RESEARCH FRONT

CSIRO PUBLISHING

Aust. J. Chem. **2013**, *66*, 145–150
http://dx.doi.org/10.1071/CH12381

Full Paper

Continuous Flow Synthesis of Difluoroamine Systems by Direct Fluorination

Christopher B. McPake,[A] *Christopher B. Murray,*[B,C] *and Graham Sandford*[A,C]

[A]Department of Chemistry, Durham University, South Road, Durham, DH1 3LE, UK.
[B]AWE, Aldermaston, Reading, Berkshire, RG7 4PR, UK.
[C]Corresponding authors. Email: christopher.murray@awe.co.uk; graham.sandford@durham.ac.uk

Continuous flow methodology for the synthesis of perfluoroaryl difluoroamine derivatives by reaction of fluorine gas with an appropriate perfluoroaniline substrate is described, further demonstrating the efficient use of flow regimes for reactions involving highly reactive and toxic reagents.

Manuscript received: 15 August 2012.
Manuscript accepted: 27 September 2012.
Published online: 17 January 2013.

Introduction

Continuous flow methods for the production of a wide range of commodity chemicals have, of course, been used extensively in many large scale manufacturing processes, but the transfer of flow techniques to the laboratory has, in contrast, only begun to develop recently to any real extent.[1,2] There are many advantages associated with using flow reactors for chemical synthesis at both the laboratory and manufacturing stages and among those often discussed[2] and debated[3] include high throughput, use of very small quantities of material when appropriate, reduced waste streams, low manufacturing, operation and maintenance costs, low power consumption, increased precision and accuracy and disposability. Miniaturisation may also lead to increased performance of a system due to optimisation of contact between reagents because of very rapid mixing in such devices. The concept of scale-up by operating reactors in parallel is advantageous, where laboratory operation would exactly mirror the manufacturing situation. The ready availability of an increasingly wider range of commercially available stand-alone flow synthesis equipment has helped the adoption of flow techniques into academic and discovery research laboratories and synthetic applications continue to develop.

Flow techniques can be particularly useful for carrying out reactions with potentially hazardous reagents because the small inventories of reagents in contact within a flow reactor channel is very small compared with a conventional batch process, minimising associated risks. In addition, exothermic reactions may be controlled much more effectively in flow processes where the opportunity for efficient heat transfer is available.

In a series of papers from Durham,[4] we have engaged in developing the use of fluorine gas as a reagent for organic synthesis and, in particular, using continuous flow methodology[5,6] for the preparation of, for example, a range of fluoroaromatic,[7] -heterocyclic,[8,9] -diketone[10] and -ketoester[11] derivatives. Scale-out of direct fluorination reactions was achieved by the fabrication and implementation of parallel multi-channel flow reactors[5] that enable large quantities of commercially valuable fluorinated fine chemicals to be prepared in high yield and purity from inexpensive fluorine gas.

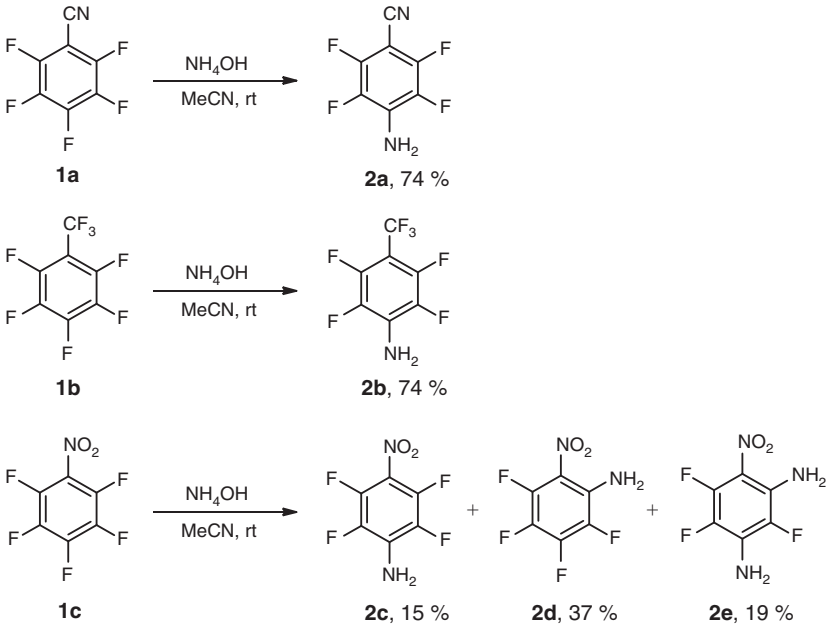
In this paper, we report the synthesis of a short series of perfluoroaryl difluoroamine systems from corresponding aniline substrates and fluorine gas by continuous flow processes. Whilst several approaches have been described for the synthesis of aliphatic difluoroamine species,[12–25] the synthesis of aryl difluoroamines has been less widely reported. Existing methodology generally involves batch fluorination with elemental fluorine in either liquid HF or acetonitrile,[26,27] although the use of nitrogen trifluoride as a difluoroaminating agent has also been explored.[28]

We chose to study the fluorination of perfluorinated aniline derivatives as model substrates due to the low reactivity of the perfluoroaryl ring towards fluorination, which would minimise competing by-product formation and as part of a wider program of research into the synthesis and properties of perfluorinated aromatic and heteroaromatic systems.[29,30]

Results and Discussion

A short series of perfluoroaniline derivatives **2** were synthesised by nucleophilic aromatic substitution reactions of appropriate perfluoroaryl substrates **1** with ammonium hydroxide in acetonitrile at room temperature (Scheme 1).

