

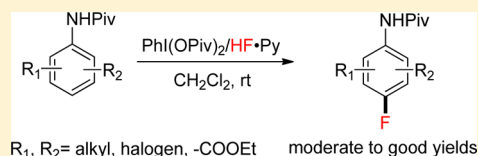
Hypervalent Iodine Mediated *para*-Selective Fluorination of Anilides

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S Supporting Information

ABSTRACT: A metal-free method for the direct regioselective fluorination of anilides has been developed. In the presence of bis(*tert*-butylcarbonyloxy)-iodobenzene (PhI(OPiv)₂) and hydrogen fluoride-pyridine, the *para*-fluorination products of anilides were obtained in moderate to good yields. Because of its operational safety and the use of readily available reagents, this new procedure provides facile access to a variety of *para*-fluorinated anilides.



Fluorinated aromatic compounds are often prepared as bioactive and pharmaceutical agents.¹ Generally, molecular fluorine and electrophilic fluorinating reagents, such as XeF₂, AcOF, CF₃OF, and CsSO₄F, are used in the direct fluorination of aromatic compounds, forming the C–F bond through electrophilic fluorination. However, these unstable fluorinating reagents are difficult to handle, and the electrophilic fluorination usually provides low regioselectivity for electron-rich aromatics; a mixture of *o/p*-isomers is obtained in most cases.² Other electrophilic fluorinating reagents such as Selectfluor (F-TEDA-BF₄), NFSi, and *N*-fluoro pyridinium salts are commercially available, easy-to-handle, and stable. Moreover, these reagents demonstrated high regioselectivity and efficiency for fluorination. Nevertheless, they are expensive.³ In order to prepare various fluorinated compounds, great efforts have been dedicated to the formation of C–F bond. More than 80 years ago, the Balz–Schiemann reaction⁴ was discovered to convert diazonium tetrafluoroborate salts into fluorinated arenes. In industry, the Halex process (halogen exchange) is a common method for the synthesis of fluorinated compounds by employing inexpensive inorganic fluoride sources.⁵ Palladium-catalyzed nucleophilic fluorination achieves C–F bond formation via reductive elimination.⁶ In addition, Ag-mediated aryl stannane⁷ and arylboronic acids⁸ fluorinations emerge as important methods for the preparation of a variety of fluorinated compounds. However, facile methods with mild conditions, high efficiency, and environmental protection are still needed.

In recent years, hypervalent iodine reagents have been widely used in oxidation synthesis, owing to their strong oxidizing properties and availability.⁹ Recently, Kikugawa et al.¹⁰ and Gu's group¹¹ reported the *para*-oxidation of anilides mediated by hypervalent iodine reagents. In 2011, Kitamura's group developed a simple, practical, and convenient method for the fluorination of 1,3-dicarbonyl compounds, achieved by direct utilization of aqueous hydrofluoric acid and iodosylbenzene (PhIO).¹² At the same time, Mtiyamoto's group reported the hypervalent phenyl-λ³-iodane mediated *para*-selective aromatic fluorination of 3-phenylpropyl ethers, via neighboring group participation of alkoxy substituents.¹³ Very recently, Gouver-

neur et al. developed a metal-free method for the oxidative fluorination of phenols mediated by hypervalent iodine.¹⁴ Hypervalent iodine reagents have also attracted the attention of our group.¹⁵ In continuation of our interest in hypervalent iodine chemistry, herein we report a new method for the direct fluorination of aromatic amines using hypervalent iodine reagents.

The fluorination was conducted by treating a mixture of a hypervalent iodine compound and fluorine sources with anilides in dichloromethane. As shown in Table 1, evaluation of different fluorine sources indicated that HF·Py afforded good

Table 1. Optimization of the Reaction Conditions^a

1a R = Ac 1b R = Piv		2a R = Ac 2b R = Piv		
entry	substrates	hypervalent iodine (equiv)	additive	yield ^b (%)
1	1a	PhI(OAc) ₂ (1.2)	HF·Py	56
2	1a	PhI(OAc) ₂ (1.5)	HF·Py	66
3	1a	PhI(OAc) ₂ (1.5)	BF ₃ ·Et ₂ O/H ₂ O	nd ^c
4	1a	PhI(OAc) ₂ (1.5)	AgF	nd ^c
5	1a	PhI(OAc) ₂ (1.5)	MgF ₂	nd ^c
6	1a	PhI(OAc) ₂ (1.5)	K ₂ HF	nd ^c
7	1a	PhI(OAc) ₂ (1.5)	LiF	nd ^c
8	1a	PhIO (1.5)	HF·Py	58
9	1a	PhI(OCOCF ₃) ₂	HF·Py	44
10	1a	PhI(OPiv) ₂ (1.5)	HF·Py	68
11	1b	PhI(OPiv) ₂ (1.5)	HF·Py	85
12	1b	PhI(OAc) ₂ (1.5)	HF·Py	42

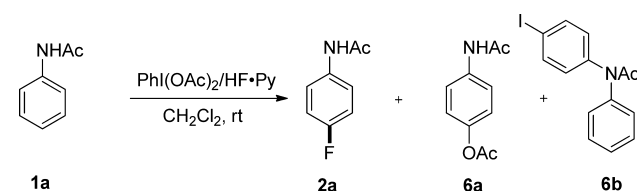
^aReaction conditions: 1a or 1b (0.5 mmol), additive (6 equiv), CH₂Cl₂ (5 mL), rt, 12 h. ^bIsolated yields. ^cNo desired product was detected by NMR analysis.

