Regular Article

Microflow Fluorinations of Benzynes: Efficient Synthesis of Fluoroaromatic Compounds

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Received July 30, 2018; accepted September 20, 2018

Fluorinated aromatic compounds are found in a variety of biologically active compounds, including clinical drugs and agrochemicals. Therefore, the synthesis of aryl fluorides is particularly important in the medicinal and process chemistry fields. In this paper, we report a method for the synthesis of aryl fluorides by benzyne fluorination under microflow conditions using the efficient Comet X-01 micromixer. In comparison to our previously reported method under ordinary batch conditions, this approach facilitates a significant reduction in reaction times, to ca. 10 s, as well as increases in the yields of fluoroarenes (by up to 51%).

Key words benzene; microflow reaction; aromatic fluorination; nonafluorobutanesulfonate; silyl group; tetra-butylammonium fluoride

A variety of fluorinated compounds are employed in the pharmaceutical and agrochemical industries.1–5 In particular, aryl fluorides, such as enzalutamide and gefitinib, among others, are the most widely used in clinical settings and have received considerable attention from medicinal chemists.6 However, the construction of C(sp²)–F bonds on arenes remains an ongoing challenge as most available methodologies employ harsh reaction conditions.10–15 Therefore, the incorporation of fluorine in biologically active aromatic compounds has most easily been achieved at the onset of the synthesis through the use of fluorinated building blocks. Given these limitations, the development of efficient methods for the fluorination of functionalized aromatic compounds under mild conditions has received increased attention over the latest decade.16–27 In fact, our research group recently developed a method for the direct preparation of fluorobenzenes 1 from 2-(trimethylsilyl)phenols 228; this method involves O-nonafluorobutenesulfonilation followed by the generation of the benzyne 4,29–34 and the immediate nucleophilic addition of a fluoride ion at 4, to yield 1. In this method, Bu₄NF(t-BuOH)₁₄ serves a dual role that generates the benzyne and then fluorinates it 35 (Chart 1-A). However, further studies were required to improve this method as the yields of aryl fluorides were relatively low, owing to the poor nucleophilicity of the fluoride ion and the instability of 4.

Continuous flow synthesis has become more prevalent in the field of organic synthesis, both in industry and academia.36–59 Flow chemistry addresses many of the challenges faced in standard synthetic procedures as it allows for efficient mixing, easy scale-up, safe handling of hazardous chemicals, and rigorous temperature management. In the context of fluorination chemistry, microflow systems enable the safe and efficient use of poisonous fluorine gas for aromatic fluorination. Moreover, flow systems prevent the formation of by-products through the efficient release of the heat associated with exothermic fluorination reactions.60,61 In the meantime, Buchwald and colleagues reported the use of a CsF packed-bed microflow reactor for the Pd-catalyzed fluorination of aryl triflates.62 Although a relatively short residence time (20 min) is required, this method still requires a large excess of expensive CsF and temperatures as high as 120°C to obtain reasonable yields (60–86%) of the aryl fluorides.

In this paper, we report an extension of our previous benzyne batch-fluorination system,5 to microflow synthesis (Chart 1-B). The latter method not only achieved very short reaction times (ca. 10 s) at room temperature, but also increases in the yields of fluorinated benzenes 1 of up to 51%. In addition, some fluorinated products 1 were exclusively obtained under microflow conditions.

Results and Discussion

In the first instance, we investigated two types of mixers, namely T-shaped (α₀6 or α₀4) and Comet X-01,64–66 for these fluorination reactions. The generation of 3,5-di-tert-butylbenzyne (4a) from 2,4-di-tert-butyl-6-(trimethylsilyl)phenyl nonafluorobutenesulfonate (nonaflate) (3a) and the subse-

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quent fluorination using 2.2 equiv of Bu$_2$NF(t-BuOH)$_4$ were monitored (Table 1, Entries 1-12). The concentrations of 3a in tetrahydrofuran (THF) and Bu$_2$NF(t-BuOH)$_4$ in THF were set to 0.10 and 0.22 M, respectively. The flow rates of 3a ($V_{3a}$) and Bu$_2$NF(t-BuOH)$_4$ ($V_p$) were set to be the same ($V_{3a}=V_p$) in most of all trial reactions. The residence time was determined by the length of the outlet tube, which had an inner diameter of 0.96 mm. All reactions provided the desired, mono-fluorinated product, 1,3-di-tert-butyl-5-fluorobenzene (1a); however, the formation of the Thia-Fries rearrangement side-product 5a could not be avoided under most of all conditions. In all cases, the starting material 3a was recovered to a greater or lesser. Nevertheless, differences in the yields of the desired product 1a were noted. The yield of 1a was 44% at a flow rate ($V_{3a}=V_p$) of 2.0 mL/min using the a06 T-shaped mixer at room temperature (Entry 1). Increases in the flow rate to 5.0 mL/min and 8.0 mL/min resulted in increases in the yield of 1a to 54 and 56%, respectively (Entries 2 and 3). In contrast, the use of the a04 T-shaped mixer at a flow rate ($V_{3a}=V_p$) of 5.0 mL/min resulted in a dramatic drop in the yield of 1a to 7% (Entry 4); therefore, the use of this mixer was not further pursued. The 52% yield of 1a obtained using the Comet X-01 mixer (Entry 7), at the same flow rate of 5.0 mL/min, was comparable to the 54% yield obtained using a06 (Entry 2); however, the yield of 5a and the recovery of 3a increased to 16 and 28%, respectively. Nevertheless, our attention was drawn to the high yield (93%) of 1a (Entry 7), based on the generated yield (93%) of 1a (Entry 7), when the Comet X-01 mixer was used (we assumed that the consumed 3a was completely transformed into 4a, except for that converted into 5a), which was significantly higher than that in Entry 2. These results suggest that the generated benzene molecules were more efficiently trapped by the fluoride ion using the Comet X-01 than the Comet mixer. Hence, the Comet X-01 mixer was chosen for further optimization studies. The use of a longer outlet tube (224 cm) resulted in an improved yield of 1a (76%), while the recovered 3a decreased to only 2% (Entry 8). These results suggest that both benzene generation and fluorination proceeded in the Comet X-01 mixer as well as in the outlet tube. It is worth noting that the yield of 1a (76%) under flow conditions (Entry 8) was higher than that under the original batch conditions (55% yield of 1a over a reaction time of 10 s, see: Entry 13). This difference is attributed mainly to the greater fluorination efficiency of 4a under these optimized flow conditions (yield of 1a based on generated 4a: 97% (Entry 8) and 68% (Entry 13)). The Thia-Fries rearrangement was completely suppressed at 0°C, however, the yield dropped to 57% (70% based on generated 4a) (Entry 9). A higher temperature, such as 60°C, resulted in a decrease in the yield of 1a to 68% (84% based on generated 4a) (Entry 10).

