Regular Article

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Microflow Fluorinations of Benzynes: Efficient Synthesis of Fluoroaromatic Compounds

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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 benzyne; microflow reaction; aromatic fluorination; nonafluorobutanesulfonate; silyl group; tetrabutylammonium fluoride

A variety of fluorinated compounds are employed in the pharmaceutical and agrochemical industries.[1–8] 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.[9] However, the construction of C(sp^2)–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 **2**[28]; this method involves *O*-nonafluorobutanesufonylation 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, $Bu_4NF(t\text{-}BuOH)_4$ 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,[35] to microflow synthesis[63] (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.

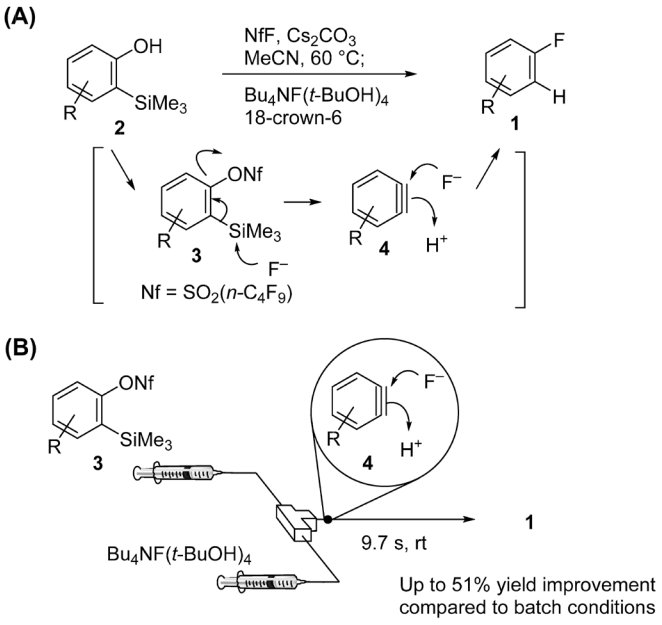

Chart 1. (A) Our Previous Work: Benzyne Fluorination under Batch Conditions; (B) This Work: Benzyne Fluorination under Microflow Conditions

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 nonafluorobutanesulfonate (nonaflate) (**3a**) and the subse-

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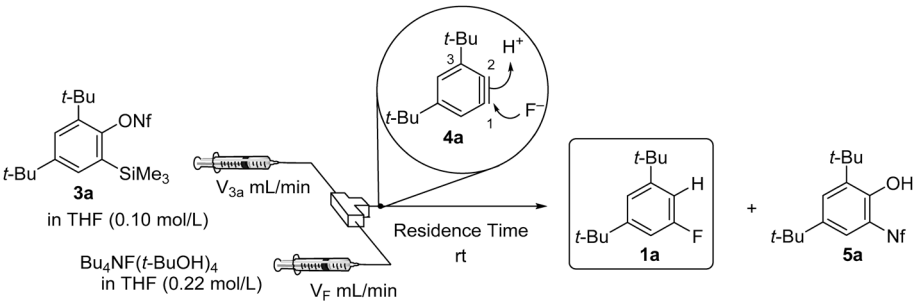
quent fluorination using 2.2 equiv of $Bu_4NF(t\text{-}BuOH)_4$ were monitored (Table 1, Entries 1–12). The concentrations of **3a** in tetrahydrofuran (THF) and $Bu_4NF(t\text{-}BuOH)_4$ in THF were set to 0.10 and 0.22 M, respectively. The flow rates of **3a** (V_{3a}) and $Bu_4NF(t\text{-}BuOH)_4$ (V_F) were set to be the same ($V_{3a}=V_F$) 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 ($V_{3a}=V_F$) of 2.0 mL/min using the *α*06 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 *α*04 T-shaped mixer at a flow rate ($V_{3a}=V_F$) 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 *α*06 (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 **4a**, 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 benzyne molecules were more efficiently trapped by the fluoride ion using the Comet X-01 than the *α*06 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 benzyne 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).[35,67] 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_F=7.5 mL/min) of the solution of **3a** (0.20 M in THF) and that of $Bu_4NF(t\text{-}BuOH)_4$ (0.147 M in THF) with keeping the molar ratio of the combined solution and the total

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



Entry	Mixer[a)]	Length (cm)[b)]	V (mL/min)		Residence Time (s)	Yield (%)[c)]			Yield of **1a** based on generated **4a**[d)]
			V_{3a}	V_F		**1a**	**5a**	Recovered **3a**	
1	*α*06	90	2.0	2.0	9.8	44	7	4	49
2	*α*06	90	5.0	5.0	3.9	54	8	6	63
3	*α*06	90	8.0	8.0	2.4	56	10	2	64
4	*α*04	90	5.0	5.0	3.9	7	8	2	8
5	Comet X-01	24	0.50	0.50	10.4	39	20	11	57
6	Comet X-01	24	1.0	1.0	5.2	54	17	24	92
7	Comet X-01	24	5.0	5.0	1.0	52	16	28	93
8	Comet X-01	224	5.0	5.0	9.7	76 (74)[e)]	20	2	97
9[f)]	Comet X-01	224	5.0	5.0	9.7	57	nd	19	70
10[g)]	Comet X-01	224	5.0	5.0	9.7	68	18	1	84
11	Comet X-01	24	2.5[h)]	7.5[h)]	1.0	71	15	7	91
12	Comet X-01	224	2.5[h)]	7.5[h)]	9.7	78	16	2	95
13	Batch[i)]	—	—	—	10	55 (53)[e)]	19	nd[j)]	68

