Elemental fluorine. Part 10.[1] Selective fluorination of pyridine, quinoline and quinoxaline derivatives with fluorine–iodine mixtures

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Selective fluorination of a range of pyridine and quinoline substrates to give corresponding 2-fluoro-derivatives can be readily achieved in high yield at room temperature using elemental fluorine–iodine mixtures. Reaction of fluorine with iodine forms, *in situ*, systems that function like sources of both iodonium and fluoride ions and fluorination of heterocyclic derivatives is suggested to proceed by fluoride ion attack on intermediate *N*-iodo-heterocyclic species. Quinoxaline derivatives react under similar conditions to give either the 2-fluoro- or 2,3-difluoro-quinoxaline derivatives depending on the ratio of fluorine passed through the solution. In related processes, pyridine can be alkoxylated upon reaction of an appropriate alcohol and fluorine.

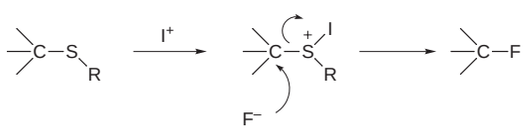
Introduction

The preparation of selectively fluorinated heterocyclic systems continues to attract considerable attention[2–7] from both industry and academia because of the profound effect that the introduction of a fluorine atom into a heterocyclic ring can have on the physical, chemical and biological properties of such substrates. This situation is reflected in the growing number of fluoro-heterocycles that are incorporated into, for example, pharmaceuticals, plant-protection agents and liquid crystals.[7]

The two most commonly used methods for the synthesis of fluoro-heterocycles are exchange of chlorine substituents by fluorine, using a source of fluoride ion (halex reactions),[8] and fluorodediazotisation of appropriate amino-heterocycles (Balz–Schiemann processes).[9] Both approaches have been used extensively and, for example, the preparation of monofluoropyridines[10] and quinolines[11–13] by halogen-exchange[12,13] and Balz–Schiemann methodology[10,11] have been reported. However, the synthetic utility of these methods depends on the availability of the appropriate halo and amino heterocyclic precursors and, furthermore, in some cases harsh reaction conditions are required to achieve fluorination.

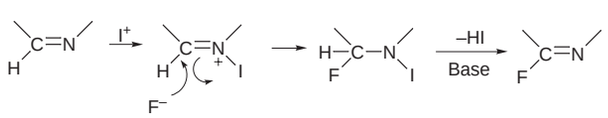
Methods for preparing fluoro-heterocycles by fluorination of the corresponding parent heterocycle, involving overall displacement of hydrogen by fluorine, have been studied as alternative routes to fluoro-heterocycles and reagents such as caesium fluoroxysulfate,[14] electrochemical fluorination[15] and *N*-fluoro-pyridinium salts,[16] have been used with varying degrees of success. Use of elemental fluorine for the synthesis of fluoro-heterocyclic systems has not been widely studied even though an industrial process, involving the preparation of the anti-cancer agent 5-fluorouracil, has been in operation for many years.[17] Direct fluorination of pyridine was described by Meinert,[18] who reported the low temperature preparation of *N*-fluoropyridinium fluoride, a solid that decomposes violently above −2 °C. However, more recently Van der Puy[19,20] reported that pyridine gave moderate yields of 2-fluoropyridine upon reaction with fluorine.

In this series of papers,[1] we are describing developments in the use of elemental fluorine as a selective fluorinating agent in organic synthesis and, in this context, we have described fluorodesulfurisation methodology for the synthesis of carbon–fluorine bonds using elemental fluorine–iodine mixtures.[21] The latter results indicate that reaction of fluorine with iodine *in situ* gives systems that function like sources of both iodonium and fluoride ions, although the precise nature of the fluorinating reagent has not been established. Transformation of carbon–sulfur bonds to carbon–fluorine bonds probably occurs by complexation of the sulfur atom with the iodonium ion, followed by the nucleophilic attack by the fluoride ion on the attached carbon atom, now a site of developing positive charge (Scheme 1).



Scheme 1

We then reasoned that if sp^2 hybridised nitrogen is employed as the heteroatom, rather than sulfur, then the nitrogen would complex with the iodonium ion. Furthermore, this complexation would activate the adjacent carbon atom to fluoride ion attack and then elimination of hydrogen iodide from this system would lead to overall substitution of hydrogen by fluorine (Scheme 2).



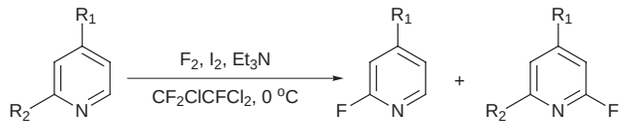
Scheme 2

Suitable substrates are, of course, aza-heterocyclic systems and in this paper, we describe the use of fluorine–iodine mixtures for the preparation of a variety of fluoro-pyridine and quinoline derivatives.

Results and discussion

Pyridine **1a** was converted to 2-fluoropyridine **2a** (major product) by simply passing fluorine gas, diluted to a 10% mixture in dry nitrogen (v/v), through a stirred, cooled (0 °C) solution of pyridine and iodine in $CF_2ClCFCl_2$ solvent (Table 1). A small quantity of 2,6-difluoropyridine (3%) was also detected by GC-MS analysis of the crude product mixture. As

Table 1 Fluorination of pyridine derivatives



1a–d **2a** **2 b–d**

Pyridine	Fluoro-pyridine	R_1	R_2	Yield[b] (%) (Conversion %)
1a	**2a**	H	H	56 (59)[a]
1b	**2b**	Et	H	54 (78)[a]
1c	**2c** + **2a**	H	Cl	**2a** 14 **2c** 70 (61)
1d	**2d** + **2a**	H	Br	**2a** 30 **2d** 59 (100)

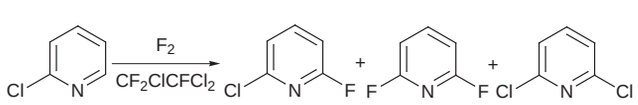
[a] Reactions performed without triethylamine present. [b] Isolated yield based on conversion of starting material.

2-fluoropyridine is significantly less basic than pyridine, separation of the fluorinated product from the starting material can be readily achieved by washing the crude product mixture with 1 M HCl solution. Similarly, fluorination of 4-ethylpyridine **1b** gave the corresponding fluoro-derivative **2b** as the major product in good yield (Table 1).

Although these reactions gave clean products in good yield, the conversion of starting material to product was moderate. However, we found that addition of a stoichiometric amount of another base, such as triethylamine, to the reaction mixture enabled a higher conversion of pyridine derivatives to the corresponding 2-fluoropyridines to be obtained in a given reaction time and, therefore, many of the reactions described below were carried out in the presence of triethylamine. Triethylamine was added to these systems to promote the elimination of hydrogen iodide, as indicated in Scheme 2.

Reaction of 2-chloropyridine **1c** with a fluorine–iodine mixture gave two products, 2-chloro-6-fluoropyridine **2c** and 2-fluoropyridine **2a**, in a ratio of 5 : 1 and, by a similar reaction, fluorination of 2-bromopyridine **1d** also gave a mixture of 2-bromo-6-fluoropyridine **2d** and 2-fluoropyridine **2a** in a ratio of 2 : 1 (Table 1).

In contrast, in direct fluorination reactions in the absence of iodine, Van der Puy reported that direct fluorination of pyridine in $CF_2ClCFCl_2$ also gives 2-fluoropyridine[19,20] but it is clear from the preceding experiments that the present fluorine–iodine methodology is different in character to reactions involving elemental fluorine alone. Although, direct fluorination of 2-chloropyridine was reported to give 2-chloro-6-fluoropyridine as the major product and various other products, including 2,6-difluoropyridine and 2,6-dichloropyridine,[19,20] no 2-fluoropyridine was observed (Scheme 3). A mechanism involving an

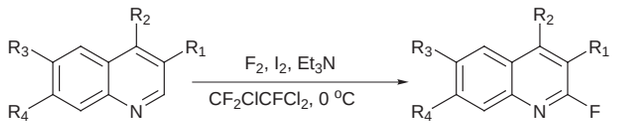


Scheme 3

addition–elimination sequence (Scheme 4) was proposed to account for these results.[19,20]

However, using the present procedure, reaction of 2-chloropyridine with a fluorine–iodine mixture, gave only two products, 2-chloro-6-fluoropyridine **2c** and 2-fluoropyridine **2a**, in a ratio of 5 : 1. In this case, nucleophilic displacement of chloride from intermediate **2e** by the fluoride ion accounts for the formation of significant amounts of 2-fluoropyridine **2a** (Scheme 5, Path a) while attack by fluoride ion at the 2-position

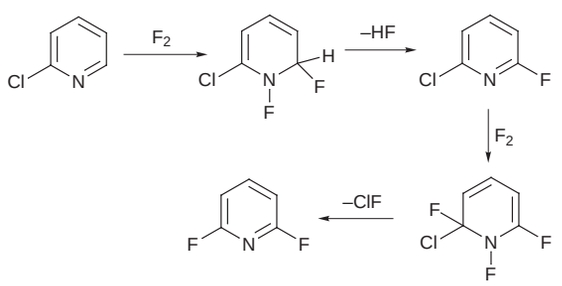
Table 2 Fluorination of quinoline derivatives



