Polyhalogenated heterocyclic compounds. Part 42.[1] Fluorinated nitrogen heterocycles with unusual substitution patterns

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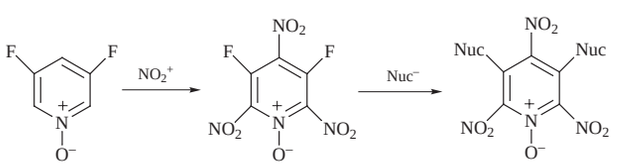
Reductive replacement of fluorine in 3,5-dichloro-2,4,6-trifluoropyridine 2a and pentafluoropyridine 2 using DIBAL and LAH leads to useful syntheses of fluoro and chlorofluoro pyridine derivatives. Replacement of fluorine by bromine using a mixture of HBr and $AlBr_3$ is extremely efficient, giving excellent routes to 2,4,6-tribromo-3,5-difluoropyridine 3. Bromofluoro-pyrimidine and -quinoxaline derivatives have also been efficiently synthesised from perfluorinated precursors. Catalytic hydrogenation of bromofluoro heterocycles gives high yields of the corresponding fluorinated heterocycles.

Reactions of nucleophiles with 3 gives surprising results. Soft nucleophiles, *e.g.* PhSNa displace bromine whereas hard nucleophiles, *e.g.* MeONa, displace fluorine.

There is a continuing search for explosives that have increased power and, equally important, reduced sensitivity. It has been noted that, because of their favourable elemental composition, heteroaromatic nitro compounds produce explosives having high performance.[2] Consequently, the aim of the work described in this paper was to provide fluorinated heterocycles with substitution patterns that have hitherto been unavailable, or difficult to obtain, in order to provide opportunities for synthetic manipulation. In particular, 3,5-difluoropyridine *N*-oxide should, in principle, undergo electrophilic nitration at the 2-, 4- and 6-positions, and then the remaining fluorinated sites should be strongly activated towards nucleophilic attack, *e.g.* by appropriate amines, as in Scheme 1.

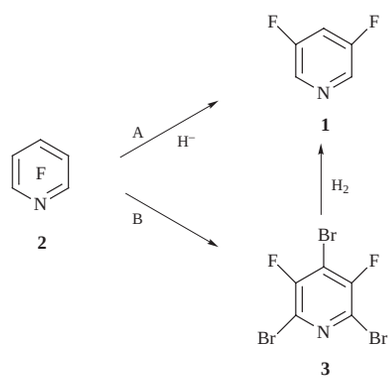


Scheme 1 Strategy for the synthesis of high energy compounds

Similar strategies could be followed for the synthesis of other aromatic nitrogen heterocycles having a high nitrogen content.

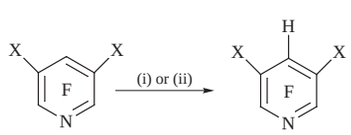
Results and discussion

We have been unable to find a description of the synthesis of 3,5-difluoropyridine **1** in the literature, although coordination compounds of **1** with platinum have been claimed[3] and 4-amino-3,5-difluoropyridine is included in a description of a drug synthesis.[4] Various methodologies were considered for synthesising **1**, including the Balz–Schiemann process[5] and the replacement of chlorine by fluorine using potassium fluoride (Halex process),[6] but these did not seem to offer viable routes to the required compound. Therefore we adopted a strategy of starting with the 3- and 5-carbon-fluorine bonds intact, as in pentafluoropyridine **2**, and then exploring routes to **1** which involve either direct replacement of fluorine by hydrogen, using nucleophilic reagents (Route A), or replacement of fluorine by bromine followed by catalytic hydrogenation (Route B), Scheme 2.



Scheme 2 Potential approaches to **1**

Reaction of **2** with diisobutylaluminium hydride (DIBAL) occurred only under vigorous conditions but was efficiently converted to 2,3,5,6-tetrafluoropyridine **4**, Scheme 3. The more



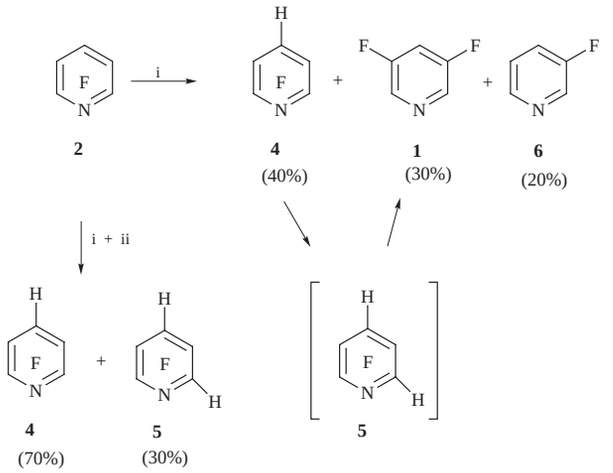
2 X = F (i)
2a X = Cl (ii)

4 X = F, 90%
4a X = Cl, >90%

Scheme 3 *Reagents and conditions*: i, DIBAL, diglyme, 100 °C, sealed tube; ii, DIBAL, CH_2Cl_2, RT

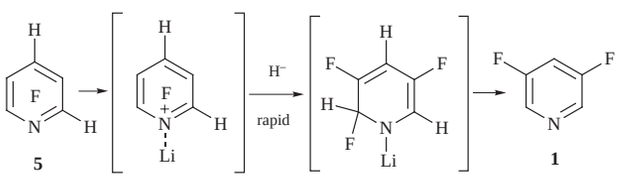
reactive 3,5-dichloro-2,4,6-trifluoropyridine **2a**[7] reacted in an analogous way but at room temperature to give **4a**. Thus, this approach now provides an efficient route to the 4-hydro derivatives, **4**[8] and **4a**,[9] but reaction is unlikely to proceed significantly further with **4** under realistic conditions.

Lithium aluminium hydride (LAH), Scheme 4, is a more



Scheme 4 *Reagents and conditions*: i, 2 equiv. $LiAlH_4$, Et_2O, 0 °C, 2 h, RT, 28 h; ii, 1.2 equiv. 12-C-4 polyether

vigorous reagent than DIBAL and reaction with **2**, even at 0 °C, proceeded through to 3-fluoropyridine **6**, together with **4** and the target difluoro derivative **1**. Surprisingly, none of the 2,4-dihydro-derivative **5** was detected in the product mixture, even though it must be an intermediate in the formation of **1** from **4**. It is well established[10] that initial attack on pentafluoropyridine **2** by most nucleophilic reagents occurs exclusively at the 4-position, followed by attack at the 2-position and hence the intermediacy of **5** is to be expected. However, it is not immediately apparent why **5** should react much faster than **4** or **1**, which must be the case in order for **5** to be absent from the product mixture. A probable explanation seems to be that lithium coordinates with the ring nitrogen in **5**, as shown in Scheme 5 and therefore selectively activates fluorine at the adjacent 2-position, Scheme 4, to further reaction.

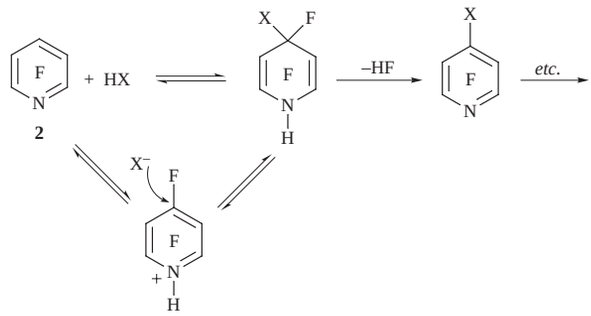


Scheme 5

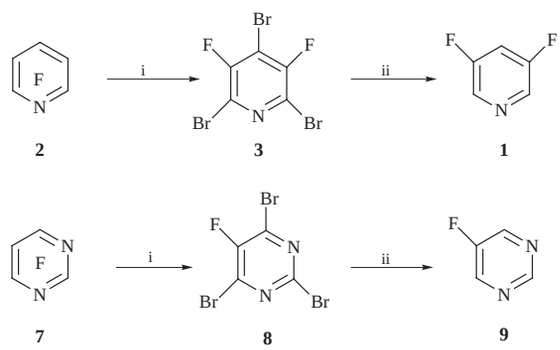
To confirm this hypothesis, we carried out an analogous reaction of pentafluoropyridine **2** with LAH in the presence of 12-crown-4 polyether in order to inhibit coordination of lithium to the ring nitrogen. Indeed, under these conditions, only 2,3,5,6-tetrafluoropyridine **4** and 2,3,5-trifluoropyridine **5** were obtained, therefore supporting the hypothesis.

The reactions of reducing agents with pentafluoropyridine described above have led to useful procedures for the preparation of various fluoropyridine derivatives, but this approach, as indicated in Route A, Scheme 2, had not achieved a viable synthesis of **1**. Consequently, we turned to Route B. Earlier work from these laboratories[11] showed that acid-induced exchange of fluorine in pentafluoropyridine **2**, for bromine, could be achieved to give **3**, albeit in only 30% yield and the process may be envisaged as that outlined in Scheme 6. However, we now find that heating **2** with a mixture of hydrogen bromide and aluminium tribromide, in an autoclave and in the absence of a solvent, gives high yields of 2,4,6-tribromo-3,5-difluoropyridine **3**. Similarly, tetrafluoropyrimidine **7** gives a good yield of 2,4,6-tribromopyrimidine **8**, under similar conditions, Scheme 7.

The next stage, catalytic reduction[8] of **3** or **8** proceeded very smoothly, giving essentially quantitative conversions of these tribromo derivatives to **1** and **9** respectively, although handling

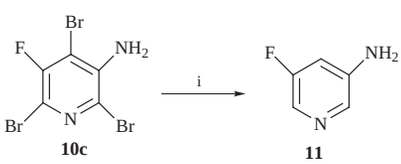


Scheme 6



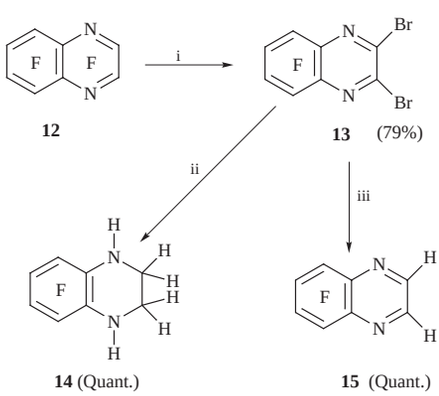
Scheme 7 *Reagents and conditions*: i, HBr, $AlBr_3$, 150 °C, Autoclave; ii, Pd/C, H_2 (4 Bar), Et_3N, CH_2Cl_2, RT

losses reduced the isolated yields. Similarly, the 3-amino derivative **10c** (see later) was converted quantitatively to **11**, Scheme 8.



