Preparation of 2-Fluoro-3-aminophenylboronates via Directed *ortho*-Metalation

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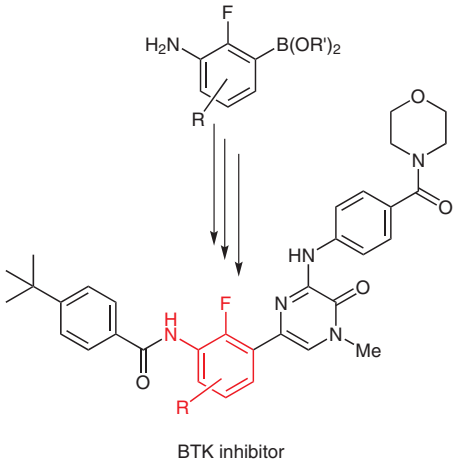
Abstract: The aromatic amine in fluoroanilines was protected with 2,2,5,5-tetramethyl-1-aza-2,5-disila-cyclopentane (stabase) in order to direct metalation *ortho* to the fluorine. A series of novel 2-fluoro-3-aminophenylboronates were prepared after quenching the metalated intermediate with triisopropylborate and deprotection in situ. The presented method is convenient and scalable, because all of the synthetic steps use crude intermediates. Several transformations are carried out in the same pot, and the final boronates are easily purified crystalline materials.

Key words: boronates, metalation, regioselectivity, protecting groups, amines

In the course of our work on the inhibitors of Bruton's tyrosine kinase (Btk),[1] we required a series of 2-fluoro-3-aminophenylboronates to form the middle portion of the inhibitor molecule (Scheme 1). To our surprise, there have been limited precedents for their synthesis in the literature.[1,2] An alternative preparation of compound **7a** using palladium chemistry was previously reported in our patent.[1] A similar method was used in the preparation of 4-chloro-3-(dimethylamino)-2-fluorophenylboronic acid.[2] However, the product was not isolated and was used without any purification in the following step.[2] In this paper, we report a simple and high-yielding preparation of these boronates via *ortho*-metalation reactions followed by a borate quench.

Because a variety of substituted 2-fluoroanilines are commercially available and inexpensive, we chose them as our starting materials. The most straightforward approach to 2-fluoro-3-aminophenylboronates is via the metalation of these 2-fluoroanilines *ortho* to the fluorine atom.[3] However, it is well-known from the work of Schlosser et al. that *tert*-butylcarbamate-protected fluoroanilines are metalated *ortho* to the nitrogen atom.[4] Pivaloyl-protected 2-fluoroaniline behaves similarly.[5] Therefore, the amine moiety has to be protected in such a way as to negate its *ortho*-directing properties. With 3- and 4-substituted anilines, this effect can be achieved through bis-TMS or bis-TES nitrogen protection.[4,6] In the case of 3-fluoroaniline and 3,5-difluoroaniline, the 2,2,5,5-tetramethyl-1-aza-2,5-disila-cyclopentane (stabase) group reduces the directing effect of the aromatic amine moiety, and lithiation occurs only at the *para*-position.[7] We decided that a similar bis-silyl protection should also be applicable to 2-fluoroanilines **1**. However, we chose the stabase group as the protecting group.[8]



Scheme 1 2-Fluoro-3-aminophenylboronate and a Btk inhibitor derived from it

One of the advantages of using stabase over bis-TES and bis-TMS is that the protection reaction does not require the use of *n*-BuLi. It can be carried out on a multigram scale under solvent-free conditions with the convenient, commercially available silylating agent 1,2-bis[(dimethylamino)dimethylsilyl]ethane (**2**; Table 1).[9]

The reported reaction conditions (140 °C, 5 h)[9] required some optimization. While they worked well with crude **2** prepared in our laboratory, the reaction with pure commercial material proceeded only sluggishly beyond the uncyclized intermediate **3**. This indicated that the cyclization of **3** to **4** could be catalyzed by impurities. Indeed, adding 7 mol% dimethylamine hydrochloride (a likely impurity in crude **2**) at the beginning of the reaction accelerated the cyclization and increased the yield of **4**. In order for the general procedure to be applicable to hindered substrates, we had to increase the amount of zinc iodide (from 1 to 25 mol%) and temperature (from 140 to 180–210 °C) as compared to the original literature.[9] Completion of the reaction was monitored by GC or NMR analysis.

Protected compound **4** was easily separated from zinc iodide, which formed a solid cake after the reaction mixture was cooled. Adding hexanes to the mixture and decanting

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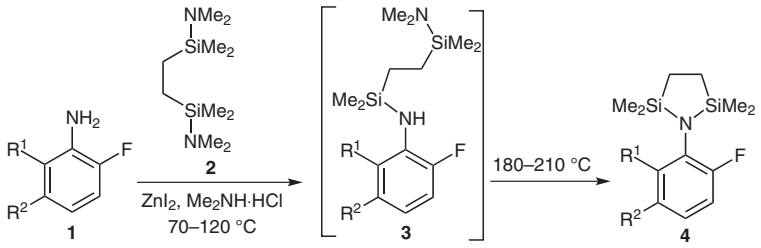
Table 1 Stabase Protection of Anilines



Entry	R^1	R^2	Product	Yield (%)
1	H	H	**4a**	100
2	H	Cl	**4b**	97
3	H	Me	**4c**	100
4	Cl	H	**4d**	99
5	F	H	**4e**	96
6	Me	H	**4f**	100

the solution afforded **4**, which was of sufficient purity (>85%) to be used in the following step directly.