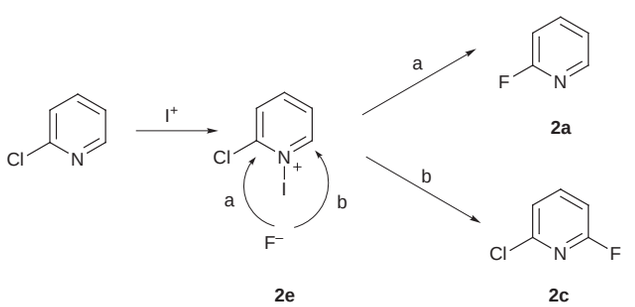
3 a–g **4 a–g**

Quinoline	Fluoro-quinoline	R_1	R_2	R_3	R_4	Yield[b] (%) (Conversion %)
3a	**4a**	H	H	H	H	54 (77)[a]
3b	**4b**	Br	H	H	H	85 (56)
3c	**4c**	H	Cl	H	H	90 (76)
3d	**4d**	H	Me	H	H	49 (58)[a]
3e	**4e**	H	H	Cl	H	82 (81)
3f	**4f**	H	Cl	H	Cl	88 (69)
3g	**4g**	H	Cl	H	CF_3	84 (74)

[a] Reactions performed without added triethylamine present. [b] Isolated yield based on conversion of a starting material.



Scheme 4



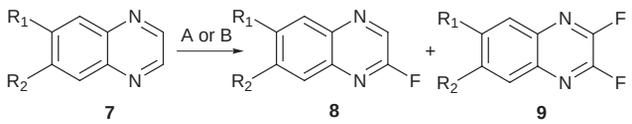
Scheme 5

in **2e**, followed by elimination of hydrogen iodide (Scheme 5, Path b), gives the major product **2c** (Scheme 5).

Studies concerning direct fluorination of quinoline systems have not, to our knowledge, been reported. However, extension of the fluorine–iodine methodology to the selective fluorination of quinolines **3a**–**g** gave a range of corresponding 2-fluoroquinoline derivatives **4a**–**g**, containing various substituent groups, in high conversion and yield (Table 2). In each reaction, trace amounts of other impurities were detected by fluorine NMR and GC analysis of crude product mixtures but all of the fluorinated quinolines could be purified by either column chromatography or fractional distillation under reduced pressure. The identities of all products **4a**–**g** follow directly from ^{19}F NMR spectroscopy because the observed chemical shifts of fluorine on carbon atoms α to the ring nitrogen are characteristically in the region of −55 to −70 ppm.[22] The structures of all products **4a**–**g** were also confirmed by ^{1}H and ^{13}C NMR spectroscopy and other analytical techniques (see Experimental section). By an analogous procedure, phenanthridine **5** gave 6-fluorophenanthridine **6** as the only product upon reaction with the fluorine–iodine mixture (Scheme 6).

Diazines have, of course, additional sites that are α to the ring nitrogen atom and could, in principle, give poly-fluorinated

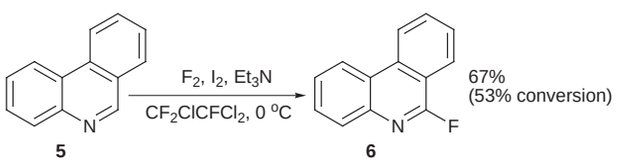
Table 3 Fluorination of quinoxaline derivatives



7 8 9

Quinoxaline	R_1	R_2	Conditions[a]	Conversion	Yield **8** (%)	Yield **9** (%)
7a	H	H	A	91	**8a**, 48	**9a**, 11
7a	H	H	B	100	**8a**, 8	**9a**, 33
7b	CH_3	H	A	43	**8b** ($R_1 = CH_3$, $R_2 = H$), 16 **8c** ($R_1 = H$, $R_2 = CH_3$), 29	**9b**, 7
7b	CH_3	H	B	71	**8b** + **8c**, 16 (total)	**9b**, 23
7c	CH_3	CH_3	A	75	**8d**, 40	**9c**, 5
7c	CH_3	CH_3	B	90	**8d**, 14	**9c**, 12
7d	Cl	H	A	64	**8e** ($R_1 = Cl$, $R_2 = H$), 28 **8f** ($R_1 = H$, $R_2 = Cl$), 16	**9d**, 3
7d	Cl	H	B	94	**8e** + **8f**, 25 (total)	**9d**, 19

[a] Conditions A: quinoxaline (1 equiv.), I_2 (1 equiv.), Et_3N (1 equiv.), F_2 (1.5 equiv.); Conditions B: quinoxaline (1 equiv.), I_2 (1 equiv.), Et_3N (2 equiv.), F_2 (3 equiv.).



5 6

Scheme 6

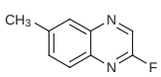
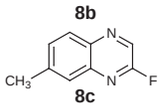
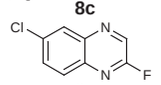
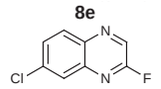
products upon reaction with the fluorine–iodine mixture. However, using analogous procedures to those that were successful for the fluorination of pyridine and related systems described above, pyrazine, pyrimidine and pyridazine were all recovered unchanged. In contrast, quinoxaline **7a**, gave a mixture of both the monofluoro- **8a** and difluoro-quinoxaline **9a** derivatives as the only fluorine containing products upon reaction with iodine, triethylamine and a slight excess of fluorine (Conditions A, Table 3). Several quinoxaline derivatives **7b**–**d** were fluorinated under the same conditions to give the corresponding monofluoro **8b**–**f** and difluorinated products **9a**–**d** (Table 3). Methyl- **7b** and chloro- **7d** quinoxaline gave mixtures of two monofluoro isomers **8b**,**c** and **8e**,**f** respectively and the major products, **8c** and **8e** respectively, in each case derived from fluoride ion attack at the carbon site adjacent to the most nucleophilic ring nitrogen atom, a process consistent with the mechanism outlined in Scheme 2.

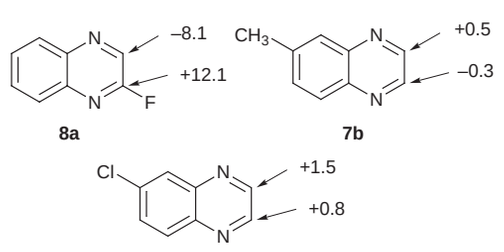
Quinoxalines containing strong electron withdrawing substituents, such as 6-nitroquinoxaline and 6,7-dichloroquinoxaline, did not react with the fluorine–iodine system under the present reaction conditions and this is presumably due to the decreased nucleophilicity of the ring nitrogen atoms in such substrates.

Difluoroquinoxalines **9a**–**d** were prepared upon passing excess fluorine through a solution of quinoxaline **7a**–**d**, triethylamine and iodine in $CF_2ClCFCl_2$ (Conditions B, Table 3), although, in these reactions, yields were relatively low due to increased substrate degradation. Purification of all fluoroquinoxalines **8**,**9** was achieved by column chromatography on silica gel.

Fluoroquinoxaline **8a** could be identified by the presence of a characteristic ^{19}F NMR resonance which appears as a doublet centred at −74.4 ppm ($^3J_{HF} = 7.6$ Hz). Furthermore, in the ^{13}C NMR spectrum of **8a**, the resonances attributed to C-2 and C-3 can be assigned at 156.3 and 136.1 ppm respectively because of the presence of diagnostic coupling patterns ($^1J_{CF}$ 256 Hz and $^2J_{CF}$ 42.5 Hz respectively). A comparison of ^{13}C NMR shift data for C-2 and C-3 in fluoroquinoxaline **8a** with the ^{13}C NMR data observed for quinoxaline ($\delta_{C\text{-}2} = \delta_{C\text{-}3} = 144.2$ ppm) allows the substituent chemical shift for fluorine on the C-2 and C-3 sites to be calculated (Scheme 7). Substituent chemical shift

Table 4 Calculated and observed ^{13}C NMR data for **8b**,**c**,**e**,**f**

		δ_C C-2	δ_C C-3
 **8b**	Calc.	156.0	136.6
	Observed	156.2	134.6
 **8c**	Calc.	156.8	135.8
	Observed	156.7	135.8
 **8e**	Calc.	157.1	137.6
	Observed	156.7	137.4
 **8f**	Calc.	157.8	136.9
	Observed	157.2	136.5



8a 7b 7d

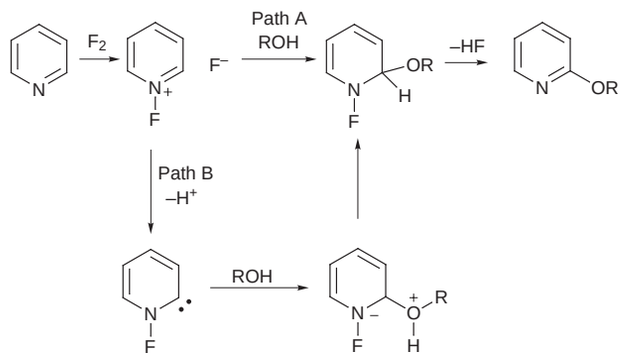
Scheme 7 Substituent chemical shift values in ppm for C-2 and C-3 relative to quinoxaline ($\delta_C = 144.2$ ppm). Positive values indicate δ(derivative) > δ(quinoxaline).

values for 6-methyl and 6-chloro substituents were also calculated (Scheme 7) and, consequently, predictions for the ^{13}C NMR shifts of C-2 and C-3 in **8b**,**c**,**e**,**f** were calculated based upon the additivity of these substituent effects[23] (Table 4). A comparison of calculated chemical shift values for C-2 and C-3 in **8b**,**c**,**e**,**f** show close agreement with the ^{13}C NMR resonances observed and, consequently, full assigment of the ^{13}C NMR spectra of each mono-fluorinated isomer followed readily.