Scheme 8 *Reagents and conditions*: Pd/C, H_2 (4 Bar), Et_3N, CH_2Cl_2, RT

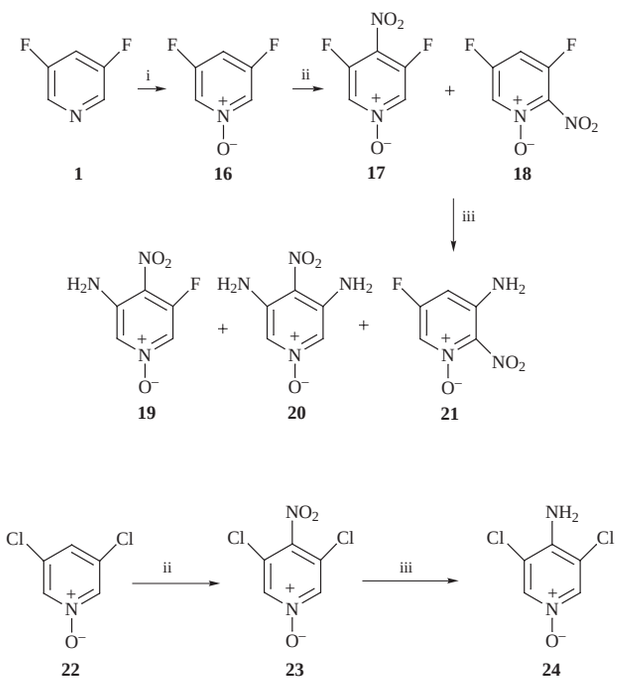
Hexafluoroquinoxaline **12** behaved slightly differently; the dibromo derivative **13** was formed in high yield simply by using hydrogen bromide, because **12** is a stronger base than pentafluoropyridine **2**,[12] and subsequent reduction of **13** over palladium gave the partially saturated product, **14**. However, tetrafluoroquinoxaline **15** was obtained quantitatively from **13**, using a Lindlar catalyst, Scheme 9.



Scheme 9 *Reagents and conditions*: i, HBr, CH_3CN, 70 °C; ii, H_2, Pd/C; iii, H_2, Lindlar cat.

The studies described above have provided viable routes to a range of hydrofluoro- and bromofluoro-heterocycles which are potentially functional systems and, following, are some preliminary studies on their reactions.

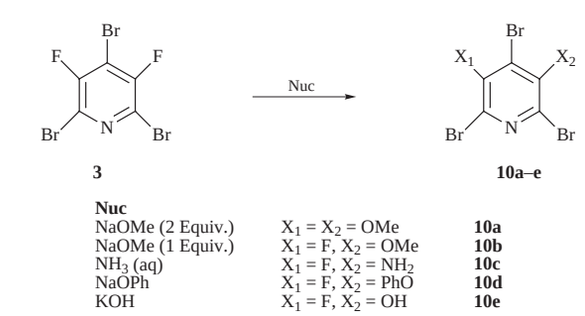
First, 3,5-difluoropyridine was converted into its *N*-oxide **16**, in order to activate the system to electrophilic attack, which was nitrated to give the 4-nitro derivative **17** as the major isomer, together with the 2-nitro isomer **18**. These compounds, now very reactive towards nucleophilic attack, were then treated with ammonia to give the amino derivatives **19**, **20** and **21** resulting from *the exclusive replacement of fluorine*, Scheme 10. Thus, the strategic value of starting with 3,5-difluoropyridine was demonstrated because when we carried out a corresponding series of reactions starting with 3,5-dichloropyridine **22**, then treatment of the derived nitro-compound **23** with ammonia resulted in *exclusive replacement of the nitro group*, giving the amino derivative **24**, Scheme 10.



Scheme 10 *Reagents and conditions*: i, CH_3CO_3H, $CHCl_3$; ii, fuming H_2SO_4–HNO_3; iii, NH_3, CH_3CN

These results are consistent with the established understanding that, in nucleophilic aromatic substitution of relatively reactive systems, the mobility order is $F > NO_2 > Cl$.[13–15] Clearly, the amino nitro derivative **20** is now activated towards further nitration and the strategy outlined in Scheme 1 is clearly available for the synthesis of new high energy compounds, although their preparation is outside the scope of the present study.

Reactions of the tribromo derivative **3** with nucleophiles provided some surprises and the results are summarised in Schemes 11 and 12. Harder nucleophiles *e.g.* NaOMe, and aqueous

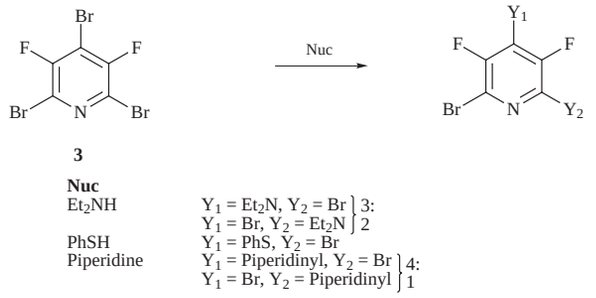


Nuc		
NaOMe (2 Equiv.)	$X_1 = X_2 = OMe$	**10a**
NaOMe (1 Equiv.)	$X_1 = F, X_2 = OMe$	**10b**
NH_3 (aq)	$X_1 = F, X_2 = NH_2$	**10c**
NaOPh	$X_1 = F, X_2 = PhO$	**10d**
KOH	$X_1 = F, X_2 = OH$	**10e**

Preferential replacement of F (Hard nucleophiles)

Scheme 11

ammonia, gave *exclusive displacement of fluorine* (Scheme 11), in spite of the activating influence of the ring nitrogen on the brominated sites. However, softer nucleophiles *e.g.* Et_2NH, PhSNa *etc*. gave *exclusive displacement of bromine* (Scheme 12). This is a remarkable observation arising from the nature of the nucleophile and we are unable to attribute this selectivity to any effect other than the well known preference of hard nucleophiles to attack hard centres (C–F) and soft nucleophiles to attack soft centres (C–Br).[16,17]

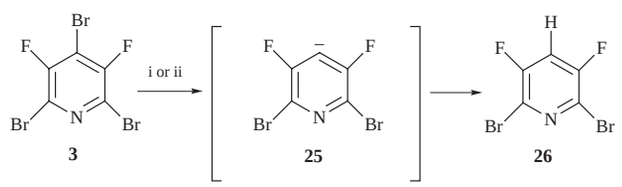


Nuc		
Et_2NH	$Y_1 = Et_2N, Y_2 = Br$	3:
	$Y_1 = Br, Y_2 = Et_2N$	2
PhSH	$Y_1 = PhS, Y_2 = Br$	
Piperidine	Y_1 = Piperidinyl, $Y_2 = Br$	4:
	$Y_1 = Br, Y_2$ = Piperidinyl	1

Preferential replacement of Br (Soft nucleophiles)

Scheme 12

Surprisingly, halophilic reactions of **3**, Scheme 13, occurred

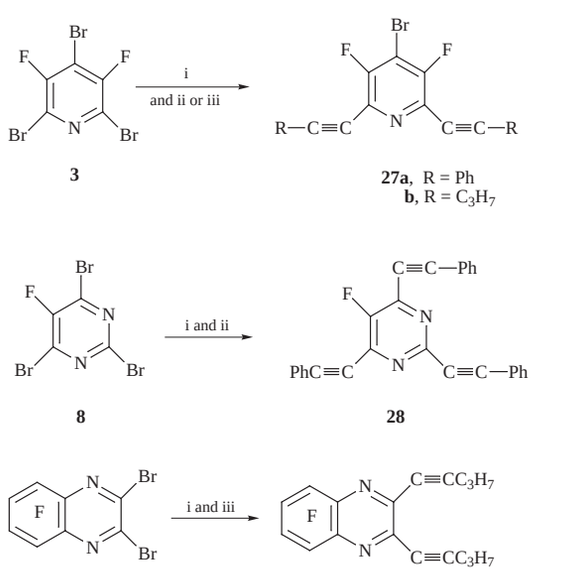


Scheme 13 *Reagents and conditions*: i, $NaNH_2$, CH_3CN, reflux; ii, 1-(trimethylsilyloxy)cyclohexene, KF, CH_3CN, 60 °C

both with sodium amide and with the enolate anion derived from cyclohexanone; in each case only *reduction* occurred, giving **26** as the sole product, *via* **25**. In principle **26** could be obtained *via* a SET process but when reactions were carried out in the dark and also with the addition of dinitrobenzene, no change in the reaction products could be discerned.

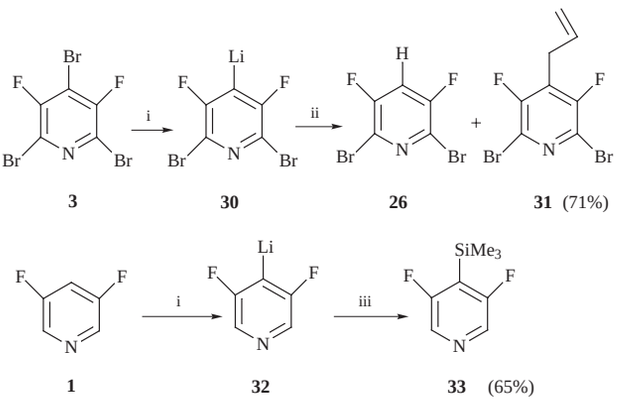
Displacement of bromine in bromofluoroheterocycles **3**, **8** and **13** was found to occur readily in palladium-induced processes. Thus, reaction with phenylacetylene or pent-1-yne and **3** resulted in the selective displacement of 2- and 6-bromine atoms, which suggests a directing role by the ring nitrogen. Additional examples are shown in Scheme 14.

In contrast, with butyllithium, lithium–bromine exchange occurred readily with **3**, exclusively at the 4-position, giving the



Scheme 14 *Reagents and conditions*: i, CuI, $(Ph_3P)_3PdCl_2$, Et_3N; ii, PhC≡CH; iii, $C_3H_7C{\equiv}CH$

lithium derivative **30** [δ_F −87.5 (s); *cf.* −103.17 (s) for **3**] which decomposed only slowly at room temperature. Reaction of **30** with allyl bromide gave a mixture containing the 4-allyl derivative **31** as the major product, together with a smaller amount of the 4-hydro-derivative **26**, Scheme 15.



Scheme 15 *Reagents and conditions*: i, BuLi, Et_2O, −78 °C; ii, CH_2=$CHCH_2Br$, −78 °C to RT; iii, Me_3SiCl, −78 °C to RT

When 3,5-difluoropyridine **1** was treated with butyllithium, hydrogen–lithium exchange occurred, again exclusively at the 4-position to give **32** as demonstrated by conversion to the silyl derivative **33** (Scheme 15). A solution of the lithio-derivative **32**, showed a single resonance at δ_F −94.5 in its NMR spectrum, compared to a value of δ_F −124.1 for the starting material **1**.

These preliminary experiments demonstrate that the halogenated heterocyclic compounds described in this paper are indeed very useful synthons for further application.

Experimental

All starting materials were obtained commercially and used as received. ^{19}F and ^{1}H NMR spectra were recorded using either a Bruker AC 250, a Varian VXR 400S, or a Bruker AMX 500 spectrometer. ^{13}C NMR spectra were recorded using either a Varian VXR 400S or a Bruker AMX 500 spectrometer. [Unless stated otherwise, all spectra were run in $CDCl_3$, chemical shifts are measured in ppm from $CFCl_3$ (^{19}F) or $SiMe_4$ (^{1}H) and coupling constants, *J*, are given in Hz.] Infrared spectra were recorded on a Perkin-Elmer 1600 FTIR spectrometer using KBr discs (solid samples) or thin films between two KBr plates (liquid samples). GLC mass spectra were obtained using a VG Trio 1000 spectrometer linked to a Hewlett Packard 5890 Series II gas chromatograph fitted with a 25 m cross-linked silicone elastomer (SE 30) capillary column. Carbon, hydrogen and nitrogen elemental analyses were obtained using a Carlo Erba 440 Elemental Analyser.