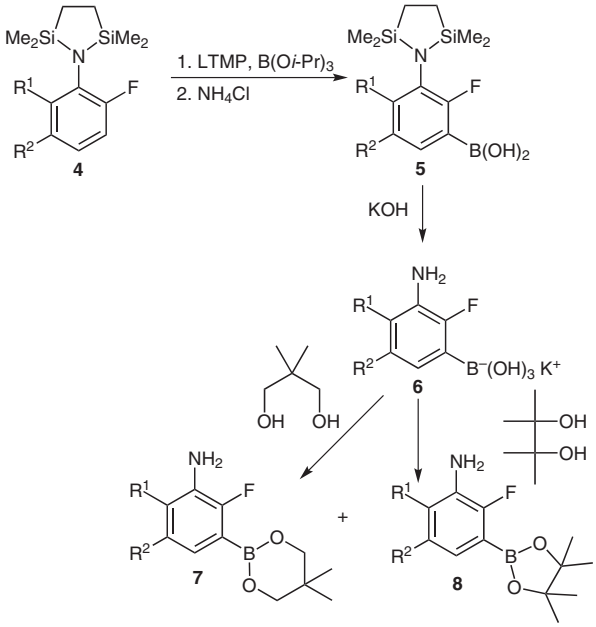
We first attempted to use *s*-BuLi to metalate **4a** (–78 °C, 1 h), with subsequent quenching of the resulting anion with triisopropyl borate. Unfortunately, a significant amount of side product formed, and, after workup, a mixture of the corresponding boronic and borinic acids was isolated in approximately 60% yield.

Unsatisfied with this result, we turned to the in situ quench protocol, which employs a milder base lithium 2,2,6,6-tetramethylpiperidine (LTMP).[10] The application of these conditions was successful. Boronic acid **5**, which formed after treating the reaction mixture with ammonium chloride, was not isolated. The stabase protecting group was removed by treating the crude mixture with aqueous potassium hydroxide (in most cases) or hydrochloric acid (for **5d** and **5f**; Table 2). An advantage of using a base is that the resulting polar 'ate' complexes **6** migrated into the aqueous phase, while all the impurities remained in the organic layer.

It was more convenient to isolate ester **7** or **8** rather than the aminophenylboronic acid, which is water soluble. The standard procedure would involve extracting the boronic acid and treatment with a diol in the presence of a drying agent. However, we discovered that highly crystalline neopentyl glycolates **7a–e** and pinacolate **8e** readily precipitated from an aqueous solution of **6a–e** after treatment with neopentyl glycol or pinacol followed by acetic acid. As the formation of boronates is reversible, acidification to approximately neutral pH 6.5–7.9 and use of a concentrated solution of **6** and excess diol was necessary to obtain good yields.

It is noteworthy that *all six steps* of the synthesis: stabase protection, lithiation, borate quench, aqueous quench, stabase deprotection, and borate ester formation were performed with crude mixtures and did not involve crystallization or chromatography. Nevertheless, the final products **7** and **8** were obtained as pure crystalline compounds in high overall yield.

Table 2 Preparation of Boronates



Entry	R^1	R^2	Product	Yield (%)
1	H	H	**7a**	75
2	H	Cl	**7b**	70
3	H	Me	**7c**	84
4	Cl	H	**7d**	73
5	F	H	**7e**	84
6	F	H	**8e**	84
7	Me	H	**8f**	80

To improve the base-induced deprotection of hindered derivatives **5d** and **5f**, which was sluggish and required prolonged times, a more robust acidic deprotection procedure for **5d** and **5f** employing HCl in a mixture of tetrahydrofuran (THF) and water was also developed. The resulting crude boronic acids were converted into esters **7d** and **8f** following standard procedures. Although **8f** required chromatographic purification, pinacolates **8** have the advantage of being more stable than neopentyl glycolates **7**. This may be important if **7** or **8** are to be further derivatized while preserving the boronate group.

In conclusion, a convenient, high-yielding method for the preparation of 2-fluoro-3-aminophenylboronates was developed. The method, which avoids purification or isolation of the intermediates, consists of the lithiation of stabase-protected 2-fluoroanilines, followed by deprotection of the stabase group. The desired 2-fluoro-3-aminophenylboronates are precipitated in high purity from the resulting aqueous solutions with a diol.