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yields of fluorination products, while $\text{BF}_3\cdot\text{Et}_2\text{O}$ and other villiamites produced no fluorination product.

Specifically, we first employed PIDA as the hypervalent iodine reagent for its chemical stability and easy availability. After **1a** (1 mmol) was mixed with $\text{HF}\cdot\text{Py}$ (55%, 6 mmol) in CH_2Cl_2 (5 mL), $\text{PhI}(\text{OAc})_2$ (1.2 mmol) was added, and the mixture was stirred at room temperature for 12 h. After purification by column chromatography, **2a** was obtained in 56% yield; meanwhile, starting materials and some byproducts, *para*-acetoxylation product **6a** and *N*-iodophenylation product **6b**, were detected^{10,11a} (Scheme 1). The yield was increased to

Scheme 1. Reaction of Acetanilide with $\text{PhI}(\text{OAc})_2$



66% by using 1.5 mmol $\text{PhI}(\text{OAc})_2$ under the same condition. When other hypervalent iodine reagents such as $\text{PhI}(\text{OCOCF}_3)_2$, $\text{PhI}(\text{OPiv})_2$, and PhIO (Table 1, entries 8–10) were employed in this reaction, moderate yields were also obtained. Gratifyingly, when **1b** was subjected to the reaction in the presence of $\text{PhI}(\text{OPiv})_2$, the side reactions were inhibited and the product **2b** was obtained in 85% yield (Table 1, entry 11).

In order to investigate the effect of protecting groups, a series of aniline derivatives with different protecting groups were subjected to the reaction. As summarized in Table 2, the results showed that the pivaloyl substrate (**1b**) provided the highest yield (entry 2). When trifluoroacetyl was used as the protecting group, a 36% yield was obtained (entry 3). As for **1d** and **1e** with the sulfonyl protecting groups, the reaction formed complex mixtures, and only trace amounts of desired products

Table 2. *para*-Fluorination of Aniline with Different Protecting Groups^a

entry	substrates	R group	yield ^b (%)
1	1a	Ac-	68
2	1b	Piv-	85
3	1c	$\text{CF}_3\text{CO}-$	36
4	1d	Ts-	nd ^c
5	1e	Ms-	nd ^c
6	1f	$\text{EtOCO}-$	nd ^c
7	1g	Bz-	53
8	1h	$4\text{-Cl-C}_6\text{H}_4\text{CO}-$	54
9	1i	$4\text{-C}_6\text{H}_5\text{-C}_6\text{H}_4\text{CO}-$	53
10	1j	$4\text{-Br-C}_6\text{H}_4\text{CO}-$	52
11	1k	$4\text{-NO}_2\text{-C}_6\text{H}_4\text{CO}-$	50
12	1l	2-naphthoyl-	13

^aReaction conditions: **1a–l** (0.5 mmol), $\text{PhI}(\text{OPiv})_2$ (1.5 equiv), $\text{HF}\cdot\text{Py}$ (6 equiv), and CH_2Cl_2 (5 mL) at room temperature, 12 h.

^bIsolated yields. ^cNo desired product was detected by NMR analysis.

were obtained (entries 4 and 5). Furthermore, carbonate protected aniline also formed a complex mixture, and no target product was detected. We also tried some benzoyl-type protecting groups, and the fluorination procedure usually afforded products in moderate yields (entries 7–11). However, the naphthoyl substrate furnished the product in only 13% yield (entry 12).

To explore the scope of the fluorination reaction, several aromatic amines were used. The results are summarized in Table 3. We found that this reaction was tolerant to various functional groups, such as alkyl, halogen, and ester groups. The fluorination of pivaloanilide with a methyl group at the *ortho*-position provided **4a** in 80% yield (entry 1). Due to steric effect, the reaction afforded **4b** in 70% yield when the methyl group was at the *meta*-position of pivaloanilide (entry 2). Moreover, anilide with an *o*-ethyl group was fluorinated to give **4h** in 64% yield (entry 8). In addition, reaction of disubstituted anilides **3g** and **3i** proceeded smoothly to produce the *para*-fluorinated products **4g** and **4i** in 78% and 72% yields, respectively (entries 7 and 9). When the substrates contained electron-withdrawing groups, such as halogen and ester groups, moderate yields were obtained. The reaction mixture was more complex and byproducts of *para*-pivaloylation and *N*-iodophenylation were detected. These observations indicated that the electronegativity of anilide substituent may have a great impact on the reaction (entries 3–6 and 10). Furthermore, for anilides with *o*-halogen substituents (entries 3 and 4), prolonged reaction time was needed to finish the conversion. We attempted the reaction with 3,4-dimethyl-*N*-pivaloylanilines **3n**; however, no desired products were detected.