Cyano- and trifluoromethyl-benzene derivatives **1a** and **1b** gave the corresponding 4-amino derivatives **2a** and **2b** respectively, regiospecifically in high yield, reflecting the activating influence of fluorine atoms *ortho* and *meta* to the site of nucleophilic attack in S_NAr processes involving perfluorinated aryl systems, following well established principles.[31] Amination of perfluoronitrobenzene **1c** gave a mixture of products **2c**–**e** arising from substitution of fluorine *ortho* and *para* to the



Scheme 1. Synthesis of perfluoroaniline substrates **2**.

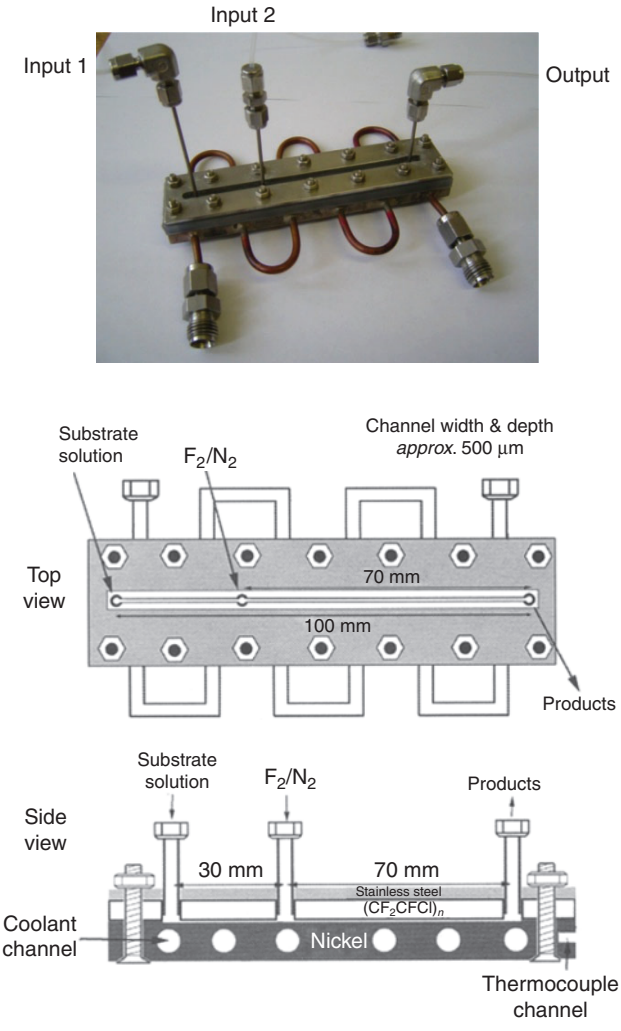


Fig. 1. Single channel continuous flow device for direct fluorination processes.

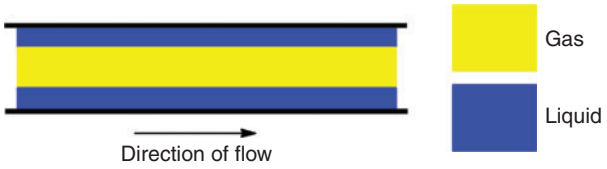
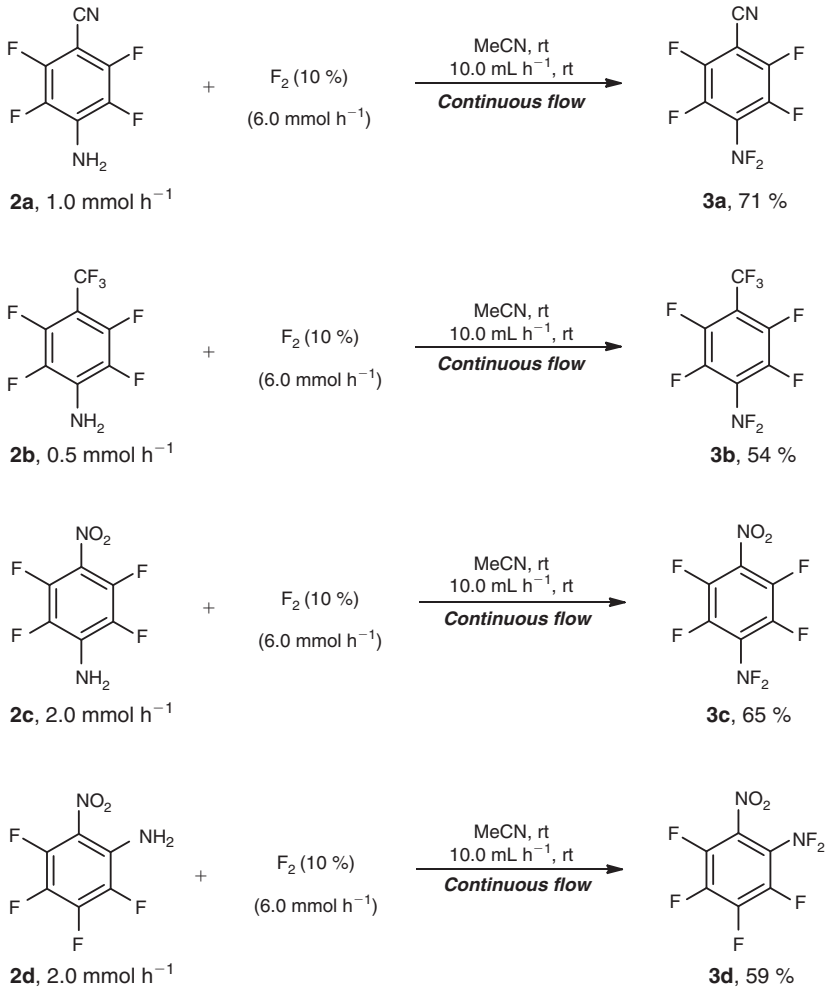


Fig. 2. 'Pipe-flow' within continuous flow reactor.

nitro group, demonstrating the very effective *ortho* activating influence of nitro groups in these systems. All products were isolated by recrystallisation or column chromatography as appropriate and NMR spectral data was consistent with the structures proposed.

