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Elemental Fluorine. Part 21.[1] Direct Fluorination of Benzaldehyde Derivatives

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Abstract:

Direct fluorination of a range of benzaldehyde derivatives gives mixtures of fluorobenzaldehyde and benzoyl fluoride products in ratios that depend upon the nature of the ring substituent. Electron-withdrawing substituents give predominantly benzoyl fluoride derivatives, whereas electron-donating substituents lead to fluoroarene systems. Separation of ring-fluorinated products can be easily accomplished by esterification of the benzoyl fluoride side products. Scale-up of these processes to provide significant quantities of appropriate fluorobenzaldehyde systems has also been achieved using continuous flow techniques.

1. Introduction

Many selectively fluorinated molecules, that is, systems bearing CF, CF_2 or CF_3 units, are commercially very important products,[2] and for instance, it is estimated that nearly one-fifth of pharmaceuticals currently the focus of clinical trials possess at least one fluorine atom in their structures.[3] Fluorinated units are present in several leading drugs such as Prozac and Ciprofloxacin, and many commercially successful plant protection agents exemplify the importance of fluorine containing molecules to the life science industries.[3,4]

The synthesis of fluorinated molecules often presents some unique challenges.[2,4] and in any synthetic strategy towards a particular target molecule the chemist must decide between introducing fluorine atoms into a molecule at a late stage, by carrying out carbon−fluorine bond formation using an appropriate fluorinating agent,[2,4] or at an early stage, by using a suitable fluorinated building bock for appropriate carbon−carbon bond-forming reactions.[5] Of course, whichever route is chosen, a carbon−fluorine bond must be synthesised at some stage of the synthetic sequence to either form a target molecule directly or to produce an appropriate functionalised fluorinated building block. Whilst many fluorinating reagents are available to the synthetic chemist for the selective fluorination of a variety of molecular targets and functional group transformations,[4] large-scale manufacture of fluorinated compounds requires the application of readily available and, especially, inexpensive fluorinating agents. Consequently, HF and KF are the major fluorinating agents that are used by industry despite the specialist equipment that is required to handle the highly corrosive anhydrous HF and the frequently harsh conditions required for reactions involving KF. There is, therefore, a continued requirement for the development of other cost-effective, selective fluorinating agents for industrial use to make a wider range of functional fluorinated building blocks available at a realistic cost.

Elemental fluorine gas, F_2, is generated inexpensively by electrolysis from HF on a very large scale for the nuclear power industry.[6] Fluorine could, in principle, be used widely for industrial fluorination processes, but although 5-fluorouracil, a leading drug in the treatment of solid tumours, has been synthesised by direct fluorination of uracil[3] in acetic acid for over 40 years, the use of fluorine in industry has not developed to any great extent, mainly due to the continued perception that has built up over the years that reactions of elemental fluorine are uncontrollable. Now, efficient thermal control of reactions using dilute mixtures of fluorine in inert gases as well as using appropriate aprotic or acidic reaction media is changing this widely held view. At Durham,[1,7,8] we have utilised formic and sulfuric acid and acetonitrile media for the selective fluorination of a range of aromatic,[9,10] heterocyclic,[11–13] carbonyl,[14] dicarbonyl,[15] hydrocarbon[16] and carbohydrate[17] derivatives. In particular, direct fluorination of ketoesters, first reported in 1996,[18] was subsequently scaled up in a remarkably short time period by F2 Chemicals Ltd. (UK) to provide the fluorinated building block necessary for incorporation into Veroconazole, a Pfizer product.[19]

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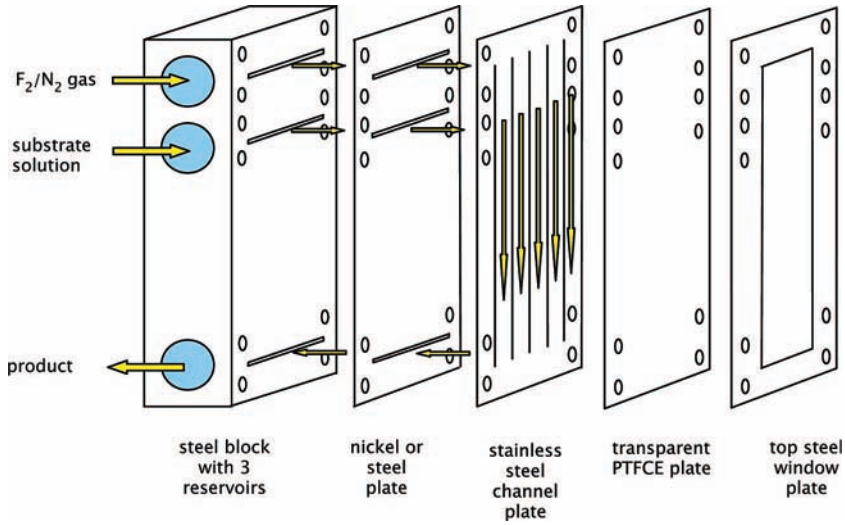

Figure 1. **Schematic representation of modular microreactor device.**

Furthermore, whilst batch-wise processes, involving passage of fluorine diluted in nitrogen into a rapidly stirred solution of substrate, have been used successfully for fluorination processes, continuous flow reactors have been developed at Durham that enable very effective, simple scale-up of gas/liquid reactions.[20–25] A multichannel device,[20] where gas and liquid reagents are supplied to many channels from single feedstock reservoirs, allowing the large-scale synthesis of fluorinated derivatives (e.g., 100 g of fluorinated ketoesters can be produced from a single 9-channel device in a 24 h period), is shown in Figure 1.