Next, we examined a similar reaction with a 1:3 flow rate ($V_{3a}=2.5$ mL/min, $V_p=7.5$ mL/min) of the solution of 3a (0.20 M in THF) and that of Bu$_2$NF(t-BuOH)$_4$ (0.147 M in THF) with keeping the molar ratio of the combined solution and the total

Table 1. Optimizing the Reaction Conditions for Benzene Fluorination under Flow Conditions

| Entry | Mixer$^{a)}$ | Length (cm)$^b$ | $V_{3a}$ (mL/min) | $V_p$ (mL/min) | Residence Time (s) | Yield (%)$^c$ | Yield of 1a based on generated 4a$^d$ |
|-------|-------------|----------------|------------------|----------------|-------------------|-------------|---------------------------------|
| 1     | a06         | 90             | 2.0              | 2.0            | 9.8               | 44          | 7                              |
| 2     | a06         | 90             | 5.0              | 5.0            | 3.9               | 54          | 8                              |
| 3     | a06         | 90             | 8.0              | 8.0            | 2.4               | 56          | 10                             |
| 4     | a04         | 90             | 5.0              | 5.0            | 3.9               | 7           | 8                              |
| 5     | Comet X-01  | 24             | 0.50             | 0.50           | 10.4              | 39          | 20                             |
| 6     | Comet X-01  | 24             | 1.0              | 1.0            | 5.2               | 54          | 17                             |
| 7     | Comet X-01  | 24             | 5.0              | 5.0            | 1.0               | 52          | 16                             |
| 8     | Comet X-01  | 224            | 5.0              | 5.0            | 9.7               | 76 (74)$^e$ | 20                             |
| 9$^{f)}$ | Comet X-01  | 224            | 5.0              | 5.0            | 9.7               | 57          | nd                             |
| 10$^{g)}$ | Comet X-01  | 224            | 5.0              | 5.0            | 9.7               | 68          | 19                             |
| 11    | Comet X-01  | 24             | 2.5$^h$          | 7.5$^h$        | 9.7               | 78          | 16                             |
| 12    | Comet X-01  | 224            | 2.5$^h$          | 7.5$^h$        | 9.7               | 78          | 16                             |

$^{a)}$ A solution of 3a in THF (0.10 M, 5.0 mL/min) and a separate solution of Bu$_2$NF(t-BuOH)$_4$ in THF (0.22 M, 5.0 mL/min) were mixed at room temperature using the a06, a04, and Comet X-01 mixers. $^b$ Length of the outlet tube with an inner diameter of 0.96 mm. $^c$ Determined by 3$^H$-NMR analysis of the crude reaction mixture using 1,1,2,2-tetrachloroethane as the internal standard. $^d$ Determined by 3$^H$-NMR analysis of the crude reaction mixture using 1,1,2,2-tetrachloroethane as the internal standard. $^e$ Isolated yield. $^f$ The reaction was conducted at 0°C. $^g$ The reaction was conducted at 60°C. $^h$ A solution of 3a in THF (0.20 M, 2.5 mL/min) and a separate solution of Bu$_2$NF(t-BuOH)$_4$ in THF (0.147 M, 7.5 mL/min) were mixed. $^i$ 2.0 mmol of 3a and 4.4 mmol of Bu$_2$NF(t-BuOH)$_4$ were reacted at 60°C for 10 s in a flask. $^j$ Not detected.
flow rate in the outlet tube ($V_{3a+F} = 10\text{mL/min}$) (Entries 11 and 12). Importantly, the initial reaction rate became obviously higher (Entry 11) than that at the 1:1 flow rate (Entry 7), whereas, the yield of 1a (78, 95% based on generated 4a) for the residence time of 9.7s using a longer outlet tube (224 cm) (Entry 12) was eventually comparable to that of Entry 8. Complete regioselectivity was observed during the formation of 1a, which is attributable to the steric effect of the large tert-butyl group at the C3 position in 4a.