Several of the fluorination reactions described above were also performed using an inert solvent such as hexafluorobenzene, although conversions to fluorinated products were lower in this medium. Other solvents such as dichloromethane, dimethylformamide, tetrahydrofuran and nitromethane were found to be unsuitable solvents for reactions using the fluorine–iodine system, largely because of the insolubility of iodine in these media.

Alkoxylation of pyridine derivatives

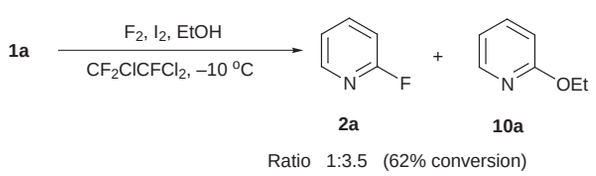
Fluorination of pyridine and related systems by fluorine–iodine mixtures, in which intermediate *N*-iodo-pyridinium ions are attacked by nucleophilic fluoride ion (Scheme 2), constitutes an unusual method for the overall nucleophilic displacement of hydrogen. In principle, *N*-fluoropyridinium fluoride, formed upon reaction of pyridine with fluorine, could react with other nucleophiles which, after elimination of hydrogen fluoride, also lead to overall nucleophilic substitution of hydrogen (Scheme 8,



Scheme 8

Path A). Indeed, Strekowski[24] has reported products arising from carboximidation of N-heterocycles in which acetonitrile acts as the nucleophile, by processes that could be interpreted according to Scheme 8, Path A, although a mechanism involving a carbene intermediate was suggested[24] (Scheme 8, path B).

We have now discovered that reaction of pyridine **1a** with fluorine in a mixture of ethanol and $CF_2ClCFCl_2$ results in the formation of significant quantities of 2-ethoxy-pyridine **10a** as well as 2-fluoropyridine **2a** in a ratio of 3.5 : 1 (Scheme 9).



Scheme 9

Several alkoxypyridines **10b–d** were prepared in an analogous manner by passing fluorine through a stirred, cooled (−10 °C) solution of pyridine and an alcohol or derivative in $CF_2ClCFCl_2$ (Table 5).

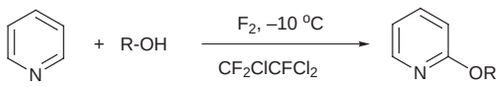
In a separate experiment, we established that, 2-ethoxypyridine **10a** could not be formed by ethoxylation of 2-fluoropyridine. When a mixture of ethanol and 2-fluoropyridine in $CF_2ClCFCl_2$ was stirred for 8 hours at 40 °C only unchanged 2-fluoropyridine was recovered. In the light of our earlier experiments with iodine and fluorine, we consider that the formation of all the alkoxylated derivatives are most reasonably accounted for by the mechanism shown in Scheme 8, Path A.

In summary, selective fluorination of various pyridine, quinoline and quinoxaline derivatives, involving replacement of hydrogen atoms by fluorine at positions α to the heteroatom, can be achieved using elemental fluorine–iodine mixtures. This methodology further extends the use of elemental fluorine as a viable reagent for selective fluorination reactions.[25]

Experimental

All starting materials were obtained commercially (Aldrich) and all solvents were dried using literature procedures. NMR spectra were recorded in deuteriochloroform, unless otherwise stated, on either a Varian Gemini 200, a Varian VXR 400S or a Bruker AC250 NMR spectrometer with tetramethylsilane and

Table 5 Alkoxylation of pyridine



10

R-OH	**10** Yield (%) (Conversion %)
CH_3CH_2OH	**10a**, 50 (62)
CH_3–OH	**10b**, 54 (67)
$CH_3CH_2CH_2CH_2$–OH	**10c**, 58 (86)
CF_3–CH_2–OH	**10d**, 60 (63)

trichlorofluoromethane as internal standards. Spectral assignments were made with the aid of data collected by ^{1}H–^{1}H COSY and ^{1}H–^{13}C HETCOR experiments and coupling constants are given in Hz. In ^{19}F NMR spectra, upfield shifts are quoted as negative. Mass spectra were recorded on either a VG 7070E spectrometer or a Fissons VG Trio 1000 spectrometer coupled with a Hewlett Packard 5890 series II gas chromatograph. Elemental analyses were obtained on either a Perkin-Elmer 240 or a Carlo Erba elemental analyser. Melting points were recorded at atmospheric pressure and are uncorrected. Superscript numbers given as part of boiling point data indicate the pressure (in mmHg) during measurement. Column chromatography was carried out on silica gel (Merck No. 1-09385, 230–400 mesh) using dichloromethane as eluant and TLC analysis was performed on silica gel TLC plates using dichloromethane as eluant.

Fluorination of pyridine and quinoline derivatives

General procedure. A solution consisting of the pyridine or quinoline, iodine, triethylamine (if required) and $CF_2ClCFCl_2$ was placed in a fluorination apparatus fitted with an overhead stirrer and a drying tube filled with soda lime. Elemental fluorine (165 mmol) as a 10% mixture in dry nitrogen was then passed through the stirred, cooled (0–5 °C) solution using narrow bore PTFE tubing at *ca.* 40 ml min^{-1}. After fluorine had been passed into the solution, the mixture was poured into 10% aqueous sodium metabisulfite solution, neutralised with sodium bicarbonate and continuously extracted with dichloromethane. The organic extracts were dried ($MgSO_4$) and evaporated to leave the crude product. The composition of a weighed crude reaction mixture was determined by GC-MS analysis and the conversion of starting material was calculated from GC peak intensities. The amount of fluoro-heterocycle in the crude product was determined by adding a known amount of fluorobenzene to a weighed amount of the crude product mixture. Comparison of the relative intensities of the appropriate ^{19}F NMR resonances gave the yield of fluoroheterocycle, based upon the conversion obtained above. Purification of the desired fluoro-heterocycle could be achieved by either (i) washing the crude product with 1 M HCl solution followed by column chromatography on silica gel using dichloromethane as eluant, (ii) vacuum transfer followed by column chromatography on silica gel using dichloromethane as eluant or (iii) fractional distillation under reduced pressure. Yields of fluoro-heterocycle are quoted as isolated yields based on the conversion of starting material.

Pyridine 1a. Pyridine **1a** (9.5 g, 120 mmol) and iodine (30.0 g, 118 mmol) in $CFCl_2CF_2Cl$ (150 ml) and fluorine (165 mmol) gave, after washing the crude product in dichloromethane with 1 M HCl and vacuum transfer, 2-fluoropyridine **2a** (6.5 g, 56%, 59% conversion) as a yellow oil in >95% purity by GC; δ_H(200 MHz) 6.9 (1 H, m, H-3), 7.2 (1 H, m, H-5), 7.8 (1 H, m, H-4), 8.2 (1 H, m, H-6); δ_C(50 MHz) 109.4 (d, $^2J_{CF}$ 37.1, C-3), 121.3 (d, $^4J_{CF}$ 4.2, C-5), 141.2 (d, $^3J_{CF}$ 7.7, C-4), 147.5 (d, $^2J_{CF}$ 14.5,

C-6), 163.5 (d, $^1J_{CF}$ 237.4, C-2); δ_F(235 MHz) −67.9 (s); *m/z* (EI$^+$) 97 (M$^+$, 100%), 70 (68), 69 (12), 57 (18), 50 (29), 39 (22); as compared to the literature data;[10] and 2,6-difluoropyridine (3% by GC); *m/z* (EI$^+$) 115 (M$^+$, 100%), 88 (22), 70 (54), 57 (13).