In this paper, we continue our studies on the use of elemental fluorine[1] as a viable reagent for organic synthesis in studies concerning the direct fluorination of a variety of benzaldehyde derivatives using both batch and continuous flow techniques. Fluoroaromatic systems, which may be accessed by direct fluorination rather than multistep fluorodediazoniation processes, are very important building blocks for application in the life science and materials industries.[26] Direct fluorination of various methoxy benzaldehyde derivatives have been reported previously to give the corresponding fluoroaromatic products.[9]

2. Results and Discussion

Direct fluorination of benzaldehyde **1a** in acetonitrile at 0 °C gave a mixture of four products **2a**−**d** in 48% conversion in the ratio 0.9:5.2:1.9:1, arising from displacement of the *ortho*, *meta*, *para* and aldehydic hydrogen atoms, respectively. Reaction conversion and ratio of products was measured by GCMS and ^{19}F NMR analysis of the crude reaction mixture with an added internal reference and comparison with literature data. Benzoyl fluoride **2d** was detected ($\delta_F = +20.3$ ppm), and since benzoyl fluoride is readily hydrolysed, making isolation difficult, 3,5-dinitrobenzyl alcohol and pyridine were added to the crude reaction mixture, which was then heated to room temperature in order to transform the acid fluoride into an easily isolable, hydrolytically stable ester **3a** for characterisation purposes. It is, therefore, a very simple procedure in principle to separate out ring fluorinated products from side chain fluorinated systems due to the ready hydrolysis of acid fluorides. The yield of the ester **3a** is calculated from the two-step reaction of **1a**.

Fluorinations of a range of *para*-substituted benzaldehyde derivatives **1** were performed under similar conditions, and where appropriate, esters **3** formed upon addition of dinitrobenzyl alcohol and pyridine to the reaction mixture for characterization. In each case the ratios of products were measured by ^{19}F NMR analysis before reaction work-up so handling losses are not reflected in the results (Table 1). Fluoroarenes **2f,g,h,k** were isolated by column chromatography and identified by comparison with authentic samples.

Both 4-methyl- and 4-methoxy-benzaldehyde, **1b** and **1c**, gave fluoroaromatic products **2e,f** and **2g,h**, respectively, consistent with an electrophilic substitution process, and no benzoyl fluoride derivatives were observed in either case. In contrast, 4-trifluoromethyl- and 4-cyano-benzaldehyde, **1d** and **1e**, gave the corresponding acid fluorides **2j** and **2l** in significant quantities, and these were characterised as esters **3c** and **3d**, respectively.

By similar processes, a short series of *meta*-substituted benzaldehyde derivatives **4** in which both substituents are electron-withdrawing groups gave mixtures of the corresponding 5-fluoroaromatic and benzoyl fluoride products **5**. The benzoyl fluorides were isolated and characterised as the corresponding esters **6** by the techniques described above, and fluoroarenes **5a,c,e** were isolated by column chromatography and identified by comparison with authentic samples (Table 2).

The results in Tables 1 and 2 indicate that the relative proportions of products arising from fluorination of the aromatic ring or the aldehyde group depends on the nature of the ring substituent. In all cases, when a strong electron-withdrawing group is attached to the ring (NO_2, CN), then fluorination occurs preferentially on the carbonyl group to give the corresponding

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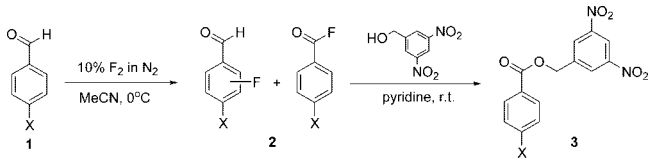
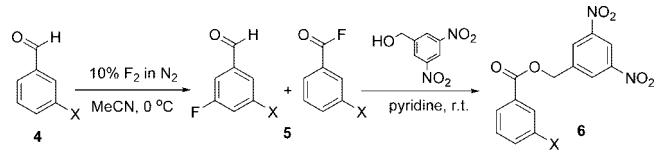
Table 1. **Fluorination of *para*-substituted benzaldehyde derivatives 1[a]**



Benzaldehyde **1**	Conv. (%)	Products **2** (Ratio and isolated yield %)	Benzoate product **3**
1b	58%	**2e*** **2f**, 73% **2e** : **2f**, 1 : 7.3	-
1c	66%	**2g**, 79% **2h**, 12% **2g** : **2h**, 5 : 1	-
1d	35%	**2i*** **2j*** **2i** : **2j**, 1 : 2	**3c**, 61%
1e	44%	**2k**, 12% **2l*** **2k** : **2l**, 1 : 4	**3d**, 54%

[a] Asterisk (*) denotes compound was not isolated.