Reactions of pentafluoropyridine 2

With lithium aluminium hydride. Lithium aluminium hydride (2.0 g, 53 mmol), pentafluoropyridine **2** (4.2 g, 25 mmol) and diethyl ether (40 cm^3) were stirred, under nitrogen, initially at 0 °C, then at room temperature for 28 h before dilute sulfuric acid was added slowly at 0 °C. The mixture was filtered and solvent was removed at reduced pressure to yield a liquid (2.0 g) which was shown to consist of 2,3,5,6-tetrafluoropyridine **4**[8] (40%), 3,5-difluoropyridine **1** (30%) and 3-fluoropyridine **6** (20%), identified by comparing their fluorine NMR spectra and GC–MS chromatographs against authentic samples (see later).

With lithium aluminium hydride and 12-crown-4 polyether. A solution of pentafluoropyridine **2** (0.6 g, 3.6 mmol) in diethyl ether (5 cm^3) was added to a mixture of lithium aluminium hydride (5 cm^3, 5 mmol of 1.0 M solution in diethyl ether) and 12-crown-4 polyether (1.0 g, 5.7 mmol) in diethyl ether (10 cm^3) at 0 °C, with stirring, under an atmosphere of dry nitrogen. The mixture was stirred at 0 °C for 10 min, then at room temperature for 19 h. Iced water was then added and the mixture extracted into diethyl ether. The extracts were dried ($MgSO_4$), evaporated and were shown by GC to contain two compounds which were isolated by preparative scale GC. (10% SE 30, 40 °C); (i) 2,3,5,6-tetrafluoropyridine **4**[8] (70%) (Found: C, 39.8; H, 0.6; N, 9.3. C_5HF_4N requires C, 39.7; H, 0.7; N, 9.3%); δ_H(400 MHz) 7.60 (t, $^3J_{HF}$ 7.2); δ_C(100 MHz) 119.01 (tt, $^2J_{CF}$ 20.3, $^3J_{CF}$ 3.0, 4-*C*H), 143.33 (d, $^1J_{CF}$ 245.1, 3-*C*F), 141.62 (dm, $^1J_{CF}$ 260.5, 2-*C*F); δ_F(376 MHz) −91.11 (2F, s, 2-C*F*), −139.93 (2F, A part of AA′MM′X, 3-C*F*); *m*/*z* 151 (M$^+$, 100%), and (ii) 2,3,5-trifluoropyridine **5**[18] (30%) (Found: C, 44.9; H, 1.3; N, 10.5. Calc. for $C_5H_2F_3N$: C, 45.1; H, 1.5; N, 10.5%); ν_{max}/cm^{-1} 1649, 1605, 1471, 1295, 1256, 1192, 1159; δ_H(400 MHz) 7.87 (1H, s, 6-C*H*), 7.40 (1H, ABdd, J_{AB} 15.2, 7.6, $^4J_{HF}$ and $^4J_{HH}$ 2.4, 1.2, 4-C*H*); δ_C(100 MHz) 115.35 (ddd, $^2J_{CF}$ 17.9, 24.0, $^3J_{CF}$ 3.4, 2-*C*H), 128.51 (ddd, $^3J_{CF}$ 13.7, $^2J_{CF}$ 26.8, $^4J_{CF}$ 5.9, 4-*C*H), 144.65 (ddd, $^1J_{CF}$ 266.6, $^2J_{CF}$ 31.7 and $^3J_{CF}$ 7.2, 5-*C*F), 147.95 (dd, $^1J_{CF}$ 235.9, $^2J_{CF}$ 14.1, 6-*C*F), 156.43 (d, $^1J_{CF}$ 256.3, 3-*C*F); δ_F(376 MHz) −89.66 (1F, t, $^3J_{FF}$ 25.6, 2-C*F*), −127.37 (1F, ddd, $^5J_{FF}$ 29.4, $^3J_{FH}$ 7.2 and $^3J_{FF}$ 3.0, 3-C*F*), −134.16 (1F, ddd, $^3J_{FH}$ 26.0, $^3J_{FH}$ 8.7 and $^4J_{FF}$ 3.0, 5-C*F*); *m*/*z* 133 (M$^+$, 100%).

With diisobutylaluminium hydride. A Carius tube was charged with pentafluoropyridine **2** (1.0 g, 6.mmol), DIBAL (10 cm^3, 10 mmol of 1.0 M solution in DCM) and diglyme (10 cm^3). The DCM distilled off at reduced pressure and the tube was heated at 100 °C for 24 h. The tube was cooled, and transfer under reduced pressure gave 2,3,5,6-tetrafluoropyridine **4** (0.7 g, 77%).

Preparation of 3,5-dichloro-2,6-difluoropyridine 4a

3,5-Dichlorotrifluoropyridine **2a** (3.0 g, 15 mmol) was added to a solution of diisobutylaluminium hydride (DIBAL) (30 cm^3, 30 mmol of 1.0 M solution in dichloromethane) in dry diethyl ether (30 cm^3) at 0 °C, under nitrogen, with stirring. After 68 h the mixture was cooled to 0 °C and dilute sulfuric acid added slowly. This was filtered and the product was extracted with dichloromethane (DCM). The DCM solution was dried ($MgSO_4$) and evaporated to dryness giving 3,5-dichloro-2,6-difluoropyridine **4a**[9] (2.4 g, 90%) (Found: C, 32.1; H, 0.39. $C_5HCl_2F_2N$ requires C, 32.6; H, 0.54%); ν_{max}/cm^{-1} 3081–2668, 1585, 1443, 1409, 1376, 1307, 1261, 1104, 903, 765, 730; δ_H(400 MHz) 7.99 (t, $^4J_{HF}$ 7.6); δ_C(100 MHz) 154.52 (dd, $^1J_{CF}$ 247.0, $^3J_{CF}$ 13.0, 2,6-*C*F), 143.82 (t, $^3J_{CF}$ 1.9, 4-*C*H), 113.76 (dd, $^2J_{CF}$ 37.5 and $^4J_{CF}$ 2.5, 3,5-*C*Cl); δ_F(376 MHz) −72.32 (d, $^4J_{FH}$ 6.0); *m*/*z* 183 (M$^+$, 100%).

Synthesis of bromofluoroheterocycles

2,4,6-Tribromo-3,5-difluoropyridine 3. A Hastalloy autoclave (equipped with a copper gasket and an Inconel bursting disc) was charged with aluminium bromide (50.0 g, 187 mmol), pentafluoropyridine **2** (20.0 g, 118 mmol) and hydrogen bromide (25.0 g, 309 mmol). The autoclave was heated at 150 °C for 84 h, cooled, then excess gaseous hydrogen bromide was neutralised by release through a column of soda lime. The autoclave was opened and ice water cautiously added to the solid contents. This mixture was extracted with DCM, and the dried extracts were evaporated to give 2,4,6-tribromo-3,5-difluoropyridine **3**[11] (38.0 g, 91%), mp 110–111 °C [from DCM–light petroleum (bp 40–60 °C), 1:1] (lit.,[11] 105.5–106.5 °C) (Found: C, 17.3; N, 4.1. Calc. for $C_5Br_3F_2N$: C, 17.0; N, 4.0%); ν_{max}/cm^{-1} 1559, 1419, 1388, 1347, 1131, 1053, 771, 700, 651, 548; δ_C(100 MHz) 110.08 (t, $^2J_{CF}$ 24.0, 4-*C*Br), 122.54 (X part of ABX, 2-*C*Br), 153.64 (dd, $^1J_{CF}$ 263.6 and 1.11, 3- or 5-*C*F); δ_F(376 MHz) −103.17 (s); *m*/*z* 355 (M$^+$, 32%), 353 (97), 351 (100), 349 (34).

2,4,6-Tribromo-5-fluoropyrimidine 8. The above procedure was followed except that tetrafluoropyrimidine **7** (10.9 g, 72 mmol), aluminium bromide (25.0 g, 94 mmol) and anhydrous hydrogen bromide (8.0 g, 100 mmol) were used and the vessel was heated for 43 h. The crude solid product was recrystallised from toluene to give 2,4,6-*tribromo*-5-*fluoropyrimidine* **8** (19.0 g,

57 mmol, 79%), mp 133 °C (Found: C, 14.4; H, 0. $C_4Br_3FN_2$ requires C, 14.3; H, 0%); ν_{max}/cm^{-1} 1507, 1375, 1359, 1284, 1201, 851, 753, 676, 619; δ_C($CDCl_3$) 140.36 (d, $^2J_{CF}$ 23.6, 4-*C*Br), 143.44 (d, $^4J_{CF}$ 7.2, 2-*C*Br), 153.53 (d, $^1J_{CF}$ 268.6, 5-*C*F); δ_F(376 MHz) −114.91 (s); *m*/*z* 338 (M^+, 32%), 336 (97), 334 (100), 332 (34).

2,3-Dibromo-5,6,7,8-tetrafluoroquinoxaline 13. A Carius tube containing hexafluoroquinoxaline **12** (1.1 g, 4.6 mmol), acetonitrile (3 cm^3) and hydrogen bromide (1.8 g, 23 mmol) was heated in a rotating oil bath at 75 °C for 42 h. The mixture was added to dilute aqueous sodium hydrogen carbonate (20 cm^3) and extracted into DCM. The DCM solution was dried ($MgSO_4$) and evaporated to give 2,3-*dibromo*-5,6,7,8-*tetrafluoroquinoxaline* **13** (1.3 g, 79%), mp 96 °C (from DCM) (Found: C, 26.4; N, 7.9. $C_8Br_2F_4N_2$ requires C, 26.7; N, 7.8%); ν_{max}/cm^{-1} 1669, 1534, 1505, 1485, 1434, 1338, 1249, 1166, 1145, 1049, 769, 644, 570, 455; δ_C(125.8 MHz) 127.89 (m, 4a-*C*), 140.91 (dm, $^1J_{CF}$ 262.9, 5- or 6-*C*F), 142.03 (dm, $^1J_{CF}$ 257.8, 5- or 6-*C*F), 143.44 (s, 2-*C*Br); δ_F(235 MHz) −149.15 (1 F, s), −149.50 (1 F, s); *m*/*z* 362 (M^+, 61%), 360 (96), 358 (62), 52 (100).

General procedure for the catalytic hydrogenation of bromofluoro heterocycles

A solution of the substrate in DCM was stirred with activated carbon and filtered. A palladium catalyst (5% Pd/C unless otherwise stated) and triethylamine were added to the filtrate and the mixture hydrogenated on a Parr apparatus at 4 Bar. The mixture was filtered, water added and extracted into DCM.