Direct fluorination of anilines **2** was carried out using a flow reactor constructed from nickel metal and narrow bore nickel and PTFE tubing as described previously[5] in detail and shown in Fig. 1. Briefly, fluorine gas, diluted to 10 % *v/v* solution in nitrogen was added via a mass flow controller to the micro-channel via Input A, the aniline substrate **2**, dissolved in acetonitrile, was added at a prescribed flow rate by syringe pump into the flow channel via Input B and reacts with fluorine as both these starting materials pass down the reactor channel in a 'pipe flow' regime (Fig. 2), as observed in previous direct fluorination reactions using this reactor design.[5] The crude reaction mixture was then passed into a vessel containing water to quench the reaction. Work-up by extraction of the crude reaction mixture by dichloromethane, drying and evaporation of the organic solvent gave a crude product that could be further purified by column chromatography.

After our initial experiments involving fluorination of cyanoaniline **2a**, we found that passing a 6-fold excess of fluorine at a rate of 6 mmol h^{-1} and aniline **2a** at 1 mmol h^{-1} gave good yield of difluoroamine product **3a** (Scheme 2). ^{19}F NMR analysis of the crude product mixture before work-up showed very high conversion of **2a** to **3a** (Fig. 3) and subsequent column chromatography gave pure **3a**. A ^{19}F NMR resonance observed



Scheme 2. Synthesis of difluoroamine systems **3**.

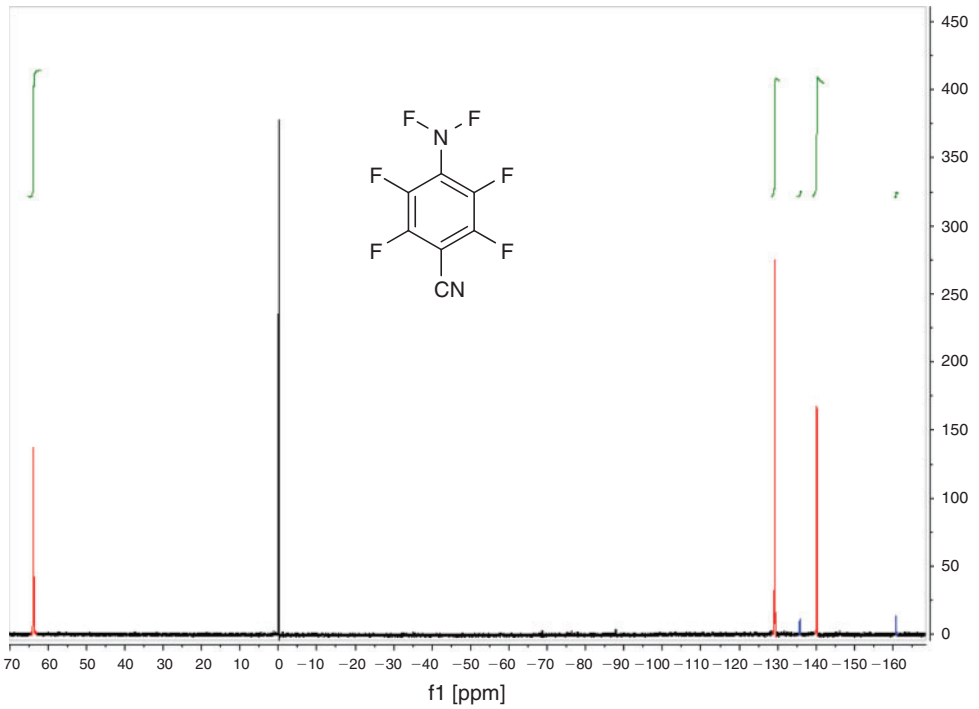
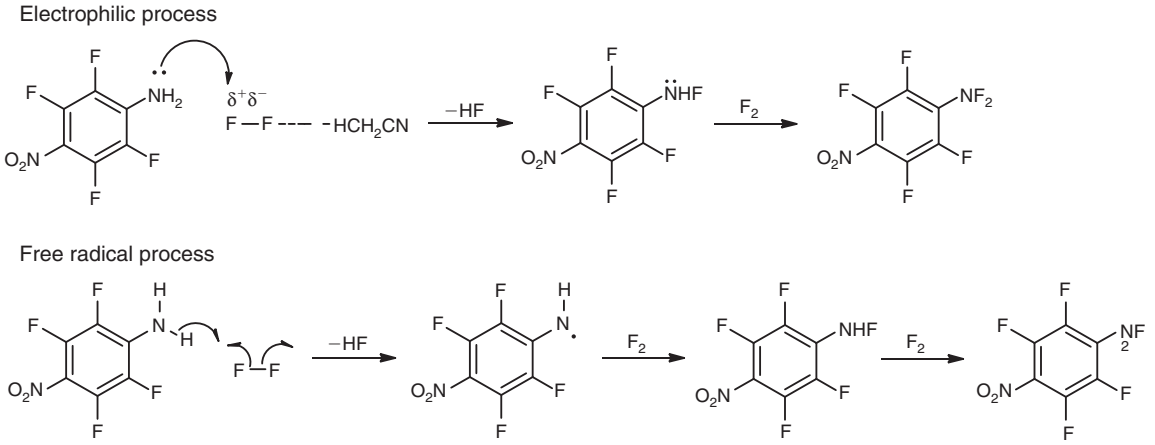


Fig. 3. ^{19}F NMR analysis of crude reaction mixture of fluorination of 4-aminobenzonitrile derivative **2a**.