Having optimized the flow conditions (Table 1, Entry 8), the substrate scope of the reaction was examined. For this purpose, the benzyne precursors, 2-(trimethylsilyl)phenyl nonaflate 3b–3f and triflate 3g′ were used and their immediate fluorinations were examined (Table 2). Symmetrical benzenes 4b, 4c, and 4e, generated from 3b, 3c, and 3e (Entries 1, 2 and 4), and asymmetrically substituted benzenes 4d, 4f, and 4g, from 3d, 3f, and 3g′ (Entries 3, 5 and 6), respectively, were trapped by fluoride ions to produce the corresponding fluorinated aromatic compounds 1b–g. It is noteworthy that all reactions under these flow conditions provided fluoroarenes 1 in higher yields than those under batch conditions (Table 2). Furthermore, perfect regioselectivities were observed during reactions involving 3-(benzyloxy)benzyne 4d and 3-borylbenzyne 4g, to afford meta-1d and ortho-1g, respectively, under both batch and flow conditions (Entries 3 and 6). In these cases, the reactive sites of the benzenes were completely controlled by the electron-withdrawing and electron-donating inductive effects of the C3-alkoxy and C3-boryl group, respectively.

The fluorination of 3-(tert-butyldimethylsilyl)benzyne 4f gave a mixture of meta-1f and ortho-1f in a 6.4:1 ratio under both batch and flow conditions (Entry 5). In this case, the regiochemistry is believed to be mainly controlled by the steric bulkiness of the C3-silyl group of 4f.

Despite extensive examples in the literature involving the reactions of halobenzenes with a range of arynophiles, the nucleophilic fluorination of halobenzenes 4h–4k, generated from 3h, 3i, 3j′, and 3k′, with Bu$_4$NF(t-BuOH)$_4$ under normal batch conditions produced complex mixtures, and the yields of the expected fluorobenzenes 1 were very poor (Table 3). In stark contrast, the reaction of 5-chloro-3-(tert-butyldimethylsilyl)benzyne (4h), generated from 3h, with Bu$_4$NF(t-BuOH)$_4$ under the optimized flow conditions produced 1h in 51% yield as a mixture of two regioisomers (meta-1h/ortho-1h = 1.2:1, Entry 1). Multi-substituted fluorobenzenes 1i (meta-1i/ortho-1i = 1.5:1, Entry 2) and 1j (single product, Entry 3) were similarly prepared from 3i and 3j′ in yields of 53 and 50%, respectively. Despite the success of this methodology, the diiodobenzyne precursor 3k′ could not be converted into the fluorodiodobenzene 1k, rather a complex mixture of products resulted (Entry 4). The completely regioselective formation of meta-1j from 4j is attributed to synergism involving the C3-bromine atom that acts as an inductive electron-withdrawing substituent and is sterically bulky; consequently it directs the nucleophile into the least-hindered meta position (Entry 3). The preference for meta-1h over ortho-1h (1.2:1 ratio) was lower than that observed for 1f (meta-1f/ortho-1f = 6.4:1, Table 2, Entry 5), due to differences in the electronic natures of their C5-substituents. Indeed, the

Table 2. Comparing the Substrate Scopes of Benzyne Fluorination under Flow and Batch Conditions

| Entry | Substrate 3 | Major Product 1 | Yield (%) of 1$^\text{a}$ | Flow | Batch |
|-------|-------------|-----------------|--------------------------|------|-------|
| 1     | MeO          | MeO             | 71 (91)$^\text{f}$       | 64$^\text{e}$ (87)$^\text{f}$ | |
| 2     | Br           | Br              | 74 (%)                   | 67$^\text{f}$ | |
| 3     | OMe          | OMe             | 73$^\text{f}$ (64)$^\text{a}$ | | |

$^\text{a}$Conditions for flow: A solution of 3 in THF (0.10 M, 5.0 mL/min) and a separate solution of Bu$_4$NF(t-BuOH)$_4$ in THF (0.22 M, 5.0 mL/min) were mixed using the Combi-401 mixer at room temperature, and the total residence time was 9.7s. Conditions for batch: A solution of 3 (1 equiv) and Bu$_4$NF(t-BuOH)$_4$ (2.2 equiv) in THF (0.05 M) were stirred at 60 °C for 1 h. $^\text{b}$Isolated yield of 1 unless otherwise noted. $^\text{c}$Determined by GC. $^\text{d}$Yield reported in reference 7. $^\text{e}$Only one regiosomer was observed by $^\text{f}$H NMR and $^\text{g}$F NMR analysis of the crude product. $^\text{h}$Total isolated yield of regiosomers (meta-1f/ortho-1f = 6.4:1). $^\text{i}$B(dan) = 1H-naphtho[1,8-de][1,3,2]diazaborin-2(3H)-yl.
chlorine atom in a 5-chlorobenzyne is known to preferentially drive nucleophilic addition to the C2 position \(^93,94\); hence the additional chlorine substituent in \(4h\) hampers the preferential formation of \(\text{meta-1h}\). On the other hand, the 2,5-dioxoranyl group at the C5 position of \(4f\) has very little effect on the observed regioselectivity; therefore, the silyl group mainly drives the addition of the fluoride ion to the C1 position due to its steric bulkiness. Similar logic can be used to explain the formation of the mixture of regioisomers observed for \(1i\) (\(\text{meta-1i}/\text{ortho-1i} = 1.5 : 1\), Entry 2).

