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Design and Application of a Low-Temperature Continuous Flow Chemistry Platform

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Supporting Information

ABSTRACT: A flow reactor platform technology applicable to a broad range of low temperature chemistry is reported. The newly developed system captures the essence of running low temperature reactions in batch and represents this as a series of five flow coils, each with independently variable volume. The system was initially applied to the functionalization of alkynes, Grignard addition reactions, heterocycle functionalization, and heteroatom acetylation. This new platform has then been used in the preparation of a 20-compound library of polysubstituted, fluorine-containing aromatic substrates from a sequential metalation-quench procedure and can be readily adapted to provide gaseous electrophile inputs such as carbon dioxide using a tube-in-tube reactor.

INTRODUCTION

The field of flow chemistry continues to attract interest in both the synthesis and engineering communities as it occupies a special position where the two disciplines overlap.[1−8] Continued partnership between these two groups is vital to the understanding of relevant parameters and limitations of the technology. Flow processing should not be seen as a direct competitor to batch chemistry; rather it is a complementary tool to assist modern synthesis programs and is often best used when fully integrated into the overall reaction sequence.[9−11]

Recent publications suggest a trend towards more specialized applications. Topics such as multistep (telescoped) synthesis,[12−28] hazardous chemistry,[29−35] pumping organometallic reagents,[36−42] downstream processing,[43−52] and scaling processes[53−56] are attracting serious interest from the academic community. From our own laboratories we have also reported solutions for handling solids[57−60] or gases,[61−72] real-time in-line analysis,[73−77] and linked biological assays.[78,79] In addition, recent publications show a trend towards operating more complex flow systems.[80−87]

We have additionally described the application of two new cryo-flow units that can be used in conjunction with existing flow chemistry equipment to facilitate low-temperature processing without the need for cryogenic consumables (such as liquid N_2 or solid CO_2).[88] Specifically, a lithium/halogen exchange reaction with an in situ quench with a boron-containing electrophile was investigated.[89] With these tools we subsequently extended both the scope and throughput capabilities by increasing the diameter of the tubing with which the device was fabricated to 2.44 mm i.d. This meant that problematic substrates, which tended to block the narrow-bore (1.0 mm i.d.) tubing, could now be used. These modifications also permitted increased throughput, where for one example we prepared 26 g within 30 min. In addition, not all of the lithium/halogen exchange borylation reactions we studied proceed well under certain in situ quenching conditions, consequently a sequential addition process was explored. These modifications were combined with an in-house liquid/liquid separator in order to capitalize on the time savings made by running a fully continuous approach. Simultaneously, work also began on the investigation of the use of thermocouples mounted at tee-pieces to accurately monitor reaction exotherms which improved both reaction safety and process control.[90] As these methods developed, we gained further understanding of the key facets which contributed to the reactor design; of these, both convenience and broad applicability best serve the synthesis chemist. Indeed these criteria dictated the design of a new platform technology for low temperature reactions under continuous flow conditions. Processing of organometallic reactions fits nicely with the benefits that these new systems offer, such as favorable surface area-to-volume ratios, while maintaining a low reactive intermediate inventory. The ability to add further downstream quenching and workup processes is also a clear bonus. Given these opportunities we set out to design a flow chemistry platform which could harness a large selection of organometallic reactions. We began by considering how low-temperature reactions are more typically conducted in batch mode (Figure 1, part 1). On scales typically greater than one millimole the process can be represented by 5 operations, involving steps 1 and 2 consisting of precooling both the latent organometallic reagent and the organometallic species prior to step 3, adding one of these to the other, often the latter to the former. Step 4 is precooling of the appropriate electrophile, before step 5 which is addition of the cooled electrophile to the previous reaction pot. With this series of low-temperature batch operations in mind a flow schematic which represented this was devised (Figure 1, part 2). By using five separate coils that could

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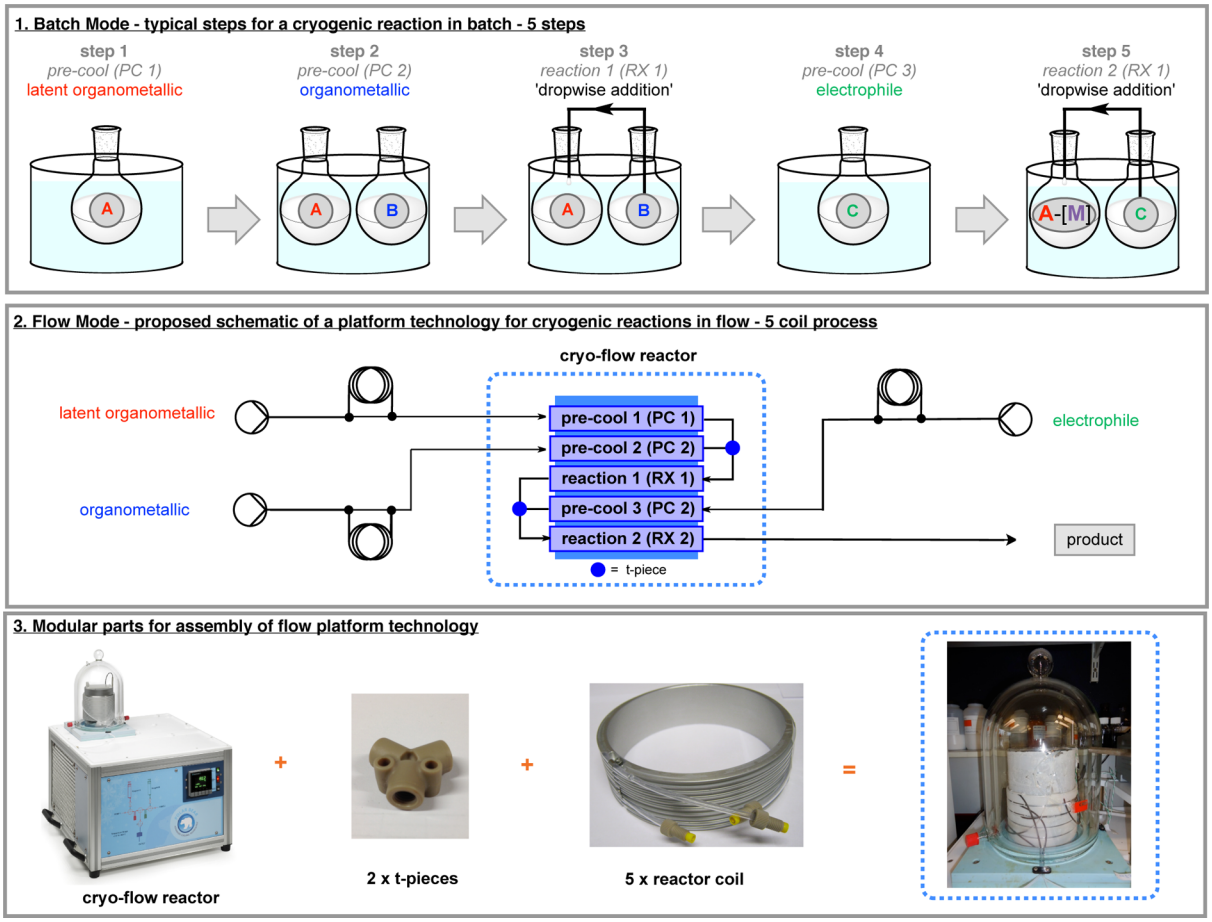

Figure 1. Design of a flow platform technology for cryogenic reactions.

be stacked over a central cryo-cooling device the reagent streams could be precooled independently and then combined at the appropriate points using two tee- or y-pieces and then passed in to the appropriate reactor coil (Figure 1, part 3). Under this arrangement the three reagents are delivered directly to the three precooling-coils prior to mixing and passage through the reaction coils (Figure 1, part 3). Notably, the modular approach also accommodates variation in the volume of individual coils.