Hydrogenation of 2,4,6-tribromo-3,5-difluoropyridine 3. 2,4,6-Tribromo-3,5-difluoropyridine **3** (34.0 g, 97 mmol), DCM (200 cm^3), palladium catalyst (3.4 g) and triethylamine (45 cm^3, 31.5 g, 312 mmol) were hydrogenated for 21 h. Distillation of the DCM solution on Fischer–Spaltrohr apparatus gave 3,5-*difluoropyridine* **1** (7.0 g, 61 mmol, 63%), bp 92.5 °C (Found: C, 52.2; H, 3.0; N, 12.2. $C_5H_3F_2N_2$ requires C, 52.2; H, 3.0; N, 12.2%); ν_{max}/cm^{-1} 3065, 2974, 1593, 1489, 1467, 1434, 1287, 1221, 1133, 1024, 973, 875, 691; δ_H(250 MHz) 7.22 (1H, tt, $^3J_{HF}$ 8.8, $^4J_{HH}$ 2.3, 4-C*H*), 8.37 (2H, d, $^3J_{HF}$ 2.0, 2,6-C*H*); δ_C(100 MHz) 111.14 (t, $^2J_{CF}$ 21.1, 4-*C*H), 134.21 (4 lines showing X part of ABX, 2-*C*H), 159.07 (dd, $^1J_{CF}$ 261.7, $^3J_{CF}$ 5.7, 3-*C*F); δ_F(235 MHz) −124.11 (s); *m*/*z* 115 (M^+, 100%).

Hydrogenation of 2,4,6-tribromo-5-fluoropyrimidine 8. 2,4,6-Tribromo-5-fluoropyrimidine **8** (9.7 g, 30 mmol), DCM (30 cm^3), tri-*n*-butylamine (21 cm^3, 17 g, 90 mmol) and the catalyst (1.0 g) were hydrogenated for 24 h giving 5-fluoropyrimidine **9** (100% conversion). A sample of 5-fluoropyrimidine was obtained by preparative scale GLC (10% SE 30, 40 °C) and identified by comparison of its proton and fluorine NMR spectra with published data;[19] δ_H(250 MHz) 8.64 (2H, s, 4,6-C*H*), 9.08 (1H, d, $^5J_{HF}$ 3.3, 2-C*H*) [lit.,[19] 8.71 (2H, d, $^3J_{FH}$ 0.8), 9.14 (1H, d, $^5J_{FH}$ 3.5)]; δ_C(100 MHz) 144.83 (d, $^2J_{CF}$ 19.5, 4,6-*C*H), 154.77 (d, $^4J_{CF}$ 6.1, 2-*C*H), 157.86 (d, $^1J_{CF}$ 266.6, 5-*C*F); δ_F(235 MHz) −137.4 (s) [lit.,[19] −135.2 (d, $^5J_{FH}$ 3.5)]; *m*/*z* 98 (M^+, 100%).

Hydrogenation of 2,3-dibromo-5,6,7,8-tetrafluoroquinoxaline 13 (with Pd catalyst). 2,3-Dibromo-5,6,7,8-tetrafluoroquinoxaline **13** (1.3 g, 3.6 mmol), palladium catalyst (0.1 g), triethylamine (1 cm^3) and DCM (20 cm^3) were hydrogenated for 64 h. The DCM solution was dried ($MgSO_4$), evaporated to dryness and recrystallised from chloroform to give 1,2,3,4-tetrahydro-5,6,7,8-tetrafluoroquinoxaline **14**[20] (0.9 g, >95%), mp 137–138 °C (from chloroform) (lit.,[20] 148–150 °C) (Found: C, 46.3; H, 3.2. $C_8H_6F_4N_2$ requires C, 46.6; H, 3.2%); ν_{max}/cm^{-1} 3407, 2946, 2895, 1523, 1432, 1307, 1234, 1047, 926; δ_H(250 MHz) 3.42 (2H, s), 3.79 (1H, s); δ_C(100 MHz) 118.70 (m, 9-*C*), 133.50 (dm, $^1J_{CF}$ 240.4, 5- or 6-*C*F), 136.41 (dm, $^1J_{CF}$ 241.4, 5- or 6-*C*F), 40.32 (s, 2-*C*H); δ_F(235 MHz) −167.16 (1F, s), −175.72 (1F, s); *m*/*z* 206 (M^+, 100%).

Hydrogenation of 2,3-dibromo-5,6,7,8-tetrafluoroquinoxaline 13 (with Lindlar catalyst). 2,3-Dibromo-5,6,7,8-tetrafluoroquinoxaline **13** (0.6 g, 1.7 mmol), Lindlar catalyst (0.1 g), triethylamine (1 cm^3) and DCM (30 cm^3) were hydrogenated for 120 h. The DCM solution was dried ($MgSO_4$), evaporated to dryness, sublimed, and recrystallised from ethyl acetate to give 5,6,7,8-tetrafluoroquinoxaline **15**[21] (0.15 g, 44%), mp 89 °C (from chloroform) (lit.,[21] 90–91 °C); ν_{max}/cm^{-1} 1500, 1054; δ_H(200 MHz) 8.93 (d, $^3J_{HH}$ 5.4); δ_C(100 MHz) 130.0 (s, 5-*C*), 141.4 (dm, $^1J_{CF}$ 262.5, 6- and 7-*C*F), 145.8 (s, 2-*C*H); δ_F(376 MHz) −151.65 (m); *m*/*z* 202 (M^+, 69%), 148 (100).

Hydrogenation of 3-amino-2,4,6-tribromo-5-fluoropyridine 10c. 3-Amino-2,4,6-tribromo-5-fluoropyridine **10c** (0.9 g, 2.6 mmol), triethylamine (1.1 cm^3, 7.9 mmol), palladium catalyst (0.1 g) and DCM (15 cm^3) were hydrogenated for 18 h. The DCM solution was dried ($MgSO_4$) and evaporated giving 3-*amino*-5-*fluoropyridine* **11** (0.3 g, >95%), mp 86 °C (from DCM) (Found: C, 53.6; H, 4.6; N, 25.0. $C_5H_5FN_2$ requires C, 53.6; H, 4.5; N, 25.0%); ν_{max}/cm^{-1} 3335, 3146, 1605, 1582, 1336, 1295, 1265, 1184, 1167, 1021, 872, 847, 691, 527, 460; δ_H(250 MHz) 3.84 (2 H, br s, NH_2), 6.70 (1 H, dd, $^3J_{HF}$ 10.3 and $^4J_{HH}$ 2.2, 4-C*H*), 7.87–7.90 (2 H, 3 lines, 2- and 6-C*H*); δ_C(100 MHz) 108.19 (d, $^2J_{CF}$ 21.0, 4-*C*H), 127.51 (d, $^2J_{CF}$ 23.6, 2-*C*H), 133.25 (s, 6-*C*H), 144.00 (d, $^3J_{CF}$ 6.1, 5-*C*NH_2), 160.12 (d, $^1J_{CF}$ 254, 3-*C*F); δ_F(235 MHz) −128.34 (s); *m*/*z* 113 (M^+, 100%).

Preparation of *N*-oxides

Preparation of 3,5-difluoropyridine *N*-oxide 16. A solution of **1** (0.37 g, 3 mmol), peracetic acid (1.5 cm^3 of a 40% solution in acetic acid) in acetic acid (5 cm^3) and chloroform (10 cm^3) was heated at 50 °C, with stirring, for 24 h. The mixture was neutralised by the addition of dilute aqueous sodium hydroxide to the chilled mixture, then remaining peroxides were destroyed by the addition of sodium metabisulfite (2 g). Following extraction into DCM, the solution was dried ($MgSO_4$) and evaporated to dryness giving a solid which was recrystallised from DCM–light petroleum (1 : 1) to yield 3,5-*difluoropyridine* N-*oxide* **16** (0.3 g, 71%), mp 136.5 °C (Found: C, 45.5; H, 2.3. $C_5H_3F_2NO$ requires C, 45.8; H, 2.3%); ν_{max}/cm^{-1} 3099, 3042, 1638, 1626, 1574, 1533, 1458, 1181, 1143, 1019, 996, 869, 835, 666, 607, 517; δ_H(250 MHz) 6.95 (1H, t, $^3J_{HF}$ 7.9, 4-C*H*), 8.05 (2H, s, 2-C*H*); δ_C(100 MHz) 103.58 (t, $^2J_{CF}$ 23.8, 4-*C*H), 126.98 (d, $^2J_{CF}$ 36.9, 2-*C*H), 160.25 (dd, $^1J_{CF}$ 254.1, $^3J_{CF}$ 15.3, 3-*C*F); δ_F(235 MHz) −118.2 (s); *m*/*z* 131 (M^+, 100%).

Preparation of 3,5-dichloropyridine *N*-oxide 22. The method for the preparation of **16** was followed, except that 3,5-dichloropyridine (7.5 g, 51 mmol), chloroform (50 cm^3) and peracetic acid (39 cm^3) gave, after 67 h, 3,5-*dichloropyridine* N-*oxide* **22** (8.0 g, 96%), mp 111.0 °C (from DCM) (Found: C, 36.3; H, 1.7; N, 8.1. $C_5H_3Cl_2NO$ requires C, 36.6; H, 1.8; N, 8.5%); ν_{max}/cm^{-1} 3109, 3050, 3010, 1592, 1540, 1448, 1406, 1271, 1132, 1109, 1089, 1007, 969, 892, 837, 821, 663, 557, 539, 435; δ_H(200 MHz) 8.16 (2 H, d, $^4J_{HH}$ 1.6, 2-C*H*), 7.31 (1 H, t, $^4J_{HH}$ 1.2, 4-C*H*); δ_C(100 MHz) 125.95 (s, 2-*C*H), 133.21 (s, 4-*C*H), 137.34 (s, 3-*C*Cl); *m*/*z* 165 (M^+, 57%), 163 (92), 73 (100).

Nitration of *N*-oxides

Nitration of 3,5-difluoropyridine *N*-oxide 16. 3,5-Difluoropyridine *N*-oxide **16** (2.0 g, 15.2 mmol) was added to a mixture of fuming sulfuric acid (15 cm^3) and fuming nitric acid (10 cm^3) at 0 °C, with stirring. The mixture was heated at 100 °C for 4 h, then added to iced water (10 cm^3) and neutralised with aqueous sodium hydrogen carbonate. The mixture was continuously extracted into DCM, after which the DCM solution was dried ($MgSO_4$) and evaporated. Column chromatography (DCM–ethyl acetate) on silica gel gave **16** (0.25 g, 13%), 3,5-*difluoro*-4-*nitropyridine* N-*oxide* **17** (0.75 g, 32% based on 87% conversion), mp 124 °C (Found: C, 34.2; H, 1.2; N, 15.9. $C_5H_2F_2N_2O_3$ requires C, 34.1; H, 1.1; N, 15.9%); ν_{max}/cm^{-1} 3125, 3025, 1633, 1580, 1520, 1335, 1189, 1076, 858, 639; δ_H(300.1 MHz) 8.14 (d, $^3J_{HH}$ 3.8); δ_C(100.58 MHz) 153.02 (d, $^1J_{CF}$ 267.8, 3-*C*F), 128.33 (d, $^2J_{CF}$ 34.7, 2-*C*H), 104.16 (t, $^2J_{CF}$ 23.0, 4-*C*NO_2);

δ_F(235 MHz) −128.12 (s); *m*/*z* 176 (M^+, 44%), 75 (100) and 3,5-difluoro-2-nitropyridine *N*-oxide **18** (0.07 g, 3% based on 87% conversion); δ_H(250 MHz) 8.24 (2 H, d, $^3J_{HF}$ 2.3, 2-C*H*), 7.55 (1 H, ddd, $^3J_{HF}$ 8.7 and 7.2 and $^4J_{HH}$ 2.3, 4-C*H*); δ_C(100.58 MHz) 116.14 (dd, $^2J_{CF}$ 21.7 and 22.1, 4-*C*H), 132.71 (dd, $^3J_{CF}$ 25.9 and $^4J_{CF}$ 4.9, 2-*C*H), 141.80 (s, 6-*C*NO_2), 152.50 (dd, $^1J_{CF}$ 281.5 and $^3J_{CF}$ 8.0, 3-*C*F), 161.82 (dd, $^1J_{CF}$ 271.6 and $^3J_{CF}$ 4.9, 5-*C*F); δ_F(235 MHz) −111.58 (1 F, s), −115.83 (1 F, s).