2-(Trimethylsilyl)phenyl trimethylsilyl ether \(6a\), which is a new benzyne precursor that was recently reported by our group,\(^95\) was also successfully used in the benzyne fluorination reaction under microflow conditions using three syringes with two Comet X-01 micromixers, as shown in Chart 2. Hence, a solution of \(6a\) (0.20 M) and nonafluorobutanesulfonyl fluoride (NfF) (0.30 M) in MeCN/THF (2:1) was mixed with a 0.020 M solution of \(\text{Bu}_4\text{NF(t-BuOH)}_4\) (TBAT) in MeCN/THF (2:1) at 60°C to generate 2-(trimethylsilyl)phenyl nonaflate \(3a\) in the first mixer and outlet tube (10 m, residence time of 94 s). This reaction mixture was subsequently mixed with a solution of \(\text{Bu}_4\text{NF(t-BuOH)}_4\) (0.22 M) in THF in the second mixer and outlet tube (224 cm, residence time of 9.7 s) to form benzyne \(4a\), which was immediately trapped by fluoride to afford aryl fluoride \(1a\) in 72% isolated yield.

When compared to batch conditions, significant improvements in the yields of aryl fluorides \(1\) were observed under microflow conditions (Tables 1–3). The use of microflow chemistry addressed various challenges associated with these reactions. The generation of benzyynes from \(3\) using \(\text{Bu}_4\text{NF(t-BuOH)}_4\) is very fast, even at room temperature, and the resulting benzyynes are extremely reactive, which can lead to...
decomposition and/or self-polymerization. Furthermore, the fluoride ion is a poor nucleophile, and the fluorination step can be reversible\(^{24}\) (Chart 3). Microflow conditions facilitate highly efficient mixing, rapid fluoride addition, and immediate protonation, to provide good yields. On the other hand, under batch conditions (Table 1, Entry 13), the reaction mixture is not completely homogenous in the microscopic sense, which is more obvious during and immediately following the addition of \(\text{Bu}_4\text{NF(t-BuOH)}_4\) (Fig. 1-A). When the concentration of the fluoride ion in the microscopic vicinity of a generated benzyne is low, the reactive benzyne molecule may polymerize or react with other arynophiles such as adventitious water, generated phenols, and solvents, resulting in poor yields of 1. In comparison, a microflow system at a high flow rate affords greater reaction-mixture homogeneity due to highly efficient mixing. Hence, benzyne reacts rapidly with fluoride ions followed by immediate protonation by \(\text{t-BuOH}\) (or adventitious water) to produce 1 in high yields (Fig. 1-B). The application of two different flow rates may realize more efficient mixing and made the benzyne generation and fluorination faster (Table 1, Entry 11). This efficient mixing was particularly beneficial during the microflow reactions of halogenated benzyynes\(^{4h-4j}\) (Table 3, Entries 1–3), resulting in the suppression of characteristic side-reactions of halobenzynes, such as the halogen dance reaction,\(^{96}\) Thia-Fries rearrangement,\(^{93,97,98}\) and the further formation of other benzyynes.\(^{99-102}\) The reaction of 3,5-iodobenzyne (4k) seems to be too difficult to be achieved even under microflow conditions probably because of the high leaving ability of the iodo group.

In summary, we developed a method for the synthesis of aromatic fluorinated compounds that involves the generation of a benzyne and its immediate fluorination in a microflow reactor. The yields of aryl fluorides obtained under flow conditions were generally higher than those obtained under batch conditions. To the best of our knowledge, this is the first report involving fluoride-ion-mediated generation of benzyynes under microflow conditions. The use of this microflow fluorination procedure in route to biologically active molecules, and in other benzyne reactions, is currently underway in our laboratory.

**Experimental**

**General** All reactions were carried out under an atmosphere of argon or nitrogen. A flask containing a stirrer bar and fitted with a three-way stopcock was used as the reactor. Anhydrous THF and MeCN were purchased from Kanto Chemical Co., Inc., Japan, and purified with a GlassContour\textsuperscript{TM} solvent purification system (Nikko Hansen & Co., Ltd., Japan) using two columns packed with activated molecular sieves. Commercial 18-crown-6 was purified by recrystallization from MeCN. \(\text{Bu}_4\text{NF(t-BuOH)}_4\),\(^{103}\) benzyne precursors 3a–3f, \(3g\) and \(3i\)\(^{35}\) were prepared according to a literature procedure. All other reagents were purchased from Kanto Chemical Co., Inc., FUJIFILM Wako Pure Chemical Industries, Ltd., Japan, Tokyo Chemical Industry Co., Ltd., Japan, Sigma-Aldrich Co., LLC., U.S.A., Nacalai Tesque, Inc., Japan or Kishida Chemical Co., Ltd., Japan, and were used without further purification. Flash chromatography was performed using 60N spherical neutral (40–50 µm) silica gel purchased from Kanto Chemical Co., Inc. All reactions were monitored by TLC on glass-backed 0.2-mm silica gel 60F\(\text{254}\) plates (Merck), and compounds were visualized under UV light (254 nm).