RESULTS AND DISCUSSION

The initial reactor setup facilitated work in a segmented flow fashion whereby reagent loading loops are filled and emptied in sequence. Working in this manner necessitates good matching of dispersion curves to ensure a good reagent stoichiometry of the output from reaction coil 1 (RX 1) with the output of the electrophile from precooling coil 3 (PC 3). Previously, we have reported on the use of in-line IR monitoring to accurately control this stoichiometry problem.[32,37,65,73,76,77] This approach is particularly useful when: (a) there is significant dispersion within the system, due to extensive tubing networks or the presence of polymer supported reagents and/or (b) the third stream reagent is precious and it is therefore important not to over add the material, and/or (c) the third stream reagent is difficult to remove from the product. In the particular case reported here the reactor path was sufficiently short that it was easy to control by simply staggering the start times of the appropriate reagent pumps. A simple dye experiment can be used to check timings of such events, as outlined in Figure 2, accompanied by a series of images which detail how this can be achieved. Thus, stream 1 was loaded with a blue dye, while stream 2 was left colorless and stream 3 contained a red dye. It was anticipated that the precoolers would take on the corresponding color while the reactors would contain a mixture of the two, pale blue for RX 1 and purple for RX 2 (although in this case the strength of the red dye seemed to dominate that of the blue). In addition to deliberately staggering the pump start times, we could also increase the volume of the inexpensive electrophile loading loop whose excess can be easily removed from the product in the normal way.

With the optimized setup and timings in place we turned attention to establishing the proof of concept using a small selection of starting materials, organometallic reagents, and quenching electrophiles. Initially, a series of monosubstituted aryl-alkynes were introduced into the loading loops as the latent organometallic reagents along with *n*-butyllithium. The combination of these on exiting RX 1 meet a stream containing any of TMSCl, CF_3CO_2Me, or $ClCO_2Et$ to provide the corresponding disubstituted alkynes in good yield (Figure 3, entries 1−5). Importantly the equipment was simple to operate and reliable, involving drawing the reagents into a syringe, dispensing them into the loading loop, and then switching the loops in-line (corresponding to the timings determined by the flowing dye experiments for each series of flow rates and loop volumes).

Congruent with previous reports using Grignard reagents under flow chemical conditions, use of vinyl magnesium bromide as a nucleophile for addition to an aromatic aldehyde necessitated use at room temperature to ensure sufficient conversion and prevent later blockages.[36,37,41] In the event, the

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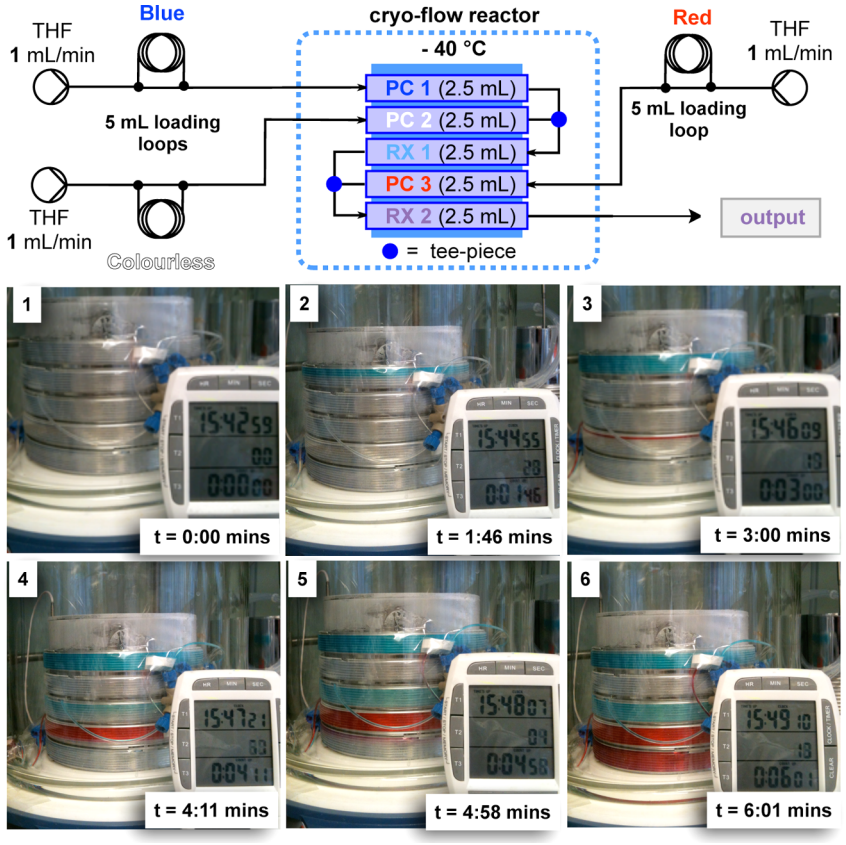

Figure 2. An example of using dyes in timing experiments to ensure accurate meeting of flow streams when several flow streams are bought together. 1. (t = 0:00 min)/Pumps 1 and 2 initiated. 2. t = (1:46 min) PC 1 filling. 3. (t = 3:00 min) PC 1 full, PC 3 starts filling. 4. (t = 4:11 min) RX 1 filling. 5. (t = 4:58 min) PC 1, PC 3 and RX 1 full, RX 2 starts filling. 6. (t = 6:01 min) RX 1 and RX 2 full, PC 1 emptying. Pump 3 was initiated at t = 2:00 min, lines connecting loading loops to PC coils approximately 0.5 mL volume.

magnesium alkoxide intermediate could be capped with an acid chloride delivered through the electrophile stream to provide the ester product (**4a**) in good yield (Figure 3, entry 6). Deprotonation of *N*-methylimidazole at the 2 position with *n*-butyllithium followed by quenching with *N*,*N*-dimethylacetamide furnished the acetylated imidazole product (**5a**) in good yield (Figure 3, entry 7). Similarly an Evans oxazolidinone auxiliary was acetylated within the reactor in moderate yield (Figure 3, entry 8, **6a**).