4-Ethylpyridine 1b. 4-Ethylpyridine **1b** (12.8 g, 120 mmol) and iodine (30.5 g, 120 mmol) in $CFCl_2CF_2Cl$ (150 ml) and fluorine (165 mmol) gave a yellow oil (9.54 g) which contained **1b**, 2-fluoro-4-ethylpyridine **2b** and other minor products by GC-MS The oil was redissolved in dichloromethane and washed with 2 M HCl solution, dried ($MgSO_4$) and evaporated to give 2-fluoro-4-ethylpyridine **2b** (6.3 g, 54%, 78% conversion) as a clear oil in >95% purity by GC; δ_H(200 MHz) 1.26 (3 H, t, $^3J_{HH}$ 7.6, CH_3), 2.69 (2 H, q, $^3J_{HH}$ 7.6, CH_2), 6.75 (1 H, s, H-3), 7.02 (1 H, dm, $^3J_{H5,H6}$ 5.1, H-5), 8.09 (1 H, d, $^3J_{H5,H6}$ 5.1, H-6); δ_C(50 MHz) 14.1 (s, CH_3), 28.2 (d, $^4J_{CF}$ 2.7, CH_2), 108.5 (d, $^2J_{CF}$ 36.5, C-3), 121.3 (d, $^4J_{CF}$ 3.9, C-5), 147.3 (d, $^3J_{CF}$ 15.2, C-6), 159.3 (d, $^3J_{CF}$ 7.8, C-4), 164.2 (d, $^1J_{CF}$ 236.3, C-2); δ_F(235 MHz) −69.9 (s); *m/z* (EI$^+$) 125 (M$^+$, 100%), 110 (47), 97 (15), 83 (13); as compared to the literature data.[19]

2-Chloropyridine. 2-Chloropyridine **1c** (3.0 g, 26 mmol), iodine (6.7 g, 26 mmol) and triethylamine (2.7 g, 26 mmol) in $CFCl_2CF_2Cl$ (150 ml) and fluorine (35 mmol) gave a brown oil (2.5 g) which contained **2a** (10%) and 2-chloro-6-fluoropyridine **2c** (50%) by GC-MS analysis. Purification by column chromatography gave 2-chloro-6-fluoropyridine **2c** (1.25 g, 70%, 61% conversion) as white crystals; mp 35–36 °C (lit.,[26] 34–36 °C); R_f 0.77; δ_H(200 MHz) 6.86 (1 H, ddd, $J_{H4,H5}$ 8.1, $J_{H5,F}$ 2.7, $J_{H3,H5}$ 0.6, H-5), 7.21 (1 H, ddd, $J_{H3,H4}$ 7.7, $J_{H3,F}$ 1.6, $J_{H3,H5}$ 0.6, H-3), 7.75 (1 H, pseudo q, $J_{H3,H4} = J_{H4,H5} = J_{H4,F} = 7.9$, H-4); δ_C(50 MHz) 109.8 (d, $^2J_{CF}$ 34.8, C-5), 123.6 (s, C-3), 145.0 (d, $^3J_{CF}$ 7.5, C-4), 150.8 (d, $^3J_{CF}$ 13.5, C-2), 164.2 (d, $^1J_{CF}$ 244.2, C-6); δ_F(235 MHz) −66.3 (s); *m/z* (EI$^+$) 131 (M$^+$, 100%), 133 (M$^+$, 33), 96 (64), 76 (20), 51 (14); as compared to the literature data.[16,19]

2-Bromopyridine 1d. 2-Bromopyridine **1d** (4.1 g, 26 mmol), iodine (6.7 g, 26 mmol), triethylamine (2.7 g, 26 mmol) in $CFCl_2CF_2Cl$ (150 ml) and fluorine (35 mmol) gave a brown oil which contained triethylamine (23%), **2a** (25%) and 2-bromo-6-fluoropyridine **2d** (51%) by GC-MS analysis. Purification by column chromatography gave 2-bromo-6-fluoropyridine **2d** (2.7 g, 59%, 100% conversion) as white crystals; mp 30–32 °C; R_f 0.78; δ_H(200 MHz) 6.90 (1 H, ddd, $J_{H4,H5}$ 8.0, $J_{H4,F}$ 2.7, $J_{H3,H5}$ 0.5, H-5), 7.37 (1 H, m, H-3), 7.66 (1 H, pseudo q, $J_{H3,H4} = J_{H4,H5} = J_{H4,F} = 7.9$, H-4); δ_C(50 MHz) 110.2 (d, $^2J_{CF}$ 34.6, C-5), 127.5 (d, $^4J_{CF}$ 4.8, C-3), 140.6 (d, $^3J_{CF}$ 13.5, C-Br), 144.8 (d, $^3J_{CF}$ 7.5, C-4), 164.1 (d, $^1J_{CF}$ 245.1, C-F); δ_F(235 MHz) −65.5 (s); *m/z* (CI$^+$, NH_3) 176 (M$^+$ + 1, 26%), 178 (M$^+$ + 1, 22), 98 (100).

Quinoline 3a. Quinoline **3a** (18.0 g, 139 mmol) and iodine (35.3 g, 139 mmol) in $CFCl_2CF_2Cl$ (250 ml) and fluorine (165 mmol) gave an orange oil (12.4 g). Distillation afforded 2-fluoroquinoline **4a** (8.3 g, 54%, 77% conversion) as a pale yellow oil; bp^{30} 134–136 °C (lit.,[11] bp^{30} 133 °C); δ_H(400 MHz) 7.05 (1 H, dd, $J_{H3,H4}$ 8.8, $J_{H3,F}$ 2.8, H-3), 7.51 (1 H, ddd, $J_{H5,H6}$ 8.0, $J_{H6,H7}$ 6.8, $J_{H6,H8}$ 0.8, H-6), 7.71 (1 H, ddd, $J_{H7,H8}$ 8.0, $J_{H6,H7}$ 7.6, $J_{H5,H7}$ 1.2, H-7), 7.81 (1 H, d, $J_{H5,H6}$ 8.0, H-5), 7.94 (1 H, d, $J_{H7,H8}$ 8.4, H-8), 8.20 (1 H, dd, $J_{H3,H4} = J_{H4,F}$ 8.4, H-4); δ_C(100 MHz) 110.0 (d, $^2J_{CF}$ 42.1, C-3), 126.1 (d, $^4J_{CF}$ 2.6, C-8), 126.8 (d, $^4J_{CF}$ 1.9, C-4a), 127.5 (s, C-6), 128.0 (d, $^5J_{CF}$ 1.2, C-5), 130.6 (d, $^5J_{CF}$ 0.8, C-7), 141.9 (d, $^3J_{CF}$ 9.9, C-4), 145.7 (d, $^3J_{CF}$ 16.7, C-8a), 161.1 (d, $^1J_{CF}$ 240.5, C-2); δ_F(250 MHz) −63.2 (s); *m/z* (EI$^+$) 147 (M$^+$, 100%); as compared to the literature data.[11,27]

3-Bromoquinoline 3b. 3-Bromoquinoline **3b** (1.0 g, 4.8 mmol), iodine (1.22 g, 4.8 mmol) and triethylamine (0.48 g, 4.8 mmol) in $CFCl_2CF_2Cl$ (30 ml) and fluorine (5 mmol) gave a brown oil (0.95 g). Column chromatography gave 2-fluoro-3-bromoquinoline **4b** (0.52 g, 85%, 56% conversion) as white needles; mp 75–76 °C (vacuum sublimation oil bath temp. 50 °C/<1 mmHg); R_f 0.69 (Found: C, 47.5; H, 2.1; N, 6.2. C_9H_5BrFN requires: C, 47.8; H, 2.2; N, 6.2%); δ_H(400 MHz) 7.55 (1 H, dd, $J_{H5,H6} = J_{H6,H7}$ 8.0, H-6), 7.74 (1 H, ddd, $J_{H7,H8}$ 8.4, $J_{H6,H7}$ 7.2, $J_{H5,H7}$ 1.2, H-7), 7.76 (1 H, d, $J_{H5,H6}$ 8.0, H-5), 7.91 (1 H, dd, $J_{H7,H8}$ 8.4, $J_{H6,H8}$ 0.8, H-8), 8.42 (1 H, d, $J_{H4,F}$ 8.4, H-4); δ_C(100 MHz) 104.0 (d, $^2J_{CF}$ 43.2, C-3), 126.6 (s, C-6), 127.0 (d, $^4J_{CF}$ 2.7, C-8), 128.0 (d, $^5J_{CF}$ 1.9, C-5) 128.0 (d, $^4J_{CF}$ 2.2, C-4a), 130.9 (d, $^5J_{CF}$ 1.1, C-7), 143.5 (d, $^3J_{CF}$ 3.7, C-4), 144.2 (d, $^3J_{CF}$ 15.1, C-8a), 157.3 (d, $^1J_{CF}$ 238.1, C-2); δ_F(235 MHz) −60.8 (s); *m/z* (EI$^+$) 225 (M$^+$, 100%), 227 (M$^+$, 74), 146 (56), 126 (23), 101 (18), 75 (14).