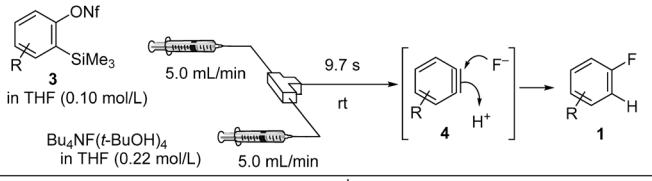
a) A solution of **3a** in THF (0.10 M, 5.0 mL/min) and a separate solution of $Bu_4NF(t\text{-}BuOH)_4$ in THF (0.22 M, 5.0 mL/min) were mixed at room temperature using the *α*06, *α*04, and Comet X-01 mixers. *b*) Length of the outlet tube with an inner diameter of 0.96 mm. *c*) Determined by ^{1}H-NMR analysis of the crude reaction mixture using 1,1,2,2-tetrachloroethane as the internal standard. *d*) In determining the yield of **1a** based on generated **4a**, the total amount of recovered **3a**, and **3a** that was converted into **5a**, was first subtracted, and the remaining amount of **3a** was then used to calculate the yield of **1a**. *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 $Bu_4NF(t\text{-}BuOH)_4$ in THF (0.147 M, 7.5 mL/min) were mixed. *i*) 2.0 mmol of **3a** and 4.4 mmol of $Bu_4NF(t\text{-}BuOH)_4$ were reacted at 60°C for 10 s in a flask. *j*) Not detected.

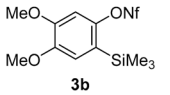
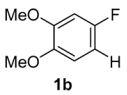
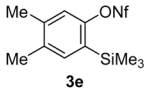
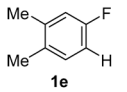
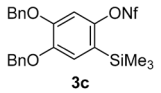
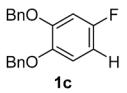
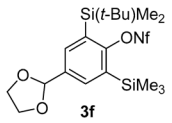
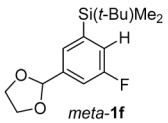
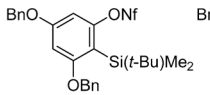
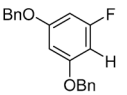
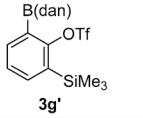
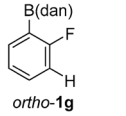
flow rate in the outlet tube (V_{3a+F}=10 mL/min) (Entries 11 and 12). Importantly, the initial reaction rate became obviously higher (Entry 11) than that at the 1 : 1 flow rate (Entry 7), whereas, the yield of **1a** (78, 95% based on generated **4a**) for the residence time of 9.7 s using a longer 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 nonaflates **3b**–**3f** and triflate **3g′** were used and their immediate fluorinations were examined (Table 2). Symmetrical benzynes **4b**, **4c**, and **4e**, generated from **3b**, **3c**, and **3e** (Entries 1, 2 and 4), and asymmetrically substituted benzynes **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 benzynes were completely controlled by the electron-withdrawing and electron-donating inductive effects of the C3-alkoxy and C3-boryl group, respectively.[68–78] 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**.[68]

Despite extensive examples in the literature involving the reactions of halobenzynes with a range of arynophiles,[79–92] the nucleophilic fluorination of halobenzynes **4h**–**4k**, generated from **3h**, **3i**, **3j′**, and **3k′**, with $Bu_4NF(t\text{-}BuOH)_4$ 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 $Bu_4NF(t\text{-}BuOH)_4$ 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 fluorodiiodobenzene **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[a]



Entry	Substrate **3**	Major Product **1**	Yield (%) of **1**[b] Flow	Batch	Entry	Substrate **3**	Major Product **1**	Yield (%) of **1**[b] Flow	Batch
1	 **3b**	 **1b**	71 (91)[c]	64 (87)[c,d]	4	 **3e**	 **1e**	57[c]	51[c]
2	 **3c**	 **1c**	74	67[d]	5	 **3f**	 *meta*-**1f**	60[f]	44[d,f]
3	 **3d**	 *meta*-**1d**	73[e]	64[d,e]	6[g]	 **3g′**	 *ortho*-**1g**	66[e]	60[d,e]

[a]Conditions for flow: A solution of **3** in THF (0.10 M, 5.0 mL/min) and a separete solution of $Bu_4NF(t\text{-}BuOH)_4$ in THF (0.22 M, 5.0 mL/min) were mixed using the Comet-X01 mixer at room temperature, and the total residence time was 9.7 s. Conditions for batch: A solution of **3** (1 equiv) and $Bu_4NF(t\text{-}BuOH)_4$ (2.2 equiv) in THF (0.05 M) were stirred at 60 °C for 1 h. [b]Isolated yield of **1** unless otherwise noted. [c]Determined by GC. [d]Yield reported in reference 7. [e]Only one regioisomer was observed by ^{1}H NMR and ^{19}F NMR analysis of the crude product. [f]Total isolated yield of regioisomers (*meta*-**1f**/*ortho*-**1f** = 6.4:1). [g]B(dan) = 1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl.

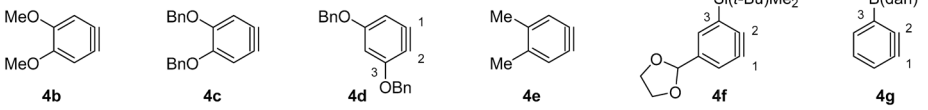
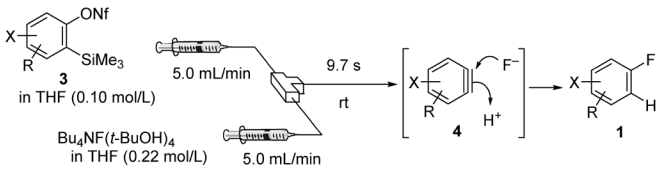
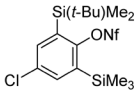
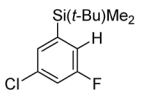
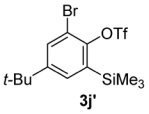
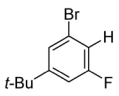
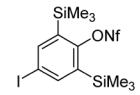
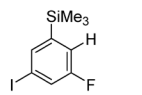
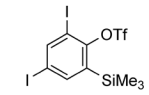
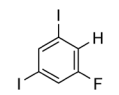
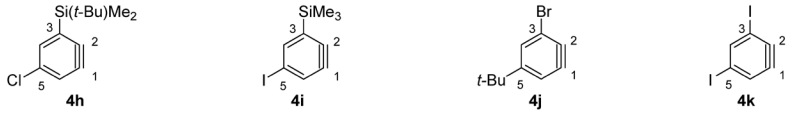