Scheme 3. Possible fluorination mechanisms.

at +63.8 ppm is the diagnostic signal corresponding to an NF_2 group as compared with literature data for other N–F bonds.[32] Syntheses of other difluoroamine systems were carried out by similar processes after adjusting flow rates of fluorine to achieve full conversion of the aniline starting material.

Certain difluoroamine compounds are known to be sensitive explosives.[14,28] Whilst no difficulties were encountered in this work and, indeed, standard work-up and chromatographic purification techniques were utilised to isolate the difluoroamine products **3**, appropriate precautions should be taken when handling potentially explosive materials.

The mechanism of these fluorination processes is unclear but we can postulate both electrophilic and free radical pathways (Scheme 3).

Whilst fluorine is considered to act as an effective electrophile in acetonitrile media,[10] the low nucleophilicity of the perfluoroaniline substrates provides support for a free radical process in which the intermediate radical may be stabilised by conjugation with the aryl ring and this is consistent with a similar mechanism proposed previously.[26]

Conclusions

Efficient synthesis of perfluoroaryl difluoroamine derivatives **3** is possible using fluorination of appropriate anilines **2** in continuous flow techniques, further demonstrating the possibilities for flow syntheses using highly reactive, yet potentially very useful, reagents.

Experimental

General

Unless otherwise noted, commercially available reagents were used without purification. DMF was purified and dried using an Innovative Technology Inc. Solvent Purification System fitted with a Metrohm 831 Karl Fischer Coulometric Titrator. Hexane and DCM were purchased from Fischer and used without further purification. Flash column chromatography was performed using Fluorochem silicagel LC60A (40–63 micron). Proton, carbon and fluorine nuclear magnetic resonance spectra (^{1}H NMR, ^{13}C NMR and ^{19}F NMR) were recorded on a Varian Inova-500 (^{1}H NMR, 500 MHz; ^{13}C NMR, 126 MHz; ^{19}F NMR, 470 MHz) or a Varian DD-700 (^{1}H NMR, 700 MHz; ^{13}C NMR, 176 MHz; ^{19}F NMR, 658 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR, $CHCl_3$ at 7.26 ppm; ^{13}C NMR, $CDCl_3$ at 77.26 ppm; ^{19}F NMR, $CFCl_3$ at 0.00 ppm). ^{1}H, ^{13}C and ^{19}F spectroscopic data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constants (Hz), integration, and assignment. GC-MS analysis was performed on a Thermoquest Trace GC-MS device (Thermo-Finnigan Corp.) operating in electron impact ionisation (EI^+) mode and accurate mass analysis was achieved with a Xevo QtoF mass spectrometer (Waters Ltd, UK) equipped with an accurate solids analysis probe (ASAP). Elemental analysis data was collected using an Exeter Analytical E-440 Elemental Analyser. Infrared spectra were recorded on a Perkin Elmer Spectrum RX1 fitted with an ATR attachment whilst X-ray analysis was performed using a Rigaku R-Axis SPIDER IP diffractometer equipped with Cryostream (Oxford Cryosystems) low-temperature device at 120 K using graphite-monochromated MoK_α-radiation ($\lambda = 0.71073$ A). All reactions were heated in a Biotage Initiator^{TM} Sixty microwave.

Synthesis of Perfluoroaniline Derivatives ***2***

General Procedure

The perfluoroarene **1** was added to a flask that was then sealed and purged with argon. Ammonium hydroxide and MeCN were added and the reaction mixture was stirred at room temperature for 22 h. The reaction mixture was quenched with water (40 mL) and extracted with DCM (3 × 50 mL). The organic extracts were washed with water (150 mL) and brine (150 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product. Column chromatography on silica gel and recrystallisation gave the pure aniline derivative.

4-Amino-2,3,5,6-tetrafluorobenzonitrile ***2a***

Pentafluorobenzonitrile **1a** (6.0 g, 31.0 mmol), ammonium hydroxide (7.0 mL, 40 mmol) and MeCN (40 mL), after column chromatography on silica gel using hexane/ethyl acetate (4 : 1) as the eluent and recrystallisation (chloroform), gave *4-amino-2,3,5,6-tetrafluorobenzonitrile* **2a** (4.41 g, 74 %) as white crystals, mp 95–96°C (lit.[33] 95–96°C). ν_{max} (neat)/cm^{-1} 3228, 3358 and 3476 (NH_2), 2236 (CN), 1168, 1315, 1506 and 1640. δ_H (400 MHz, $CDCl_3$) 4.64 (br, 2H, N*H*$_2$). δ_C (176 MHz, $CDCl_3$) 80.4 (tm, $^2J_{CF}$ 17.6, C-4), 109.0 (t, $^3J_{CF}$ 3.6, -*C*N), 132.6 (tt, $^2J_{CF}$ 13.4, $^3J_{CF}$ 4.6, C-1), 135.6 (dddd, $^1J_{CF}$ 242.0, $^2J_{CF}$ 14.4, $^3J_{CF}$ 6.0, $^4J_{CF}$ 3.9, C-3), 147.9 (dddd, $^1J_{CF}$ 256.4, $^2J_{CF}$ 10.0, $^3J_{CF}$ 5.8, $^4J_{CF}$

3.7, C-2). δ_F (376 MHz, $CDCl_3$) −135.5–(−135.6) (m, 2F, F-2), −160.7–(−160.9) (m, 2F, F-3). *m/z* (EI^+) 190 ($[MH]^+$, 100 %), 162 (20), 143 (24), 124 (18).