Nitration of 3,5-dichloropyridine *N*-oxide 22. The procedure for the preparation of **17** and **18** was followed, except that 3,5-dichloropyridine *N*-oxide **22** (1.0 g, 6.1 mmol) after 5 h, gave 3,5-*dichloro*-4-*nitropyridine* N-*oxide* **23** (0.9 g, 71%), mp 141 °C (from $CHCl_3$) (Found: C, 28.6; H, 0.9; N, 13.1. $C_5H_2Cl_2N_2O_3$ requires C, 28.7; H, 1.0; N, 13.4%); ν_{max}/cm^{-1} 3116, 3047, 2992, 1581, 1549, 1423, 1353, 1297, 1172, 1067, 843, 636; δ_H(250 MHz) 8.18 (s); δ_C(100 MHz) 125.89 (s), 138.76 (s); *m*/*z* 210 (M^+, 33%), 208 (52), 97 (100).

Preparation of the amino derivatives 19, 20 and 21

Reaction of ammonia with 17 and 18. Ammonia gas was bubbled through a stirred solution of **17** (1.0 g, 5.7 mmol) and **18** (0.1 g, 0.6 mmol) in acetonitrile at 70 °C for 3 h. The mixture was filtered and the solid was washed with acetonitrile. The resulting solid (1.25 g) was washed with water (to remove ammonium fluoride), filtered, dried, and recrystallised from dimethyl sulfoxide and water to give 3,5-*diamino*-4-*nitropyridine* N-*oxide* **20** (0.55 g, 57%), mp >300 °C (decomp.) (HRMS Found: M^+, 170.044 53. $C_5H_6N_4O_3$ requires M^+, 170.043 99); ν_{max}/cm^{-1} 3543, 3403, 1627, 1567, 1269, 1162, 1109, 1037, 785, 652; δ_H(400 MHz; [$^2H_6$]DMSO) 7.39 (2 H, s, NH_2),† 7.11 (1 H, s, 2-C*H*); δ_C(100.58 MHz, [$^2H_6$]DMSO) 114.84 (s, 2-*C*H), 116.92 (s, 4-*C*NO_2), 144.38 (s, 3-*C*NH_2); *m*/*z* 171 (M^+, 44%), 170 (47), 154 (100). The filtrate from the acetonitrile washing was evaporated to dryness giving a solid (0.34 g). Chromatography on silica gel with acetonitrile and ethyl acetate (50 : 50) as the eluent gave 3-*amino*-5-*fluoro*-2-*nitropyridine* N-*oxide* **21** (0.07 g, 8%), mp decomp. (from ethyl acetate–acetonitrile) (Found: C, 34.6; H, 2.4; N, 24.2. $C_5H_4FN_3O_3$ requires C, 34.7; H, 2.3; N, 24.3%); ν_{max}/cm^{-1} 3470, 3271, 3105, 1646, 1567, 1538, 1269, 1129, 612; δ_H(400 MHz; [$^2H_6$]DMSO) 8.03 (1 H, dd, $^3J_{HF}$ 4.4 and $^4J_{HH}$ 2.4, 6-C*H*), 6.79 (2 H, s, NH_2), 6.77 (1H, dd, $^3J_{HF}$ 10.0 and $^4J_{HH}$ 2.0, 4-C*H*);† δ_C(100.58 MHz, [$^2H_6$]DMSO) 101.63 (d, $^2J_{CF}$ 24.4, 4-*C*H), 117.97 (d, $^2J_{CF}$ 39.7, 6-*C*H), 138.81 (s, 2-*C*NO_2), 139.60 (d, $^3J_{CF}$ 15.2, 3-*C*NH_2), 159.64 (d, $^1J_{CF}$ 247, 5-*C*F); δ_F(376 MHz; [$^2H_6$]DMSO) −120.16 (dd, $^3J_{FH}$ 10.4 and 4.5); *m*/*z* 174 (M^+, 34%), 173 (96), 111 (100) and 3-*amino*-5-*fluoro*-4-*nitropyridine* N-*oxide* **19** (0.15 g, 15%), mp >200 °C (decomp.); (HRMS Found: M^+, 173.0237. $C_5H_4FN_3O_3$ requires M^+, 137.0237); ν_{max}/cm^{-1} 3430, 3297, 3118, 1640, 1567, 1481, 1269, 1182, 1096, 659, 533; δ_H(400 MHz; [$^2H_6$]DMSO) 7.84 (1 H, 2 lines, 2,6-C*H*), 7.62 (1 H, s, NH_2); δ_C(100.58 MHz; [$^2H_6$]DMSO) 117.96 (d, $^2J_{CF}$ 38.2, 6-*C*H), 119.22 (s, 4-*C*NO_2), 125.52 (s, 2-*C*H), 143.45 (s, 3-*C*NH_2), 155.03 (d, $^1J_{CF}$ 260.0, 5-*C*F); δ_F(376 MHz; [$^2H_6$]DMSO) −131.09 (d, $^3J_{FH}$ 6.4); *m*/*z* 173 (M^+, 100%).

Reaction of aqueous ammonia with 4-nitro-3,5-dichloropyridine *N*-oxide 23. A sealed Carius tube containing 4-nitro-3,5-dichloropyridine *N*-oxide **23** (0.4 g, 1.9 mmol), aqueous ammonia (1 cm^3 of a 0.88 g dm^{-3} solution) and acetonitrile (1 cm^3) was heated in a rotating oil bath at 70 °C for 3 h. The mixture was filtered giving a solid which was washed with water. The remaining solid (0.1 g) was recrystallised from hot methanol giving 4-*amino*-3,5-*dichloropyridine* N-*oxide* **24** (0.1 g, 30%), mp 210 °C (from MeOH) (Found: M^+, 177.9701. $C_5H_4Cl_2N_2O$ requires M^+, 177.9701); ν_{max}/cm^{-1} 3315, 3177, 1653, 1499, 1213, 1110, 1037, 967, 818; δ_H(250 MHz; [$^2H_6$]-DMSO) 8.26 (1 H, s, 2-C*H*), 6.65 (1 H, s, NH_2); δ_C(100.58 MHz; [$^2H_6$]DMSO) 114.77 (s, 2-*C*), 136.85 (s, 4-*C*), 140.77 (s, 3-*C*); *m*/*z* 182 (M^+, 14%), 181 (37), 180 (60), 179 (56), 178 (86), 52 (100).

Reactions of 2,4,6-tribromo-3,5-difluoropyridine 3 with nucleophiles

With a ten-fold excess of sodium methoxide. A tube containing 2,4,6-tribromo-3,5-difluoropyridine **3** (0.4 g, 1.1 mmol) and a ten-fold excess of sodium methoxide in methanol was sealed and left standing at room temperature for 48 h. Water (20 cm^3) was added and the mixture was extracted into DCM. The DCM solution was evaporated to dryness giving a solid which upon recrystallisation from DCM–light petroleum (1 : 1) gave 2,4,6-*tribromo*-3,5-*dimethoxypyridine* **10a** (0.4 g, 100%), mp 145–146 °C (Found: C, 22.5; H, 1.4; N, 3.3. $C_7H_6Br_3NO_2$ requires C, 22.3; H, 1.6; N, 3.7%); ν_{max}/cm^{-1} 2943, 2857, 1508, 1455, 1443, 1357, 1110, 975, 919, 770, 751, 718, 630; δ_H[400 MHz; $(CD_3)_2CO$] 3.95 (s); δ_C[100 MHz; $(CD_3)_2CO$] 61.34 (s, *C*H_3), 125.93 (s, 4-*C*Br), 130.50 (s, 2-*C*Br), 153.31 (s, 3-*C*OMe); *m*/*z* 379 (M^+, 32%), 377 (98), 375 (100), 373 (35).

With one equivalent of sodium methoxide. A solution of **3** (1.0 g, 2.6 mmol) and sodium methoxide (0.184 g, 3.4 mmol) in methanol (3 cm^3) was stirred at room temperature for 60 h. Methanol was evaporated, water (20 cm^3) added and the mixture was extracted into DCM. The DCM solution was dried ($MgSO_4$) and evaporated to dryness. Chromatography on silica gel with DCM–light petroleum (1 : 4) as the eluent yielded 2,4,6-*tribromo*-3-*fluoro*-5-*methoxypyridine* **10b** (0.7 g, 70%), mp 116–118 °C (Found: C, 20.0; H, 0.8; N, 3.7. $C_6H_3Br_3FNO$ requires C, 19.8; H, 0.8; N, 3.9%); ν_{max}/cm^{-1} 2942, 1541, 1451, 1394, 1366, 1121, 1063, 945, 767, 749, 695, 664, 628, 557; δ_H(400 MHz) 3.97 (s); δ_C(100 MHz) 61.21 (s, *C*H_3), 117.29 (d, $^2J_{CF}$ 19.8, 4- or 6-*C*Br), 122.41 (d, $^2J_{CF}$ 26.7, 4- or 6-*C*Br), 130.15 (d, $^4J_{CF}$ 3.8, 2-*C*Br), 152.38 (s, 3-*C*OCH_3), 153.74 (d, $^1J_{CF}$ 249.8, 5-*C*F); δ_F(376 MHz) −103.6 (s); *m*/*z* 367 (M^+, 32%), 365 (99), 363 (100), 361 (35).

With potassium hydroxide. A mixture of **3** (1.0 g, 2.8 mmol), potassium hydroxide pellets (0.6 g) and 2-methylpropan-2-ol (8 cm^3) was stirred under reflux for 3 h. The mixture was cooled and acidified with dilute hydrochloric acid (30 cm^3). The mixture was extracted into DCM, then the DCM solution was dried ($MgSO_4$) and evaporated to dryness. Recrystallisation gave 2,4,6-*tribromo*-3-*fluoro*-5-*hydroxypyridine* **10e** (1.0 g, 97%), mp 96–97 °C (from DCM) (Found: C, 17.2; H, 0.2. C_5HBr_3FNO requires C, 17.2; H, 0.3%); ν_{max}/cm^{-1} 3491 (O–H), 3000–2800, 1463, 1377, 1283, 1172, 722; δ_C(100 MHz) 108.49 (d, $^2J_{CF}$ 23.6, 4- or 6-*C*Br), 117.80 (d, $^2J_{CF}$ 27.1, 4- or 6-*C*Br), 122.11 (d, $^4J_{CF}$ 3.8, 2-*C*Br), 148.27 (s, 3-*C*OH), 153.74 (d, $^1J_{CF}$ 260.2, 5-*C*F); δ_F(376 MHz) −104.24 (d, *J* 1.9); *m*/*z* 353 (M^+, 30%), 351 (93), 349 (100), 347 (37).