4-Chloroquinoline 3c. 4-Chloroquinoline **3c** (1.0 g, 6 mmol), iodine (1.55 g, 6 mmol) and triethylamine (0.60 g, 6 mmol) in $CFCl_2CF_2Cl$ (30 ml) and fluorine (7 mmol) gave a brown oil (1.01 g). Column chromatography gave 2-fluoro-4-chloroquinoline **4c** (0.76 g, 90%, 76% conversion) as white needles; mp 60–61 °C (vacuum sublimation oil bath temp. 50 °C/<1 mmHg); R_f 0.78 (Found: C, 59.7; H, 2.9; N, 7.6. C_9H_5ClFN requires: C, 59.5; H, 2.75; N, 7.7%); δ_H(400 MHz) 7.20 (1 H, d, $J_{H3,F}$ 2.4, H-3), 7.62 (1 H, ddd, $J_{H5,H6} = J_{H6,H7}$ 7.4, $J_{H6,H8}$ 1.2, H-6), 7.78 (1 H, ddd, $J_{H6,H7} = J_{H7,H8}$ 7.8, $J_{H5,H7}$ 1.2, H-7), 7.96 (1 H, d, $J_{H7,H8}$ 8.4, H-8), 8.19 (1 H, d, $J_{H5,H6}$ 8.4, H-5); δ_C(100 MHz) 110.2 (d, $^2J_{CF}$ 45.8, C-3), 124.2 (d, $^5J_{CF}$ 0.8, C-5), 125.1 (d, $^4J_{CF}$ 2.6, C-4a), 127.0 (d, $^6J_{CF}$ 2.7, C-6), 128.5 (d, $^4J_{CF}$ 1.5, C-8), 131.6 (s, C-7), 145.9 (d, $^3J_{CF}$ 18, C-8a), 146.6 (d, $^3J_{CF}$ 12.5, C-4), 160.2 (d, $^1J_{CF}$ 242.3, C-2); δ_F(235 MHz) −61.5 (s); *m/z* (EI$^+$) 183 (M$^+$, 26%), 181 (M$^+$, 100), 146 (35), 126 (15), 75 (12), 50 (11).

4-Methylquinoline 3d.[28] 4-Methylquinoline **3d** (5.0 g, 35 mmol) and iodine (9.0 g, 35 mmol) in $CFCl_2CF_2Cl$ (30 ml) and fluorine (40 mmol) gave a brown oil (3.7 g). Column chromatography gave 2-fluoro-4-methylquinoline **4d** (1.6 g, 49%, 58% conversion) as an oil which was homogeneous by GC; δ_H(200 MHz) 2.64 (3 H, s, CH_3), 6.83 (1 H, s, H-3), 7.51 (1 H, m, H-6), 7.66 (1 H, m, H-7), 7.87 (2 H, m, H-5 and H-8); δ_C(50 MHz) 18.9 (d, $^4J_{CF}$ 2.6, CH_3), 109.9 (d, $^2J_{CF}$ 41.6, C-3), 123.8 (s, C-6), 125.8 (d, $^4J_{CF}$ 2.3, C-8), 126.8 (d, $^4J_{CF}$ 1.8, C-4a), 128.5 (d, $^5J_{CF}$ 1.5, C-5), 130.3 (s, C-7), 145.5 (d, $^3J_{CF}$ 17.5, C-8a), 151.0 (d, $^3J_{CF}$ 10.2, C-4), 161.0 (d, $^1J_{CF}$ 241.1, C-2); δ_F(235 MHz) −59.3 (s); *m/z* (EI$^+$) 161 (M$^+$, 67%), 143 (100), 133 (11), 115 (52), 89 (29).

6-Chloroquinoline 3e. 6-Chloroquinoline **3e** (1.0 g, 6.1 mmol), iodine (1.55 g, 6.1 mmol) and triethylamine (0.62 g, 6.2 mmol) in $CFCl_2CF_2Cl$ (30 ml) and fluorine (7 mmol) gave a brown solid (0.93 g). Column chromatography gave 2-fluoro-6-chloroquinoline **4e** (0.73 g, 82%, 81% conversion) as a white solid; mp 60–61 °C (vacuum sublimation oil bath temp. 60 °C/<1 mmHg); R_f 0.78 (Found: C, 59.6; H, 2.9; N, 7.5. C_9H_5ClFN requires: C, 59.5; H, 2.75; N, 7.7%); δ_H(400 MHz) 7.12 (1 H, dd, $J_{H3,H4}$ 8.8, $J_{H3,F}$ 2.8, H-3), 7.67 (1 H, dd, $J_{H7,H8}$ 9.2, $J_{H5,H7}$ 2.4, H-7), 7.82 (1 H, d, $J_{H5,H7}$ 2.4, H-5), 7.87 (1 H, d, $J_{H7,H8}$ 9.0, H-8), 8.16 (1 H, dd, $J_{H3,H4} = J_{H4,F}$ 8.8, H-4); δ_C(100 MHz) 111.1 (d, $^2J_{CF}$ 42.3, C-3), 126.3 (s, C-5), 127.3 (s, C-4a), 129.6 (s, C-8), 131.4 (s, C-7), 131.9 (s, C-6), 141.0 (d, $^3J_{CF}$ 9.9, C-4), 144.1 (d, $^3J_{CF}$ 16.8, C-8a), 161.2 (d, $^1J_{CF}$ 243.8, C-2); δ_F(235 MHz) −61.5 (s); *m/z* (EI$^+$) 181 (M$^+$, 100%), 183 (M$^+$, 32), 146 (34), 126 (11).

4,7-Dichloroquinoline 3f. 4,7-Dichloroquinoline **3f** (1.0 g, 5 mmol), iodine (1.28 g, 5 mmol) and triethylamine (0.51 g, 5.1 mmol) in $CFCl_2CF_2Cl$ (30 ml) gave a brown oil (1.06 g). Column chromatography gave 2-fluoro-4,7-dichloroquinoline **4f** (0.66 g, 88%, 69% conversion) as white crystals; mp 105–106 °C (vacuum sublimation oil bath temp. 60 °C/<1 mmHg); R_f 0.72 (Found: C, 49.7; H, 1.7; N, 6.3. $C_9H_4Cl_2FN$ requires: C, 50.0; H, 1.85; N, 6.5%); δ_H(400 MHz) 7.20 (1 H, d, $J_{H3,F}$ 2.4, H-3), 7.58 (1 H, dd, $J_{H5,H6}$ 9.0, $J_{H6,H8}$ 2.2, H-6), 7.95 (1 H, d, $J_{H6,H8}$ 2.0, H-8), 8.13 (1 H, d, $J_{H5,H6}$ 9.2, H-5); δ_C(100 MHz) 110.38 (d, $^2J_{CF}$ 45.8, C-3), 123.6 (d, $^4J_{CF}$ 2.3, C-4a), 125.5 (s, C-6), 127.6 (d, $^5J_{CF}$

1.2, C-5), 128.1 (d, $^4J_{CF}$ 2.6, C-8), 137.9 (s, C-7), 146.4 (d, $^3J_{CF}$ 24.6, C-4), 146.6 (d, $^3J_{CF}$ 18.5, C-8a), 160.9 (d, $^1J_{CF}$ 244.1, C-2); δ_F(235 MHz) −60.0 (s); *m/z* (EI$^+$) 215 (M$^+$, 100%), 217 (M$^+$, 61), 219 (M$^+$, 11), 182 (14), 180 (40), 145 (18).

4-Chloro-7-trifluoromethylquinoline 3g. 4-Chloro-7-trifluoromethylquinoline **3g** (1.0 g, 4.3 mmol), iodine (1.1 g, 4.3 mmol) and triethylamine (0.43 g, 4.3 mmol) in $CFCl_2CF_2Cl$ (30 ml) and fluorine (6 mmol) gave a brown solid (1.08 g). Column chromatography gave 2-fluoro-4-chloro-7-trifluoromethylquinoline **4g** (0.67 g, 84%, 74% conversion) as white needles; mp 94–95 °C (vacuum sublimation oil bath temp. 50 °C/<1 mmHg); R_f 0.81 (Found: C, 47.7; H, 1.3; N, 5.5. $C_{10}H_4ClF_4N$ requires: C, 48.1; H, 1.6; N, 5.6%); δ_H(400 MHz) 7.32 (1 H, d, $J_{H,F}$ 2.4, H-3), 7.79 (1 H, dd, $J_{H5,H6}$ 8.8, $J_{H6,H8}$ 1.6, H-6), 8.23 (1 H, m, H-8), 8.32 (1H, d, $J_{H5,H6}$ 8.8, H-5); δ_C(50 MHz) 112.3 (d, $^2J_{CF}$ 45.5, C-2), 122.9 (m, C-6), 123.4 (q, $^1J_{CF}$ 272.7, CF_3), 125.6 (s, C-5), 126.2 (m, C-8), 126.7 (s, C-4a), 133.4 (q, $^2J_{CF}$ 33.2, C-7), 145.2 (d, $^3J_{CF}$ 18.7, C-8a), 146.7 (d, $^3J_{CF}$ 12.9, C-4), 160.9 (d, $^1J_{CF}$ 245.3, C-2); δ_F(235 MHz) −59.7 (1 F, s, F-2), −63.9 (3 F, s, CF_3); *m/z* (EI$^+$) 249 (M$^+$, 100%), 251 (M$^+$, 33), 230 (26), 214 (18), 201 (11), 199 (33), 194 (12).