To further demonstrate the synthetic applicability of our new fluorination method, deprotection of the pivaloyl group of **2b** was examined. After treatment with 6 N HCl in aqueous solution under reflux, the product 4-fluoroaniline **5** was isolated in 82% yield (Scheme 2).

Based on our results and previous literature studies,^{10,11} a possible mechanism for the *para*-fluorination of anilide is shown in Scheme 3. The anilide first undergoes nucleophilic attack by $\text{PhI}(\text{OPiv})_2$, forming the intermediate A. Cleavage of the N–I bond releases PhI and generates nitrenium ion intermediate B. As stabilized by the phenyl ring, the charge delocalized intermediate C is preferred. Finally, the intermediate C was trapped by HF to give the *para*-fluorination product.

In conclusion, we have developed a straightforward regioselective metal-free method for the synthesis of *para*-fluorinated anilides. By employing commercially available $\text{PhI}(\text{OPiv})_2$ in the presence of $\text{HF}\cdot\text{Py}$, the *para*-selective fluorination of anilides was achieved. This convenient procedure provides a new access to the construction of *para*-fluorinated aromatic amines.

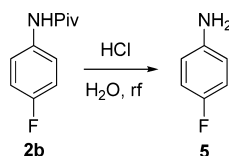
EXPERIMENTAL SECTION

General Experimental Methods. All chemicals were purchased as reagent grade and used without further purification, unless otherwise noted. Dichloromethane was distilled over calcium hydride. Analytical TLC was performed on silica gel60 F₂₅₄ precoated on glass plates, with detection by fluorescence and/or by staining with 5% concentrated sulfuric acid in EtOH. Column chromatography was performed employing silica gel (230–400 mesh). ¹H NMR spectra were recorded on Advance spectrometers at 25 °C. Chemical shifts (in ppm) were referenced with tetramethylsilane (δ = 0 ppm) in deuterated chloroform and deuterated dimethyl sulfoxide (δ = 2.50 ppm). ¹³C NMR spectra were obtained by using the same NMR

Table 3. *para*-Fluorination of Anilides Using $\text{PhI}(\text{OPiv})_2/\text{HF}\cdot\text{Py}$ System^a

$\text{R}-\text{C}_6\text{H}_4-\text{NHPiv} \xrightarrow[\text{CH}_2\text{Cl}_2, \text{rt}]{\text{PhI}(\text{OPiv})_2/\text{HF}\cdot\text{Py}} \text{R}-\text{C}_6\text{H}_3(\text{F})-\text{NHPiv}$							
Entry	Substrate	Product	Yield ^b (%)	Entry	Substrate	Product	Yield ^b (%)
1			80	6			43 ^c
2			70	7			78
3			40 ^c	8			64
4			48 ^c	9			72
5			55	10			51
				11			n.d. ^d

^aReaction conditions: **3a–n** (0.5 mmol), $\text{PhI}(\text{OPiv})_2$ (1.5 equiv), $\text{HF}\cdot\text{Py}$ (6 equiv), and CH_2Cl_2 (5 mL) at room temperature. ^bIsolated yields. ^cThe reaction was carried out for 24 h. ^dNo desired product was detected by NMR analysis.

Scheme 2. Deprotection of 4-Fluoro-*N*-pivaloylaniline^a

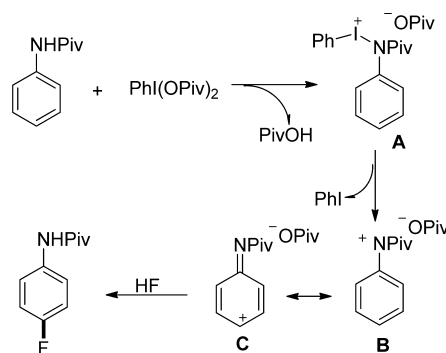
^aReaction conditions: **2b** (0.5 mmol), HCl (6 M, 2.5 mL) at refluxing temperature.

spectrometers and were calibrated with CDCl_3 ($\delta = 77.00$ ppm) and DMSO ($\delta = 39.52$ ppm). High-resolution mass spectrometry was performed on FTICR mass spectrometer.

General Procedure A for Fluorination of Anilides. To a solution of acetylaniline (0.5 mmol) and $\text{HF}\cdot\text{Py}$ (270 μL , 3 mmol) in CH_2Cl_2 (2.0 mL) was added a solution of $\text{PhI}(\text{OPiv})_2$ (305 mg, 0.75 mmol) in CH_2Cl_2 (3.0 mL). The reaction mixture was stirred at room temperature for 12 h followed by quenching with 0.2 equiv of Et_3N . After the solvent was removed under vacuum, the residue was purified by flash column chromatography on aluminum oxide (pH 10) eluted with EtOAc /hexane.