2,3,5,6-Tetrafluoro-4-(trifluoromethyl)aniline ***2b***

Octafluorotoluene **1b** (3.0 g, 12.72 mmol), ammonium hydroxide (12.0 mL, 120 mmol) and MeCN (10 mL), after column chromatography on silica gel using hexane/ethyl acetate 4 : 1 as the eluent, gave *2,3,5,6-tetrafluoro-4-(trifluoromethyl) aniline* **2b** (1.43 g, 48 %) as a clear orange oil. ν_{max} (neat)/cm^{-1} 3600 and 3428 (NH_2), 1127, 1330, 1506 and 1654. δ_H (400 MHz, $CDCl_3$) 4.38 (br, 2H, N*H*$_2$). δ_C (176 MHz, $CDCl_3$) 97.0 (qt, $^2J_{CF}$ 34.8, $^2J_{CF}$ 21.6, C-4), 121.8 (qm, $^1J_{CF}$ 272.7, CF_3), 130.2 (tt, $^2J_{CF}$ 13.9, $^3J_{CF}$ 4.4, C-1), 136.3 (ddm, $^1J_{CF}$ 240.0, $^2J_{CF}$ 16.0, C-3), 144.9 (dm, $^1J_{CF}$ 255.3, C-2). δ_F (376 MHz, $CDCl_3$) −55.3 (t, 3F, $^4J_{FF}$ 21.1, CF_3); −144.0–(−144.3) (m, 2F, F-3), −162.0–(−162.2) (m, 2F, F-2). *m/z* (EI^+) 233 ($[M]^+$, 42 %), 214 (82), 183 (64), 117 (34), 69 (100); and as compared with literature data.[34]

Tetrafluoro-4-nitroaniline ***2c*** *and Tetrafluoro-6-nitroaniline* ***2d***

Pentafluoronitrobenzene **1c** (2.3 g, 10.8 mmol), ammonium hydroxide (2.2 mL, 22 mmol) and THF (20 mL), after column chromatography on silica gel using hexane/ethyl acetate (2 : 1) as eluent, gave **2c**, **2d**, and **2e**. *Tetrafluoro-4-nitroaniline* **2c** (0.37 g, 15 %) as yellow crystals, mp 105–106°C (lit.[35] 106–108°C). δ_H (400 MHz, $CDCl_3$) 4.62 (br, 2H, N*H*$_2$). δ_C (176 MHz, $CDCl_3$) 119.6–120.2 (m, C-1), 131.2 (tt, $^2J_{CF}$ 13.9, $^3J_{CF}$ 4.1, C-4), 135.3 (ddm, $^1J_{CF}$ 243.6, $^2J_{CF}$ 14.2, C-3), 142.1 (dddd, $^1J_{CF}$ 260.6, $^2J_{CF}$ 13.4, $^3J_{CF}$ 4.0, $^4J_{CF}$ 2.6, C-2). δ_F (376 MHz, $CDCl_3$) −147.6–(−147.8) (m, 2F, F-2), −161.6–(−161.8) (m, 2F, F-3). *m/z* (EI^+) 210 ($[M]^+$, 80 %), 180 (67), 164 (57), 144 (42), 137 (100). *Tetrafluoro-6-nitroaniline* **2d** (0.85 g, 37 %) as red crystals, mp 45–46°C (lit.[36] 43–44°C). δ_H (400 MHz, $CDCl_3$) 5.87 (br, 2H, N*H*$_2$). δ_C (176 MHz, $CDCl_3$) 120.7–121.1 (m, C-6), 132.12 (dddd, $^1J_{CF}$ 245.6, $^2J_{CF}$ 16.5, $^3J_{CF}$ 13.7, $^4J_{CF}$ 2.9, C-2), 132.3 (ddd, $^2J_{CF}$ 13.2, $^3J_{CF}$ 3.8, $^4J_{CF}$ 1.9, C-1), 136.2 (dddd, $^1J_{CF}$ 243.2, $^2J_{CF}$ 12.5, $^3J_{CF}$ 5.5, $^4J_{CF}$ 2.3, C-5), 143.7 (ddt, $^1J_{CF}$ 262.4, $^2J_{CF}$ 12.8, $^3J_{CF}$ 4.7, C-3 or C-4), 144.2 (dtd, $^1J_{CF}$ 260.2, $^2J_{CF}$ 13.9, $^3J_{CF}$ 4.6, C-4 or C-3). δ_F (376 MHz, $CDCl_3$) −145.5 (dt, $^3J_{FF}$ 22.6, $^4J_{FF}$ 8.9, 1F, F-3 or F-4), −147.5 (td, $^3J_{FF}$ 21.4, $^4J_{FF}$ 8.9, 1F, F-3 or F-4), −160.5 (ddd, $^3J_{FF}$ 20.6, $^4J_{FF}$ 8.9, $^5J_{FF}$ 5.9, 1F, F-2 or F-5), −164.3 (td, $^3J_{FF}$ 22.4, $^4J_{FF}$ 5.8, 1F, F-2 or F-5). *m/z* (EI^+) 207 ($[M]^+$, 81 %), 177 (50), 161 (58), 134 (100). *2,4,5-Trifluoro-6-nitrobenzene-1,3-diamine* **2e** (0.42 g, 19 %) as yellow crystals, mp 145–147°C (lit.[35] 147–148°C). δ_H (400 MHz, $CDCl_3$) 4.48 (br, 2H, N*H*$_2$), 5.86 (br, 2H, N*H*$_2$). δ_C (176 MHz, $CDCl_3$) 113.6–113.9 (m, C-3), 131.8 (ddd, $^1J_{CF}$ 234.5, $^2J_{CF}$ 16.4, $^3J_{CF}$ 7.9, C-4), 133.0 (dm, $^1J_{CF}$ 226.2, C-2), 133.0 (td, $^2J_{CF}$ 15.0, $^3J_{CF}$ 4.5, C-3), 143.6 (ddd, $^1J_{CF}$ 254.8, $^2J_{CF}$ 12.9, $^4J_{CF}$ 3.2, C-5). δ_F (376 MHz, $CDCl_3$) −147.9 (dd, $^3J_{FF}$ 21.5, $^4J_{FF}$ 8.9, 1F, F-4), −163.4 (dd, $^4J_{FF}$ 8.9, $^5J_{FF}$ 2.0, 1F, F-2), −172.2 (dd, $^3J_{FF}$ 21.5, $^5J_{FF}$ 2.0, 1F, F-5). *m/z* (EI^+) 207 ($[M]^+$, 81 %), 177 (50), 161 (58), 134 (100).