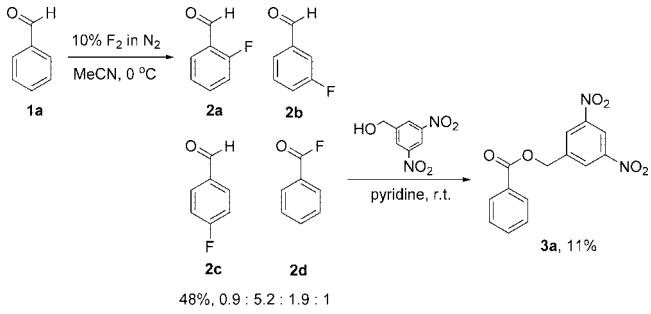
Table 2. **Fluorination of *meta*-substituted benzaldehyde derivatives 4[a]**



Benzaldehyde **4**	Conv. (%)	Products **5** (Ratios and isolated yields)	Benzoate product **6**
4a	39%	**5a**, 15% **5b*** **5a** : **5b**, 1 : 4.1	**6a**, 64%
4b	34%	**5c**, 23% **5d*** **5c** : **5d**, 1 : 3.2	**6b**, 75%
4c	38%	**5e**, 24% **5f*** **5e** : **5f**, 1 : 2.3	**6c**, 61%
4d	16%	**5g*** **5h*** **5g** : **5h**, 1.6 : 1	**6d**, 37%

[a] Asterisk (*) denotes isolated yield.

Scheme 1. **Fluorination of benzaldehyde 1a**

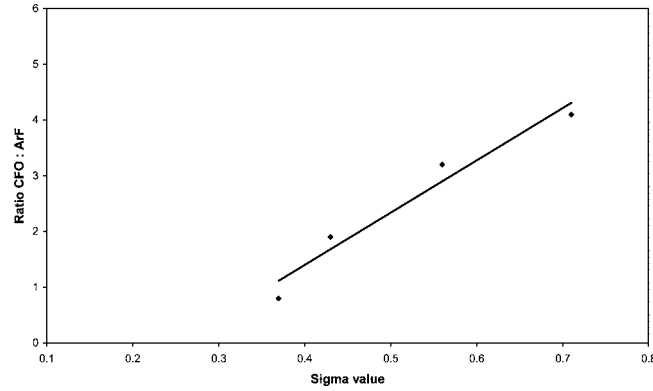


benzoyl fluoride derivative, whereas for fluoroarenes bearing electron-donating substituents (CH_3, OCH_3), fluorination of the aromatic ring occurs exclusively. The electronic effects of substituents may be described by σ-values, and a plot of the ratio of benzoyl fluoride to ring fluorination against σ_m value shows that there is a reasonable correlation between the amount of benzoyl fluoride derivative formed and σ_m value (Scheme 2).

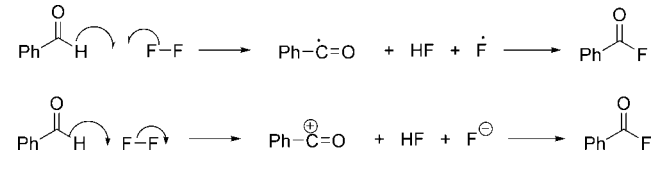
These results suggest that aromatic rings bearing electron-withdrawing groups are too deactivated towards electrophilic attack, and consequently, competing reaction at the aldehyde group is favoured. Conversely, systems bearing electron-donating groups are sufficiently activated towards electrophilic attack for electrophilic aromatic substitution to predominate.

Whilst fluorination of the arene ring is consistent with an electrophilic substitution process, the mechanism for the fluorination of the aldehyde group is less clear, and either an

Scheme 2. **Correlation between fluorination product ratio and σ_m values**

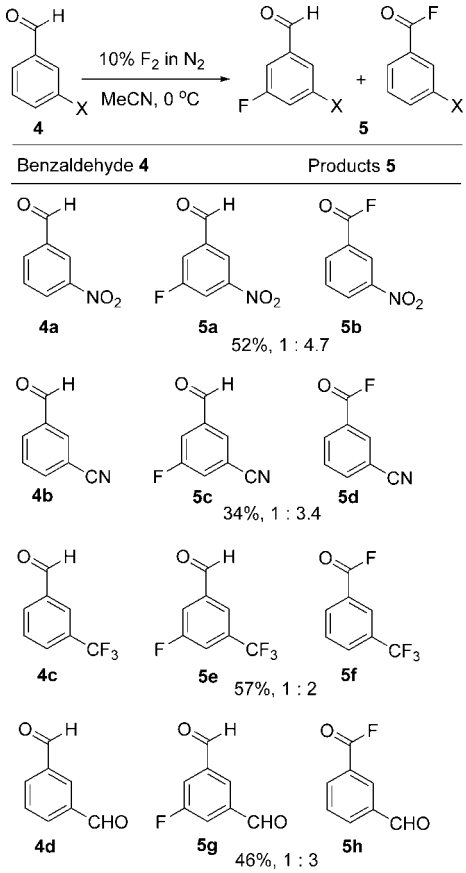


Scheme 3. **Possible mechanisms for substitution of aldehydic protons**



electrophilic or a radical process can be envisaged (Scheme 3). However, the selectivity of the process suggests the electrophilic process is more likely especially under the reaction conditions that have been established to favour an electrophilic process.[10,18]

Table 3. **Fluorinations of *m*-benzaldehydes 4 using a 9-channel microreactor**



Fluorination of several benzaldehyde derivatives were carried out using the 9-channel continuous flow reactor shown in Figure 1, and these results are collated in Table 3. In all cases, the ratio of fluorinated aromatic ring to benzoyl fluoride products remains similar to those obtained using the conventional batch techniques outlined above.