General Procedure B for Fluorination of Anilides (3j). To a solution of **3j** (0.5 mmol) and $\text{HF}\cdot\text{Py}$ (270 μL , 3 mmol) in CH_2Cl_2 (2.0 mL) was added a solution of $\text{PhI}(\text{OPiv})_2$ (305 mg, 0.75 mmol) in CH_2Cl_2 (3.0 mL). The reaction mixture was stirred at room

Scheme 3. Proposed Reaction Mechanism



temperature for 12 h. The reaction mixture was poured into CH_2Cl_2 (10 mL), neutralized with NaHCO_3 , and extracted with CH_2Cl_2 (6 mL $\times$ 3). The combined organic layer was washed with saturated salt water and dried over anhydrous Na_2SO_4 . The residue was purified by flash column chromatography on aluminum oxide (pH 10) eluted with EtOAc /hexane.

4-Fluoroacetanilide (2a). Using general procedure A, compound **2a** was isolated in 68% yield (52.0 mg, white solid); ^1H NMR (400 MHz, CDCl_3) δ 7.62 (s, 1H), 7.50–7.38 (m, 2H), 6.99 (t, $J = 8.7$ Hz, 2H), 2.16 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 168.5, 158.1,

133.8, 121.8, 115.6, 24.3; ^{19}F NMR (376 MHz, CDCl_3) δ -118.0. These spectroscopic data correspond to previously reported data.¹⁶

4-Fluoro-*N*-pivaloylaniline (2b). Using general procedure A, compound **2b** was isolated in 85% yield (83.0 mg, white solid); ^1H NMR (400 MHz, CDCl_3) δ 7.48 (m, 2H), 7.28 (s, 1H), 7.02 (m, 2H), 1.32 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 121.8, 121.8, 115.6, 115.4, 27.6; ^{19}F NMR (376 MHz, CDCl_3) δ -118.3. These spectroscopic data correspond to previously reported data.¹⁷

4-Fluorotrifluoroacetanilide (2c). Using general procedure A, compound **2c** was isolated in 36% yield (37.3 mg, white solid); ^1H NMR (400 MHz, CDCl_3) δ 8.12 (s, 1H), 7.53 (ddd, J = 10.2, 5.1, 2.7 Hz, 2H), 7.08 (m, 2H), corresponding to previously reported data;¹⁸ ^{13}C NMR (101 MHz, CDCl_3) δ 161.8, 159.3, 131.0, 122.6, 122.6, 116.3, 116.1, 114.3; ^{19}F NMR (376 MHz, CDCl_3) δ -75.7, -114.7, corresponding to previously reported data.¹⁸

***N*-(4-Fluorophenyl)-benzamide (2g).** Using general procedure A, compound **2g** was isolated in 53% yield (57.0 mg, colorless crystal); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.32 (s, 1H), 7.95 (m, 2H), 7.80 (m, 2H), 7.59 (dd, J = 5.0, 3.6 Hz, 1H), 7.53 (m, 2H), 7.20 (m, 2H); ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ 166.1, 160.1, 157.7, 136.2, 136.1, 135.4, 132.2, 129.0, 128.2, 122.8, 122.8, 115.9, 115.6, 40.7, 40.5, 40.3, 40.1, 39.9, 39.7, 39.5; ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) δ -118.9. These spectroscopic data correspond to previously reported data.¹⁹

4-Chloro-*N*-(4-fluorophenyl)-benzamide (2h). Using general procedure A, compound **2h** was isolated in 54% yield (67.4 mg, colorless crystal); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.37 (s, 1H), 7.98 (m, 2H), 7.78 (m, 2H), 7.61 (m, 2H), 7.20 (t, J = 8.9 Hz, 2H); ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ 164.0, 136.1, 134.9, 133.1, 129.2, 128.1, 121.9, 121.8, 115.0, 114.7; ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) δ -118.7. These spectroscopic data correspond to previously reported data.²⁰

***N*-(4-fluorophenyl)-[1,1'-biphenyl]-4-carboxamide (2i).** Using general procedure A, compound **2i** was isolated in 53% yield (77.2 mg, colorless crystal); mp 232.0–234.5 °C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.35 (s, 1H), 8.06 (d, J = 8.4 Hz, 2H), 7.82 (ddd, J = 7.1, 6.7, 4.2 Hz, 4H), 7.76 (m, 2H), 7.51 (t, J = 7.5 Hz, 2H), 7.43 (d, J = 7.2 Hz, 1H), 7.21 (dd, J = 12.2, 5.6 Hz, 2H); ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ 165.7, 160.1, 157.7, 143.8, 139.7, 136.1, 134.2, 129.7, 129.0, 128.8, 127.5, 127.2, 122.9, 122.8, 115.9, 115.7; ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) δ -118.9. HRMS (ESI) m/z calcd for $\text{C}_{19}\text{H}_{14}\text{FNNaO}$ [$\text{M} + \text{Na}$] $^+$: 314.0951, found 314.0952.