Synthesis of Difluoramine Derivatives ***3***

General Procedure

***CAUTION*:** Although 10 % *v/v* fluorine in nitrogen is relatively easy to handle as described previously,[37] it is still a potent oxidising agent and must be treated as such. Appropriate precautions must also be taken with regards to HF handling, including the provision of calcium gluconate antidote gel. Whilst fluorine is less toxic than widely used chlorine gas,[39] appropriate safety precautions using standard research grade fume cupboards are required.

Certain difluoroamine compounds are known to be sensitive explosives.[14,38] Whilst no difficulties were encountered in this work, appropriate precautions should be taken when handling potentially explosive materials.

Using the continuous flow device shown in Fig. 3, fluorine in N_2 (10 % *v/v*) was passed into the flow reactor channel via inlet 1 at an appropriate rate, which was controlled by a gas flow meter (Brooks®) and, simultaneously, aniline derivative **2** in MeCN was added via inlet 2 at a rate controlled by syringe pump over a period of 30 min. All liquid products were collected in a vessel containing water (25 mL), whilst excess gasses were vented through a soda lime scrubber. The reactants were extracted from the aqueous layer using DCM (3 × 25 mL) and the organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield the crude product as an orange oil. Purification by column chromatography on silica gel gave the difluoroamine **3**.

4-(Difluoroamino)-2,3,5,6-tetrafluorobenzonitrile ***3a***

F_2 (10 % in N_2, 6.0 mmol h^{-1}), MeCN (10.0 mL h^{-1}) and 4-amino-2,3,5,6-tetrafluorobenzonitrile **2a** (0.283 g, 1.50 mmol, 10.0 mL h^{-1}, 1.0 mmol h^{-1}) in DCM (15.0 mL), after column chromatography on silica gel using hexane/DCM (2 : 1) as the eluent, gave *4-(difluoroamino)-2,3,5,6-tetrafluorobenzonitrile* **3a** (0.24 g, 71 %) as a clear oil. δ_C (126 MHz, $CDCl_3$) 98.9 (tt, $^2J_{CF}$ 17.1, $^3J_{CF}$ 2.1, C-1), 106.1 (s, CN), 130.1 (t, $^2J_{CF}$ 8.9, C-4), 142.5 (dddd, $^1J_{CF}$ 267.9, $^2J_{CF}$ 21.5, $^3J_{CF}$ 14.3, $^4J_{CF}$ 8.1, C-2), 147.7 (ddm, $^1J_{CF}$ 268.0, $^2J_{CF}$ 12.6, C-3). δ_F (376 MHz, $CDCl_3$) 63.8 (t, $^4J_{FF}$ 10.3, 2F, NF_2), −129.3 (ddm, $^3J_{FF}$ 20.8, $^4J_{FF}$ 10.4, 2F, F-3), −140.2 (ddm, $^3J_{FF}$ 20.3, $^4J_{FF}$ 10.3, 2F, F-2). *m/z* (ASAP) 227 ($[MH]^+$, 5 %), 207 (100), 191 (40), 160 (17).

2,3,5,6-Tetrafluoro-4-(trifluoromethyl)difluoramine ***3b***

F_2 (10 % in N_2, 6.0 mmol h^{-1}), MeCN (10.0 mL h^{-1}) and 2,3,5,6-tetrafluoro-4-(trifluoromethyl)aniline **2b** (0.06 g, 0.25 mmol, 5.0 mL h^{-1}, 0.5 mmol h^{-1}) in DCM (2.5 mL), after column chromatography on silica gel using hexane/DCM (2 : 1) as the eluent, gave *2,3,5,6-tetrafluoro-4-(trifluoromethyl) difluoramine* **3b** (0.04 g, 54 %) as a clear oil. δ_C (126 MHz, $CDCl_3$) 95.1 (tt, $^2J_{CF}$ 17.0, $^3J_{CF}$ 3.8, C-1), 103.1 (m, CF_3), 129.0 (t, $^2J_{CF}$ 9.4, C-4), 143.8 (ddd, $^1J_{CF}$ 262.0, $^2J_{CF}$ 20.5, $^3J_{CF}$ 14.0, C-2), 147.7 (ddm, $^1J_{CF}$ 268.0, $^2J_{CF}$ 12.3, C-3). δ_F (376 MHz, $CDCl_3$) 64.0 (t, $^4J_{FF}$ 10.2, 2F, NF_2), −57.1 (t, $^2J_{FF}$ 22.3, 3F, CF_3), −137.7 (ddm, $^3J_{FF}$ 22.1, $^4J_{FF}$ 9.4, 2F, F-2), −141.8 (ddm, $^3J_{FF}$ 19.3, $^4J_{FF}$ 9.7, 2F, F-3); *m/z* (ASAP) 270 ($[MH]^+$, 18 %), 217 (53).