Phenanthridine 5. Phenanthridine **5** (1.0 g, 5.6 mmol), iodine (1.4 g, 5.6 mmol) and triethylamine (0.56 g, 5.6 mmol) in $CFCl_2CF_2Cl$ (30 ml) and fluorine (7 mmol) gave a brown oil (0.92 g). Column chromatography gave 6-fluorophenanthridine **6** (0.39 g, 67%, 53% conversion) as a white solid; mp 84–87 °C; R_f 0.78 (Found: C, 79.0; H, 4.1; N, 7.3. $C_{13}H_8FN$ requires C, 79.2; H, 4.1; N, 7.1%); δ_H(400 MHz) 7.61 (1 H, ddd, $J_{H1,H2}$ = $J_{H2,H3}$ = 7.8, $J_{H2,H4}$ 1.2, H-2), 7.69 (2 H, m, H-3 and H-9), 7.88 (1 H, ddd, $J_{H7,H8}$ 8.4, $J_{H8,H9}$ 7.2, $J_{H8,H10}$ 1.4, H-8), 7.97 (1 H, dd, $J_{H3,H4}$ 8.0, $J_{H2,H4}$ 1.2, H-4), 8.21 (1 H, dd, $J_{H9,H10}$ 8.0, $J_{H8,H10}$ 1.4, H-10) 8.45 (1 H, dd, $J_{H1,H2}$ 8.0, $J_{H1,H3}$ 0.8, H-1), 8.52 (1 H, dd, $J_{H7,H8}$ 8.4, $J_{H7,H9}$ 1.2, H-7); δ_C(100 MHz) 117.3 (d, $^2J_{CF}$ 35.1, C-6a), 122.2 (d, $^3J_{CF}$ 3.8, C-7), 122.2 (s, C-1), 123.9 (d, $^4J_{CF}$ 1.9, C-10b), 124.2 (s, C-10), 126.5 (d, $^6J_{CF}$ 2.3, C-2), 127.9 (s, C-9), 128.7 (d, $^4J_{CF}$ 1.6, C-4), 129.4 (s, C-3), 132.1 (s, C-8), 136.5 (d, $^3J_{CF}$ 7.2, C-10a), 141.5 (d, $^3J_{CF}$ 17.9, C-4a), 158.1 (d, $^1J_{CF}$ 248.7, C-6); δ_F(376 MHz) −68.2 (s); *m/z* (EI$^+$) 197 (M$^+$, 100%).

Preparation of quinoxalines

General procedure. A solution of a phenylenediamine in water (55 ml), was added to a stirred, heated (70 °C) solution of glyoxal sodium bisulfite monohydrate (glyoxal) in water (35 ml). After 1 h the reaction mixture was cooled to room temperature, neutralised with sodium carbonate and extracted using dichloromethane (3 × 30 ml). Solvent was evaporated from the combined, dried ($MgSO_4$) organic extracts to leave a crude product which was further purified by distillation, recrystallisation or sublimation to give the desired quinoxaline.

6-Methylquinoxaline 7b.[29] 4-Methylphenylene-1,2-diamine (5.12 g, 42 mmol) and glyoxal (11.20 g, 42 mmol) gave an orange oil which was distilled to afford 6-methylquinoxaline **7b** (4.42 g, 73%) as a pale yellow oil; bp[14] 125 °C (lit.,[29] bp[1] 86 °C); δ_H(400 MHz) 2.51 (3 H, s, CH_3), 7.51 (1 H, dd, $^3J_{H7,H8}$ 8.8, $^4J_{H5,H7}$ 2.0, H-7), 7.79 (1 H, br s, H-5), 7.91 (1 H, d, $^3J_{H7,H8}$ 8.8, H-8), 8.69 (1 H, d, $^3J_{H2,H3}$ 2.0, H-3), 8.72 (1 H, d, $^3J_{H2,H3}$ 2.0, H-2); δ_C(100 MHz) 21.6 (s, CH_3), 128.1 (s, C-5), 128.8 (s, C-8), 132.2 (s, C-7), 140.4 (s, C-6), 141.3 (s, C-8a), 142.9 (s, C-4a), 143.9 (s, C-2), 144.7 (s, C-3); *m/z* (EI$^+$) 144 (M$^+$, 100%), 117 (30), 90 (61); as compared to literature data.[30]

6,7-Dimethylquinoxaline 7c.[31] 4,5-Dimethylphenylene-1,2-diamine (2.86 g, 21 mmol) and glyoxal (5.60 g, 21 mmol) gave, after recrystallisation, 6,7-dimethylquinoxaline **7c** (2.59 g, 78%) as a white solid; mp 96–98 °C (lit.,[31] 100–101 °C) (from ethanol); δ_H(400 MHz) 2.42 (3 H, s, CH_3), 7.76 (1 H, s, H-5), 8.66 (1 H, s, H-2); δ_C(100 MHz) 20.3 (s, CH_3), 128.3 (s, C-5), 140.6 (s, C-6), 141.9 (s, C-4a), 143.9 (s, C-2); *m/z* (EI$^+$) 158 (M$^+$, 100%), 143 (53); as compared to literature data.[23]

6-Chloroquinoxaline 7d. 4-Chlorophenylene-1,2-diamine (4.99 g, 35 mmol) and glyoxal (9.95 g, 35 mmol) gave after sublimation (vacuum sublimation oil bath temp. 45 °C/<1 mmHg), 6-chloroquinoxaline (4.55 g, 79%) as a white solid; mp 62–63 °C (lit.,[29] 63.8–64.3 °C); δ_H(400 MHz) 7.67 (1 H, dd, $^3J_{H7,H8}$ 9.0, $^4J_{H5,H7}$ 2.4, H-7), 8.00 (1 H, d, $^3J_{H7,H8}$ 9.0, H-8), 8.06 (1 H, d, $^4J_{H5,H7}$ 2.4, H-5), 8.78 (1 H, d, $^3J_{H2,H3}$ 1.6, H-2), 8.80 (1 H, d, $^3J_{H2,H3}$ 1.6, H-3); δ_C(100 MHz) 128.4 (s, C-5), 130.8 (s, C-7), 131.2 (s, C-8), 136.0 (s, C-6), 141.5 (s, C-8a), 143.2 (s, C-4a), 145.0 (s, C-2), 145.7 (s, C-3); *m/z* (EI$^+$) 164 (M$^+$, 100%), 137 (45), 110 (52); as compared to literature data.[29,30]

6,7-Dichloroquinoxaline 7e. 4,5-Dichlorophenylene-1,2-diamine (3.72 g, 21 mmol) and glyoxal (5.60 g, 21 mmol) gave after recrystallisation, 6,7-dichloroquinoxaline **7e** (3.26 g, 78%) as white lustrous needles; mp 209–210 °C (lit.,[31] 210 °C) (from acetone); δ_H(400 MHz) 8.25 (2 H, s, H-5), 8.85 (2 H, s, H-2); δ_C(100 MHz) 130.2 (s, C-5), 134.9 (s, C-6), 141.7 (s, C-4a), 145.9 (s, C-2); *m/z* (EI$^+$) 198 (M$^+$, 100%), 171 (44), 144 (52).

6-Nitroquinoxaline 7f. 4-Nitrophenylene-1,2-diamine (3.21 g, 21 mmol) and glyoxal (5.60 g, 21 mmol) gave after recrystallisation, 6-nitroquinoxaline **7f** (3.27 g, 89%) as white needles; mp 177–178 °C (lit.,[32] 177–179 °C) (from ethanol); δ_H(400 MHz) 8.27 (1 H, d, $^3J_{H7,H8}$ 9.2, H-8), 8.57 (1 H, dd, $^3J_{H7,H8}$ 9.2, $^4J_{H5,H7}$ 2.8, H-7), 9.02 (1 H, d, $^3J_{H2,H3}$ 8.0, H-2), 9.03 (1 H, d, $^3J_{H2,H3}$ 8.0, H-3), 9.04 (1 H, d, $^4J_{H5,H7}$ 2.8, H-5); δ_C(100 MHz) 123.5 (s, C-7), 126.0 (s, C-5), 131.4 (s, C-8), 141.9 (s, C-4a), 145.3 (s, C-8a), 147.0 (s, C-3), 147.7 (s, C-6), 147.8 (s, C-2); *m/z* (EI$^+$) 175 (M$^+$, 100%); as compared to literature data.[30]

Fluorination of quinoxalines

General procedure. Fluorination of quinoxalines followed the procedure described above. Pure fluoroquinoxalines **8a**–**f** and **9a**–**d** were isolated by column chromatography on silica gel using dichloromethane as eluent.