4-Bromo-*N*-(4-fluorophenyl)-benzamide (2j). Using general procedure A, compound **2j** was isolated in 52% yield (76.5 mg, colorless crystal); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.36 (s, 1H), 7.90 (d, J = 8.6 Hz, 2H), 7.77 (ddd, J = 15.6, 9.4, 5.1 Hz, 4H), 7.19 (t, J = 8.8 Hz, 2H); ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ 165.1, 160.2, 157.8, 135.9, 134.4, 132.0, 130.4, 126.0, 122.9, 122.8, 115.9, 115.7, 40.8, 40.5, 40.3, 40.1, 39.9, 39.7, 39.5; ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) δ -118.6. HRMS (ESI) m/z calcd for $\text{C}_{13}\text{H}_{10}\text{BrFNO}$ [$\text{M} + \text{Na}$] $^+$: 293.9925, found 293.9924.

4-Nitro-*N*-(4-fluorophenyl)-benzamide (2k). Using general procedure A, compound **2k** was isolated in 50% yield (65.1 mg, colorless crystal); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.62 (s, 1H), 8.37 (m, 2H), 8.19 (m, 2H), 7.80 (m, 2H), 7.22 (dd, J = 12.2, 5.6 Hz, 2H); ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ 164.4, 160.4, 158.0, 149.8, 141.0, 135.6, 129.8, 124.2, 123.0, 123.0, 116.0, 115.8, 40.8, 40.6, 40.3, 40.1, 39.9, 39.7, 39.5; ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) δ -118.2. These spectroscopic data correspond to previously reported data.²⁰

***N*-(4-Fluorophenyl)-2-naphthalenecarboxamide (2l).** Using general procedure A, compound **2l** was isolated in 13% yield (17.2 mg, colorless crystal); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.63 (s, 1H), 8.19 (m, 1H), 8.08 (d, J = 8.2 Hz, 1H), 8.02 (m, 1H), 7.85 (dd, J = 8.7, 5.0 Hz, 2H), 7.76 (d, J = 7.0 Hz, 1H), 7.60 (m, 3H), 7.23 (t, J = 8.8 Hz, 2H); ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ 167.8, 160.1, 157.7, 136.3, 135.2, 133.8, 130.8, 130.2, 129.0, 127.6, 127.0, 126.1, 125.7, 125.6, 122.3, 122.2, 116.0, 115.8, 40.8, 40.5, 40.3, 40.1, 39.9, 39.7, 39.5. These spectroscopic data correspond to previously reported data.²¹ ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) δ -118.8.

***N*-Pivaloyl-4-fluoro-2-methylaniline (4a).** Using general procedure A, compound **4a** was isolated in 80% yield (83.7 mg, white solid); mp 96.2–98.3 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.67 (dd, J = 9.7, 5.4 Hz, 1H), 7.13 (s, 1H), 6.90 (d, J = 8.6 Hz, 2H), 2.23 (s, 3H), 1.34 (s, 9H), corresponding to previously reported data;²² ^{13}C NMR (101 MHz, CDCl_3) δ 176.6, 158.7, 132.20, 131.6, 125.2, 117.0, 116.8, 113.3, 113.1, 39.6, 27.7, 17.8; ^{19}F NMR (376 MHz, CDCl_3) δ -117.6; HRMS (ESI) m/z calcd for $\text{C}_{12}\text{H}_{17}\text{FNO}$ [$\text{M} + \text{H}$] $^+$: 210.1289, found 210.1290.

***N*-Pivaloyl-4-fluoro-3-methylaniline (4b).** Using general procedure A, compound **4b** was isolated in 70% yield (73.2 mg, white solid); mp 112.5–114.8 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.42 (dd, J = 6.6, 2.0 Hz, 1H), 7.30 (s, 1H), 7.23 (m, 1H), 6.93 (t, J = 9.0 Hz, 1H), 2.25 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 176.6, 159.1, 156.7, 133.6, 125.3, 125.1, 123.4, 123.3, 119.1, 119.0, 115.1, 114.9, 39.5, 27.6, 14.6, 14.6; ^{19}F NMR (376 MHz, CDCl_3) δ -122.5; HRMS (ESI) m/z calcd for $\text{C}_{12}\text{H}_{17}\text{FNO}$ [$\text{M} + \text{H}$] $^+$: 210.1292, found 210.1289.