With these preliminary studies in hand, we could confidently expect that this system could be used as a more generic platform for conducting similar experiments following appropriate reaction scouting of concentration and temperature. For example the reactor was readily incorporated into an ongoing collaborative project as a workhorse device. The aims here were to investigate cryogenic flow chemical methods to provide early scale-up and deliver quantities of material suitable for application testing. Furthermore, there is an opportunity to employ such tools as a way of harvesting early kinetic data, relevant to large-scale production in batch or flow mode. Here we discuss our initial findings and report how the new platform can be used for the preparation of several structurally similar aromatic products, using a fluorine-directed *ortho*-metalation approach.[91−93] This reaction can be particularly troublesome in batch since the intermediate *ortho*-fluorinated aryl lithium species undergo *ortho*-elimination if the temperature is not accurately controlled.[94] The resulting unstable benzyne intermediate and the associated highly exothermic decomposition process poses a significant safety risk, especially on scale. Flow processing is ideally suited for containment of these chemistries, as the thermal capacity of the cold zone can be designed to dominate over the natural thermal capacity of the reacting mixture.

Using the same reactor and reagent loading loop setup described above, the PEEK y-pieces were exchanged for stainless steel fittings to provide better thermal capacity at the point of mixing. The initial temperature and concentration screening using trisubstituted, 1-chloro-3-fluoro-2-methoxybenzene (**7**) and trimethyl borate as an electrophile, highlighted the need for a temperature of −50 °C and a reagent stream concentration of 1.0 M (w.r.t. the latent nucleophile). Under these conditions we were also able to use *n*-butyllithium directly from the reagent bottle, and the desired boronic acid (**7a**) was obtained in 92% yield (Figure 4). Higher temperatures were found to give lower yields and some colored impurities (77% at −40 °C) congruent with decomposition along an exothermic benzyne pathway. Substrate **7** showed excellent compatibility with different electrophiles using the same setup; for example, boronic ester **7b** (from treatment of the aryl lithium species with 4,4,5,5-tetramethyl-1,3,2-dioxaborolane) was accessed in 92% yield and aldehyde **7c** (from treatment with dimethylformamide) in a yield of 88%. Expanding the scope of substrates to other polysubstituted fluorobenzenes proved fruitful (Figure 4). 1-Chloro-3-fluoro-5-methoxybenzene (**8**) underwent successful lithiation and quench with each electrophile as did the disubstituted 1,2- and 1,4-chlorofluorobenzenes **10** and **11**. Notably, 4-chloro-2-fluoro-1-methoxybenzene (**9**) required a lower temperature of −60 °C to provide good yields, presumably

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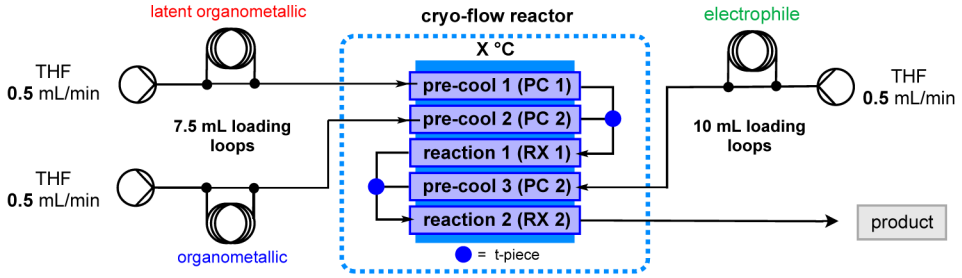


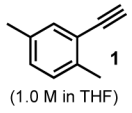
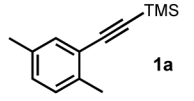
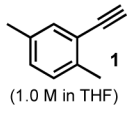
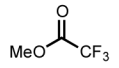
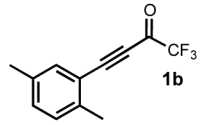
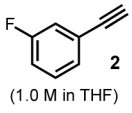
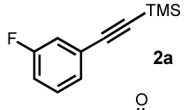
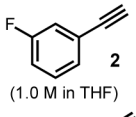
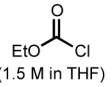
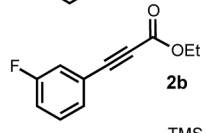
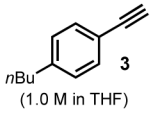
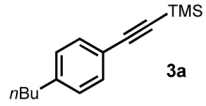
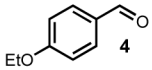
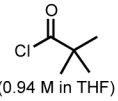
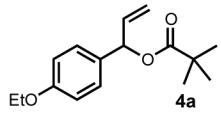
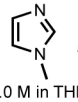
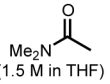
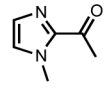
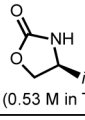
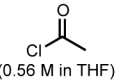
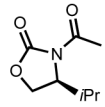
entry	latent organometallic	organometallic	electrophile	temp (°C)	product	% isolated yield
1	 1 (1.0 M in THF)	*n*BuLi (1.2 M in hexanes)	TMS−Cl (1.5 M in THF)	-40	 **1a**	90%
2	 1 (1.0 M in THF)	*n*BuLi (1.2 M in hexanes)	 (2.0 M in THF)	-40	 **1b**	86%
3	 2 (1.0 M in THF)	*n*BuLi (1.2 M in hexanes)	TMS−Cl (2.5 M in THF)	-40	 **2a**	90%
4	 2 (1.0 M in THF)	*n*BuLi (1.2 M in hexanes)	 (1.5 M in THF)	-40	 **2b**	89%
5	 3 (1.0 M in THF)	*n*BuLi (1.2 M in hexanes)	TMS−Cl (2.5 M in THF)	-40	 **3a**	90%
6	 4 (0.83 M in THF)	 (1.0 M in THF)	 (0.94 M in THF)	rt	 **4a**	81%
7	 5 (1.0 M in THF)	*n*BuLi (1.6 M in hexanes)	 (1.5 M in THF)	-60	 **5a**	75%
8	 6 (0.53 M in THF)	*n*BuLi (0.54 M in hexanes)	 (0.56 M in THF)	-30	 **6a**	53%

Figure 3. Preliminary application of the 5 coil setup.

due to the lower stability of the intermediate aryl lithium species. Compounds **9a**−**c** were all prepared as one regioisomer at this temperature, in yields of 77 (**9a**), 68 (**9b**), and 70% (**9c**). In each case the electrophile was incorporated *ortho* to fluorine despite the presence of protons *ortho* to the potentially competing directing methyl ether group. Other alterations were required for the lithiation of 2-chloro-6-fluorobenzonitrile (**12**). Given the incompatibility of the nitrile group present in substrate **12** to butyllithium (under these flow conditions), the base was switched to lithium diisopropylamide (LDA), providing access to compounds **12a**−**c** in yields of 76, 73, and 80%, respectively. A higher temperature of −40 °C was required in these cases, owing to precipitation occurring in the LDA stream at −50 °C.