**Analytical Methods** Melting points were recorded on a Büchi M-565 or a Yanagimoto melting point apparatus and are uncorrected. IR spectra were acquired on a Shimadzu FTIR-8400S and Shimadzu IRAffinity-1S. \(^1\)H-NMR and \(^1\)C-NMR spectra were recorded on a Jeol JMN-ECA-500.
A flame-dried THF (0.050 M) was added to a crude product (1H-NMR yield, 75%) and a stirrer bar, capped with a rubber septum, and evacuated and back-filled with nitrogen. Anhydrous THF (40 mL, 0.050 M) was stirred for 10 s at 60°C. 1,1,2,2-Tetrachloroethane (0.21 mL, 0.20 mmol) was added to its assigned structure. 1H-NMR spectra and melting points were recorded. All new products were further characterized by high-resolution (HR)-MS.

General Procedure A for the Optimized Flow Synthesis of Aryl Fluoride 1 from Nonaflate 3 (Tables 1–3 and Chart 4) A 0.10 M THF solution of 2-(trimethylsilyl)phenyl nonaflate 3 (1.0 equiv) and a 0.22 M THF solution of Bu₄NF(t-BuOH)₄ (2.2 equiv) were mixed under microflow conditions, and the mixture was collected as a white solid (0.14 g, 0.29 mmol, 55% yield) from our previous report. The 1H-NMR spectra of the obtained material was identical to that in our previous report. Following the General Procedure A (Flow Conditions, Table 1, Entry 8), 2,4-di-tert-butyl-6-(trimethylsilyl)phenyl nonaflate 3a (0.10 M in THF) and Bu₄NF(t-BuOH)₄ (0.22 M in THF) were mixed under microflow conditions, and the mixture was collected for 24 s [total volume 4.0 mL, 0.20 mmol of 3a, 0.44 mmol of Bu₄NF(t-BuOH)₄]. 1,1,2,2-Tetrachloroethane (21 μL, 0.20 mmol) was added to a crude mixture, and the yields of the products were determined based on 1H-NMR data as follows, 1a: 76%, 5a: 20% and 3a: 2%. The crude mixture was purified by flash column chromatography on silica gel (hexane/etOAc=20:1) to provide the titled compound 1a (31 mg, 0.15 mmol, 74%) as a colorless oil. The 1H-NMR spectra of the obtained material was identical to that in our previous report.

Following the General Procedure B (Batch Conditions, Table 1, Entry 13), a mixture of 2,4-di-tert-butyl-6-(trimethylsilyl)-phenyl nonaflate 3a (1.1 g, 2.0 mmol), Bu₄NF(t-BuOH)₄ (1.3 g, 4.4 mmol) in THF (40 mL, 0.050 M) was stirred for 10 s at 60°C. 1,1,2,2-Tetrachloroethane (0.21 mL, 0.20 mmol) was added to a crude product (1H-NMR yield, 55%, 5a: 19% and 3a: not detected). The crude mixture was purified by flash column chromatography on silica gel (hexane) to provide the titled compound 1a (0.22 g, 1.1 mmol, 53%) as a colorless oil. The 1H-NMR spectra of the obtained material was identical to that in our previous report.

General Procedure B for the Batch Synthesis of Aryl Fluoride 1 from Nonaflate 3 (Tables 1–3) A flame-dried flask was charged with 2-(trialkylsilyl)phenyl nonaflate 3 (1.0 equiv) and a stirrer bar, capped with a rubber septum, and evacuated and back-filled with nitrogen. Anhydrous THF (0.050 M) was added via a syringe, and the mixture was heated to 60°C. Bu₄NF(t-BuOH)₄ (2.2 equiv) was quickly added by opening the septum. After stirring at 60°C for the indicated amount of time, the reaction mixture was cooled to room temperature and then passed through a short pad of silica gel using EtOAc as the eluent. The mixture was extracted with hexane and washed with water. The aqueous phase was extracted twice with hexane. The combined organic phase was washed with a saturated NaCl solution and dried over anhydrous Na₂SO₄. The mixture was filtered and the solvents were removed under reduced pressure. The crude product was purified by silica-gel flash column chromatography (eluent: hexane, a mixture of hexane and EtOAc, or CH₂Cl₂) to afford the fluorinated product 1.