2,3,5,6-Tetrafluoro-4-nitro-1-difluoramine ***3c***

F_2 (10 % in N_2, 6.0 mmol h^{-1}), MeCN (10.0 mL h^{-1}) and 2,3,5,6-tetrafluoro-4-nitroaniline **2c** (0.21 g, 1.0 mmol, 10.0 mL h^{-1}, 2.0 mmol h^{-1}) in DCM (5.0 mL), after column chromatography on silica gel using hexane/DCM (4 : 1) as the eluent, gave *2,3,5,6-tetrafluoro-4-nitro-1-difluoramine* **3c** (0.16 g, 65 %) as a yellow oil. δ_C (126 MHz, $CDCl_3$) 128.3 (t, $^2J_{CF}$ 9.7, C-4), 133.0–133.4 (m, 1C, C-1), 140.4 (ddd, $^1J_{CF}$ 266.0, $^2J_{CF}$ 14.8, $^3J_{CF}$ 6.1, C-3), 142.9 (ddd, $^1J_{CF}$ 270.0, $^2J_{CF}$ 12.9, $^3J_{CF}$ 6.8, C-2). δ_F (376 MHz, $CDCl_3$) 64.2 (t, $^4J_{FF}$ 10.0, 2F, NF_2), −138.8–(−139.3) (m, 2F, F-2), −143.8–(−144.1)

(m, 2F, F-3), *m/z* (ASAP) 247 ($[MH]^+$, 25 %), 217 (100), 194 (33), 84 (81).

2,3,4,5-Tetrafluoro-6-nitro-1-difluoramine ***3d***

F_2 (10 % in N_2, 6.0 mmol h^{-1}), MeCN (10.0 mL h^{-1}) and 2,3,4,5-tetrafluoro-6-nitroaniline **2d** (0.63 g, 3.0 mmol, 10.0 mL h^{-1}, 2.0 mmol h^{-1}) in DCM (15.0 mL), after column chromatography on silica gel using hexane/DCM (2 : 1) as the eluent, gave *2,3,4,5-tetrafluoro-6-nitro-1-difluoramine* **3d** (0.44 g, 59 %) as a pale yellow oil. δ_C (126 MHz, $CDCl_3$) 124.2–124.5 (m, C-6), 132.1–132.9 (m, C-1), 140.3 (ddd, $^1J_{CF}$ 264.5, $^2J_{CF}$ 13.8, $^3J_{CF}$ 5.7, C-2/5), 143.4 (dt, $^1J_{CF}$ 265.0, C-3/4), 143.7 (dm, 270.0, C-2/5), 144.4 (dt, $^1J_{CF}$ 268.5, C-3/4). δ_F (376 MHz, $CDCl_3$) 64.2 (t, $^4J_{FF}$ 10.0, 2F, NF_2), −136.1–(−136.9) (m, 1F, F-2/5), −141.6 (tm, $^3J_{FF}$ 20.6, 1F, F-3/4) −145.2 (ddd, $^3J_{FF}$ 21.7, $^4J_{FF}$ 9.2, $^5J_{FF}$ 5.4, 1F, F-5/2), −145.6 (td, $^3J_{FF}$ 20.5, $^4J_{FF}$ 5.3, 1F, F-4/3). *m/z* (ASAP) 247 ($[MH]^+$, 27 %), 217 (100), 194 (44), 84.0 (70).

Acknowledgements

We thank AWE and Durham University for funding (studentship to C. B. McPake).