Table 3. Scope and Limitations of Halogenated-Benzyne Fluorinations[a]



Entry	Substrate 3	Major Product 1	Yield (%)[b] Flow	Batch	Entry	Substrate 3	Major Product 1	Yield (%)[b] Flow	Batch
1	 **3h**	 *meta*-**1h**	51[c]	nd[d]	3	 **3j'**	 *meta*-**1j**	50[g]	nd[d]
2	 **3i**	 *meta*-**1i**	53[e]	5[f]	4	 **3k'**	 *meta*-**1k**	nd[d]	nd[d]

[a]Conditions for flow: A solution of **3** in THF (0.10 M, 5.0 mL/min) and a separate solution of $Bu_4NF(t\text{-}BuOH)_4$ in THF (0.22 M, 5.0 mL/min) were mixed using the Comet-X01 mixer at room temperature, and the total residence time was 9.7 s. Conditions for batch: A solution of **3** (1 equiv) and $Bu_4NF(t\text{-}BuOH)_4$ (2.2 equiv) in THF (0.05 M) were stirred at 60 °C for 1 h. [b]Isolated yield of **1**. [c]Total isolated yield of regioisomers (*meta*-**1h**/*ortho*-**1h** = 1.2:1). [d]Not detected. [e]Total isolated yield of regioisomers (*meta*-**1i**/*ortho*-**1i** = 1.5:1). [f]Determined by ^1H NMR. [g]*meta*-**1j** was obtained with high selectivity (another possible regioisomer was not detected by ^1H NMR and ^{19}F NMR analysis of the crude pruduct).



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 *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** (*meta*-**1i**/*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 $Bu_4NPh_3SiF_2$ (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 $Bu_4NF(t\text{-}BuOH)_4$ (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 benzynes from **3** using $Bu_4NF(t\text{-}BuOH)_4$ is very fast, even at room temperature, and the resulting benzynes are extremely reactive, which can lead to

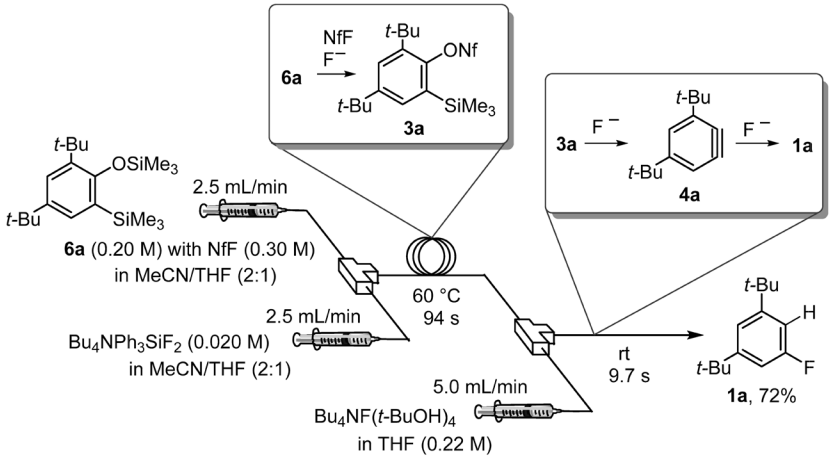


Chart 2. Generation of Benzyne **4a** from Silyl Ether **6a** and Its Fluorination under Flow Conditions

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 $Bu_4NF(t\text{-BuOH})_4$ (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, benzynes react rapidly with fluoride ions followed by immediate protonation by *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 benzynes **4h**–**j** (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 benzynes.[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 benzynes under microflow conditions. The use of this microflow fluorination procedure *en route* to biologically active molecules, and in other benzyne reactions, is currently underway in our laboratory.

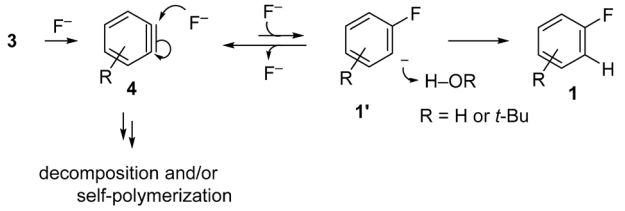


Chart 3. Steps in the Fluorination of a Benzyne

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™ 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. $Bu_4NF(t\text{-BuOH})_4$,[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 60 F^{254} plates (Merck), and compounds were visualized under UV light (254 nm). The Comet X-01 micromixing device and dual syringe pumps (Catamaran HII-10) were obtained from Techno Applications Co., Ltd., 34-16-204 Hon, Denenchofu, Oota, Tokyo, 145-0072, Japan (e-mail: yukio-matsubara@nifty.com). The α06 (channel width 600 μm) and α04 (Channel width 400 μm) micromixing devices were purchased from MiChS Co., Ltd., Japan.