1,3-Di-tert-butyl-5-fluorobenzene (1a) Following the General Procedure A (Flow Conditions, Table 1, Entry 8), 2,4-di-tert-butyl-6-(trimethylsilyl)phenyl nonaflate 3a (0.10 M in THF) and Bu₄NF(t-BuOH)₄ (0.22 M in THF) were mixed under microflow conditions, and the mixture was collected for 24 s [total volume 4.0 mL, 0.20 mmol of 3a, 0.44 mmol of Bu₄NF(t-BuOH)₄]. 1,1,2,2-Tetrachloroethane (21 μL, 0.20 mmol) was added to a crude mixture, and the yields of the products were determined based on 1H-NMR data as follows. 1a: 76%, 5a: 20% and 3a: 2%. The crude mixture was purified by flash column chromatography on silica gel (hexane/etOAc=20:1) to provide the titled compound 1a (31 mg, 0.15 mmol, 74%) as a colorless oil. The 1H-NMR spectra of the obtained material was identical to that in our previous report. Following the General Procedure B (Batch Conditions, Table 1, Entry 13), a mixture of 2,4-di-tert-butyl-6-(trimethylsilyl)-phenyl nonaflate 3a (1.1 g, 2.0 mmol), Bu₄NF(t-BuOH)₄ (1.3 g, 4.4 mmol) in THF (40 mL, 0.050 M) was stirred for 10 s at 60°C. 1,1,2,2-Tetrachloroethane (0.21 mL, 0.20 mmol) was added to a crude product (1H-NMR yield, 55%, 5a: 19% and 3a: not detected). The crude mixture was purified by flash column chromatography on silica gel (hexane) to provide the titled compound 1a (0.22 g, 1.1 mmol, 53%) as a colorless oil. The 1H-NMR spectra of the obtained material was identical to that in our previous report.
for 12 s [total volume 2.0 mL, 0.10 mmol of 3b, 0.22 mmol of Bu₄NF(−BuOH)₄, n-Decane (19 µL, 0.10 mmol) was added to the reaction mixture and diluted with EtOAc (ca. 5 mL). A part of the mixture was filtered through a silica gel pad and the filtrate was measured by GC (91% GC yield of 1b). The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc = 1:1) to provide the titiled compound 1b (11 mg, 70 µmol, 71%) as a colorless oil. The 1H-NMR spectra of the obtained material was identical to that in our previous report. 35)

4-Fluoro-1,2-bis(benzyloxy)benzene (1c) (Table 2, Entry 2) 35) Following the General Procedure A (Flow Conditions), 4,5-bis(benzyloxy)-2-(trimethylsilyl)phenyl nonaflate (3c) 35) (0.10 mmol in THF) and Bu₄NF(−BuOH)₄ (0.22 mmol in THF) were mixed under microflow conditions, and the mixture was collected for 24 s [total volume 4.0 mL, 0.20 mmol of 3c, 0.44 mmol of Bu₄NF(−BuOH)₄]. The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc = 10:1) to provide the starting compound 1c (46 mg, 0.15 mmol, 74%) as a colorless solid. The 1H-NMR spectra of the obtained material was identical to that in our previous report. 35)

1-Fluoro-3-chloro-5-(tert-butyldimethylsilyl)benzene (meta-1h) and 1-Fluoro-4-chloro-2-(tert-butyldimethylsilyl)benzene (ortho-1h) (Table 3, Entry 1) Following the General Procedure A (Flow Conditions), 4-chloro-2-(tert-butyldimethylsilyl)-6-(trimethylsilyl)phenyl nonaflate (3h) (0.10 mmol in THF) and Bu₄NF(−BuOH)₄ (0.22 mmol in THF) were mixed under microflow conditions, and the mixture was collected for 24 s [total volume 4.0 mL, 0.20 mmol of 3h, 0.44 mmol of Bu₄NF(−BuOH)₄]. The crude product (meta-1h/ortho-1h = 1:2.1, determined by 300 MHz 1H-NMR analysis) was purified by flash column chromatography on silica gel (hexane/EtOAc = 5:1) to provide a 1:3:1 mixture of the titled compounds, meta-1h and ortho-1h (24 mg, 0.11 mmol, 51%) as a colorless oil. 1H-NMR (300 MHz, CDCl₃) δ = 2.6 (6H×4/9, s), 0.30 (6H×5/9, s), 0.86 (9H×4/9, s), 0.88 (9H×5/9, s), 6.85–6.95 (1H×4/9, m), 7.03–7.08 (2H×5/9, m), 7.20 (1H×5/9, dd, d = 1.5, 1.5 Hz), 7.25–7.30 (2H×4/9, m).

19F-NMR (283 MHz, CDCl₃) δ = −6.3, −5.4, 16.8, 17.2, 26.3, 26.5, 116.37 (d, J = 29.0 Hz), 116.43 (d, J = 24.0 Hz), 119.0 (d, J = 18.0 Hz), 126.3 (d, J = 33.5 Hz), 129.0 (d, J = 2.5 Hz), 129.8 (d, J = 2.5 Hz), 130.9 (d, J = 8.5 Hz), 134.5 (d, J = 8.5 Hz), 135.7 (d, J = 12.0 Hz), 142.8 (d, J = 9.5 Hz), 162.2 (d, J = 252.0 Hz), 165.6 (d, J = 241.0 Hz).

IR (neat): 1574, 1253, 1231 cm⁻¹. HR-MS: [M]⁺ = 326.0849, 326.0855 (Two regioisomers, ortho/meta = 5 : 1) to provide a 2 : 1 mixture of the titled compounds, meta-1h and ortho-1h which could not be detected in a crude mixture by 1H-NMR spectroscopy.

4-Fluoro-1,2-dimethylbenzene (1e) (Table 2, Entry 4) 35) Following the General Procedure A (Flow Conditions), 4,5-dimethyl-2-(trimethylsilyl)phenyl nonaflate (3e) 35) (0.10 mmol in THF) and Bu₄NF(−BuOH)₄ (0.22 mmol in THF) were mixed under microflow conditions, and the mixture was collected for 12 s [total volume 2.0 mL, 0.1 mmol of 3e, 0.42 mmol of Bu₄NF(−BuOH)₄]. n-Decane (19 µL, 0.10 mmol) was added to the reaction mixture and diluted with EtOAc (ca. 5 mL). A part of the mixture was filtered through a silica gel pad and the filtrate was measured by GC (91% GC yield of 1e). The retention time was identical with the commercial one.