To further extend the substrate scope and explore the modularity of the platform, the device configuration was altered to include an AF-2400 tube-in-tube reactor, capable of delivering carbon dioxide as the electrophile.[64,95,96] This was achieved simply by swapping the electrophile loading loop for a Teflon AF-2400 gas permeable membrane tube-in-tube reactor and addition of a back pressure regulator to the output of the whole flow platform (Figure 5). A pressure of 10 bar of CO_2 was applied to the outer tube with a liquid pressure of 8 bar (as set by the back pressure regulator). A flowing stream of THF at 0.5 mL/min proved to dissolve sufficient CO_2 to quench the aryl lithium intermediate (as evidenced by outgassing of the remaining CO_2, after passing through the BPR). The back-pressure regulator is essential here and serves to ensure that the CO_2 remains dissolved in solution (homogeneous) inside the reactor; this can in some instances, however, lead to fouling particularly in combination with low temperatures. Under these conditions substrates **7**, **10**, and **11** all processed to provide the corresponding carboxylic acids in yields of 64 (**7d**), 71 (**10d**), and 74% (**11d**), respectively. Carboxylic acid **12d** could be prepared from **12** in 76% yield (Figure 5); again, however,

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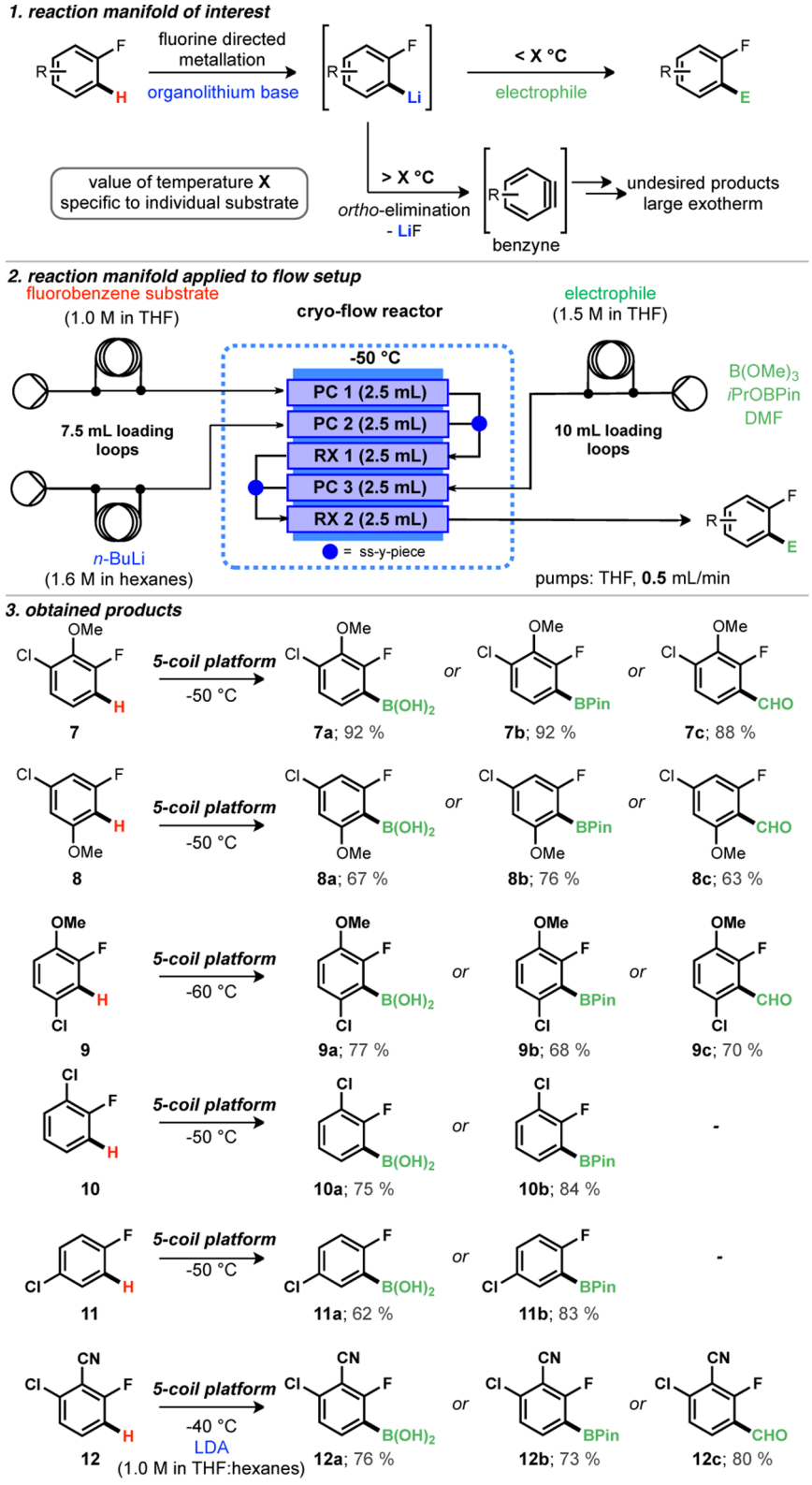

Figure 4. Cryogenic flow platform for the preparation of aromatic building blocks using a fluorine directed *ortho*-lithiation approach.

substituting LDA for butyl lithium was required to avoid addition to the nitrile group.

The successful application of the reported flow platform to this specific reaction manifold resulting in the preparation of a number of substrate analogues supports the notion that this tool can be operated as a supportive device in a research environment.

CONCLUSION

A flow platform to enable low-temperature sequential metalation and electrophilic quenching has been established. The system was initially demonstrated to be applicable to functionalisation of alkynes, Grignard addition, heterocycle functionalisation, and heteroatom acetylation. The technology has been used for the