In summary, direct fluorination of a range of benzaldehyde derivatives by either conventional batch or continuous flow processes give mixtures of fluoroarenes and benzoyl fluoride products in ratios that depend upon the nature of the ring substituent. Whilst various batch wise direct fluorination processes have been scaled-up to multikilogram scale,[19] the use of continuous flow process techniques would, in principle, also allow the production of very large quantities of appropriate fluorinated products.

3. Experimental Section

3.1. General. All starting materials were obtained commercially, and all solvents were dried using literature procedures. NMR spectra were recorded in deuteriochloroform, unless otherwise stated, on a Varian VXR 400S NMR spectrometer with tetramethylsilane and trichlorofluoromethane as internal standards. Spectral assignments were made with the aid of data collected by $^1H-^1H$ COSY and $^1H-^{13}C$ HETCOR experiments, and coupling constants are given in hertz. In ^{19}F NMR spectra, upfield shifts are quoted as negative. Mass spectra were recorded on either a VG 7070E spectrometer or a Fisons VG Trio 1000 spectrometer coupled with a Hewlett-Packard 5890 series II gas chromatograph. Accurate mass measurements were performed by the EPSRC National Mass Spectrometry service, Swansea, UK. 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. Column chromatography was carried out on silica gel (Merck No. 1-09385, 230–400 mesh), and TLC analysis was performed on silica gel TLC plates using dichloromethane as eluant.

3.2. Batch Reactions with Elemental Fluorine with Benzaldehyde Derivatives. General Procedure. Elemental fluorine, as a 10% (v/v) mixture with nitrogen, was passed at a rate of ca. 50 mL min^{-1} through a stirred, cooled (0 °C) mixture that consisted of the benzaldehyde substrate and acetonitrile. After addition of the fluorine, the reaction mixture was poured into water (100 mL), neutralised ($NaHCO_3$) and extracted with dichloromethane (3 × 40 mL). The combined, dried ($MgSO_4$) organic extracts were evaporated to give a crude product. The composition of a weighed crude reaction mixture was determined by GCMS analysis, and the conversion of starting material was calculated from GC peak intensities. The amount of fluorinated product in the crude product was determined by adding a known amount of fluorobenzene to a weighed amount of the crude product mixture, and comparison of the relative intensities of the appropriate ^{19}F NMR resonances gave the yield and ratios of fluorinated derivative, based upon the conversion obtained above. Analytical samples of fluorinated products were obtained by either preparative-scale GC or column chromatography. Yields of fluorinated products are based on the conversion of starting material and identified by comparison with an authentic sample.

Where appropriate, 3,5-dinitrophenylmethanol and pyridine (1 mL) were added to the reaction mixture, which was then stirred for 2 h. The reaction mixture was poured into water, extracted by dichloromethane (3 × 100 mL), dried ($MgSO_4$) and evaporated to give a dark brown crude product, which was purified as the ester by column chromatography on silica gel.

*Fluorination of Benzaldehyde **1a.*** Elemental fluorine (56 mmol) and benzaldehyde **1a** (1.4 g, 13 mmol) in acetonitrile (150 mL) gave a crude reaction mixture (48% conv) that contained 2-fluorobenzaldehyde **2a**, δ_F −120.4 (dd, $^3J_{HF}$ = 9.48, $^3J_{HF}$ = 7.81); 3-fluorobenzaldehyde **2b**, δ_F −111.6 (dd, $^3J_{HF}$ = 9.48, $^3J_{HF}$ = 7.81); 4-fluorobenzaldehyde **2c**, δ_F −103.3 (dd, $^3J_{HF}$ = 9.48, $^3J_{HF}$ = 7.81); and benzoyl fluoride **2d**, δ_F 20.3 (s); in the ratio 0.9: 5.2: 1.9: 1.

After reaction with 3,5-dinitrophenylmethanol and pyridine (1 mL), purification by column chromatography gave 3,5-dinitrobenzyl-benzoate **3a** (0.21 g, 11%) as a white solid; mp 164–165 °C; (found C, 55.6; H, 3.3; N, 9.2. $C_{14}H_{10}N_2O_6$ requires C, 55.6; H, 3.3; N, 9.3); δ_H 5.56 (2H, s, CH_2), 7.50 (2H, m, H-3), 7.61 (1H, m, H-4), 8.08 (2H, m, H-2), 8.66 (2H, m, H-2′), 9.03 (1H, m, H-4′); δ_c 64.5 (s, CH_2), 118.8 (s, C-4′), 128.1 (s, C-3), 128.9 (s, C-2′) 129.2 (s, C-1), 130.0 (s, C-2), 134.0 (s, C-4), 140.9 (s, C-1′), 149.2 (s, C-3′), 166.1 (s, *C*=O); *m/z* (EI^+) 302 ($[M]^+$, 18%), 104 (100), 77 (72).

*Fluorination of para-Substituted Benzaldehydes **1**. 4-Methyl Benzaldehyde 1b.* Elemental fluorine (37.5 mmol) and 4-methyl benzaldehyde **1b** (1.5 g, 12.5 mmol) in acetonitrile (150 mL)

gave a crude reaction mixture (58% conv) that contained 2-fluoro-4-methylbenzaldehyde **2e**, δ_F −126.9 (t, $^3J_{HF}$ = 6.77), and 3-fluoro-4-methylbenzaldehyde **2f**, δ_F −116.5 (qt, $^3J_{HF}$ = 10.16, $^5J_{HF}$ = 2.07), in the ratio 1:7.3.