3-(1,3-Dioxolan-2-yl)-1-fluoro-5-(tert-butyldimethylsilyl)benzene (meta-1f) 35) and 4-(1,3-Dioxolan-2-yl)-1-fluoro-2-(tert-butyldimethylsilyl)benzene (ortho-1f) (Table 2, Entry 5) Following the General Procedure A (Flow Conditions), 2-(tert-butyldimethylsilyl)-4-(1,3-dioxolan-2-yl)-6-(trimethylsilyl)phenyl nonaflate (3f) 35) (0.10 mmol in THF) and Bu₄NF(−BuOH)₄ (0.22 mmol in THF) were mixed under microflow conditions, and the mixture was collected for 24 s [total volume 4.0 mL, 0.20 mmol of 3f, 0.44 mmol of Bu₄NF(−BuOH)₄]. The crude product (meta-1f/ortho-1f = 6.4:1, determined by 300 MHz 1H-NMR analysis) was purified by flash column chromatography on silica gel (hexane) to provide a 6.4:1 mixture of the titled compounds, meta-1f and ortho-1f (33 mg, 0.12 mmol, 60%) as a green oil. The 1H-NMR spectra of the obtained material was identical to that in our previous report. 35)

2-(2-Fluorophenyl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinin (ortho-1g) 35) (Table 2, Entry 6) Following the General Procedure A (Flow Conditions), 2-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)-6-(trimethylsilyl)phenyl triflate (3g) 35) (0.10 mmol in THF) and Bu₄NF(−BuOH)₄ (0.22 mmol in THF) were mixed under microflow conditions, and the mixture was collected for 24 s [total volume 4.0 mL, 0.20 mmol of 3g, 0.44 mmol of Bu₄NF(−BuOH)₄]. The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc = 5:1) to provide the titled compound ortho-1g (34 mg, 0.13 mmol, 66%) as a colorless solid. The 1H-NMR spectra of the obtained material was identical to that in our previous report. 35)
Following the General Procedure B (Batch Conditions), a mixture of 4-iodo-2,6-bis(trimethylsilyl)phenyl nonaflate (3j) \(^{35}\) (0.26 g, 0.40 mmol), Bu₄NF(t-BuOH)₄ (0.49 g, 0.88 mmol) in THF (8.0 mL, 0.050 M) was stirred for 1 h at 60°C. However, only 5% of the titled compounds, meta-II and ortho-II was detected in a crude mixture by \(^1\)H-NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard (meta-II-ortho-II=1:5:1).

1-Bromo-3-tert-butyl-5-fluorobenzene (meta-I) \(^{36}\) (Table 3, Entry 3) Following the General Procedure A (Flow Conditions), 2-bromo-4-tert-butyl-6-(trimethylsilyl)phenyl triflate (3j') (0.10 M in THF) and Bu₄NF(t-BuOH)₄ (0.22 M in THF) were mixed under microflow conditions, and the mixture was collected for 48 s [total volume 8.0 mL, 0.40 mmol of 3j', 0.88 mmol of Bu₄NF(t-BuOH)₄]. The crude product (meta-I/ortho-I=98:2, determined by 300 MHz \(^1\)H-NMR analysis) was purified by flash column chromatography on silica gel (hexane/CH₂Cl₂=100:1) to provide the titled compound meta-I (46 mg, 0.20 mmol, 50%) as a brown oil. \(^1\)H-NMR spectrum of the obtained material was identical to that in our previous report. \(^{35}\)

General Procedures C and D for the Synthesis of Benzene Precursors 3h, 3j' and 3k' 

General Procedure C
An oven dried flask was charged with 2-bromophenol (1.0 equiv) and capped with an inlet adapter with a 3-way stopcock and then evacuated and back-filled with argon. Anhydrous THF (0.10–0.50 M), Et₃N (1.5 equiv) and Me₃SiCl (1.5 equiv) were added via syringes and the reaction mixture was stirred for a few hours at room temperature. The reaction mixture was concentrated under reduced pressure. Hexane was added to the residue and the mixture was filtered through a silica gel pad and washed with hexane. The solution was evaporated to give 2-bromophenyl trimethylsilyl ether. Without purification of the obtained material, anhydrous THF (0.10–0.33 M) was added to the flask and the mixture was cooled to −78°C. n-BuLi (1.6 M hexane solution, 1.2 equiv) was added dropwise at −78°C and the reaction was allowed to warm up to room temperature and stirred for several hours. To the reaction mixture was added a saturated aqueous solution of NH₄Cl for quenching. The mixture was extracted with EtOAc (this process was repeated three times) and combined organic phase was dried over anhydrous Na₂SO₄. The organic phase was filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc) to provide 2-(trimethylsilyl)phenol 2.

General Procedure D
An oven dried flask was charged with 2-(trialkylsilyl)phenol 2 (1.0 equiv), 18-crown-6 (1.0 equiv) and capped with rubber septum, and then evacuated and back-filled with argon. Anhydrous THF (0.10 M) and sodium hydride (NaH) (60% in mineral oil, 1.5 equiv) was added into the flask, and the reaction mixture was stirred for a few minutes. NfF (1.5 equiv) was added via a syringe, and the resulting mixture was stirred at 60°C. After the reaction completed, the mixture was cooled to 0°C. Water was added into the reaction mixture and the mixture was extracted with hexane (this process was repeated...
three times). Organic phase was combined and it was dried over anhydrous Na$_2$SO$_4$. The mixture was filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc) to afford 2-(triaklyl)silylphenyl nonaflate 3.