With aqueous ammonia. A Carius tube containing **3** (1.0 g, 2.8 mmol), aqueous ammonia (2 cm^3) and acetonitrile (5 cm^3) was heated in a rotating oil bath at 75 °C for 72 h. Water (20 cm^3) was added and the mixture was extracted into DCM. The DCM solution was dried ($MgSO_4$) and evaporated to dryness giving a solid which was sublimed and recrystallised from DCM giving 2,4,6-*tribromo*-3-*amino*-5-*fluoropyridine* **10c** (0.9 g, 93%), mp 125.5–126.5 °C (Found: C, 17.3; H, 0.6. $C_5H_2Br_3FN_2$ requires C, 17.2; H, 0.6%); δ_H(500 MHz) 4.73 (br s, NH_2); δ_C(126 MHz) 105.09 (d, $^2J_{CF}$ 23.9, 4- or 6-*C*Br), 113.00 (d, $^2J_{CF}$ 27.7, 4- or 6-*C*Br), 119.68 (d, $^3J_{CF}$ 3.8, 3-*C*NH_2), 141.03 (s, 2-*C*Br), 153.35 (d, $^1J_{CF}$ 256.6, 5-*C*F); δ_F(376 MHz) −106.16 (s); *m*/*z* 352 (M^+, 41%), 350 (100), 348 (100), 346 (43).

With sodium phenoxide. Sodium phenoxide was freshly prepared by adding sodium metal to phenol (0.45 g, 4.8 mmol) dissolved in diethyl ether (15 cm^3), under an atmosphere of dry nitrogen. This was refluxed with **3** (1.0 g, 2.8 mmol) for 23 h. Following evaporation of the diethyl ether, water (20 cm^3) was added and the mixture was extracted into DCM. The DCM solution was dried ($MgSO_4$) and evaporated to give a solid

† Assignment confirmed by shaking with D_2O (NH_2 signal collapses, hence observation of the aromatic protons is possible).

(1.2 g). Fractional sublimation and recrystallisation from acetonitrile gave unreacted 2,4,6-tribromo-3,5-difluoropyridine (0.8 g, 80%) and 2,4,6-*tribromo*-3-*fluoro*-5-*phenoxypyridine* **10d** (0.2 g, 20%), mp 100 ± 1 °C (Found: C, 31.3; H, 1.1; N, 2.9. $C_{11}H_5Br_3FNO$ requires C, 31.0; H, 1.2; N, 3.3%); ν_{max}/cm^{-1} 2851, 1588, 1533, 1462, 1375, 1191, 826, 754; δ_H(400 MHz) 7.34 (2H, dd, $^3J_{HH}$ 8.4 and 7.2, 9-C*H*), 7.13 (1H, t, $^3J_{HH}$ 7.2, 10-C*H*), 6.83 (2H, d, $^3J_{HH}$ 8.0, 8-C*H*); δ_C(100 MHz) 115.22 (s, 8-*C*H), 118.23 (d, $^2J_{CF}$ 21.3, 4- or 6-*C*Br), 123.63 (s, 10-*C*H), 123.86 (d, $^2J_{CF}$ 26.4, 4- or 6-*C*Br), 129.96 (s, 9-*C*H), 130.94 (d, $^4J_{CF}$ 3.8, 2-*C*Br), 147.70 (d, $^3J_{CF}$ 1.5, 3-*C*O), 155.48 [s, 7-*C*(Ph)O], 153.96 (d, $^1J_{CF}$ 262.8, 5-*C*F); δ_F(235 MHz) −104.5 (s); *m*/*z* 429 (M$^+$, 2.9%), 427 (11), 425 (11), 423 (3.3), 77 (100).

With diethylamine. A Carius tube charged with diethylamine (5 cm^3) and **3** (0.5 g, 1.4 mmol) was heated in a rotating oil bath at 50 °C for 95 h. Excess diethylamine was evaporated to leave a solid. Water (50 cm^3) was added and the mixture was extracted into DCM. The DCM solution was dried ($MgSO_4$) and evaporated to dryness, giving a solid (0.5 g), shown to consist of 2,6-dibromo-4-diethylamino-3,5-difluoropyridine (61% by fluorine NMR spectroscopy) and 4,6-dibromo-2-diethylamino-3,5-difluoropyridine (39% by fluorine NMR spectroscopy). Chromatography on silica gel with DCM–light petroleum (1:1) as the eluent yielded, (i) 2,6-*dibromo*-4-*diethylamino*-3,5-*difluoropyridine* (0.3 g, 60%), mp 41–42 °C (Found: C, 31.4; H, 2.9; N, 8.2. $C_9H_{10}Br_2F_2N_2$ requires C, 31.4; H, 2.9; N, 8.1%); ν_{max}/cm^{-1} 2921, 1573, 1463, 1393, 1268, 1194, 1022, 951, 807, 725; δ_H(400 MHz) 1.18 (3H, t, $^3J_{HH}$ 7.2, CH_3), 3.39 (2H, qt, $^3J_{HH}$ 7.2 and $^5J_{HF}$ 1.6, CH_2); δ_C(100 MHz) 13.72 (t, $^5J_{CF}$ 1.9, *C*H$_3$), 46.40 (t, $^4J_{CF}$ 4.9, *C*H$_2$), 135.88 (t, $^2J_{CF}$ 11.5, 4-*C*NEt$_2$), 147.96 (dd, $^1J_{CF}$ 257.1, $^3J_{CF}$ 4.2, 3-*C*F), 123.22 (6 lines showing X part of ABX system, 2-*C*H); δ_F(376 MHz) −121.05 (s); *m*/*z* 346 (M$^+$, 14%), 344 (29), 342 (14), 329 (100) and (ii) 4,6-*dibromo*-2-*diethylamino*-3,5-*difluoropyridine* (0.2 g, 30%) (Found: M$^+$, 341.9179. $C_9H_{10}Br_2F_2N_2$ requires *M*$^+$, 341.9179); δ_H(400 MHz) 1.19 (3H, t, $^3J_{HH}$ 6.8, CH_3), 3.47 (2H, qd, $^3J_{HH}$ 7.2 and $^5J_{HF}$ 2.0, CH_2); δ_C(100 MHz) 13.57 (s, *C*H$_3$), 44.28 (d, $^4J_{CF}$ 5.7, *C*H$_2$), 109.33 (t, $^2J_{CF}$ 24.0, 4-*C*Br), 118.44 (dd, $^2J_{CF}$ 24.8 and 3.4, 6-*C*Br), 144.66 (dd, $^1J_{CF}$ 249.4, $^3J_{CF}$ 2.7, 3- or 5-*C*F), 143.68 (dd, $^2J_{CF}$ 260.2, $^3J_{CF}$ 2.3, 3- or 5-*C*F), 144.43 (br dd, $^2J_{CF}$ 8.8, 2-*C*NEt$_2$); δ_F(376 MHz) −122.47 (1F, d, $^4J_{FF}$ 4.5, 5-C*F*), −125.92 (1F, br dt, $^4J_{FF}$ 4.5,‡ 3-C*F*); *m*/*z* 331 (M$^+$ − 15, 13%), 329 (26), 327 (14).

With sodium thiophenolate. A solution of **3** (1.0 g, 2.8 mmol), benzenethiol (0.33 g, 3.0 mmol), acetonitrile (5 cm^3) and sodium carbonate (0.3 g) was stirred under reflux for 19 h. Water (20 cm^3) was added, then the mixture was extracted into DCM. The DCM solution was dried ($MgSO_4$) and evaporated to dryness. Chromatography on silica gel (DCM–hexane, 30:70) yielded 2,6-*dibromo*-3,5-*difluoro*-4-*phenylthiopyridine* (0.9 g, 85%), mp 65.5–66.5 °C (Found: C, 34.45; H, 1.3. $C_{11}H_5Br_2F_2NS$ requires C, 34.7; H, 1.3%); ν_{max}/cm^{-1} 3059, 2964, 1139, 1023, 1001, 791, 749, 697, 687; δ_H(400 MHz) 7.33–7.40 (3H, m), 7.48–7.49 (2H, m); δ_C(100 MHz) 122.67 (6 lines showing X part of ABX, 2-*C*Br), 126.04 (t, $^2J_{CF}$ 20.0, 4-*C*SPh), 129.343 [s, *C*(phenyl)H], 129.589 [s, *C*(phenyl)H], 132.767 [s, *C*(phenyl)H], 154.07 (d, $^1J_{CF}$ 263.1, 3-*C*F); δ_F(376 MHz) −104.845 (s); *m*/*z* 383 (M$^+$, 37%), 381 (86), 379 (35), 221 (100).

With piperidine. A solution of **3** (1.0 g, 2.8 mmol), piperidine (0.3 cm^3, 0.3 g, 3.0 mmol) and acetonitrile (5 cm^3) was stirred at reflux for 23 h. Water (20 cm^3) was added and the mixture was extracted into DCM. The DCM solution was dried ($MgSO_4$) and evaporated to dryness. Chromatography on silica gel with DCM–hexane (1:1) as the eluent yielded 2,4,6-tribromo-3,5-difluoropyridine (0.6 g, 60%) and 2,6-*dibromo*-3,5-*difluoro*-4-*piperidinylpyridine*§ (0.4 g, 40%), mp 107–109 °C (Found: C, 33.6; H, 3.1. $C_{10}H_{10}Br_2F_2N_2$ requires C, 33.7; H, 2.8%); ν_{max}/cm^{-1} 2955, 2854, 1575, 1462, 1374, 1050, 964, 725; δ_H(400 MHz) 1.60 (3H, s), 3.29 (2H, s); δ_C(100 MHz) 123.18 (6 lines showing X part of ABX, 2-*C*Br), 137.06 (t, $^2J_{CF}$ 11.5, 4-*C*N), 147.36 (dd, $^1J_{CF}$ 257.5, $^3J_{CF}$ 3.4, 3-*C*F), 23.91 (s, 10-*C*H), 26.31 (s, 8-*C*H), 51.57 (s, 9-*C*H); δ_F(376 MHz) −121.02 (s); *m*/*z* 358 (M$^+$, 29%), 357 (53), 356 (61), 355 (100), 354 (34), 353 (50).