The reaction mixture was poured into water, extracted by dichloromethane (3 × 100 mL), dried ($MgSO_4$) and evaporated to give a dark crude product. Purification by column chromatography gave 3-fluoro-4-methylbenzaldehyde **2f** (0.73 g, 73%) as a bright yellow liquid; (found C 69.3; H, 5.4. C_8H_7FO requires C, 69.5; H, 5.1); δ_F −116.5 (qt, $^3J_{HF}$ = 10.16, $^5J_{HF}$ = 2.07); δ_H 2.23 (3H, d, $^4J_{HF}$ = 1.90, CH_3), 7.21 (1H, m, H-5), 7.36 (1H, m, H-2), 7.45 (1H, m, H-6), 9.87 (1H, br s, CHO); δ_c 14.5 (d, $^3J_{CF}$ = 3.52, CH_3), 122.5 (d, $^2J_{CF}$ = 22.9, C-2), 126.1 (d, $^4J_{CF}$ = 3.0, C-6), 132.3 (d, $^3J_{CF}$ = 4.78, C-5), 132.2 (d, $^2J_{CF}$ = 18.8, C-4), 136.2 (d, $^3J_{CF}$ = 5.21, C-1), 160.6 (d, $^1J_{CF}$ = 246.3, C-F), 191.0 (d, $^4J_{CF}$ = 2.03, CHO); *m/z* (EI^+) 138 ($[M]^+$, 100%), 137 (88), 113 (98).

4-Methoxy-benzaldehyde ***1c.*** Elemental fluorine (44 mmol) and 4-methoxy-benzaldehyde **1c** (2.0 g, 14.7 mmol) in acetonitrile (150 mL) gave a crude reaction mixture (66% conv) that contained 3-fluoro-4-methoxybenzaldehyde **2g**, δ_F −133.8 (m), and 3,5-difluoro-4-methoxy-benzaldehyde **2 h**, δ_F 126.9 (m), in the ratio 5:1.

Purification by column chromatography gave 3-fluoro-4-methoxybenzaldehyde **2g** (1.18 g. 79%) as a yellow liquid; δ_F −133.9 (m); δ_H 3.89 (3H, br s, OCH_3), 7.01 (1H, m, H-5), 7.51 (2H, m, H-2,6), 9.77 (1H, br s, CHO); δ_c 56.5 (s, OCH_3), 118.6 (d, $^3J_{CF}$ = 9.9, C-5), 115.7 (d, $^2J_{CF}$ = 24.3, C-2), 128.3 (d, $^4J_{CF}$ = 3.37, C-6), 130.3 (d, $^3J_{CF}$ = 4.8, C-1), 152.6 (d, $^1J_{CF}$ = 248.3, C-F), 153.3 (d, $^2J_{CF}$ = 11.01, C-4), 190.0 (d, $^4J_{CF}$ = 2.13, CHO); *m/z* (EI^+) 156 (2), 154 (88), 153 (98) and 3,5-difluoro-4-methoxy-benzaldehyde **2h**[27] (0.18 g, 12%) as a yellow liquid; δ_H 4.07 (3H, br s, OCH_3), 7.39 (2H, m, H-2), 9.76 (1H, br s, CHO); δ_c 60.7 (s, OCH_3), 112.1 (m, C-2), 129.1 (m, C-1), 141.5 (t, $^2J_{CF}$ = 13.5, C-4), 156.2 (dd, $^1J_{CF}$ = 252.1, $^3J_{CF}$ = 5.96, C-3), 188.2 (s, *C*=O); *m/z* (EI^+) 172 ($[M]^+$, 2%) 172 (84), 171 (100).

4-Trifluoromethyl-benzaldehyde ***1d.*** Elemental fluorine (24mmol) and 4-trifluoromethyl-benzaldehyde **1d** (1.4 g, 8 mmol) in acetonitrile (150 mL) gave a crude reaction mixture (35% conv) that contained 2-fluoro-4-trifluoromethyl-benzaldehyde **2i**, δ_F −115.6 (dd, $^3J_{FF}$ = 10.48, $^3J_{HF}$ = 9.83) and 4-trifluoromethyl-benzoyl fluoride **2j**, δ_F 21.3 (s), in the ratio 1:2.

After reaction with 3,5-dinitrophenylmethanol and pyridine (1 mL), purification by column chromatography gave 4-trifluoromethyl-(3,5-dinitrobenzyl)-benzoate **3c** (0.63 g, 61%) as a white solid; mp 149–151 °C; (found C, 48.7; H, 2.4; N, 7.6. $C_{15}H_9F_3N_2O_6$ requires C, 48.6; H, 2.4; N, 7.6); δ_H 5.75 (2H, s, CH_2), 7.89 (2H, AX, $^3J_{HH}$ = 8.85, H-3), 8.31 (2H, AX, $^3J_{HH}$ = 7.75, H-2), 8.86 (2H, m, H-2′), 8.92 (1H, m, H-4′); δ_c 65.2 (s, CH_2), 118.2 (q, $^1J_{CF}$ = 245.2, CF_3) 118.7 (s, C-4′), 125.3 (q, $^3J_{CF}$ = 3.75, C-3), 128.3 (s, C-2′), 130.4 (s, C-2), 130.7 (s, C-1), 135.3 (q, $^2J_{CF}$ = 32.5, C-4), 140.6 (s, C-1′), 148.8 (s, C-3′), 164.7 (s, *C*=O), *m/z* (EI^+) 370 ($[M]^+$, 8%) 330 (24), 180 (100), 150 (42).