Quinoxaline 7a. Quinoxaline **7a** (3.90 g, 30 mmol), iodine (7.62 g, 30 mmol), triethylamine (3.03 g, 30 mmol) and fluorine (45 mmol) gave 2-fluoroquinoxaline **8a** (1.94 g, 48%, 91% conversion) as a pale yellow oil; bp[8] 120 °C; R_f 0.60 (Found: M$^+$, 148.0437. $C_8H_5FN_2$ requires M, 148.0437); δ_F(376 MHz) −74.40 (d, $^3J_{FH}$ 7.6); δ_H(400 MHz) 7.73 (1 H, pseudo t, $^3J_{HH}$ 6.8, H-6 or H-7), 7.77 (1 H, pseudo t, $^3J_{HH}$ 6.8, H-6 or H-7), 7.93 (1 H, d, $^3J_{H5,H6}$ 8.0, H-5), 8.13 (1 H, d, $^3J_{H7,H8}$ 8.0, H-8), 8.67 (1 H, d, $^3J_{FH}$ 7.6, H-3); δ_C(100 MHz) 128.1 (s, C-5), 129.1 (s, C-8 and C-6 or C-7), 131.3 (s, C-6 or C-7), 136.1 (d, $^2J_{CF}$ 42.5, C-3), 139.4 (d, $^3J_{CF}$ 10.6, C-8a), 141.2 (s, C-4a), 156.3 (d, $^1J_{CF}$ 256.0, C-2); *m/z* (EI$^+$) 148 (M$^+$, 100%), 129 (16); and, after column chromatography and sublimation (vacuum sublimation oil bath temp. 60 °C/<1 mmHg), 2,3-difluoroquinoxaline **9a** (0.50 g, 11%) as a white solid; mp 89–90 °C; R_f 0.82 (Found: C, 57.5; H, 2.3; N, 16.8. $C_8H_4F_2N_2$ requires: C, 57.8; H, 2.4; N, 16.9%); δ_F(235 MHz) −83.60 (s); δ_H(400 MHz) 7.79 (1 H, m, H-6), 7.99 (1 H, m, H-5); δ_C(100 MHz) 127.8 (s, C-5), 130.4 (s, C-6), 138.3 (m, C-4a), 146.1 (dd, $^1J_{CF}$ 263.7, $^2J_{CF}$ 39.8, C-2); *m/z* (EI$^+$) 166 (M$^+$, 100%), 76 (13). Quinoxaline **7a** (3.25 g, 25 mmol), iodine (6.35 g, 25 mmol), triethylamine (5.06 g, 50 mmol) and fluorine (75 mmol) gave 2,3-difluoroquinoxaline **9a** (1.07 g, 33%, 100% conversion) and 2-fluoroquinoxaline **8a** (0.30 g, 8%); spectral data as above.

6-Methylquinoxaline 7b. 6-Methylquinoxaline **7b** (4.12 g, 29 mmol), iodine (7.26 g, 29 mmol), triethylamine (2.89 g, 29 mmol) and fluorine (35 mmol) gave after sublimation (vacuum sublimation oil bath temp. 30 °C/<1 mmHg), an isomeric

mixture of 2-fluoro-6-methylquinoxaline **8b** (0.32 g, 16%) and 2-fluoro-7-methylquinoxaline **8c** (0.57 g, 29%, 43% conversion) as white needles; mp 61–63 °C; R_f 0.58 (Found: M^+, 162.0593 $C_9H_7FN_2$ requires M, 162.0593); 2-fluoro-6-methylquinoxaline **8b**; δ_F(376 MHz) −76.67 (d, $^3J_{FH}$ 7.5); δ_H(400 MHz) 2.59 (3 H, s, CH_3), 7.63 (1 H, dd, $^3J_{H7,H8}$ 8.3, $^4J_{H5,H7}$ 2.0, H-7), 7.78 (1 H, d, $^3J_{H7,H8}$ 8.3, H-8), 7.92 (1 H, br s, H-5), 8.65 (1 H, d, $^3J_{FH}$ 8.0, H-3); δ_C(100 MHz) 21.6 (s, CH_3), 127.6 (s, C-8), 128.1 (s, C-5), 133.6 (s, C-7), 134.6 (d, $^2J_{CF}$ 43.0, C-3), 137.6 (d, $^3J_{CF}$ 13.7, C-8a), 139.7 (s, C-4a), 141.3 (s, C-6), 156.2 (d, $^1J_{CF}$ 256.0, C-2); 2-fluoro-7-methylquinoxaline **8c**; δ_F(376 MHz) −75.45 (d, $^3J_{FH}$ 7.5); δ_H(400 MHz) 2.59 (3 H, s, CH_3), 7.58 (1 H, dd, $^3J_{H5,H6}$ 8.4, $^4J_{H6,H8}$ 1.6, H-6), 7.72 (1 H, br s, H-8), 8.03 (1 H, d, $^3J_{H5,H6}$ 8.3, H-5), 8.62 (1 H, d, $^3J_{FH}$ 8.0, H-3); δ_C(100 MHz) 21.8 (s, CH_3), 127.1 (s, C-8), 128.6 (s, C-5), 131.4 (s, C-6), 135.8 (d, $^2J_{CF}$ 42.3, C-3), 137.6 (d, $^3J_{CF}$ 13.7, C-8a), 139.7 (s, C-4a), 142.3 (s, C-7), 156.7 (d, $^1J_{CF}$ 255.1, C-2); *m*/*z* (EI^+) 162 (M^+, 100%), 135 (10); and 2,3-difluoro-6-methylquinoxaline **9b** (0.16 g, 7%) as a white solid; mp 81–82 °C; R_f 0.64 (Found: C, 59.75; H, 3.25; N, 15.4. $C_9H_6F_2N_2$ requires: C, 60.0; H, 3.4; N, 15.6%); δ_F(375 MHz) −83.20 (1 F, d, $^3J_{FF}$ 30.5, F-2 or F-3), −84.56 (1 F, d, $^3J_{FF}$ 30.5, F-2 or F-3); δ_H(400 MHz) 7.59 (1 H, dd, $^3J_{H7,H8}$ 8.8, $^4J_{H5,H7}$ 1.4, H-7), 7.74 (1 H, s, H-5), 7.85 (1 H, d, $^3J_{H7,H8}$ 8.4, H-8); δ_C(100 MHz) 21.7 (s, CH_3), 126.9 (s, C-5), 127.2 (s, C-8), 132.4 (s, C-7), 136.5 (d, $^3J_{CF}$ 6.1, C-4a or C-8a), 138.4 (d, $^3J_{CF}$ 6.1, C-4a or C-8a), 141.1 (s, C-6), 145.7 (dd, $^1J_{CF}$ 257.6, $^2J_{CF}$ 35.8, C-2 or C-3), 146.1 (dd, $^1J_{CF}$ 257.6, $^2J_{CF}$ 35.8, C-2 or C-3); *m*/*z* (EI^+) 180 (M^+, 100%).

6-Methylquinoxaline **7b** (1.56 g, 11 mmol), iodine (2.74 g, 11 mmol), triethylamine (2.18 g, 22 mmol) and fluorine (33 mmol) gave 2,3-difluoro-6-methylquinoxaline **9b** (0.32 g, 23%, 71% conversion) and fluoromethylquinoxaline **8b,c** (0.29 g, 16%); spectral data as above.

6,7-Dimethylquinoxaline 7c. 6,7-Dimethylquinoxaline **7c** (1.60 g, 10 mmol), iodine (2.57 g, 10 mmol), triethylamine (1.02 g, 10 mmol) and fluorine (15 mmol) gave after sublimation (vacuum sublimation oil bath temp. 60 °C/<1 mmHg) 2-fluoro-6,7-dimethylquinoxaline **8d** (0.31g, 40%, 75% conversion) as a white solid; mp 94–95 °C; R_f 0.54 (Found: C, 68.1; H, 5.0; N, 16.0. $C_{10}H_9FN_2$ requires: C, 68.15; H, 5.15; N, 16.0%); δ_F(235 MHz) −83.90 (s); δ_H(400 MHz) 2.42 (6 H, s, CH_3), 7.63 (1 H, s, H-5), 7.81 (1 H, s, H-8), 8.52 (1 H, d, $^3J_{FH}$ 6.4, H-3); δ_C(100 MHz) 20.2 (s, CH_3), 20.4 (s, CH_3), 127.2 (s, C-5), 128.2 (s, C-8), 134.7 (d, $^2J_{CF}$ 42.5, C-3), 138.2 (d, $^3J_{CF}$ 10.7, C-8a), 139.5 (d, $^4J_{CF}$ 3.1, C-4a), 140.2 (s, C-6 or C-7), 142.2 (s, C-6 or C-7), 156.4 (d, $^1J_{CF}$ 253.8, C-2); *m*/*z* (EI^+) 176 (M^+, 100%), 161 (100); and, after sublimation (vacuum sublimation oil bath temp. 50 °C/<1 mmHg), 2,3-difluoro-6,7-dimethylquinoxaline **9c** (0.07 g, 5%) as a white solid; mp 150–151 °C; R_f 0.61 (Found: C, 61.4; H, 4.0; N, 14.4. $C_{10}H_8F_2N_2$ requires: C, 61.6; H, 4.2; N, 14.4%); δ_F(376 MHz) −85.05 (s); δ_H(400 MHz) 2.47 (3 H, s, CH_3), 7.70 (1 H, s, H-5); δ_C(100 MHz) 20.3 (s, CH_3), 127.0 (s, C-5), 136.9 (t, $^3J_{CF}$ 5.3, $^4J_{CF}$ 5.3, C-4a), 140.9 (s, C-6), 145.7 (dd, $^1J_{CF}$ 249.5, $^2J_{CF}$ 39.1, C-2); *m*/*z* (EI^+) 194 (M^+, 52%), 179 (100).

6,7-Dimethylquinoxaline **7c** (1.79 g, 11 mmol), iodine (2.87 g, 11 mmol), triethylamine (2.28 g, 22 mmol) and fluorine (33 mmol) gave 2,3-difluoro-6,7-dimethylquinoxaline **9c** (0.23 g, 12%, 90% conversion) and, 2-fluoro-6,7-dimethylquinoxaline **8d** (0.24 g, 14%); spectral data as above.