With 1-(trimethylsilyloxy)cyclohexene and potassium fluoride. 1-(Trimethylsilyloxy)cyclohexene (0.7 g, 3.9 mmol) was added to a mixture of **3** (0.5 g, 1.4 mmol), dry potassium fluoride (0.5 g) and acetonitrile, at room temperature, with stirring under nitrogen. The mixture was stirred at room temperature for 16 h, then at 60 °C for 8 h. Water (20 cm^3) was added and the mixture extracted into DCM. Evaporation of the dried DCM solution gave 2,6-*dibromo*-3,5-*difluoropyridine* **26** (0.3 g, 79%), mp 99–100 °C [from DCM–light petroleum (bp 40–60 °C), 1:1] (Found: C, 21.9; H, 0.3; N, 4.8. $C_5HBr_2F_2N$ requires C, 22.0; H, 0.4; N, 5.1%); ν_{max}/cm^{-1} 3056, 1404, 1346, 1261, 1241, 1163, 1093, 889, 802, 657, 577; δ_H(400 MHz) 7.31 (1H, t, $^3J_{HF}$ 6.4); δ_C(100 MHz) 113.73 (t, $^2J_{CF}$ 23.8, 4-*C*H), 122.68 (dd, X part of ABX, 2-*C*Br), 155.51 (dd, $^1J_{CF}$ 265.5, $^3J_{CF}$ 4.5, 3-*C*F); δ_F(376 MHz) −109.10 (d, $^3J_{FH}$ 6.8, 3-C*F*); *m*/*z* 275 (M$^+$, 49%), 273 (100), 271 (52). This reaction was repeated except 1,3-dinitrobenzene (0.4 g, 2.4 mmol) was added to a mixture of **3** (0.5 g, 1.4 mmol), potassium fluoride (3.0 g) and 1-(trimethylsilyloxy)-cyclohexene (1.0 g, 6 mmol) in acetonitrile (10 cm^3) and the reaction was carried out in the dark to afford a solid (0.4 g), shown to contain **26** (100% conv., 51% yield).

With 2-(trimethylsilyloxy)pent-2-en-4-one and potassium fluoride. 2-Trimethylsilyloxypent-2-en-4-one (1.0 g, 5.6 mmol) was added to a mixture of **3** (1.0 g, 2.8 mmol), dry potassium fluoride (1.5 g) and acetonitrile (15 cm^3), at room temperature, with stirring under nitrogen. After stirring at 60 °C for 18 h, water (20 cm^3) was added and the mixture was extracted with DCM. Evaporation of the dried DCM solution gave a solid (1.2 g) which was shown to be **26** (>90%) by comparison of its fluorine and proton NMR spectra and GC–MS data with an authentic sample.

With sodium amide. A solution of **3** (0.8 g, 2.3 mmol) in acetonitrile (10 cm^3) was added to sodium amide (0.7 g, 18 mmol) at 0 °C, with stirring, under nitrogen, then heated to reflux for 1 h. Water (20 cm^3) was added and the mixture extracted into DCM. The solution was evaporated giving a solid (0.8 g), consisting of unreacted **3** (68%) and 2,6-dibromo-3,5-difluoropyridine **26** (32%) by fluorine NMR spectroscopy against an internal standard (2-fluoropyridine). Repeating this experiment in the dark with the addition of 1,3-dinitrobenzene (0.4 g, 2.4 mmol) gave the same result as the reaction carried out in the absence of 1,3-dinitrobenzene and in the presence of light.

Lithiations

Preparation of 2,6-dibromo-3,5-difluoro-4-lithiopyridine 30. Either a solution of butyllithium (2.2 cm^3, 3.5 mmol of 1.6 M solution in hexanes) or lithium diisopropylamide (1.8 cm^3 of 2.0 M solution in THF–heptanes–ethylbenzene) was added to **3** (1.0 g, 2.8 mmol) in diethyl ether (10 cm^3) at −78 °C, with stirring, under an atmosphere of dry nitrogen.

Preparation of 4-allyl-2,6-dibromo-3,5-difluoropyridine 31. Allyl bromide (0.8 cm^3) was added to a solution of **30** in diethyl ether and the mixture was stirred for 0.5 h at −78 °C, then warmed to room temperature. Water (40 cm^3) was added and the mixture was extracted into DCM. The DCM solution was dried ($MgSO_4$) and evaporated to give a residue which after chromatography on silica gel with ethyl acetate and hexane (20:80) as eluent yielded 4-*allyl*-2,6-*dibromo*-3,5-*difluoropyridine* **31** (0.6 g, 71%) (Found: M$^+$, 312.8736. $C_8H_5Br_2F_2N$ requires *M*$^+$, 312.8736); ν_{max}/cm^{-1} 3085, 2983, 2930, 2511, 1642, 1582, 1381, 1255, 1197, 1096, 989, 928, 887, 699, 653, 577; δ_H(376 MHz) 3.53 (2 H, d, $^3J_{HH}$ 4.8, 9-CH_2), 5.16 (2 H, s, 7-C*H*), 5.86 (1 H, dd, $^3J_{HH}$ 16.0 and 8.8, 8-C*H*); δ_C(100 MHz) 27.72

‡ Adjacent N broadens signal.

§ There were traces of the 2-piperidinyl isomer, however, insufficient quantities were recovered for characterisation.

(s, 7-*C*H), 118.53 (s, 9-*C*H), 122.30 (4 lines showing X part of ABX, 2-*C*Br), 127.31 (t, $^2J_{CF}$ 20.0, 4-*C*CH_2), 130.97 (s, 8-*C*H), 154.12 (dd, $^1J_{CF}$ 262.4 and $^3J_{CF}$ 2.6, 3-*C*F); δ_F(376 MHz) −114.4 (s), and **4d** (<0.1 g) by comparison with an authentic sample.

Attempted decomposition of the anion 30

A solution of **30** was prepared at −78 °C, then warmed to room temperature and stirred for 3 h. A fluorine NMR spectrum of the crude mixture clearly showed the presence of the anion **30**; δ_F(235 MHz) −87.5 (s) and the 4-hydro derivative, **26**, in a ratio of 3 : 1. Hydrolysis with water and work-up gave **26** (0.6 g, 77%).

Lithiation of 3,5-difluoropyridine 1 (in diethyl ether)

A solution of 3,5-difluoropyridine **1** (0.37 g, 3.2 mmol) in diethyl ether (5 cm^3) was added to a solution of butyllithium (2.5 cm^3, 4 mmol of 1.6 M solution in hexanes) and tetramethylethylenediamine (TMEDA) (0.8 cm^3, 0.62 g, 5 mmol) in dry diethyl ether at −78 °C, with stirring, under an atmosphere of dry nitrogen. After 1.25 h, trimethylsilyl chloride (0.8 cm^3) was added and the mixture stirred at −78 °C for 1.5 h, then at room temperature for 0.5 h. Water (20 cm^3) was added and the mixture extracted into diethyl ether. The ethereal solution was dried ($MgSO_4$) and evaporated to give an oil. Chromatography on silica gel with DCM as the eluent yielded 3,5-*difluoro*-4-*trimethylsilylpyridine* **33** (0.4 g, 65%) (Found: M^+, 187.0629. $C_8H_{11}F_2NSi$ requires M^+, 187.0629); δ_H(400 MHz) 0.33 (9H, s, CH_3), 8.16 (2H, s, 2-C*H*); δ_C(100 MHz) −0.41 (s, *C*H_3), 122.69 (t, $^2J_{CF}$ 30.5, 4-*C*Si), 133.51 (4 lines showing X part of ABX, 2-*C*H), 162.77 (d, $^1J_{CF}$ 259.8, 3-*C*F); δ_F(376 MHz) −113.10 (s); *m*/*z* 187 (M^+, 21%), 81 (100).

Lithiation of 3,5-difluoropyridine 1 (in THF)

A solution of **1** (0.45 g, 3.9 mmol) in tetrahydrofuran (5 cm^3) was added to a solution of butyllithium (3.0 cm^3, 4.8 mmol of 1.6 M solution in hexanes) and TMEDA (0.8 cm^3, 0.62 g, 5 mmol) in dry tetrahydrofuran (10 cm^3), at −78 °C, with stirring, under an atmosphere of dry nitrogen. After 2 h, a sample for NMR spectroscopy was taken and allowed to warm to room temperature.¶ To the remaining solution, trimethylsilyl chloride (0.8 cm^3) was added. Work-up of the reaction mixture as above afforded **33** (0.4 g, 100% conversion).

Palladium mediated coupling of alkynes with bromofluoro heterocyclic compounds

Preparation of 2,4-dibromo-3,5-difluoro-6-(phenylacetylenyl)-pyridine and 4-bromo-3,5-difluoro-2,6-bis(phenylacetylenyl)-pyridine 27a. A mixture of **3** (1.0 g, 2.8 mmol), phenylacetylene (0.5 g, 5 mmol), copper(I) iodide (0.01 g, 0.05 mmol), bis-(triphenylphosphine)palladium dichloride (0.04 g, 0.06 mmol) and triethylamine (10 cm^3) was stirred, under an atmosphere of dry nitrogen, at room temperature for 16 h. Water (30 cm^3) was added and the mixture was filtered and extracted into DCM. The DCM solution was dried ($MgSO_4$) and evaporated giving a solid (1.1 g). Chromatography on alumina with hexane as the eluent yielded 2,4-*dibromo*-3,5-*difluoro*-6-(*phenylacetylenyl*)-*pyridine* (0.4 g, 38%), mp 156 °C (from DCM) (Found: C, 42.2; H, 1.3; N, 3.5. $C_{13}H_5Br_2F_2N$ requires C, 41.8; H, 1.3; N, 3.8%); ν_{max}/cm^{-1} 2227, 2203, 1490, 1428, 1411, 1327, 1218, 758, 687; δ_H(250 MHz) 7.61 (2 H, m), 7.43 (3 H, m); δ_C(100 MHz) 80.30 [d, $^4J_{CF}$ 6.0, 8-*C*(alkyne)], 97.37 [dd, $^3J_{CF}$ 5.7 and $^5J_{CF}$ 2.3, 7-*C*(alkyne)], 109.23 (t, $^2J_{CF}$ 23.4, 4-*C*Br), 120.99 [s, 9-*C*(phenyl)], 123.60 (dd, $^2J_{CF}$ 25.1 and $^4J_{CF}$ 3.8, 2-*C*N), 128.34 (dd, $^2J_{CF}$ 21.0 and $^4J_{CF}$ 5.7, 6-*C*Br – partially obscured by singlet at 128.49), 128.49 [s, 10- or 11-*C*(phenyl)], 129.90 [s, 12-*C*(phenyl)], 132.18 [s, 10- or 11-*C*(phenyl)], 153.13 (d, $^1J_{CF}$ 265.9, 3- or 5-*C*F), 157.21 (d, $^1J_{CF}$ 266.6, 3- or 5-*C*F); δ_F(235 MHz) −101.27 (1 F, s), −110.36 (1 F, s); *m*/*z* 375 (M^+, 50%), 373 (100), 371 (62) and 4-*bromo*-3,5-*difluoro*-2,6-*bis*(*phenylacetylenyl*)*pyridine* **27a** (0.5 g, 45%), mp 188 °C (from chloroform) (Found: C, 64.1; H, 2.3; N, 3.4. $C_{21}H_{10}BrF_2N$ requires C, 64.0; H, 2.5; N, 3.6%); ν_{max}/cm^{-1} 3055, 2223, 1555, 1493, 1439, 1427, 1227, 864, 754, 687; δ_H(250 MHz) 7.33–7.44 (3 H, m), 7.60–7.63 (2 H, m); δ_C(100 MHz) 81.60 [4 lines showing X part of ABX, 8-*C*(alkyne)], 96.25 [t, $^3J_{CF}$ 3.8, 7-*C*(alkyne)], 108.35 (t, $^2J_{CF}$ 22.7, 4-*C*-Br), 121.27 [s, 9-*C*(phenyl)], 128.45 [s, 11-*C*(phenyl)], 128.90 (dd, $^2J_{CF}$ 16.4 and $^4J_{CF}$ 5.7, 2,6-*C*N), 156.82 (d, $^1J_{CF}$ 269, 3,5-*C*F), 129.69 (s, 12-*C*-Ar), 132.16 (s, 10-*C*-Ar); δ_F(235 MHz) −108.21 (s); *m*/*z* 395 (M^+, 94%), 393 (100).