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4-Formylbenzonitrile ***1e.*** Elemental fluorine (33 mmol) and 4-formylbenzonitrile **1e** (1.5 g, 11 mmol) in acetonitrile (150 mL) gave a crude reaction mixture (44% conv) that contained 3-fluoro-4-formylbenzonitrile **2k**, δ_F −119.6 (dd, $^3J_{HF}$ = 9.48, $^3J_{HF}$ = 7.81), and 4-cyanobenzoyl fluoride **2l**, δ_F 20.3 (s), in the ratio 1:4.

After reaction with 3,5-dinitrophenylmethanol and pyridine (1 mL), purification by column chromatography gave 3-fluoro-4-formylbenzonitrile **2l**[28] (0.09 g, 12%) as a pale yellow solid; mp 71–72 °C; δ_F −119.6 (dd, $^3J_{HF}$ = 9.5, $^4J_{HF}$ = 7.8); δ_H 7.45 (1H, m, H-2), 7.51 (1H, m, H-6), 7.92 (1H, m, H-5), 10.33 (1H, s, CHO); δ_c 115.5 (d, $^4J_{CF}$ = 2.7, CN), 118.6 (d, $^3J_{CF}$ = 9.9, C-1), 119.7 (d, $^2J_{CF}$ = 24.3, C-2), 127.1 (d, $^2J_{CF}$ = 33.7, C-4), 127.4 (d, $^4J_{CF}$ = 4.2, C-6), 128.9 (d, $^3J_{CF}$ = 2.6, C-5), 162.5 (d, $^1J_{CF}$ = 241.3, C-F), 182.5 (m, CHO); *m/z* (EI^+) 150 ($[M]^+$, 36%), 130 (100), 102 (58) and 4-cyano-3,5-dinitrobenzyl-benzoate **3d** (0.85 g, 54%) as a white solid; mp 199.9–201.6 °C; (found C, 54.9; H, 2.7; N, 12.9. $C_{15}H_9N_3O_6$ requires C, 55.0; H, 2.7; N, 12.8); δ_H 5.51 (2H, s, CH_2), 7.60 (2H, AX, $^3J_{HH}$ = 8.05, H-3), 8.15 (1H, AX, $^3J_{HH}$ = 7.21, H-2), 8.50 (2H, m, H-2′), 9.02 (1H, m, H-4′); δ_c 69.2 (s, CH_2), 116.2 (s, CN), 116.7 (s, C-4), 117.4 (s, C-4′), 128.3 (s, C-2′), 130.0 (s, C-2), 131.4 (s, C-3), 134.7 (s, C-1), 142.3 (s, C-1′), 148.8 (s, C-3′), 168.7 (s, *C*=O); *m/z* (EI^+) 327 ($[M]^+$, 11%) 131 (100), 92 (59).

Fluorination of meta-Substituted Benzaldehydes ***4****. 3-Nitrobenzaldehyde* ***4a.*** Elemental fluorine (45 mmol) and 3-nitrobenzaldehyde **4a** (2.5 g, 15 mmol) in acetonitrile (150 mL) gave a crude reaction mixture (39% conv) that contained 3-fluoro-5-nitrobenzaldehyde **5a**, δ_F −103.2 (t, $^3J_{HF}$ = 7.8), and 3-nitrobenzoyl fluoride **5b**, δ_F 20.3 (s), in the ratio 1:4.1.

After reaction with 3,5-dinitrophenylmethanol and pyridine (1 mL), purification by column chromatography gave 3-fluoro-5-nitrobenzaldehyde **5a** (0.15 g, 15%) as an orange solid; mp 47–49 °C; (found C, 49.2; H, 2.4; N, 8.1. $C_7H_4FNO_3$ requires C, 49.2; H, 2.3; N, 8.2); δ_F −103.2 (t, $^3J_{HF}$ = 7.8); δ_H 7.95 (1H, m, H-2), 8.15 (1H, m, H-4), 8.47 (1H, m, H-6), 10.03 (1H, s, CHO); δ_c 116.9 (d, $^2J_{CF}$ = 25.3, C-4), 120.7 (d, $^2J_{CF}$ = 3.37, C-6), 121.5 (d, $^2J_{CF}$ = 22.4, C-2), 139.1 (d, $^3J_{CF}$ = 6.1, C-1), 149.9 (d, $^3J_{CF}$ = 8.14, C-5), 164.1 (d, $^1J_{CF}$ = 254.3, C-F), 188.8 (d, $^4J_{CF}$ = 1.9, CHO); *m/z* (EI^+) 170 ($[M]^+$, 18%), 140 (100), 96 (48) and 3-nitro-3,5-dinitrobenzyl-benzoate **6a** (1.45 g, 64%) as an orange solid; mp 135.4–137.1 °C; (found C, 48.3; H, 2.5; N, 12.3. $C_{14}H_9N_3O_8$ requires C, 48.4; H, 2.6; N, 12.1); δ_H 5.79 (2H, m, CH_2), 7.89 (1H, m, H-5), 8.51 (1H, m, H-4), 8.54 (1H, m, H-6), 8.82 (1H, t, $^3J_{HH}$ = 1.64, H-2), 8.88 (2H, m, H-2′), 8.95 (1H, m, H-4′); δ_c 65.0 (s, CH_2), 118.2 (s, C-4′), 124.3 (s, C-2′), 128.1 (s, C-2), 128.9 (s, C-4), 130.7 (s, C-5), 131.2 (s, C-1), 135.6 (s, C-6), 140.6 (s, C-3), 148.6 (s, C-1′), 148.9 (s, C-3′), 164.2 (s, *C*=O); *m/z* (EI^+) 347 ($[M]^+$, 5%) 330 (24), 180 (100), 150 (42).