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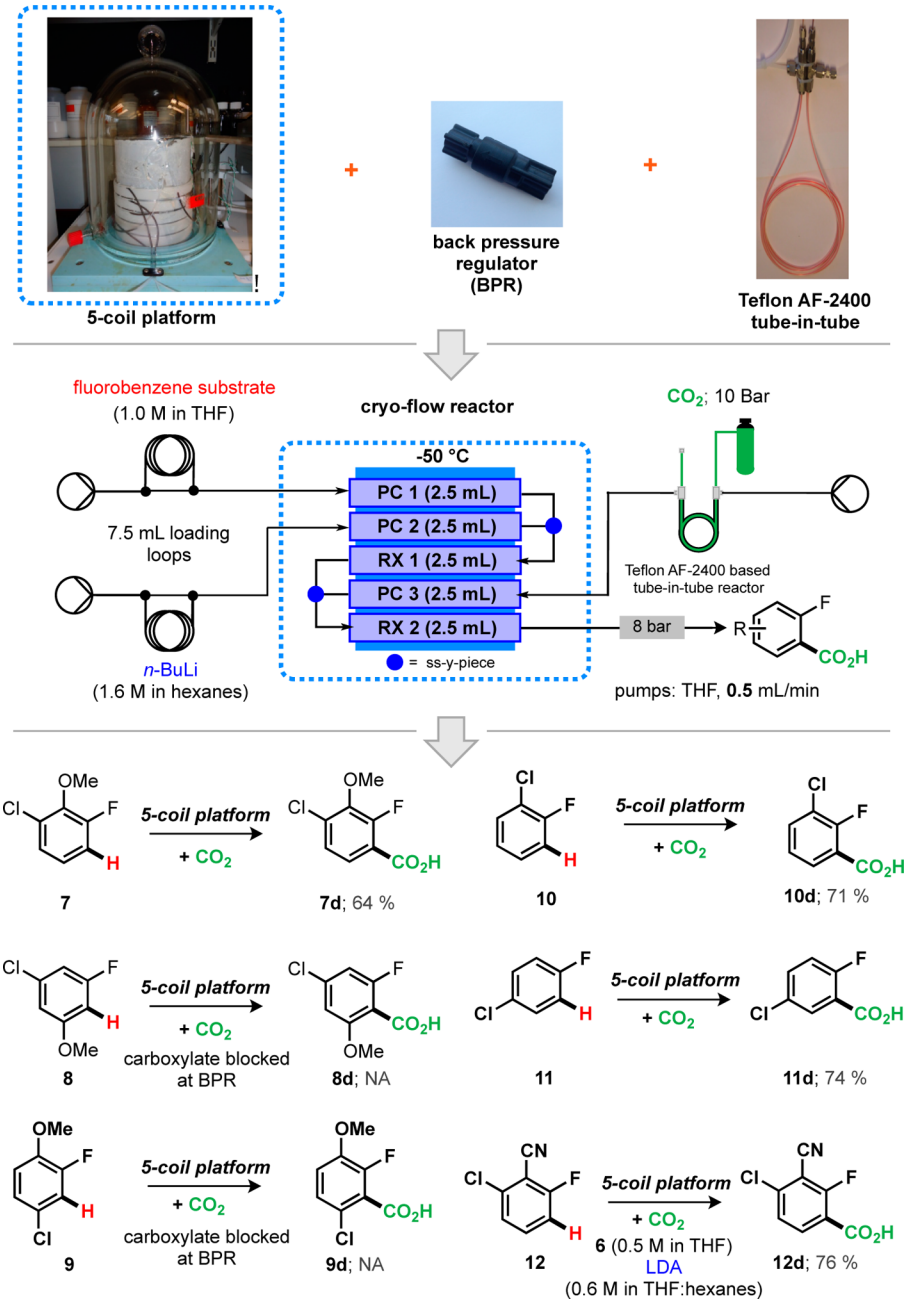

Figure 5. Cryogenic flow platform coupled with a tube-in-tube reactor to deliver CO_2 as the electrophile.

preparation of a library of 20 polyfunctionalized fluorine-bearing aromatic compounds, including boronic acids, boronic esters, and aldehydes. At the time of writing, 14 of these compounds are unreported. By switching the electrophile loading loop to a Teflon AF-2400 tube-in-tube reactor and addition of a back-pressure regulator, carbon dioxide could be conveniently used as an electrophile, providing access to carboxylic acids on the same platform apparatus with no other modifications to the device required.

Further work towards reconfiguring this same reactor platform in a modular fashion for scale-up of problematic low temperature reactions will be reported in the following publication.[100]

EXPERIMENTAL DETAILS

General Procedures. Reagents and solvents were commercial grade used as supplied. Thin layer chromatographic analysis (TLC) was performed using Merck Silica Gel 60 F-254 thin layer plates, visualizing by UV fluorescence (λ = 254 nm) or by staining with acidic potassium permanganate. ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR data were recorded on a Bruker Advance (400 MHz for ^{1}H, ^{19}F, and 125 MHz for ^{13}C NMR) spectrometer using the residual solvent peak as the internal reference ($CDCl_3$ = 7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C; d^{6}-DMSO = 2.50 ppm for ^{1}H and 39.4 ppm for ^{13}C). Data are reported as follows: chemical shift in ppm (δ), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br = broad signal, or combinations of thereof), coupling constant (Hz). Infrared spectra were obtained on a PerkinElmer Spectrum One FT-IR spectrometer using Universal ATR sampling accessories, and absorptions are reported in reciprocal centimeters. High-resolution mass spectrometry (HRMS) was performed using a Waters Micromass LCT Premier spectrom-

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eter using time-of-flight with positive ESI, to within a tolerance of 5 ppm of the theoretically calculated value.

*((2,5-Dimethylphenyl)ethynyl)trimethylsilane (**1a**).* Colourless oil. IR (cm^{-1}, thin film): 2960, 2150, 1495, 1250, 1120; ^1H NMR (400 MHz, $CDCl_3$): δ 7.33 (1H, s), 7.12 (1H, d J = 8 Hz), 7.07 (1H, d J = 8 Hz), 2.46 (3H, s), 2.33 (3H, s), 0.34 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.4, 134.8, 132.5, 129.3, 129.2, 122.7, 104.3, 97.6, 20.6, 20.1, 0.1; HRMS (ESI+) m/z: Calcd for $C_{13}H_{19}Si$ $[M + H^+]$ 203.1251, found 203.1248.

*4-(2,5-Dimethylphenyl)-1,1,1-trifluorobut-3-yn-2-one (**1b**).* Colourless oil. IR (cm^{-1}, thin film): 2930, 1695, 1610, 1570, 1495, 1455, 1260, 1210, 1135, 1150, 1045, 985, 910; ^1H NMR (400 MHz, $CDCl_3$): δ 7.43 (1H, s), 7.26 (1H, d J = 8 Hz), 7.19 (1H, d J = 8 Hz), 2.47 (3H, s), 2.34 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1 (q J_{C-F} = 42 Hz), 140.9, 135.9, 134.7, 133.7, 130.0, 116.4, 115.0 (q J_{C-F} = 289 Hz), 100.5 (q J_{C-F} = 1 Hz), 87.0, 20.4, 19.7; HRMS (ESI +) m/z: Calcd for $C_{10}H_{10}OF_3$ $[M + H^+]$ 227.0678, found 227.0684.

*((3-Fluorophenyl)ethynyl)trimethylsilane (**2a**).* Colourless oil. IR (cm^{-1}, thin film): 2965, 2160, 1610, 1580, 1485, 1430, 1265, 1250, 947; ^1H NMR (400 MHz, $CDCl_3$): δ 7.26–7.19 (2H, m), 7.14 (1H, dd J = 2, 9 Hz), 7.05–6.94 (1H, m), 0.24 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.3 (d J_{C-F} = 246.5 Hz), 129.8 (d J_{C-F} = 8.5 Hz), 127.8 (d J_{C-F} = 3 Hz), 125.0 (d J_{C-F} = 9.5 Hz), 118.7 (d J_{C-F} = 23 Hz), 115.8 (d J_{C-F} = 21 Hz), 103.6 (d J_{C-F} = 3 Hz), 95.4, −0.1; HRMS (ESI+) m/z: Calcd for $C_{11}H_{14}FSi$ $[M+H^+]$ 193.0843, found 193.0841.