***N*-Pivaloyl-2,4-difluoroaniline (4c).** Using general procedure A, compound **4c** was isolated in 40% yield (42.6 mg, yellow oil); ^1H NMR (400 MHz, CDCl_3) δ 8.26 (td, J = 9.0, 6.0 Hz, 1H), 7.49 (s, 1H), 6.86 (m, 2H), 1.33 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 176.8, 159.8, 159.7, 157.4, 157.3, 154.1, 153.9, 151.5, 123.0, 123.0, 122.9, 122.9, 111.4, 111.4, 111.2, 111.2, 103.8, 103.5, 103.5, 103.3, 40.0, 27.7; ^{19}F NMR (376 MHz, CDCl_3) δ -115.5, -115.5, -127.2, -127.2; HRMS (ESI) m/z calcd for $\text{C}_{11}\text{H}_{14}\text{F}_2\text{NO}$ [$\text{M} + \text{H}$] $^+$: 214.1042, found 214.1038.

***N*-Pivaloyl-2-chloro-4-fluoroaniline (4d).** Using general procedure A, compound **4d** was isolated in 48% yield (55.0 mg, slight yellow oil); ^1H NMR (400 MHz, CDCl_3) δ 8.36 (dd, J = 9.2, 5.7 Hz, 1H), 7.86 (s, 1H), 7.13 (dd, J = 8.0, 2.9 Hz, 1H), 7.00 (ddd, J = 9.1, 8.0, 2.9 Hz, 1H), 1.34 (s, 9H); ^{13}C (101 MHz, CDCl_3) δ 176.7, 159.6, 157.2, 131.4, 123.7, 122.9, 122.8, 116.4, 116.2, 114.9, 114.6, 40.2, 27.7; ^{19}F NMR (376 MHz, CDCl_3) δ -116.7; HRMS (ESI) m/z calcd for $\text{C}_{11}\text{H}_{14}\text{ClFNO}$ [$\text{M} + \text{H}$] $^+$: 230.0749, found 230.0742.

***N*-Pivaloyl-3-chloro-4-fluoroaniline (4e).** Using general procedure A, compound **4e** was isolated in 55% yield (63 mg, slight yellow solid); ^1H NMR (400 MHz, CDCl_3) δ 7.71 (d, J = 6.4 Hz, 1H), 7.50 (s, 1H), 7.31 (dd, J = 6.8, 2.1 Hz, 1H), 7.04 (t, J = 8.7 Hz, 1H), 1.30 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 176.9, 155.9, 153.4, 134.6, 134.6, 122.6, 120.0, 119.9, 116.5, 116.2, 39.6, 27.5; ^{19}F NMR (376 MHz, CDCl_3) δ -116.6; HRMS (ESI) m/z calcd for $\text{C}_{11}\text{H}_{14}\text{ClFNO}$ [$\text{M} + \text{H}$] $^+$: 230.0748, found 230.0742.

***N*-Pivaloyl-5-chloro-4-fluoro-2-methylaniline (4f).** Using general procedure A, compound **4f** was isolated in 43% yield (52.2 mg, slight yellow solid); mp 107.2–109.4 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.88 (d, J = 7.2 Hz, 1H), 7.18 (s, 1H), 6.95 (d, J = 9.4 Hz, 1H), 2.20 (s, 3H), 1.32 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 176.6, 156.2, 153.8, 132.2, 130.0, 130.0, 125.2, 117.8, 117.6, 39.6, 27.6, 17.3; ^{19}F NMR (376 MHz, CDCl_3) δ -120.4; HRMS (ESI) m/z calcd for $\text{C}_{12}\text{H}_{16}\text{ClFNO}$ [$\text{M} + \text{H}$] $^+$: 244.0904, found 244.0899.

***N*-Pivaloyl-4-fluoro-2,5-dimethylaniline (4g).** Using general procedure A, compound **4g** was isolated in 78% yield (87.0 mg, white solid); mp 116.5–117.8 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.46 (d, J = 7.5 Hz, 1H), 7.21 (s, 1H), 6.79 (d, J = 10.0 Hz, 1H), 2.20 (s, 3H), 2.14 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 176.7, 159.6, 157.1, 131.1, 129.7, 129.6, 126.9, 126.8, 122.5, 122.3, 116.4, 116.2, 39.4, 27.5, 17.2, 14.1, 14.1; ^{19}F NMR (376 MHz, CDCl_3) δ -121.9; HRMS (ESI) m/z calcd for $\text{C}_{13}\text{H}_{19}\text{FNO}$ [$\text{M} + \text{H}$] $^+$: 224.1445, found 224.1446.

***N*-Pivaloyl-2-ethyl-4-fluoroaniline (4h).** Using general procedure A, compound **4h** was isolated in 64% yield (71.7 mg, slight yellow solid); mp 103.5–104.0 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.58 (dd, J = 8.6, 5.5 Hz, 1H), 7.28 (d, J = 6.8 Hz, 1H), 6.87 (m, 2H), 2.53 (q, J = 7.5 Hz, 2H), 1.30 (s, 9H), 1.20 (t, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 176.8, 161.5, 159.1, 138.5, 138.4, 131.0, 130.9, 126.2, 126.1, 114.9, 114.7, 113.0, 112.8, 77.3, 77.0, 76.7, 39.4, 27.5, 24.2, 13.4; ^{19}F NMR (376 MHz, CDCl_3) δ -117.0; HRMS (ESI) m/z calcd for $\text{C}_{13}\text{H}_{19}\text{FNO}$ [$\text{M} + \text{H}$] $^+$: 224.1445, found 224.1445.