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 ^{13}C-NMR spectra were recorded on a Jeol JMN-ECA-500

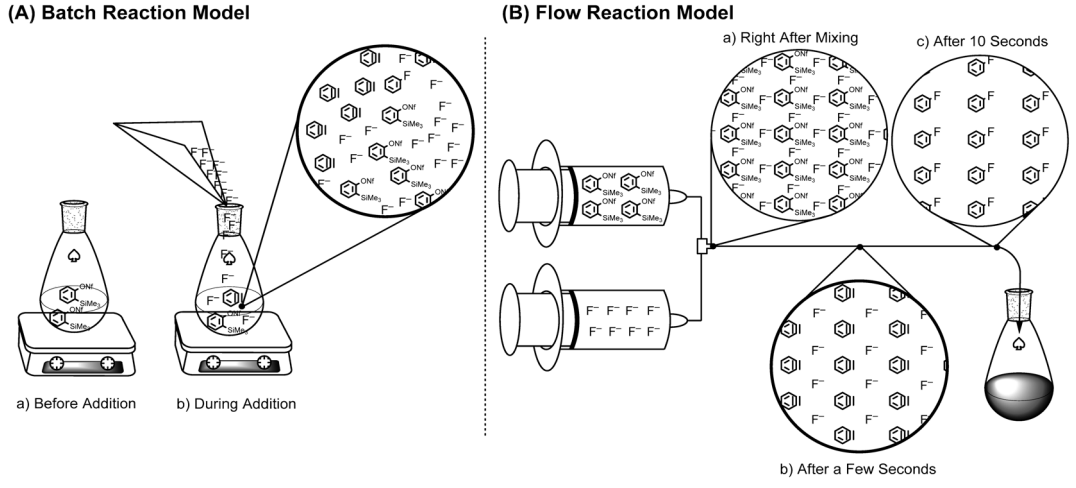


Fig. 1. Illustrating the Microscopic Differences between the Batch Reaction (A) and the Microflow Reaction (B)

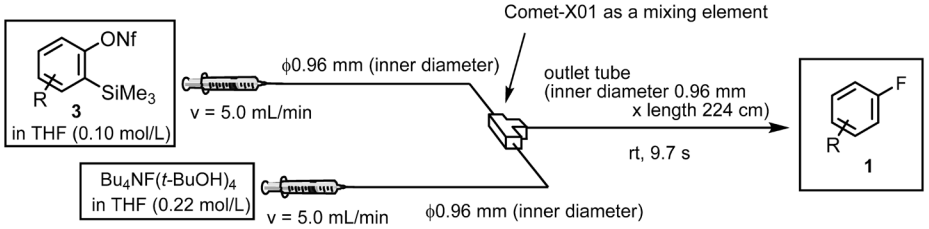


Chart 4. Flow Reactor for Tables 1–3

(^{1}H: 500 MHz, ^{13}C: 125 MHz, ^{19}F: 470 MHz), a Jeol JMN-ECS-400 (^{1}H: 400 MHz, ^{13}C: 100 MHz, ^{19}F: 376 MHz), or a Jeol ECS-300 (^{1}H: 300 MHz, ^{13}C: 75 MHz, ^{19}F: 282 MHz) spectrometer. Chemical shifts are reported in ppm and are referenced against the chemical shifts of residual protonated solvent (^{1}H) or deuterated solvent (^{13}C) (an internal standard was not used for the ^{19}F-NMR spectra as the JMN-ECA and ECS instruments do not require this). GC was performed using a Shimadzu GC-2010 instrument. Mass spectra were acquired on a Jeol JMS-S3000 (matrix assisted laser desorption/ionization (MALDI)), a Jeol JMS-700 (FAB and electron ionization (EI)), or a JMS-T100TD (APCI) spectrometer. "Yield" refers to the isolated yield of a compound exhibiting at most only trace peaks in its ^{1}H-NMR spectrum that are not attributable to its assigned structure. ^{1}H-NMR spectra and melting points (where applicable) of all known compounds 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 $Bu_4NF(t\text{-}BuOH)_4$ (2.2 equiv) were mixed and reacted at room temperature in a continuous flow reactor consisting of a dual syringe pump set to 5.0 mL/min, a Comet X-01 mixing element, and an outlet tube (inner diameter 0.96 mm, outer diameter 1.56 mm, length 224 cm, and residence volume 1.62 mL). The effective residence time was 9.7 s. The crude reaction mixture was collected into a test tube containing *ca.* 1 mL of a saturated NH_4Cl solution for 24 s [total volume 4.0 mL, 0.20 mmol of **3**, 0.44 mmol of $Bu_4NF(t\text{-}BuOH)_4$] from at least 10 s after the commencement of solution flow. 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 Na_2SO_4. The mixture was filtered and the solvent was removed under reduced pressure. The crude product was purified by silica-gel flash column chromatography (eluent: hexane, a mixture of hexane and EtOAc, or CH_2Cl_2) to afford the fluorinated product **1**.

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. $Bu_4NF(t\text{-}BuOH)_4$ (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 Na_2SO_4. 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 CH_2Cl_2) to afford the fluorinated product **1**.

1,3-Di-*tert*-butyl-5-fluorobenzene (1a)[104] Following the General Procedure A (Flow Conditions (Table 1, Entry 8)), 2,4-di-*tert*-butyl-6-(trimethylsilyl)phenyl nonaflate (**3a**)[35] (0.10 M in THF) and $Bu_4NF(t\text{-}BuOH)_4$ (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 $Bu_4NF(t\text{-}BuOH)_4$]. 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 ^{1}H-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 ^{1}H-NMR spectra of the obtained material was identical to that in our previous report.[35]

Following the General Procedure B (Batch Conditions (Table 1, Entry 13)), a mixture of 2,4-di-*tert*-butyl-6-(trimethylsilyl)-phenyl nonaflate (**3a**)[35] (1.1 g, 2.0 mmol), $Bu_4NF(t\text{-}BuOH)_4$ (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 (^{1}H-NMR yield, **1a**: 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 ^{1}H-NMR spectra of the obtained material was identical to that in our previous report.[35]

2,4-Di-*tert*-butyl-6-(nonafluorobutanesulfonyl)phenol (5a) (Table 1, Entry 13) **5a** was obtained from above mentioned reaction mixture as a white solid (0.14 g, 0.29 mmol, 15%). *Rf*: 0.6 (hexane/EtOAc=10 : 1). mp: 64–66°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.31 (9H, s), 1.42 (9H, s), 7.55 (1H, d, J=2.5 Hz), 7.77 (1H, d, J=2.5 Hz), 8.98 (1H, br s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 29.2, 30.3, 34.6, 35.8, 104.2–122.8 (4C, m), 113.0, 125.5, 134.9, 139.6, 143.2, 156.1. ^{19}F-NMR (376 MHz, $CDCl_3$) δ: −126.08–(−125.82) (2F, m), −121.12–(−120.82) (2F, m), −112.82–(−112.68) (2F, m), −80.81–(−80.65) (3F, m). IR (neat): 3381, 1471 cm^{-1}. HR-MS (APCI): m/z Calcd for $C_{18}H_{22}F_9O_3S$ $[M]^+$: 488.1062. Found: 488.1066.