*Ethyl 3-(3-fluorophenyl)propiolate (**2b**).* Colourless oil. IR (cm^{-1}, thin film): 2985, 1705, 1605, 1370, 1300, 1210, 1020; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39–7.29 (2H, m), 7.29–7.21 (1H, m), 7.19–7.08 (1H, m), 4.29 (2H, q J = 7 Hz), 1.34 (3H, t J = 7.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.1 (d J_{C-F} = 248.0 Hz), 153.6, 130.2 (d J_{C-F} = 3.5 Hz), 128.8 (d J_{C-F} = 3.5 Hz), 121.4 (d J_{C-F} = 9.5 Hz), 119.5 (d J_{C-F} = 23.5 Hz), 118.0 (d J_{C-F} = 21.0 Hz), 84.1 (d J_{C-F} = 3.5 Hz), 81.2, 62.2, 14.0 ppm; HRMS (ESI +) m/z: Calcd for $C_{11}H_{10}O_2F$ $[M + H^+]$ 193.0659, found 193.0660.

*((4-Butylphenyl)ethynyl)trimethylsilane (**3a**).* Colourless oil. IR (cm^{-1}, thin film): 2960, 1505, 1465, 1250, 860; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38 (2H, d J = 8 Hz), 7.11 (2H, d J = 8 Hz), 2.60 (2H, t J = 8 Hz), 1.58 (2H, quin J = 7.5 Hz,), 1.34 (2H, sex J = 7.5 Hz), 0.92 (3H, t J = 7.5 Hz), 0.25 (9H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.6, 131.9, 128.3, 120.3, 105.4, 93.2, 35.6, 33.3, 22.3, 13.9, 0.0; HRMS (ESI+) m/z: Calcd for $C_{15}H_{23}Si$ $[M + H^+]$ 231.1564, found 231.1561.

*1-(4-Ethoxyphenyl)allyl Pivalate (**4a**).* Colourless oil. IR (cm^{-1}, thin film): 3420, 1675, 955, 915; ^1H NMR (400 MHz, $CDCl_3$) δ 7.13 (1H, s), 7.00 (1H, s), 4.00 (3H, s), 2.65 (3H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 158.7, 136.7, 131.2, 128.3, 116.0, 114.4, 75.4, 63.4, 38.5, 27.0, 14.8. HRMS (TOF^+) found 285.1466, $C_{16}H_{22}O_3Na^+$ requires 285.1471.

*1-(1-Methyl-1H-imidazol-2-yl)ethan-1-one (**5a**).* Colourless oil. IR (cm^{-1}, thin film): 3420, 1675, 1625, 1105; ^1H NMR (400 MHz, $CDCl_3$) δ 7.13 (1H, s), 7.00 (1H, s), 4.00 (3H, s), 2.65 (3H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.3, 143.1, 128.8, 126.9, 36.0, 27.0. HRMS (TOF+) found 194.0788, $C_8H_{12}O_3Na^+$ requires 193.0709.

*(S)-3-Acetyl-4-isopropyloxazolidin-2-one (**6a**).* Colourless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 4.41 (1H, d J = 8.4 Hz), 4.23 (2H, dt J = 2, 9 Hz), 2.50 (3H, s), 0.88 (6H, m) ppm; HRMS (TOF^+) found 194.0718, $C_8H_{12}O_3Na^+$ requires 193.0709. Data are consistent with the literature.[96]

*(4-Chloro-2-fluoro-3-methoxyphenyl)boronic Acid (**7a**).* White solid. Mpt 236–238 °C. IR (cm^{-1}, thin film) 1440, 1040, 920, 750; ^1H NMR (400 MHz, d^6-DMSO) δ 7.26–7.20 (2H, m), 3.91 (3H, s) ppm; ^{13}C NMR (100 MHz, d^6-DMSO) δ 160.4, 158.0, 143.8 (d J_{C-F} = 246.5 Hz), 130.1 (d J_{C-F} = 10.5 Hz), 129.1 (d J_{C-F} = 3.5 Hz), 125.5 (d J_{C-F} = 3.0 Hz), 61.7 (d J_{C-F} = 4.0 Hz) ppm; ^{19}F NMR (400 MHz, d^6-DMSO) δ −120.8 ppm. HRMS (TOF+) found 205.0244, $C_7H_8BClFO_3H^+$ requires 205.0239.

*2-(4-Chloro-2-fluoro-3-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**7b**).* Colourless oil. IR (cm^{-1}, thin film) 1020, 920, 750; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.37 (1H, dd J = 5.5, 8 Hz), 7.16 (1H, dd J = 1.5, 8 Hz), 3.98 (3H, s), 1.38 (12H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3 (d J_{C-F} = 253 Hz), 144.2 (d J_{C-F} = 10 Hz), 131.7 (d J_{C-F} = 4 Hz), 130.6 (d J_{C-F} = 10 Hz), 125.2 (d J_{C-F} = 3 Hz), 84.1, 61.5 (d J_{C-F} = 8 Hz), 24.8 ppm; ^{19}F NMR (400 MHz, $CDCl_3$) δ −118.1 ppm. HRMS (TOF+) found 287.1022, $C_{13}H_{18}BClFO_3H^+$ requires 287.1022.

*4-Chloro-2-fluoro-3-methoxybenzaldehyde (**7c**).* Colourless oil. IR (cm^{-1}, thin film) 1730, 1020, 920; ^1H NMR (400 MHz, $CDCl_3$) δ 10.30 (1H, s), 7.52 (1H, dd J = 8.5, 7.0 Hz), 7.27 (1H, d J = 8.5 Hz), 4.02 (3H, s) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.0 (d J_{C-F} = 7.0 Hz), 158.3 (d J_{C-F} = 260.5 Hz), 144.9 (d J_{C-F} = 12.5 Hz), 135.5 (d J_{C-F} = 4.0 Hz), 125.9 (d J_{C-F} = 4.0 Hz), 124.2 (d J_{C-F} = 7.0 Hz), 122.6 (d J_{C-F} = 3.0 Hz), 61.8 (d J_{C-F} = 4.5 Hz) ppm; ^{19}F NMR (400 MHz, $CDCl_3$) δ −137.4 ppm. HRMS (TOF+) found 189.0119, $C_8H_7ClFO_2H^+$ requires 189.0119.