N-Pivaloyl-4-fluoro-2,6-dimethylaniline (4i). Using general procedure A, compound **4i** was isolated in 72% yield (80.7 mg, white solid); mp 124.5–126.0 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.03 (s, 1H), 6.72 (d, J = 9.1 Hz, 2H), 2.11 (s, 6H), 1.30 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 176.1, 161.4, 159.0, 137.0, 136.9, 129.2, 113.7, 113.5, 76.5, 76.2, 75.9, 38.3, 26.8, 17.5, 17.5; ^{19}F NMR (376 MHz, CDCl_3) δ –116.5; HRMS (ESI) m/z calcd for $\text{C}_{13}\text{H}_{19}\text{FNO}$ [$\text{M} + \text{H}$] $^+$: 224.1449, found 224.1445.

6-Fluoro-3-[(2,2-dimethyl-1-oxopropyl)amino]-benzoic Acid Ethyl Ester (4j). Using general procedure B, compound **4j** was isolated in 51% yield (68.4 mg, slight yellow oil); ^1H NMR (400 MHz, CDCl_3) δ 7.88 (m, 2H), 7.50 (s, 1H), 7.08 (dd, J = 10.7, 8.4 Hz, 2H), 4.37 (t, J = 7.1 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H), 1.32 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 177.0, 164.2, 159.7, 157.1, 134.2, 134.1, 126.6, 126.5, 123.3, 117.6, 117.4, 77.5, 77.2, 76.9, 61.6, 39.7, 27.7, 14.4; ^{19}F NMR (376 MHz, CDCl_3) δ –115.0; HRMS (ESI) m/z calcd for $\text{C}_{14}\text{H}_{19}\text{FNO}_3$ [$\text{M} + \text{H}$] $^+$: 268.1344, found 268.1344.

4-Fluoroaniline (5). The 4-fluoro-*N*-pivaloylaniline **2b** (97.6 mg, 0.5 mmol) was suspended in 6 N HCl (2 mL) and stirred overnight at 100 °C. The yellow solution was cooled to room temperature and diluted with water (2.5 mL), and then concentrated sodium hydroxide was added dropwise until the pH was alkaline. The reaction mixture was extracted with CH_2Cl_2 (6 mL $\times$ 3). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4 . The residue was purified by silica gel column chromatography eluted with EtOAc/hexane. Compound **5** was isolated in 82% yield (45.6 mg, yellow liquid); ^1H NMR (400 MHz, CDCl_3) δ 6.84 (m, 2H), 6.60 (m, 2H), 3.50 (s, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 157.51, 155.17, 142.35, 116.02, 115.94, 115.71, 115.48, 77.32, 77.00, 76.68; ^{19}F NMR (376 MHz, CDCl_3) δ –126.85 (m). These spectroscopic data correspond to previously reported data.²³