Preparation of 4-bromo-3,5-difluoro-2,6-bis(phenylacetylenyl)pyridine 27a. The above procedure was followed, except **3** (1.0 g, 2.8 mmol), phenylacetylene (2.0 g, 20 mmol), copper(I) iodide (0.01 g, 0.05 mmol), bis(triphenylphosphine)palladium dichloride (0.04 g, 0.06 mmol) and triethylamine (80 cm^3) gave, after 88 h and work-up, a solid (1.7 g). Chromatography on alumina with hexane–DCM (50 : 50) as eluent yielded **27a** (0.8 g, 72%) by comparison of its carbon and fluorine NMR spectra and elemental analysis, and 1,4-diphenylbuta-1,3-diyne (0.3 g), mp 85 °C (lit.,[22] 88 °C) (Found: C, 94.4; H, 4.9. $C_{16}H_{10}$ requires C, 95.0; H, 4.95%); ν_{max}/cm^{-1} 2923, 755, 685; δ_H(250 MHz) 7.33–7.36 (3 H, 2 lines), 7.51–7.54 (2 H, 3 lines); δ_C(100.58 MHz) 73.9 (s, 2-C), 81.5 (s, 1-C), 121.7 [s, C(phenyl)], 128.4 [s, C(phenyl)], 129.2 [s, C(phenyl)], 132.5 [s, C(phenyl)]; *m*/*z* 203 (M^+, 20%), 202 (100).

Preparation of 4-bromo-3,5-difluoro-2,6-dipent-1-ynylpyridine 27b. Pent-1-yne (0.5 cm^3, 6 mmol), **3** (1.0 g, 2.8 mmol), copper(I) iodide (0.1 g), palladium(II) acetate (0.04 g), triphenylphosphine (0.08 g) and triethylamine (15 cm^3) gave, after 66 h and work-up, a solid (1.1 g). Chromatography on silica gel with DCM–hexane (50 : 50) as the eluent yielded 4-*bromo*-3,5-*difluoro*-2,6-*dipent*-1-*ynylpyridine* **27b** (0.6 g, 66%), mp 84 °C (from hexane) (Found: C, 55.7; H, 4.4; N, 4.4. $C_{15}H_{14}BrF_2N$ requires C, 55.2; H, 4.3; N, 4.3%); ν_{max}/cm^{-1} 2964, 2933, 2871, 2240, 1561, 1447, 1431, 1418, 1213, 1173, 792, 667, 567; δ_H(250 MHz) 0.96 (3 H, t, $^3J_{HH}$ 7.3, CH_3), 1.59 (2 H, q, $^3J_{HH}$ 7.2, CH_2CH$_3$), 2.38 (2 H, t, $^3J_{HH}$ 7.1, CH_2CH$_2$CH$_3$); δ_C(100 MHz) 13.46 (s, 9-*C*H$_3$), 21.44 (s, 7- or 8-*C*H$_2$), 21.54 (s, 7- or 8-*C*H$_2$), 73.04 (s, 6-*C*), 98.36 (s, 5-*C*), 107.93 (t, $^2J_{CF}$ 22.9, 4-*C*Br), 128.88 (4 lines showing X part of ABX, 2-*C*), 156.50 (d, $^1J_{CF}$ 267, 3-*C*F); δ_F(376 MHz) −125.09 (s); *m*/*z* 327 (M^+, 45%), 44 (100).

Preparation of 5,6,7,8-tetrafluoro-2,3-dipent-1-ynylquinoxaline 29. Pent-1-yne (0.6 cm^3, 7 mmol), 2,3-dibromo-5,6,7,8-tetrafluoroquinoxaline **13** (0.45 g, 1.3 mmol), copper(I) iodide (0.06 g), bis(triphenylphosphine)palladium dichloride (0.04 g) and triethylamine (20 cm^3) gave, after room temperature for 16 h, then at 40 °C for 24 h and work-up, a solid (0.5 g). Chromatography on silica gel with hexane–DCM (70 : 30) as the eluent yielded 5,6,7,8-*tetrafluoro*-2,3-*dipent*-1-*ynylquinoxaline* **29** (0.3 g, 69%), mp 71–73 °C (Found: C, 64.3; H, 4.3; N, 8.2. $C_{18}H_{14}F_4N_2$ requires C, 64.7; H, 4.2; N, 8.4%); ν_{max}/cm^{-1} 2969, 2937, 2877, 2221, 1656, 1500, 1387, 1356, 1203, 1045; δ_H(400 MHz) 1.12 (3H, t, $^3J_{HH}$ 7.4, CH_3), 1.73 (2H, q, $^3J_{HH}$ 7.2, CH_2CH$_3$), 2.56 (2H, t, $^3J_{HH}$ 7.0, CH_2CH$_2$CH$_3$); δ_C(100 MHz) 13.62 (s, 15-*C*H$_3$), 21.49 (s, 13- or 14-*C*H$_2$), 21.82 (s, 13- or 14-*C*H$_2$), 78.34 [s, 12-*C*(alkyne)], 101.03 [s, 11-*C*(alkyne)], 127.10 (d, $^2J_{CF}$ 3.8, 9-*C*), 141.26 (dm, $^1J_{CF}$ 264.0, 5- or 6-*C*F), 140.83 (dm, $^1J_{CF}$ 284.9, 5- or 6-*C*F), 142.26 (s, 2-*C*N); δ_F(376 MHz) −151.64 (1F, AA′XX′), −152.39 (1F, AA′XX′); *m*/*z* 334 (M^+, 83%), 213 (100).

Preparation of 2,4,6-triphenylacetylenyl-5-fluoropyrimidine 28. Phenylacetylene (0.35 cm^3, 3.2 mmol), 2,4,6-tribromo-5-fluoropyrimidine **8** (1.0 g, 3.0 mmol), copper(I) iodide (0.1 g),

¶ The initially light colour rapidly darkened on warming. However, the unreacted 4-lithio salt **32** was observed by fluorine NMR spectroscopy at room temperature; δ_F(235 MHz) −94.5 (s), with traces (<5%) of the 2-lithio (or 2,4-dilithio) salt; δ_F(235.342 MHz, $CFCl_3$) −101.5 (s) and −113.8 (s).

bis(triphenylphosphine)palladium dichloride (0.04 g) and triethylamine (15 cm^3) gave, after room temperature for 15 h, then at 40 °C for 3 h and work-up, a solid (1.4 g). Chromatography on silica gel with hexane–DCM (50 : 50) as the eluent yielded 2,4,6-*triphenylacetylenyl*-5-*fluoropyrimidine* **28** (0.5 g, 42%), mp 234 °C (from chloroform) (Found: C, 83.9; H, 3.7; N, 6.9. $C_{28}H_{15}FN_2$ requires C, 84.4; H, 3.8; N, 7.0%); ν_{max}/cm^{-1} 2217, 1552, 1416, 1393, 755, 689; δ_H(400 MHz) 7.67 [2 H, dd, $^3J_{HH}$ 8.0 and 1.6, C(Ph)*H*], 7.43 [3 H, m, C(Ph)*H*]; δ_C(100 MHz) 80.80 [d, $^3J_{CF}$ 4.5, 13-*C*(alkyne)], 86.90 [s, 14-*C*(alkyne)], 87.87 [s, 8-*C*(alkyne)], 101.33 [d, $^5J_{CF}$ 4.6, 7-*C*(alkyne)], 120.66 [s, 15-*C*(phenyl)], 121.11 [s, 9-*C*(phenyl)], 128.43 [s, 18-*C*(phenyl)], 128.62 [s, 17-*C*(phenyl)], 129.77 [s, 12-*C*(phenyl)], 130.52 [11-*C*(phenyl)], 132.62 [s, 16-*C*(phenyl)], 132.64 [s, 10-*C*(phenyl)], 140.01 [d, $^2J_{CF}$ 15.2, 4-*C*-C(alkyne)], 148.71 [d, $^4J_{CF}$ 9.2, 2-*C*-C(alkyne)], 156.40 (d, $^1J_{CF}$ 275.6, 5-*C*F); δ_F(376 MHz) −125.09 (s); *m*/*z* 398 (M^+, 69%), 143 (100) and 1,4-diphenylbuta-1,3-diyne (0.1 g).

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References

1 For Part 41, see R. D. Chambers, A. J. Roche and M. H. Rock, *J. Chem. Soc.*, *Perkin Trans. 1*, 1996, 1095.
2 J. P. Agrawal, *Progress in Energy and Combustion Science*, in press.
3 D. Craciunescu, V. Scarcia, A. Furlani, C. Ghirvu, L. Ravalico and A. Duadrio, *Acta Pharm. Fenn.*, 1987, **96**, 157.
4 G. Fenton and M. Palfreyman, Pat. No. WO 95/04045 (Rhone-Poulenc Rorer); *Chem. Abstr.*, 1995, **123**, 143 644g.
5 M. M. Boudakian, *J. Fluorine Chem.*, 1981, **18**, 497, and references therein.
6 L. Dolby-Glover, *Chem. Ind.*, 1986, 518, and references therein.
7 R. D. Chambers, J. Hutchinson and W. K. R. Musgrave, *J. Chem. Soc.*, *Suppl. 1*, 1964, 5634.
8 R. D. Chambers, F. G. Drakesmith and W. K. R. Musgrave, *J. Chem. Soc.*, 1965, 5045.
9 G. C. Finger, L. D. Starr, D. R. Dickerson, H. S. Gutowsky and J. Hamer, *J. Org. Chem.*, 1963, **28**, 1666.
10 R. D. Chambers, J. Hutchinson and W. K. R. Musgrave, *J. Chem. Soc.*, 1964, 3736.
11 R. D. Chambers, M. Hole, W. K. R. Musgrave and J. G. Thorpe, *J. Chem. Soc.* (*C*), 1971, 61.
12 S. L. Bell, R. D. Chambers, W. K. R. Musgrave and J. G. Thorpe, *J. Fluorine Chem.*, 1971, **1**, 51.
13 J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, 1951, **49**, 273.
14 G. Bartoli and P. E. Todesco, *Acc. Chem. Res.*, 1977, **10**, 125.
15 J. Miller, *Aromatic Nucleophilic Substitution*, Elsevier, London, 1968.
16 M. Cervera, J. Marquet and X. Martin, *Tetrahedron*, 1996, **52**, 2557.
17 I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, Wiley, London, 1976.
18 P. L. Coe, A. G. Holton and J. C. Tatlow, *J. Fluorine Chem.*, 1982, **21**, 171.
19 C. Reichardt and K. Halbritter, *Liebigs Ann. Chem.*, 1975, 470.
20 J. Burdon, V. A. Damodaran and J. C. Tatlow, *J. Chem. Soc.*, 1964, 763.
21 C. G. Allison, R. D. Chambers, J. A. H. Macbride and W. K. R. Musgrave, *J. Fluorine Chem.*, 1971, **1**, 59.
22 J. B. Hendrickson and K. W. Blair, *J. Org. Chem.*, 1977, **42**, 3875.

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