*4-Chloro-2-fluoro-3-methoxybenzoic Acid (**7d**).* White solid. Mpt 136–137 °C. IR (cm^{-1}, thin film) 1654, 1025, 1010, 920; ^1H NMR (400 MHz, $CDCl_3$) δ 11.45 (1H, brs), 7.56 (1H, t J = 8 Hz), 7.35 (1H, d J = 8 Hz), 3.87 (3H, s) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.2 (d J_{C-F} = 3 Hz), 155.3 (d J_{C-F} = 260 Hz), 144.7 (d J_{C-F} = 14 Hz), 131.9 (d J_{C-F} = 3 Hz), 126.5 (d J_{C-F} = 1 Hz), 125.4 (d J_{C-F} = 0.5 Hz), 120.0, 61.7 (d J_{C-F} = 4 Hz) ppm; ^{19}F NMR (400 MHz, $CDCl_3$) δ −126.6 ppm. HRMS (TOF+) found 205.0068, $C_8H_7ClFO_3H^+$ requires 205.0068.

*(4-Chloro-2-fluoro-6-methoxyphenyl)boronic Acid (**8a**).* White solid. Mpt 187–188 °C. IR (cm^{-1}, thin film) 1435, 1040, 915, 755; ^1H NMR (400 MHz, d^6-DMSO) δ 7.05–6.69 (2H, m), 3.73 (3H, s) ppm. ^{13}C NMR (100 MHz, d^6-DMSO) δ 165.5, 163.3 (d J_{C-F} = 18 Hz), 163.2, 134.8 (d J_{C-F} = 14 Hz), 108.3 (d J_{C-F} = 52 Hz), 107.6 (d J_{C-F} = 3 Hz), 56.4 ppm; ^{19}F NMR (400 MHz, d^6-DMSO) δ −103.5 ppm. HRMS (TOF+) found 205.0240, $C_7H_8BClFO_3H^+$ requires 205.0239.

*2-(4-Chloro-2-fluoro-6-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**8b**).* Colourless oil. IR (cm^{-1}, thin film) 1015, 860. ^1H NMR (400 MHz, $CDCl_3$) δ 6.67 (1H, d J = 8.5 Hz), 6.61 (1H, s), 3.79 (3H, s), 1.37 (12H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6 (d J_{C-F} = 246 Hz), 164.3 (d J_{C-F} = 15 Hz), 137.4 (d J_{C-F} = 14 Hz), 108.7 (d J_{C-F} = 28 Hz), 107.0 (d J_{C-F} = 3 Hz), 105.3 (br, C–B), 84.2, 56.0, 22.7 ppm; ^{19}F NMR (400 MHz, $CDCl_3$) δ −102.6 ppm. HRMS (TOF+) found 287.1030, $C_{13}H_{18}BClFO_3H^+$ requires 287.1022.

*4-Chloro-2-fluoro-6-methoxybenzaldehyde (**8c**).* White solid. Mpt 46–47 °C. IR (cm^{-1}, thin film) 1635, 1015, 900; ^1H NMR (400 MHz, $CDCl_3$) δ 10.4 (1H, d J = 1.0 Hz), 7.11 (1H, dd J = 8.5, Hz), 7.27 (1H, d J = 8.5 Hz), 4.02 (3H, s) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6 (d J_{C-F} = 246 Hz), 164.3 (d J_{C-F} = 15 Hz), 137.4 (d J_{C-F} = 14 Hz), 108.7 (d J_{C-F} = 28 Hz), 107.0 (d J_{C-F} = 3 Hz), 105.3 (br, C–B), 84.2, 56.0, 22.7 ppm; ^{19}F NMR (400 MHz, $CDCl_3$) δ −102.6 ppm. HRMS (TOF+) found 189.0121, $C_8H_7ClFO_2H^+$ requires 189.0119

*(6-Chloro-2-fluoro-3-methoxyphenyl)boronic Acid (**9a**).* White solid. Mpt 204−205 °C (decomposed). IR (cm^{-1}, thin film) 1440, 925, 750; ^1H NMR (400 MHz, d^6-DMSO) δ 7.37−6.94 (2H, m), 3.80 (3H, s) ppm; ^{13}C NMR (100 MHz, d^6-DMSO) δ 151.3 (d J_{C-F} = 246 Hz), 146.7 (d J_{C-F} = 10 Hz), 126.2 (d J_{C-F} = 2 Hz), 124.9 (d J_{C-F} = 2 Hz), 116.6 (d J_{C-F} = 22 Hz), 115.1, 56.4 ppm; ^{19}F NMR (400 MHz, d^6-DMSO) δ −132.1 ppm. HRMS (TOF+) found 205.0244, $C_7H_8BClFO_3H^+$ requires 205.0239.

*2-(6-Chloro-2-fluoro-3-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**9b**).* Colourless oil. IR (cm^{-1}, thin film) 1035, 920, 745; ^1H NMR (400 MHz, $CDCl_3$) δ 7.02 (1H, dd J = 9, 1 Hz), 6.87 (1H, t J = 9 Hz), 3.82 (3H, s), 1.39 (12H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6 (d J_{C-F} = 246 Hz), 146.1 (d J_{C-F} = 12 Hz), 128.3 (d J_{C-F} = 10 Hz), 124.6 (d J_{C-F} = 4 Hz), 115.6 (d J_{C-F} = 3 Hz), 84.8, 56.5, 24.7 ppm; ^{19}F NMR (400 MHz, d^6-DMSO) δ − 124.1 ppm. HRMS (TOF+) found 287.1025, $C_{13}H_{18}BClFO_3H^+$ requires 287.1022.

*6-Chloro-2-fluoro-3-methoxybenzaldehyde (**9c**).* White solid. Mpt 61−62 °C. IR (cm^{-1}, thin film) 1635, 1010, 865; ^1H NMR (400 MHz, $CDCl_3$) δ 10.4 (1H, d J = 1.0 Hz), 7.11 (1H, dd J = 8.5, 1.0 Hz), 7.27 (1H, d J = 8.5 Hz), 4.02 (3H, s) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.2 (d J_{C-F} = 7.0 Hz), 152.5 (d J_{C-F} = 264.5 Hz), 147.3 (d J_{C-F} = 10.0 Hz), 126.7 (d J_{C-F} = 3.0 Hz), 125.9 (d J_{C-F} = 4.5 Hz), 122.0 (d J_{C-F} = 7.0 Hz), 118.3 (d J_{C-F} = 4.0 Hz), 56.8 ppm; ^{19}F NMR (400 MHz, $CDCl_3$) δ −136.2 ppm. HRMS (TOF+) found 189.0116, $C_8H_7ClFO_2H^+$ requires 189.0119.

