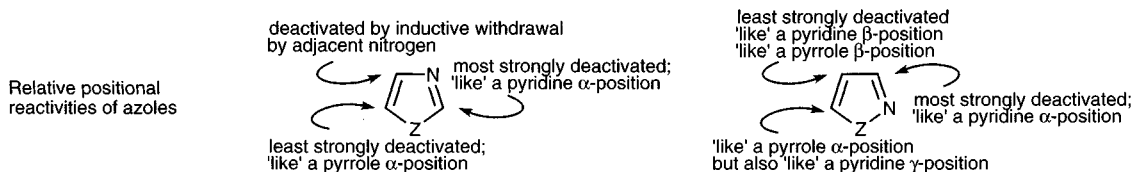


Many of the lessons to be learnt apply to both 1,3- and 1,2-azoles, though the direct linking of the two heteroatoms in the latter has a substantial inductive influence, altering properties in degree. The 1,2-azoles tend to be less nucleophilic and less basic at the imine nitrogen than their 1,3-isomers. That such electrophilic additions occur, again illustrates that the imine nitrogen lone-pair is not involved in the aromatic sextet of electrons.

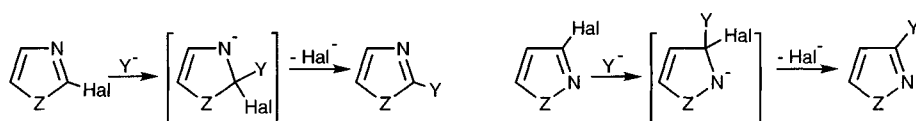


Electrophilic substitution in the azoles is intermediate in facility between pyridine on the one hand and pyrroles, thiophene and furans on the other: the presence of the electron-withdrawing imine unit has an effect on the five-membered aromatic heterocycles just as it does when incorporated into a six-membered aromatic framework, i.e. the comparison is like that between benzene and pyridine (chapter 4). The order of reactivity – pyrrole > furan > thiophene – is echoed in the azoles, though the presence of the basic nitrogen complicates such comparisons. The regiochemistry

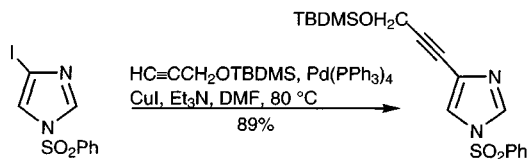
of electrophilic attack can be seen nicely by comparing the 'character' of the various ring positions – those that are activated in being five-membered in character and those that are deactivated by their similarity to  $\alpha$  and  $\gamma$  positions in pyridine.



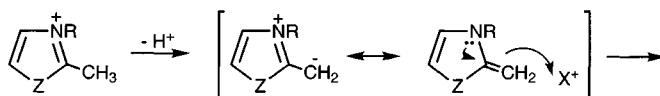
The converse of electrophilic substitution following the five-membered pattern, is that nucleophilic substitution of halogen follows the pyridine pattern i.e. it is much faster at the 2-position of 1,3-azoles and at the 3-position of 1,2-azoles, than at other ring positions. Resonance contributors to the intermediates for such substitutions make the reason for this plain: the imine nitrogen can act as an electron sink for attack only at these positions.



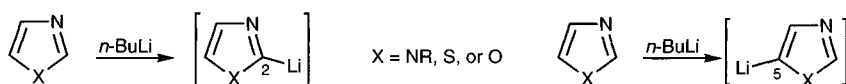
The utility of palladium(0)-catalysed processes (see section 2.7 for a detailed discussion) for the construction of azoles has been extensively developed: one simple example is shown below.



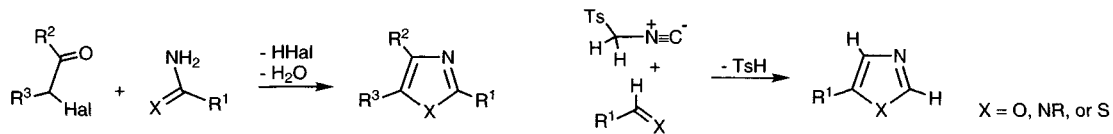
Continuing the analogy with pyridine reactivity, methyl groups at the 2-positions of 1,3-azoles and the 3-positions of 1,2-azoles carry acidified hydrogen atoms and can be deprotonated with strong bases. In further analogy with pyridines, the quaternisation of the imine nitrogen makes such deprotonations even easier; the resulting enamines react with electrophiles at the side-chain carbon.



Lithiation is regioselective for the 2-position in the 1,3-azoles and for the 5-position in the 1,2-azoles. The facility with which 1,3-diazolium cations form ylides (carbenes) by 2-deprotonation is at the heart of the biological activity of thiamine pyrophosphate.



It has long been known that 1,3-azoles can be assembled from a component providing the two heteroatoms – a thioamide or an amidine – and an  $\alpha$ -bromoketone. A much more recent route employs the interaction between the anion of an isonitrile and an aldehyde, thioaldehyde or imine.



To produce a 1,2-azole, a 1,3-dicarbonyl compound needs to be condensed with a unit providing the two heteroatoms – a hydrazine or hydroxylamine. The dipolar cycloaddition of alkynes with nitrile oxides or nitrile imines provides a route to isoxazoles and pyrazoles.