References

[1] W. Ehrfeld, V. Hessel, H. Lowe, *Microreactors: New Technology for Modern Chemistry* **2000** (Wiley-VCH: New York, NY).
[2] C. Wiles, P. Watts, *Micro Reactor Technology in Organic Synthesis* **2011** (CRC Press: Boca Raton, FL).
[3] F. E. Valera, M. Quaranta, A. Moran, J. Blacker, A. Armstrong, J. T. Cabral, D. G. Blackmond, *Angew. Chem. Int. Ed.* **2010**, *49*, 2478. doi:10.1002/ANIE.200906095
[4] G. Sandford, *J. Fluor. Chem.* **2007**, *128*, 90. doi:10.1016/J.JFLUCHEM.2006.10.019
[5] R. D. Chambers, M. A. Fox, D. Holling, T. Nakano, T. Okazoe, G. Sandford, *Lab Chip* **2005**, *5*, 191. doi:10.1039/B416400H
[6] R. D. Chambers, D. Holling, G. Sandford, *PCT/GB03/01993* **2002**.
[7] R. D. Chambers, J. Hutchinson, M. E. Sparrowhawk, G. Sandford, J. S. Moilliet, J. Thomson, *J. Fluor. Chem.* **2000**, *102*, 169. doi:10.1016/S0022-1139(99)00238-9
[8] R. D. Chambers, M. Parsons, G. Sandford, C. J. Skinner, M. J. Atherton, J. S. Moilliet, *J. Chem. Soc., Perkin Trans. 1* **1999**, 803. doi:10.1039/A809838G
[9] D. Holling, G. Sandford, A. S. Batsanov, D. S. Yufit, J. A. K. Howard, *J. Fluor. Chem.* **2005**, *126*, 1377. doi:10.1016/J.JFLUCHEM.2005.07.007
[10] R. D. Chambers, M. P. Greenhall, J. Hutchinson, *Tetrahedron* **1996**, *52*, 1. doi:10.1016/0040-4020(95)00883-A
[11] R. D. Chambers, M. A. Fox, G. Sandford, *Lab Chip* **2005**, *5*, 1132. doi:10.1039/B504675K
[12] K. Baum, *J. Am. Chem. Soc.* **1968**, *90*, 7083. doi:10.1021/JA01027A035
[13] R. K. Belter, *J. Fluor. Chem.* **2012**, *137*, 73. doi:10.1016/J.JFLUCHEM.2012.02.013
[14] R. D. Chapman, in *High Energy Density Materials* (Ed. T. M. Klapoetke) **2007**, Vol. 125, pp. 123–151 (Springer: Berlin). doi:10.1007/430_2007_058
[15] R. D. Chapman, M. C. Davis, R. Gilardi, *Synth. Commun.* **2003**, *33*, 4173. doi:10.1081/SCC-120026361
[16] R. D. Dresdner, F. N. Tlumac, J. A. Young, *J. Am. Chem. Soc.* **1960**, *82*, 5831. doi:10.1021/JA01507A016
[17] W. P. Graham, J. P. Freeman, *J. Am. Chem. Soc.* **1967**, *89*, 716. doi:10.1021/JA00979A058
[18] R. Haiges, R. D. Chapman, K. O. Christe, R. Wagner, J. A. Boatz, M. Yousufuddin, M. Etzkorn, G. K. S. Prakash, M. F. Welker, C. B. Kreutzberger, *Angew. Chem. Int. Ed.* **2006**, *45*, 5179. doi:10.1002/ANIE.200601020
[19] G. K. S. Prakash, G. A. Olah, C. Bae, M. Kroll, *J. Fluor. Chem.* **2002**, *117*, 103. doi:10.1016/S0022-1139(02)00155-0
[20] S. F. Reed, R. D. Shoults, *J. Org. Chem.* **1972**, *37*, 3326. doi:10.1021/JO00986A027
[21] C. M. Sharts, *J. Org. Chem.* **1968**, *33*, 1008. doi:10.1021/JO01267A014
[22] J. M. Shreeve, R. P. Singh, *Chem. Commun.* **2001**, 1196.
[23] A. V. Fokin, Y. N. Studnev, A. I. Rapkin, L. D. Kuznetsova, *Russ. Chem. Bull.* **1996**, *45*, 2547. doi:10.1007/BF01431113
[24] T. Takagi, M. Tamura, M. Shibakami, H. Quan, A. Sekiya, *J. Fluor. Chem.* **2000**, *101*, 15. doi:10.1016/S0022-1139(99)00191-8
[25] G. K. S. Prakash, G. A. Olah, M. Etzkorn, K. O. Christe, S. Schneider, A. Vij, *Chem. Commun.* **2002**, 1712. doi:10.1039/B203811K
[26] C. L. Coon, M. E. Hill, D. L. Ross, *J. Org. Chem.* **1968**, *33*, 1387. doi:10.1021/JO01268A019
[27] M. W. Lerom, H. M. Peters, D. L. Ross, M. E. Hill, J. Dick, *J. Chem. Eng. Data* **1974**, *19*, 389. doi:10.1021/JE60063A001
[28] R. K. Belter, *J. Fluor. Chem.* **2011**, *132*, 961. doi:10.1016/J.JFLUCHEM.2011.07.024
[29] C. A. Hargreaves, G. Sandford, R. Slater, D. S. Yufit, J. A. K. Howard, A. Vong, *Tetrahedron* **2007**, *63*, 5204. doi:10.1016/J.TET.2007.03.164
[30] G. Sandford, R. Slater, D. S. Yufit, J. A. K. Howard, A. Vong, *J. Org. Chem.* **2005**, *70*, 7208. doi:10.1021/JO0508696
[31] R. D. Chambers, *Fluorine in Organic Chemistry* **2004** (Blackwell: Oxford).
[32] W. R. Dolbier, *Guide to Fluorine NMR for Organic Chemists* **2009** (John Wiley and Sons: New York, NY).
[33] R. D. Chambers, P. A. Martin, G. Sandford, D. L. H. Williams, *J. Fluor. Chem.* **2008**, *129*, 998. doi:10.1016/J.JFLUCHEM.2008.04.009
[34] R. D. Chambers, P. A. Martin, J. S. Waterhouse, D. L. H. Williams, B. Anderson, *J. Fluor. Chem.* **1982**, *20*, 507. doi:10.1016/S0022-1139(00)82276-9
[35] G. M. Brooke, *J. Chem. Soc.* **1961**, 802. doi:10.1039/JR9610000802
[36] L. J. Belf, M. W. Buxton, J. F. Tilney-Bassett, *Tetrahedron* **1967**, *23*, 4719. doi:10.1016/S0040-4020(01)92570-0
[37] R. D. Chambers, J. Hutchinson, G. Sandford, *J. Fluor. Chem.* **1999**, *100*, 63. doi:10.1016/S0022-1139(99)00202-X
[38] R. J. Koshar, D. R. Husted, C. D. Wright, *J. Org. Chem.* **1967**, *32*, 3859. doi:10.1021/JO01287A031
[39] American Environmental Group Ltd, AEGL (Acute Exposure Guideline Level) (50) October 2 **2009**.