4-Fluoro-1,2-dimethoxybenzene (1b) (Table 2, Entry 1)[35] Following the General Procedure A (Flow Conditions), 4,5-dimethoxy-2-(trimethylsilyl)phenyl nonaflate (**3b**)[35] (0.10 M in THF) and $Bu_4NF(t\text{-}BuOH)_4$ (0.22 M in THF) were mixed under microflow conditions, and the mixture was collected

for 12 s [total volume 2.0 mL, 0.10 mmol of **3b**, 0.22 mmol of $Bu_4NF(t\text{-}BuOH)_4$]. *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/Et_2O=1 : 1) to provide the titled compound **1b** (11 mg, 70 μmol, 71%) as a colorless oil. The ^{1}H-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 M in THF) and $Bu_4NF(t\text{-}BuOH)_4$ (0.22 M in THF) were mixed under microflow conditions, and the mixture was collected for 24 s [total volume 4.0 mL, 0.2 mmol of **3c**, 0.44 mmol of $Bu_4NF(t\text{-}BuOH)_4$]. The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc=10 : 1) to provide the titled compound **1c** (46 mg, 0.15 mmol, 74%) as a colorless solid. The ^{1}H-NMR spectra of the obtained material was identical to that in our previous report.[35]

1-Fluoro-3,5-bis(benzyloxy)benzene (*meta*-1d) (Table 2, Entry 3)[35,105] Following the General Procedure A (Flow Conditions), 3,5-bis(benzyloxy)-2-(*tert*-butyldimethylsilyl)phenyl nonaflate (**3d**)[35] (0.10 M in THF) and $Bu_4NF(t\text{-}BuOH)_4$ (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 **3d**, 0.44 mmol of $Bu_4NF(t\text{-}BuOH)_4$]. The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc=10 : 1) to provide the titled compound *meta*-**1d** (45 mg, 0.15 mmol, 73%) as a colorless solid. *Rf*: 0.5 (hexane/EtOAc=6 : 1). mp: 89–92°C. The ^{1}H-NMR spectra of the obtained material was identical to that in our previous report.[35]

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**) (0.10 M in THF) and $Bu_4NF(t\text{-}BuOH)_4$ (0.22 M 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**, 0.22 mmol of $Bu_4NF(t\text{-}BuOH)_4$]. *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 (57% 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)**[35] **(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 M in THF) and $Bu_4NF(t\text{-}BuOH)_4$ (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 **3f**, 0.44 mmol of $Bu_4NF(t\text{-}BuOH)_4$]. The crude product (*meta*-**1f**/*ortho*-**1f**=6.4 : 1, determined by 300 MHz ^{1}H-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 ^{1}H-NMR spectra of the obtained material was identical to that in our previous report.[35]

2-(2-Fluorophenyl)-2,3-dihydro-1*H*-naphtho[1,8-*de*][1,3,2]-diazaborinine (*ortho*-1g)[35] **(Table 2, Entry 6)** Following the General Procedure A (Flow Conditions), 2-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)-6-(trimethylsilyl)phenyl triflate (**3g′**)[35] (0.10 M in THF) and $Bu_4NF(t\text{-}BuOH)_4$ (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 **3g′**, 0.44 mmol of $Bu_4NF(t\text{-}BuOH)_4$]. 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 ^{1}H-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 M in THF) and $Bu_4NF(t\text{-}BuOH)_4$ (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 **3h**, 0.44 mmol of $Bu_4NF(t\text{-}BuOH)_4$]. The crude product (*meta*-**1h**/*ortho*-**1h**=1.2 : 1, determined by 300 MHz ^{1}H-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. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.26 (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, *J*=1.5, 1.5 Hz), 7.25–7.30 (2H×4/9, m). ^{13}C-NMR (100 MHz, $CDCl_3$) 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). ^{19}F-NMR (283 MHz, $CDCl_3$) δ: −112.0–(−111.8) (m), −100.5–(−100.3) (m). IR (neat): 1574, 1253, 1231 cm^{-1}. HR-MS (EI) Calcd for $C_{12}H_{18}{}^{35}ClFSi$ $[M]^+$: 244.0845. Found 244.0849, 244.0855 (Two regioisomers, *ortho*-**1h** and *meta*-**1h** were separated by gas chromatography and measured by HR-MS).

Following the General Procedure B (Batch Conditions), a mixture of 4-chloro-2-(*tert*-butyldimethylsilyl)-6-(trimethylsilyl)phenyl nonaflate (**3h**) (0.12 g, 0.20 mmol), $Bu_4NF(t\text{-}BuOH)_4$ (0.25 g, 0.44 mmol) in THF (4.0 mL, 0.050 M) was stirred for 1 h at 60°C. However, the titled compounds, *meta*-**1h** and *ortho*-**1h** could not be detected in a crude mixture by ^{1}H-NMR spectroscopy.