6-Chloroquinoxaline 7d. 6-Chloroquinoxaline **7d** (1.76 g, 11 mmol), iodine (2.72 g, 11 mmol), triethylamine (1.08 g, 11 mmol) and fluorine (15 mmol) gave after sublimation (vacuum sublimation oil bath temp. 50 °C/<1 mmHg), an isomeric mixture of 6-chloro-2-fluoroquinoxaline **8e** (0.35 g, 28%) and 7-chloro-2-fluoroquinoxaline **8f** (0.20 g, 16%, 64% conversion) as white needles; mp 98–100 °C; R_f 0.53 (Found: C, 52.4; H, 2.1; N, 15.1. $C_8H_4ClFN_2$ requires: C, 52.7; H, 2.2; N, 15.4%); 6-chloro-2-fluoroquinoxaline **8e**; δ_F(376 MHz) −74.29 (d, $^3J_{FH}$ 7.6); δ_H(400 MHz) 7.75 (1 H, dd, $^3J_{H7,H8}$ 8.8, $^4J_{H5,H7}$ 2.4, H-7), 7.91 (1 H, d, $^3J_{H7,H8}$ 8.8, H-8), 8.15 (1 H, d, $^4J_{H5,H7}$ 2.4, H-5), 8.71 (1 H, d, $^3J_{FH}$ 7.6, H-3); δ_C(100 MHz) 128.5 (s, C-5), 129.5 (s, C-8), 132.6 (s, C-7), 135.3 (s, C-6), 137.4 (d, $^2J_{CF}$ 42.5, C-3), 137.7 (d, $^3J_{CF}$ 9.1, C-8a), 141.8 (s, C-4a), 156.7 (d, $^1J_{CF}$ 257.2, C-2); 7-chloro-2-fluoroquinoxaline **8f**; δ_F(376 MHz) −73.33 (d, $^3J_{FH}$ 7.5); δ_H(400 MHz) 7.71 (1 H, dd, $^3J_{H5,H6}$ 8.8, $^4J_{H6,H8}$ 2.4, H-6), 7.95 (1 H, d, $^4J_{H6,H8}$ 2.4, H-8), 8.09 (1 H, d, $^3J_{H5,H6}$ 8.8, H-5), 8.68 (1 H, d, $^3J_{FH}$ 8.0, H-3); δ_C(100 MHz) 127.4 (s, C-8), 130.6 (s, C-5 and C-6), 135.3 (s, C-7), 136.5 (d, $^2J_{CF}$ 42.5, C-3), 138.2 (d, $^3J_{CF}$ 11.0, C-8a), 140.1 (s, C-4a), 157.2 (d, $^1J_{CF}$ 257.9, C-2); *m*/*z* (EI^+) 182 (M^+, 100%) and, 6-chloro-2,3-difluoroquinoxaline **9d** (0.04 g, 3%) as a white solid; mp 89–90 °C; R_f 0.60 (Found: C, 48.1; H, 1.5; N, 13.9. $C_8H_3ClF_2N_2$ requires: C, 47.9; H, 1.5; N, 14.0%); δ_F(376 MHz) −80.88 (1 F, d, $^3J_{FF}$ 29.7, F-2 or F-3), 82.00 (1 F, d, $^3J_{FF}$ 29.7, F-2 or F-3); δ_H(400 MHz) 7.74 (1 H, dd, $^3J_{H6,H7}$ 8.8, $^4J_{H5,H7}$ 2.0, H-7), 7.92 (1 H, d, $^3J_{H7,H8}$ 8.8, H-8), 7.98 (1 H, d, $^3J_{H5,H7}$ 2.0, H-5); δ_C(100 MHz) 127.0 (s, C-5), 128.9 (s, C-8), 131.4 (s, C-7), 136.4 (s, C-6), 136.9 (d, $^3J_{CF}$ 7.1, C-4a or C-8a), 138.8 (d, $^3J_{CF}$ 7.1, C-4a or C-8a), 146.2 (dd, $^1J_{CF}$ 258.8, $^2J_{CF}$ 35.3, C-2 or C-3), 146.8 (dd, $^1J_{CF}$ 259.9, $^2J_{CF}$ 35.3, C-2 or C-3); *m*/*z* (EI^+) 200 (M^+, 100%).

6-Chloroquinoxaline **7d** (2.16 g, 14 mmol), iodine (3.43 g, 14 mmol), triethylamine (2.73 g, 28 mmol) and fluorine (42 mmol) gave 6-chloro-2,3-difluoroquinoxaline **9d** (0.50 g, 19%, 94% conversion) and, chlorofluoroquinoxaline **8e**,**f** (0.60 g, 25%); spectral data as above.

6,7-Dichloroquinoxaline. 6,7-Dichloroquinoxaline **7e** (1.52 g, 8 mmol), iodine (1.93 g, 8 mmol), triethylamine (0.82 g, 8 mmol) and fluorine (12 mmol) gave recovered starting material.

6-Nitroquinoxaline. 6-Nitroquinoxaline **7f** (0.70 g, 4 mmol), iodine (1.02 g, 4 mmol), triethylamine (0.41 g, 4 mmol) and fluorine (6 mmol) gave recovered starting material.

Alkoxylation of pyridines

General procedure. A solution consisting of pyridine (10.9 g, 137 mmol), an alcohol (0.43 mol) and $CFCl_2CF_2Cl$ (150 ml) was placed in a fluorination apparatus fitted with an overhead stirrer and a drying tube filled with soda lime. Elemental fluorine (165 mmol) as a 10% mixture in dry nitrogen was then passed through the stirred solution using narrow bore PTFE tubing at *ca*. 40 ml min^{-1}. After the fluorine had been added the solution was purged with dry nitrogen, poured into water (300 ml), neutralised with sodium bicarbonate and extracted with dichloromethane. The organic phase was dried ($MgSO_4$) and solvent was removed under reduced pressure. The crude product was analysed by GC-MS to determine the conversion of the reaction. Vacuum distillation gave pure alkoxy pyridine as colourless oils.

2-Ethoxypyridine 10a.[33] A colourless oil (4.0 g, 50%); bp[4] 36–37 °C (lit.,[33] bp[25] 64 °C); δ_H 1.1 (3 H, m, CH_3), 4.2 (2 H, m, CH_2), 6.5 (1 H, m, H-3), 6.6 (1 H, m, H-5), 7.3 (1 H, m, H-4), 7.9 (1 H, m, H-6); δ_C 14.6 (s, CH_3), 61.4 (s, CH_2), 111.1 (s, C-3), 116.4 (s, C-5), 138.4 (s, C-4), 146.9 (s, C-6), 164.0 (s, C-2); *m*/*z* (EI^+) 123 (M^+, 23%), 108 (85), 95 (42), 79 (70), 67 (100).

2-Methoxypyridine 10b.[33] A colourless oil (4.1 g, 54%); bp 140–142 °C (lit.,[33] 142 °C); δ_H 3.91 (3 H, s, CH_3), 6.71 (1 H, m, H-3), 6.80 (1 H, m, H-5), 7.49 (1 H, m, H-4), 8.15 (1 H, m, H-6); δ_C 53.5 (s, CH_3), 111.3 (s, C-3), 116.9 (s, C-5), 138.7 (s, C-4), 147.2 (s, C-6), 164.5 (s, C-2); *m*/*z* (EI^+) 109 (M^+, 72%), 108 (100), 79 (98), 52 (62).

2-*n*-Butoxypyridine 10c.[33] A colourless oil (6.4 g, 58%); bp[1] 47 °C (lit.,[34] 200 °C); δ_H 0.96 (3 H, t, $^3J_{HH}$ 7.2, CH_3), 1.47 (2 H, m, CH_2CH_3), 1.74 (2 H, m, CH_2CH_2O), 4.29 (2 H, t, $^3J_{HH}$ 6.5,

CH_2O), 6.71 (1 H, m, H-3), 6.81 (1 H, m, H-5), 7.52 (1 H, m, H-4), 8.14 (1 H, m, H-6); δ_C 13.9 (s, CH_3), 19.4 (s, CH_2CH_3), 31.3 (s, CH_2CH_2O), 65.7 (s, CH_2O), 111.1 (s, C-3), 116.6 (s, C-5), 138.5 (s, C-4), 146.9 (s, C-6), 164.1 (s, C-2); *m/z* (EI^+) 151 (M^+, 8%), 122 (27), 108 (40), 95 (100), 78 (62), 67 (90), 51 (17).

2-(2,2,2,-Trifluoroethoxy)pyridine 10d.[34] A colourless oil (3.8 g, 60%); bp[4] 41 °C; δ_H 4.76 (2 H, q, $^3J_{HF}$ 8.6, CH_2), 6.83 (1 H, m, H-3), 6.94 (1 H, m, H-5), 7.62 (1 H, m, H-4), 8.13 (1 H, m, H-6); δ_C 62.2 (q, $^2J_{CF}$ 35.0, CH_2O), 111.3 (s, C-3), 118.4 (s, C-5), 124.1 (q, $^1J_{CF}$ 275.0, CF_3), 139.4 (s, C-4), 146.8 (s, C-6), 162.0 (s, C-2); *m/z* (EI^+) 177 (M^+, 40%), 158 (28), 108 (90), 79 (100).

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