■ ASSOCIATED CONTENT

■ Supporting Information

All experimental procedures and data for compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) (a) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, 317, 1881. (b) *Fluorine and Health: Molecular Imaging, Biomedical Materials and Pharmaceuticals*; Tressaud, A., Haufe, G., Eds.; Elsevier Science: Amsterdam, 2008.
- (2) (a) Banks, R. E.; Mohialdin-Khaffaf, S. N.; Lal, G. S.; Sharif, I.; Syvret, R. G. *J. Chem. Soc., Chem. Commun.* **1992**, 595. (b) Jahnisch, K.; Baerns, M.; Hessel, V.; Ehrfeld, W.; Haverkamp, V.; Lowe, H.; Wille, C.; Guber, A. *J. Fluorine Chem.* **2000**, 105, 117. (c) Chambers, R. D. *Fluorine in Organic Chemistry*; Oxford: New York, 2004. (d) Furuya, T.; Kuttruff, C. A.; Ritter, T. *Curr. Opin. Drug Discovery Dev.* **2008**, 11, 803.
- (3) (a) Karam, O.; Jacquesy, J. C.; Jouannetaud, M. P. *Tetrahedron Lett.* **1994**, 35, 2541. (b) Stavber, S.; Jereb, M.; Zupan, M. *Synlett* **1999**, 9, 1375. (c) Nyffeler, P. T.; Durón, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C. H. *Angew. Chem., Int. Ed.* **2005**, 44, 192.
- (4) (a) Balz, G.; Schiemann, G. *Ber. Deutsch. Chem. Ges.* **1927**, 60, 1186. (b) Swain, C. G.; Rogers, R. J. *J. Am. Chem. Soc.* **1975**, 97, 799. (c) Adams, D. J.; Clark, J. H. *Chem. Soc. Rev.* **1999**, 28, 225. (d) Sandford, G. *J. Fluorine Chem.* **2007**, 128, 90.
- (5) (a) Horwitz, J. P.; Tomson, A. J. *J. Org. Chem.* **1961**, 26, 3392. (b) Barlin, G. B.; Young, A. C. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1269. (c) Pike, V. W.; Aigbirhio, F. I. *J. Chem. Soc., Chem. Commun.* **1995**, 21, 2215. (d) Shah, A.; Pike, V. W.; Widdowson, D. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2043. (e) Yamada, S.; Gavryushin, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2010**, 49, 2215.
- (6) (a) Stille, J. K.; Lau, K. S. Y. *Acc. Chem. Res.* **1977**, 10, 434. (b) Differding, E.; Wehrli, M. *Tetrahedron Lett.* **1991**, 32, 3819. (c) Lal, G. S. *J. Org. Chem.* **1993**, 58, 2791. (d) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, 128, 7134. (e) Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2008**, 130, 10060. (f) Kaspi, A. W.; Yahav-Levi, A.; Goldberg, I.; Vigalok, A. *Inorg. Chem.* **2008**, 47, 5.
- (7) (a) Furuya, T.; Strom, A. E.; Ritter, T. *J. Am. Chem. Soc.* **2009**, 131, 1662. (b) Furuya, T.; Ritter, T. *Org. Lett.* **2009**, 11, 2860.
- (8) (a) Cairns, M. A.; Dixon, K. R.; McFarland, J. J. *J. Chem. Soc., Dalton Trans.* **1975**, 1159. (b) Stille, J. K.; Lau, K. S. Y. *Acc. Chem. Res.* **1977**, 10, 434. (c) Grushin, V. V. *Chem.—Eur. J.* **2002**, 8, 1006.
- (9) (a) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, 44, 3656. (b) Richardson, R. D.; Wirth, T. *Angew. Chem., Int. Ed.* **2006**, 45, 4402. (c) Uyanik, M.; Ishihara, K. *Chem. Commun.* **2009**, 2086. (d) Pouységu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, 66, 2235. (e) Zhdankin, V. V. *J. Org. Chem.* **2011**, 76, 1185.
- (10) Itoh, N.; Sakamoto, T.; Miyazawa, E.; Kikugawa, Y. *J. Org. Chem.* **2002**, 67, 7424.
- (11) (a) Liu, H.; Wang, X.; Gu, Y. *Org. Biomol. Chem.* **2011**, 9, 1614. (b) Liu, H.; Xie, Y.; Gu, Y. *Tetrahedron Lett.* **2011**, 52, 4324.
- (12) Kitamura, T.; Kuriki, S.; Morshed, M. H.; Hori, Y. *Org. Lett.* **2011**, 13, 2392.
- (13) Saito, M.; Miyamoto, K.; Ochiai, M. *Chem. Commun.* **2011**, 47, 3410.
- (14) Gao, Z.; Lim, Y. H.; Tredwell, M.; Li, L.; Verhoog, S.; Hopkinson, M.; Kaluza, W.; Collier, T. L.; Passchier, J.; Huiban, M.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2012**, 51, 6733.
- (15) (a) Zhong, W.; Yang, J.; Meng, X.; Li, Z. *J. Org. Chem.* **2011**, 76, 9997. (b) Zhong, W.; Liu, S.; Yang, J.; Meng, X.; Li, Z. *Org. Lett.* **2012**, 14, 3336.
- (16) Tang, P.; Ritter, T. *Tetrahedron* **2011**, 67, 4449.
- (17) Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, 134, 10795.
- (18) Salazar, J.; Lopez, S. E.; Rebollo, O. *J. Fluorine Chem.* **2003**, 124, 111.
- (19) Xiao, F.; Liu, Y.; Tang, C.; Deng, G. *J. Org. Lett.* **2012**, 14, 984.
- (20) Waisser, K.; Kuneš, J.; Roman, M.; Buděšínský, M.; Exner, O. *Phosphorus, Sulfur Silicon Relat. Elem.* **1994**, 97, 71.
- (21) Gonec, T.; Bobal, P.; Suján, J.; Pavlacka, L.; Vesely, L.; Kreckova, E.; Kos, J.; Jampilek, J.; Pesko, M.; Guo, J.; Coffey, A.; Kralova, K.; Kollar, P.; Imramovsky, A.; Placek, L. *Molecules* **2012**, 17, 613.
- (22) Gilday, J. P.; Negri, J. T.; Widdowson, D. A. *Tetrahedron* **1989**, 45, 4605.
- (23) Shimizu, Y.; Morimoto, H.; Zhang, M.; Ohshima, T. *Angew. Chem., Int. Ed.* **2012**, 51, 8564.