1-Fluoro-3-iodo-5-(trimethylsilyl)benzene (*meta*-1i) and 1-Fluoro-4-iodo-2-(trimethylsilyl)benzene (*ortho*-1i) (Table 3, Entry 2) Following the General Procedure A (Flow Conditions), 4-iodo-2,6-bis(trimethylsilyl)phenyl nonaflate (**3i**)[35] (0.10 M in THF) and $Bu_4NF(t\text{-}BuOH)_4$ (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 **3i**, 0.44 mmol of $Bu_4NF(t\text{-}BuOH)_4$]. The crude product (*meta*-**1i**/*ortho*-**1i**=1.5 : 1, determined by 300 MHz ^{1}H-NMR analysis) was purified by flash column chromatography on silica gel (hexane/EtOAc=5 : 1) to provide a 2 : 1 mixture of the titled compounds, *meta*-**1i** and *ortho*-**1i** (31 mg, 0.11 mmol, 53%) as a brown oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.25 (9H×2/3, s), 0.29 (9H×1/3, m), 6.75 (1H×1/3, dd, *J*=9.0, 8.5 Hz), 7.13 (1H×2/3, ddd, *J*=8.5, 2.5, 1.5 Hz), 7.39 (1H×2/3, ddd, *J*=8.5, 2.5, 1.5 Hz), 7.54–7.57 (1H×2/3, m), 7.58–7.64 (2H×1/3, m).

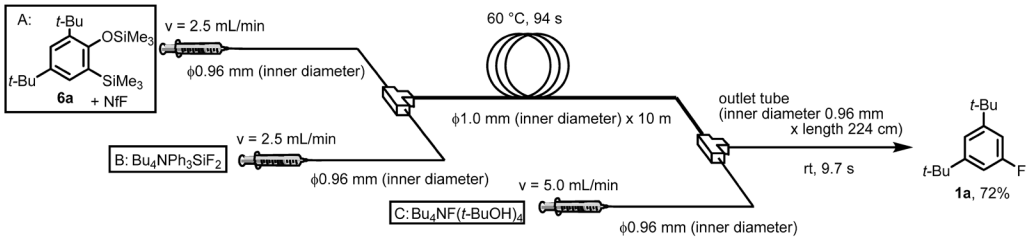


Chart 5. Flow Reactor for Chart 2

^{13}C-NMR (100 MHz, $CDCl_3$) δ: −1.3, −1.1, 88.2 (d, J=3.0 Hz), 84.5 (d, J=6.5 Hz), 117.5 (d, J=27.0 Hz), 119.1 (d, J=18.0 Hz), 125.0 (d, J=23.0 Hz), 130.2 (d, J=33.0 Hz), 137.7 (d, J=3.5 Hz), 140.0 (d, J=8.0 Hz), 143.7 (d, J=11.5 Hz), 146.3 (d, J=3.5 Hz), 162.0 (d, J=255.0 Hz), 167.2 (d, J=242.0 Hz). IR (neat): 1277, 1258 cm^{-1}. HR-MS (FAB, NBA) Calcd for $C_9H_{12}FSiI$ $[M]^+$: 293.9731. Found 293.9730.

Following the General Procedure B (Batch Conditions), a mixture of 4-iodo-2,6-bis(trimethylsilyl)phenyl nonaflate (**3i**)[35] (0.26 g, 0.40 mmol), $Bu_4NF(t\text{-}BuOH)_4$ (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*-**1i** and *ortho*-**1i** was detected in a crude mixture by ^{1}H-NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard (*meta*-**1i**–*ortho*-**1i**=1.5 : 1).

1-Bromo-3-*tert*-butyl-5-fluorobenzene (*meta*-1j)[106] (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 $Bu_4NF(t\text{-}BuOH)_4$ (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 $Bu_4NF(t\text{-}BuOH)_4$]. The crude product (*meta*-**1j**/*ortho*-**1j**=>98 : 2, determined by 300 MHz ^{1}H-NMR analysis) was purified by flash column chromatography on silica gel (hexane/CH_2Cl_2=100 : 1) to provide the titled compound *meta*-**1j** (46 mg, 0.20 mmol, 50%) as a brown oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.30 (9H, s), 7.01 (1H, ddd, J=11.0, 2.5, 1.5 Hz), 7.05 (1H, ddd, J=8.0, 2.5, 1.5 Hz), 7.28 (1H, dd, J=1.5, 1.5 Hz).

Following the General Procedure B (Batch Conditions), a mixture of 2-bromo-4-*tert*-butyl-6-(trimethylsilyl)phenyl triflate (**3j′**) (87 mg, 0.20 mmol), $Bu_4NF(t\text{-}BuOH)_4$ (0.25 g, 0.44 mmol) in THF (4.0 mL, 0.050 M) was stirred for 1 h at 60°C. However, the titled compound *meta*-**1j** could not be detected in a crude mixture by ^{1}H-NMR spectroscopy.