*(3-Chloro-2-fluorophenyl)boronic Acid (**10a**).* White solid. Mpt 220−222 °C (decomposed). IR (cm^{-1}, thin film) 1005, 760; ^1H NMR (400 MHz, d^6-DMSO) δ 7.50 (1H, t J = 4 Hz), 7.47−7.41 (1H, m), 7.13 (1H, t J = 9 Hz) ppm; ^{19}F NMR (d^6-DMSO, 400 MHz) δ −107.0 ppm. Data are in accordance with literature.[96]

*2-(3-Chloro-2-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**10b**).* Colourless oil. IR (cm^{-1}, thin film) 1140, 865; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (1H, dt J = 1.5, 7.5 Hz), 7.48 (1H, dt J = 1.5, 7.5 Hz), 7.08 (1H, t J = 7.5 Hz), 1.38 (12H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0 (J_{C-F} = 254 Hz), 134.9 (J_{C-F} = 4 Hz), 133.6, 124.4 (J_{C-F} = 4 Hz), 121.1 (J_{C-F} = 20 Hz), 84.2, 24.8 ppm; ^{19}F NMR (400 MHz, $CDCl_3$) δ −105.2 ppm.

*3-Chloro-2-fluorobenzoic Acid (**10d**).* White solid. Mpt 173−174 °C (lit. 174−176 °C). IR (cm^{-1}, thin film) 2900, 1680, 1605, 1245, 710; ^1H NMR (400 MHz, d^6-DMSO) δ 7.85−7.78 (2H, m), 7.31 (1H, t J = 8 Hz) ppm; ^{19}F NMR (400 MHz, $CDCl_3$) δ −110.9 ppm. Data are in accordance with literature.[97]

*(5-Chloro-2-fluorophenyl)boronic Acid (**11a**).* White solid. Mpt 204−205 °C (lit. 206−207 °C). IR (cm^{-1}, thin film) 1005, 760; ^1H NMR (400 MHz, d^6-DMSO) δ 7.50 (1H, t J = 4 Hz), 7.47−7.41 (1H, m), 7.13 (1H, t J = 9 Hz) ppm; ^{19}F NMR (400 MHz, d^6-DMSO δ −107.0 ppm. Data are in accordance with literature.[98]

*2-(5-Chloro-2-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**11b**).* White solid. Mpt 46−47 °C. IR (cm^{-1}, thin film) 1150, 965; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (1H, dd J = 3.0, 4.5 Hz, H^1), 7.36 (1H, ddd J = 3.0, 4.5, 8.0 Hz, H^2), 6.97 (1H, t J = 8.0 Hz, H^3), 1.35 (12H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0 (J_{C-F} = 252 Hz), 134.9 (J_{C-F} = 1 Hz), 133.6, 124.4 (J_{C-F} = 2 Hz), 121.1 (J_{C-F} = 20 Hz), 84.2, 24.8 ppm; ^{19}F NMR (400 MHz, $CDCl_3$) δ −105.9 ppm.

*5-Chloro-2-fluorobenzoic Acid (**11d**).* White solid. Mpt 148−149 °C (lit. 148−149 °C). IR (cm^{-1}, thin film) 1680, 1610, 1105, 900; ^1H NMR (400 MHz, d^6-DMSO) δ 7.81 (1H, dd J = 3, 7 Hz), 7.70 (1H, dd J = 3, 9 Hz), 7.37 (1H, t J = 9 Hz) ppm; ^{19}F NMR (400 MHz, d^6-DMSO) δ −114.6 ppm. Data are in accordance with literature.[99]

*(4-Chloro-3-cyano-2-fluorophenyl)boronic Acid (**12a**).* Pale yellow solid. Mpt 298−300 °C (decomposed). IR (cm^{-1}, thin film) 2250, 1030, 850; ^1H NMR (400 MHz, d^6-DMSO) δ 7.85 (1H, t J = 8 Hz), 7.51 (1H, d J = 8 Hz) ppm; ^{13}C NMR (100 MHz, d^6-DMSO) δ ^{13}C NMR (100 MHz, DMSO) δ 166.6 (d, J_{C-F} = 259 Hz), 141.75 (d, J_{C-F} = 12 Hz), 137.8 (d, J_{C-F} = 2 Hz), 125.9 (d, J_{C-F} = 3 Hz), 112.4, 101.8 (d, J_{C-F} = 21 Hz) ppm; ^{19}F NMR (400 MHz, d^6-DMSO) δ −95.9 ppm. HRMS (TOF+) found 200.0089, $C_7H_5BClFNO_2H^+$ requires 200.0086.

*6-Chloro-2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (**12b**).* Pale yellow solid. Mpt 60−61 °C. IR (cm^{-1}, thin film) 2250, 1040, 1015, 940; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (1H, t J = 8 Hz), 7.31 (1H, d J = 8 Hz), 1.36 (12H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6 (d J_{C-F} = 265 Hz), 141.1 (d J_{C-F} = 10 Hz), 140.4 (d J_{C-F} = 3 Hz) 124.9 (d J_{C-F} = 3 Hz), 111.0, 84.4, 60.1, 24.5 ppm; ^{19}F NMR (400 MHz, $CDCl_3$) δ −93.0 ppm. HRMS (TOF+) found 282.0868, $C_{13}H_{15}BClFNO_2H^+$ requires 282.0868.

*6-Chloro-2-fluoro-3-formylbenzonitrile (**12c**).* White solid. Mpt 76−77 °C. IR (cm^{-1}, thin film) 1605, 1040, 915; ^1H NMR (400 MHz, $CDCl_3$) δ 10.13 (1H, s), 8.06 (1H, t J = 7.5 Hz), 7.49 (1H, d J = 7.5 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.7 (d J_{C-F} = 6 Hz), 165.3 (d J_{C-F} = 272 Hz), 144.2, 133.1 (d J_{C-F} = 3 Hz), 126.6 (d J_{C-F} = 4 Hz), 122.9 (d J_{C-F} = 8 Hz), 110.1, 104.6 (d J_{C-F} = 18 Hz) ppm; ^{19}F NMR (400 MHz, $CDCl_3$) δ −112.3 ppm.

*4-Chloro-3-cyano-2-fluorobenzoic Acid (**12d**).* Pale yellow solid. Mpt 184−186 °C (decomposed). IR (cm^{-1}, thin film): 2915, 2245, 1700, 1415, 785 cm^{-1}; ^1H NMR (400 MHz, d^8-THF) δ 11.95 (1H, brs), 8.22 (1H, t J = 8 Hz), 7.59 (1H, d J = 8 Hz) ppm; ^{13}C NMR (100 MHz, d^8-THF) δ 162.2, 162.1 (d J_{C-F} = 272 Hz), 141.1 (d J_{C-F} = 2 Hz), 137.1 (d J_{C-F} = 3 Hz), 125.6 (d J_{C-F} = 4 Hz), 110.2, 104.6 (d J_{C-F} = 19 Hz) ppm; ^{19}F NMR (400 MHz, d^8-THF) δ −100.5 ppm.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and flow assembly. ^1H, ^{13}C, and ^{19}F NMR spectra for compounds **1a, 1b, 2a, 2b, 3a, 7a-d, 8a-c, 9a-c,** and **12a−d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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