4,5-Dimethyl-2-(trimethylsilyl)phenyl Nonaflate (3e) (Table 2, Entry 4) Following General Procedure C, a mixture of 4,5-dimethyl-2-bromophenol (0.26 g, 1.3 mmol), Et$_3$N (0.24 mL, 1.7 mmol), Me$_3$SiCl (1.7 mL, 20 mmol) was stirred in anhydrous THF (4.3 mL, 0.30 mol) for 1 h at room temperature. To the obtained 2-bromophenyl trimethylsilyl ether were added THF (4.3 mL, 0.30 mol) and n-BuLi (1.6 mL hexane solution, 0.98 mL, 1.6 mmol), and stirred for 1 h at room temperature. The crude mixture was purified by flash column chromatography on silica gel (hexane/EtOAc 0.98 mL, 1.6 mmol) as a colorless oil. Without purification of the crude product, anhydrous THF (0.25 L, 0.2 M) was added to the residue and the mixture was filtered through a mixture of 2,6-dibromo-4-chlorophenol (3f) (0.23 g, 90%).

Following General Procedure D, a mixture of 4-chloro-2-(tert-butyldimethylsilyl)-6-(trimethylsilyl)phenol (2h) (3.0 g, 9.7 mmol), NaH (60% in mineral oil, 0.58 g, 15 mmol), 18-crown-6 (2.5 g, 9.7 mmol) and NfF (2.5 mL, 15 mmol) was stirred in THF (50 L, 0.20 mol) at reflux for 5 h. The crude reaction mixture was purified by flash column chromatography on silica gel (hexane/EtOAc=10:1) to provide 4-chloro-2-(tert-butyldimethylsilyl)-6-(trimethylsilyl)phenol (2h) (9.0 g, 76%) as a colorless oil.

Following General Procedure D, a mixture of 4-chloro-2-(tert-butyldimethylsilyl)-6-(trimethylsilyl)phenol (2h) (3.0 g, 9.7 mmol), NaH (60% in mineral oil, 0.58 g, 15 mmol), 18-crown-6 (2.5 g, 9.7 mmol) and NfF (2.5 mL, 15 mmol) was stirred in THF (50 L, 0.20 mol) at reflux for 12 h. The crude product was purified by column chromatography (hexane) to provide the titled compound 3h (4.9 g, 85%) as a colorless oil.

**4-Chloro-2-(tert-butyldimethylsilyl)-6-(trimethylsilyl)phenol Triflate (3j)** (Table 3, Entry 2) A round-bottom flask was charged with 4-tert-butyl phenol (15 g, 0.10 mol) and stir bar. CH$_2$Cl$_2$ was added and it was cooled to 0°C. Br$_2$ (11 mL, 0.22 mol) was added to the mixture over 10 min. The mixture was warmed to room temperature and it was stirred for 4 h. The mixture was evaporated and the residue was purified by column chromatography (hexane/AcOEt=10:1) to provide 2,6-dibromo-4-tert-butylphenol (99 g, 92%) as a white solid.

**2-Bromo-4-tert-butyl-6-(trimethylsilyl)phenyl Triflate (3j)** (Table 3, Entry 2) A round-bottom flask was charged with 4-tert-butyl phenol (15 g, 0.10 mol) and stir bar. CH$_2$Cl$_2$ was added and it was cooled to 0°C. Br$_2$ (11 mL, 0.22 mol) was added to the mixture over 10 min. The mixture was warmed to room temperature and it was stirred for 4 h. The mixture was evaporated and the residue was purified by column chromatography (hexane/AcOEt=10:1) to provide 2,6-dibromo-4-tert-butylphenol (99 g, 92%) as a white solid.
butylphenol (0.40 M) and the solution was warmed to 78°C, after which it was stirred at room temperature for 2 h. The reaction mixture was evaporated under reduced pressure, and the residue was purified by flash column chromatography (hexane) to provide the titled compound 6a as a white solid (16g, 99%). mp: 64–65°C. 1H-NMR (300 MHz, CDCl3) δ: 0.30 (9H, s), 0.32 (9H, s), 1.28 (9H, s), 1.40 (9H, s), 7.24 (1H, d, J=2.5Hz). 13C-NMR (75 MHz, CDCl3) δ: 1.3, 2.9, 31.3, 31.6, 34.2, 35.1, 126.5, 130.1, 130.5, 138.6, 142.5, 156.5. IR (neat): 1413, 1254, 1223 cm−1. HR-MS (MALDI) Caled for C20H38O6Si2 [M]+: 350.2456. Found 350.2440.

Acknowledgments This work was financially supported by the JSPS KAKENHI (Grant numbers 16K01864, 15J06024, and 16H01151/18H04411 (Middle Molecular Strategy)) and Japan Agency for Medical Research and Development (AMED) (17am01010850001), and the Research Foundation for Pharmaceutical Sciences. We would also like to thank Mr. Matsubara of Techno Applications for kindly providing us with the flow reactor parts.

Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

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