Procedure for the Flow Synthesis of 1,3-Di-*tert*-butyl-5-fluorobenzene (1a)[104] from Silyl Ether 6a (Charts 2 and 5) A MeCN/THF (2 : 1) solution of 2-(trimethylsilyl)-4,6-di-*tert*-butylphenyl trimethylsilyl ether (**6a**) and NfF [**6a**: 0.20 M (1.0 equiv), NfF: 0.30 M (1.5 equiv), V=2.5 mL/min] and a 20 mM solution of $Bu_4NPh_3SiF_2$ (0.10 equiv) in THF (V=2.5 mL/min) were mixed and reacted at 60°C in a continuous flow reactor consisting of two dual syringe pumps, one set to 2.5 mL/min and the other to 5.0 mL/min, two Comet X-01 devices, an outlet tube with a 7.9 mL residence volume (inner diameter 1.00 mm, outer diameter 2.00 mm, and length 10 m), and another outlet tube with a 1.6 mL residence volume (inner diameter 0.96 mm, outer diameter 1.56 mm, and length 2.24 m). To this stream was added a stream of $Bu_4NF(t\text{-}BuOH)_4$ (2.2 equiv) in THF (0.22 M, V=5.0 mL/min) at room temperature. The effective residence time for step 1 was 94 s, and for step 2 was 9.7 s. The crude reaction mixture was collected into *ca.* 1 mL of a saturated NH_4Cl solution for 24 s [total volume 4.0 mL, 0.20 mmol of **6a**, 0.30 mmol of NfF, 20 μmol of $Bu_4NPh_3SiF_2$, 0.44 mmol of $Bu_4NF(t\text{-}BuOH)_4$] from at least 100 s after the commencement of solution flow. The mixture was extracted with hexane (three times), and the combined organic phase was dried over anhydrous Na_2SO_4. The organic phase was filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (hexane/EtOAc=20 : 1) to provide 1,3-di-*tert*-butyl-5-fluorobenzene **1a**[104] as a colorless solid (30 mg, 0.14 mmol, 72%). The ^{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 Benzyne 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), Et_3N (1.5 equiv) and Me_3SiCl (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 NH_4Cl for quenching. The mixture was extracted with EtOAc (this process was repeated three times) and combined organic phase was dried over anhydrous Na_2SO_4. 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_2SO_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-(trialkylsilyl)phenyl 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[35] (0.26 g, 1.3 mmol), Et_3N (0.24 mL, 1.7 mmol), Me_3SiCl (1.7 mL, 20 mmol) was stirred in anhydrous THF (4.3 mL, 0.30 M) for 1 h at room temperature. To the obtained 2-bromophenyl trimethylsilyl ether were added THF (4.3 mL, 0.30 M) and *n*-BuLi (1.6 M 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=10 : 1) to give 4,5-dimethyl-2-bromophenyl trimethylsilyl ether (**2e**)[35] as a colorless oil (0.23 g, 90%). *Rf*: 0.5 (hexane). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.27 (9H, s), 2.15 (6H, s), 6.65 (1H, s), 7.25 (1H, s). Following General Procedure D, a mixture of 4,5-dimethyl-2-bromophenyl trimethylsilyl ether (**2e**)[35] (0.19 g, 1.0 mmol), NaH (60% in mineral oil, 0.12 g, 3.0 mmol), 18-crown-6 (0.79 g, 3.0 mmol) and NfF (0.52 mL, 3.0 mmol) was stirred in THF (5.0 mL, 0.2 M) at reflux for 5 h. The crude reaction mixture was purified by flash column chromatography on silica gel (hexane) to provide the titled compound **3e** as a colorless oil (0.36 g, 76%). *Rf*: 0.8 (hexane). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.26 (9H, s), 2.18 (3H, s), 2.19 (3H, s), 6.99 (1H, s), 7.15 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 0.8, 19.1, 20.0, 106.5–119.4 (4C, m), 120.6, 129.2, 136.1, 136.9, 140.4, 153.4. ^{19}F-NMR (470 MHz, $CDCl_3$) δ: −125.82–(−125.64) (m), −120.79–(−120.64) (m), −110.01–(−109.82) (m), −80.73–(−80.60) (m). IR (neat): 1422, 1352 cm^{-1}. HR-MS (APCI): *m/z* Calcd for $C_{15}H_{18}F_9O_3SSi$ $[M+H]^+$: 477.0597. Found: 477.0626.

4-Chloro-2-(*tert*-butyldimethylsilyl)-6-(trimethylsilyl)-phenyl Nonaflate (3h) (Table 3, Entry 1) Following General Procedure C, a mixture of 2,6-dibromo-4-chlorophenol[107] (14 g, 50 mmol) was dissolved in THF (0.20 L, 0.25 M). Me_3SiCl (9.5 mL, 75 mmol) and Et_3N (11 mL, 75 mmol) were added to the solution and stirred at room temperature for 1 h. 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 2,6-dibromo-4-chlorophenyl trimethylsilyl ether (18 g, 98%) as a colorless oil. Without purification of the obtained material, anhydrous THF (0.25 L, 0.2 M) was added to the flask and the mixture was cooled to −78°C. *n*-BuLi (2.5 M hexane solution, 24 mL, 1.2 equiv) was added dropwise at −78°C and the reaction was allowed to warm up to room temperature and stirred for 1 h. Then the mixture was added *tert*-butyldimethylsilyl chloride (9.0 g, 60 mmol) and stirred for 12 h. Water (*ca.* 0.15 L) was added to the mixture and it was extracted with hexane (three times). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane) to provide 4-chloro-6-bromo-2-(trimethylsilyl)phenyl *tert*-butyldimethylsilyl ether (15 g, 77%) as a colorless oil. 4-Chloro-6-bromo-2-(trimethylsilyl)phenyl *tert*-butyldimethylsilyl ether (15 g, 38 mmol) was dissolved in anhydrous THF (0.19 L, 0.2 M) and the mixture was cooled to −78°C. *n*-BuLi (2.5 M hexane solution, 18 mL, 45 mmol) was added dropwise at −78°C and the reaction was allowed to warm up to room temperature and stirred for 5 h. To the reaction mixture was added a saturated aqueous solution of NH_4Cl for quenching. The mixture was extracted with hexane (this process was repeated three times) and combined organic phase was dried over anhydrous Na_2SO_4. The organic phase was filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane) 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 M) 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. *Rf*: 0.8 (hexane). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.35 (9H, s), 0.39 (6H, s), 0.80 (9H, s), 7.47–7.49 (2H, m). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: −4.0, 0.5, 18.2, 26.9, 106.5–126.9 (4C, m), 133.7, 135.3, 137.6, 137.9, 138.3, 152.7. ^{19}F-NMR (470 MHz, $CDCl_3$) δ: −125.71–(−125.56) (m), −120.86–(−120.73) (m), −106.21–(−106.12) (m), −80.54–(−80.45) (m). IR (neat): 1403, 1570, cm^{-1}. HR-MS (APCI): *m/z* Calcd for $C_{19}H_{27}{}^{35}ClF_9O_3SSi_2$ $[M+H]^+$: 597.0759. Found: 597.0781.