3-Formylbenzonitrile ***4b.*** Elemental fluorine (57 mmol) and 3-formylbenzonitrile **4b** (2.5 g, 19 mmol) in acetonitrile (150 mL) gave a crude reaction mixture (34% conv) that contained 3-fluoro-5-formyl benzonitrile **5c**, δ_F −107.2 (t, $^3J_{HF}$ = 7.2), and 3-cyanobenzoyl fluoride **5d**, δ_F 17.3 (s), in the ratio 1:3.2.

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Table 4. **Fluorination in continuous flow microreactor systems**

substrate	solvent	substrate flow[a]	F_2 flow[a]	F_2:substrate	conv (%)	product(s)
4a	CH_3CN	0.5	1.5	3	52	**5a**:**5b**, 1:4.7
4b	CH_3CN	0.5	1.5	3	34	**5c**:**5d**, 1:3.4
4c	CH_3CN	0.5	1.5	3	57	**5e**:**5f**, 1:2
4d	CH_3CN	0.5	1.5	3	46	**5g**:**5h**, 1:3

[a] Millimoles per channel per hour.

After reaction with 3,5-dinitrophenylmethanol and pyridine (1 mL), purification by column chromatography gave 3-fluoro-5-formyl benzonitrile **5c** (0.22 g, 23%) as an orange solid; δ_F −107.2 (t, $^3J_{HF}$ 7.2); δ_H 7.56 (1H, ddd, $^3J_{HF}$ = 7.6, $^4J_{HH}$ = 1.2, $^4J_{HH}$ = 1.2, H-4), 7.77 (1H, ddd, $^3J_{HF}$ = 7.9, $^4J_{HH}$ = 1.27, $^4J_{HH}$ = 1.3, H-2), 7.91 (1H, m, H-6), 9.95 (1H, br s, CHO); δ_C 114.1 (d, $^3J_{CF}$ = 8.2, C-5), 114.7 (d, $^4J_{CF}$ = 2.9, CN), 118.9 (d, $^2J_{CF}$ = 22.4, C-2), 123.8 (d, $^2J_{CF}$ = 25.5, C-4), 128.3 (d, $^4J_{CF}$ = 3.6, C-6), 138.2 (d, $^3J_{CF}$ = 5.7, C-1), 162.2 (d, $^1J_{CF}$ = 253.8, C-F), 187.8 (d, $^4J_{CF}$ = 1.9, CHO); *m/z* (EI^+) 149 ($[M]^+$, 47%), 132 (100), 105 (68) and 3-cyano-3.5 dinitrobenzyl benzoate **6b** (1.58 g, 75%) as a white solid; mp 218–220 °C; (found C, 55.3; H, 2.5; N, 12.5. $C_{15}H_9N_3O_6$ requires C, 55.0; H, 2.7; N, 12.8); δ_H 5.63 (2H, s, CH_2), 7.69 (1H, m, H-5), 7.97 (1H, m, H-4), 8.26 (1H, m, H-6), 8.35 (1H, m, H-2), 8.75 (2H, m, H-2′), 8.72 (1H, t, $^4J_{HH}$ = 2.11, H-4′); δ_c 64.6 (s, CH_2), 112.1 (s, C-3), 117.3 (s, CN), 117.9 (s, C-4′), 128.3 (s, C-2′), 129.9 (s, C-5), 130.3 (s, C-1), 132.6 (s, C-2), 133.4 (s, C-6), 136.4 (s, C-4), 139.9 (s, C-1′), 148.0 (s, C-3′), 163.6 (s, *C*=O); *m/z* (EI^+) 327 ($[M]^+$, 5%), 130 (100), 102 (56).

*3-Trifluoromethyl-benzaldehyde **4c.*** Elemental fluorine (24 mmol) and 3-trifluoromethyl-benzaldehyde **4c** (1.4 g, 8 mmol) in acetonitrile (150 mL) gave a crude reaction mixture (38% conv) that contained 3-fluoro-5-trifluoromethyl-benzaldehyde **5e**, δ_F −110.7 (1F, t, $^3J_{FF}$ = 8.9, F-5), −63.4 (3F, s, CF_3), and 3-trifluoromethyl-benzoyl fluoride **5f**, δ_F 11.3 (1F, s, CFO), −63.4 (3F, s, CF_3), in the ratio 1:2.3.