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_2Cl_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 wormed 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[108] (29 g, 92%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.26 (9H, s), 5.71 (1H, br s), 7.42 (2H, s). An oven dried flask was charged with 2,6-dibromo-4-*tert*-butylphenol[108] (5.0 g, 16 mmol) and capped with an inlet adapter with a 3-way stopcock and then evacuated and back-filled with argon. Anhydrous THF (81 mL, 0.20 M), Et_3N (3.4 mL, 24 mmol) and Me_3SiCl (3.1 mL, 24 mmol) were added *via* syringes and the reaction mixture was stirred for 1 h 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 2,6-dibromo-4-*tert*-butylphenyl trimethylsilyl ether. Without purification of the obtained material, anhydrous Et_2O (0.16 L, 0.10 M) was added to the flask and the mixture was cooled to −78°C. *n*-BuLi (2.6 M hexane solution, 6.8 mL, 18 mmol) was added dropwise at −78°C and stirred for 1 h. To the reaction mixture was added Tf_2O (4.0 mL, 24 mmol) and stirred for additional 4 h at −78°C. Saturated aqueous solution of $NaHCO_3$ was added to the reaction mixture for quenching and it was warmed to room temperature. The mixture was extracted with hexane (this process was repeated three times) and combined organic phase was dried over anhydrous $MgSO_4$. The organic phase was filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane) to provide the titled compound **3j′** (6.5 g, 92%) as a brown solid. *Rf*: 0.8 (hexane). mp: 39–41°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.40 (9H, s), 1.32 (9H, s), 7.48 (1H, d, *J*=2.5 Hz), 7.64 (1H, d, *J*=2.5 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 0.1, 31.1, 34.8, 115.9, 118.6 (1C, q, J=160 Hz), 132.6, 133.0, 136.5, 146.5, 152.3. ^{19}F-NMR (470 MHz, $CDCl_3$) δ:−71.63 (s). IR (neat): 1398, 1572 cm^{-1}. HR-MS (APCI): m/z Calcd for $C_{14}H_{21}{}^{79}BrF_3O_3SSi$ $[M+H]^+$: 433.0111. Found: 433.0107.

2,4-Diiodo-6-(trimethylsilyl)phenyl Triflate (3k′) (Table 3, Entry 4) An oven dried flask was charged with 2,4,6-triiodophenol[109] (5.0 g, 11 mmol) and capped with an inlet adapter with a 3-way stopcock and then evacuated and back-filled with argon. Anhydrous THF (53 mL, 0.20 M), Et_3N (2.2 mL, 16 mmol) and Me_3SiCl (1.0 mL, 16 mmol) were added *via* syringes and the reaction mixture was stirred for 1 h 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 2,4,6-triiodophenyl trimethylsilyl ether. Without purification of the obtained material, anhydrous Et_2O (0.11 L, 0.10 M) was added to the flask and the mixture was cooled to −78°C. *n*-BuLi (2.6 M hexane solution, 4.5 mL, 12 mmol) was added dropwise at 0°C and stirred for 1 h. To the reaction mixture was added Tf_2O (2.7 mL, 16 mmol) and stirred for additional 1.5 h at room temperature. Saturated aqueous solution of $NaHCO_3$ was added to the reaction mixture for quenching and it was warmed to room temperature. The mixture was extracted with hexane (this process was repeated three times) and combined organic phase was dried over anhydrous $MgSO_4$. The organic phase was filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane) to provide the titled compound **3k′** (5.5 g, 94%) as a white solid. *Rf*: 0.8 (hexane). mp: 46–48°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.37 (9H, s), 7.75 (1H, d, J=2.0 Hz), 8.21 (1H, d, J=2.5 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 0.15, 91.6, 95.0, 118.5 (CF_3, q, J=320.5 Hz), 140.2, 145.5, 149.9, 151.2. ^{19}F-NMR (470 MHz, $CDCl_3$) δ: −71.65 (s). IR (neat): 1215, 1408 cm^{-1}. HR-MS (FAB, NBA): m/z Calcd for $C_{10}H_{11}F_3I_2O_3SSiNa$ $[M+Na]^+$: 572.8132. Found: 572.8131.

Preparation of 2-(Trimethylsilyl)-4,6-di-*tert*-butylphenyl Trimethylsilyl Ether (6a) (Chart 2) An oven-dried round bottom flask was charged with 2-bromo-4,6-di-*tert*-butylphenol[68] (13 g, 46 mmol) and a stirrer bar. The flask was equipped with a three-way stopcock and evacuated and back-filled with nitrogen gas (three times). THF (50 mL), Me_3SiCl (8.8 mL, 69 mmol), and Et_3N (9.6 mL, 69 mmol) were sequentially added into the flask *via* a syringe. The mixture was stirred at room temperature for 1 h. The reaction mixture was evaporated under reduced pressure, and the residue was filtered through a silica gel pad. The silica gel pad was washed with hexane and the combined solution was concentrated under reduced pressure to provide 2-bromo-4,6-di-*tert*-butylphenyl trimethylsilyl ether, which was used in the next reaction without further purification. 0.12 L of anhydrous THF was added to the flask containing 2-bromo-4,6-di-*tert*-butylphenyl trimethylsilyl ether (0.40 M) and the solution was cooled to −78°C under nitrogen. *n*-BuLi (2.6 M hexane solution, 21 mL, 55 mmol) was added dropwise into the mixture at −78°C, after which it was stirred at room temperature for 2 h. Me_3SiCl (8.8 mL, 69 mmol) was added to the reaction mixture at the same temperature, with stirring at this temperature for 15 min. The mixture was concentrated under reduced pressure. The residue was purified by silica-gel flash column chromatography (hexane) to provide the titled compound **6a** as a white solid (16 g, 99%). mp: 64–65°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.30 (9H, s), 0.32 (9H, s), 1.28 (9H, s), 1.40 (9H, s), 7.24 (1H, d, J=2.5 Hz), 7.37 (1H, d, J=2.5 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) 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) Calcd for $C_{20}H_{38}OSi_2$ $[M]^+$: 350.2456. Found 350.2440.

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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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