After reaction with 3,5-dinitrophenylmethanol and pyridine (1 mL), purification by column chromatography gave 3-fluoro-5-trifluoromethyl-*m*-tolualdehyde **5e** (0.12 g. 24%) as a colorless liquid; δ_F −63.4 (3F, s, CF_3), −110.7 (1F, t, $^3J_{HF}$ = 8.9, F-3); δ_H 7.42 (1H, m, H-4), 7.54 (1H, m, H-2), 7.77 (1H, m, H-6), 9.87 (1H, s, CHO); δ_c 117.9 (dq, $^2J_{CF}$ = 25.3, $^3J_{CF}$ = 12.3, C-4), 118.8 (q, $^1J_{CF}$ = 234.5, CF_3), 120.5 (d, $^2J_{CF}$ = 22.4, C-2), 122.7 (d, $^4J_{CF}$ = 3.37, C-6), 133.1 (qd, $^2J_{CF}$ = 17.14, $^3J_{CF}$ = 8.14, C-5), 138.1 (d, $^3J_{CF}$ = 6.1, C-1), 161.1 (dm, $^1J_{CF}$ = 246.3, C-F), 190.8 (d, $^4J_{CF}$ = 1.9, CHO); *m/z* (EI^+) 192 ($[M]^+$, 3%), 191 (100), 190 (62), 173 (88), 145 (78) and 3-trifluoromethyl-(3,5-dinitrobenzyl)benzoate **6c** (0.68 g, 61%) as a white solid; mp 149–151 °C; (found C, 48.3; H, 2.5; N, 7.3. $C_{15}H_9F_3N_2O_6$ requires C, 48.6; H, 2.4; N, 7.6); δ_H 5.75 (2H, s, CH_2), 7.65 (1H, m, H-5), 7.85 (1H, m, H-6), 8.27 (1H, m, H-4), 8.31 (1H, s, H-2), 8.67 (2H, m, H-2′), 8.97 (1H, br s, H-4′); δ_c 64.6 (s, CH_2), 118.0 (s, C-4′), 118.2 (q, $^1J_{CF}$ = 273.2, CF_3), 126.9 (q, $^3J_{CF}$ = 3.97, C-2), 129.3 (s, C-2′), 129.7 (s, C-5), 130.0 (s, C-1), 130.5 (q, $^3J_{CF}$ = 3.39, C-4), 131.3 (q, $^2J_{CF}$ = 32.2, C-3), 133.2 (s, C-6), 140.6 (s, C-1′), 149.1 (s, C-3′), 165.7 (s, *C*=O); *m/z* (EI^+) 370 ($[M]^+$, 14%) 351 (100), 323 (38), 150 (42).

*Isophthaldialdehyde **4d.*** Elemental fluorine (54 mmol) and isophthaldialdehyde **4d** (2.40 g., 18 mmol) in acetonitrile (150 mL) gave a crude reaction mixture (16% conv) that contained 5-fluorobenzene-1,3-dicarboxaldehyde **5g**, δ_F −109.4 (m), and 3-formylbenzoyl fluoride **5h**, δ_F 20.3 (s), in the ratio 1.6:1.

After reaction with 3,5-dinitrophenylmethanol and pyridine (1 mL), purification by column chromatography gave 3-formyl-3.5 dinitrobenzyl-benzoate **6d** (0.38 g, 37%) as a white solid; (found C, 54.3; H, 2.8; N, 8.5. $C_{15}H_{10}N_2O_7$ requires C, 54.5; H, 3.0; N, 8.5); δ_H 5.61 (2H, s, CH_2), 7.66 (1H, m, H-5), 8.09 (1H, m, H-4), 8.25 (1H, m, H-6), 8.45 (1H, m, H-2), 8.73 (2H, m, H-2′), 8.81 (1H, m, H-4′), 10.00 (1H, s, CHO); δ_c 65.0 (s, CH_2), 118.5 (s, C-4′), 128.7 (s, C-2′), 128.1 (s, C-5), 130.5 (s, C-2), 130.8 (s, C-1), 134.1 (s, C-4), 135.0 (s, C-6), 137.3 (s, C-3), 141.6 (s, C-1′), 148.9 (s, C-3′), 165.0 (s, *C*=O), 191.7 (s, CHO); *m/z* (EI^+) 329 (5) 313 (24), 149 (42), 133 (100), 105 (64).

3.3. Continuous Flow Reactions Using Elemental Fluorine. General Procedure. The design and construction of the microreactor device has been described in detail elsewhere.[20] After purging the apparatus with nitrogen, fluorine as a 10% (v/v) mixture in nitrogen, was passed through the cooled (2 °C) microreactor via an inlet port at a prescribed flow rate that was controlled by a mass flow controller (Brooks Instruments). The microreactor and the collection vessel were cooled to the appropriate temperature by an external cryostat. Substrate mixture was injected by a mechanised syringe pump into the microreactor channel at a prescribed flow rate through the substrate inlet port. After passing through the microreactor and outlet port, excess fluorine gas and volatile waste products were passed through a scrubber filled with soda lime. Liquid products were collected in a FEP tube, and the crude product mixture was examined by ^{19}F NMR spectroscopy. Washing the dichloromethane layer with saturated $NaHCO_3$ solution, drying ($MgSO_4$) and evaporation of the solvent gave an oil, which was analysed by ^{19}F and ^1H NMR spectroscopy and GCMS. The amount of fluorinated derivative in the crude product was determined by adding a known amount of fluorobenzene to a weighed amount of the crude product mixture. Physical and spectroscopic data were compared to those recorded above. Typically, reactions would be carried out over a 16 h period, enabling 5–10 g of crude product to be collected. Substrate and fluorine gas flow used for the reactions are given in Table 4.

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