All metalation reactions were carried out under a positive pressure of nitrogen in anhydrous solvents. Stabase protection of **1**, basic deprotection of **5**, and handling of easily oxidizable basic solutions of **6** were also carried out under nitrogen. Commercially available reagents and anhydrous solvents were used as supplied without further purification. ^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded with a Bruker AVANCE 300 or a Bruker AVANCE 500 NMR spectrometer. All chemical shifts (δ) are reported in ppm, using TMS as a standard for ^{1}H, ^{13}C and ^{19}F NMR and $CFCl_3$ for ^{19}F NMR. High resolution mass spectra (HRMS) were obtained with a Waters Q-Tof micro mass spectrometer using ESI(+) ionization. Melting points were determined with an Electrothermal Mel-Temp apparatus and are uncorrected. All final compounds **7** and **8** had purity greater than 95% (area percent) as judged by HPLC analysis. Intermediates **4** had purity of 85–95% (^{1}H NMR analysis), which was sufficient for the following transformations.

Stabase Protection: 1-(2-Fluorophenyl)-2,2,5,5-tetramethyl-1,2,5-azadisilolidine (4a); Typical Procedure

A mixture of **1a** (7.62 g, 68.7 mmol), **2** (17.8 g, 76.6 mmol), freshly opened anhydrous ZnI_2 (5.50 g, 17.2 mmol), and $Me_2NH{\cdot}HCl$ (0.38 g, 4.8 mmol) was slowly heated to 190 °C over 1 h. Evolution of a gas (dimethylamine) was observed, and two layers formed. Heating was continued at 190 °C for 1 h with vigorous stirring, and the reaction was monitored by either ^{19}F or ^{1}H NMR. After cooling to r.t., the upper organic layer was decanted from the solidified zinc salts and poured into hexanes (100 mL). The solids were further washed with hexanes (3 × 5 mL), decanting every time. The combined hexanes solutions were clarified by filtering through a pad of Cellpure P65. The filtrate was evaporated under reduced pressure to afford **4a**.

Yield: 17.4 g (100%); colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.10–6.90 (m, 4 H), 0.89 (s, 4 H), 0.09 (s, 6 H), 0.08 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.4 (d, $J_{C–F}$ = 243.3 Hz), 133.8 (d, $J_{C–F}$ = 13.7 Hz), 130.4, 124.1 (d, $J_{C–F}$ = 3.5 Hz), 123.7 (d, $J_{C–F}$ = 7.4 Hz), 116.2 (d, $J_{C–F}$ = 21.9 Hz), 8.6, –0.13, –0.15.

^{19}F {^{1}H} NMR (282 MHz, $CDCl_3$): δ = –121.6.

1-(5-Chloro-2-fluorophenyl)-2,2,5,5-tetramethyl-1,2,5-azadisilolidine (4b)

Following the typical procedure and heating at 210 °C for 1.5 h, **1b** (10.0 g, 68.7 mmol) was converted into **4b**.

Yield: 19.1 g (97%); light-brown oil.

^{1}H {^{19}F} NMR (300 MHz, $CDCl_3$): δ = 6.93 (m, 3 H), 0.89 (s, 4 H), 0.11 (s, 12 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.1 (d, $J_{C–F}$ = 242.6 Hz), 135.7 (d, $J_{C–F}$ = 15.3 Hz), 129.7 (d, $J_{C–F}$ = 1.6 Hz), 128.7 (d, $J_{C–F}$ = 3.2 Hz), 123.4 (d, $J_{C–F}$ = 8.2 Hz), 116.9 (d, $J_{C–F}$ = 24.0 Hz), 8.6, –0.13, –0.15.

^{19}F {^{1}H} NMR (282 MHz, $CDCl_3$): δ = –124.0.

1-(2-Fluoro-5-methylphenyl)-2,2,5,5-tetramethyl-1,2,5-azadisilolidine (4c)

Following the typical procedure, **1c** (8.60 g, 68.7 mmol) was converted into **4c**, affording **4c** as a brown oil, which solidified on standing.

Yield: 18.5 g (100%); purple solid; mp 20–25 °C.

^{1}H {^{19}F} NMR (300 MHz, $CDCl_3$): δ = 6.90 (d, J = 7.9 Hz, 1 H), 6.76 (m, 2 H), 2.27 (s, 3 H), 0.89 (s, 4 H), 0.09 (s, 12 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.1 (d, $J_{C–F}$ = 240.3 Hz), 133.4 (d, $J_{C–F}$ = 3.5 Hz), 133.1 (d, $J_{C–F}$ = 13.9 Hz), 130.9, 124.1 (d, $J_{C–F}$ = 7.1 Hz), 115.6 (d, $J_{C–F}$ = 21.9 Hz), 20.9, 8.6, –0.10, –0.12.

^{19}F {^{1}H} NMR (282 MHz, $CDCl_3$): δ = –126.6.

1-(2-Chloro-6-fluorophenyl)-2,2,5,5-tetramethyl-1,2,5-azadisilolidine (4d)

Following the typical procedure and heating at 190 °C for 2 h, **1d** (7.00 g, 47.9 mmol) was converted into **4d**.

Yield: 13.8 g (97%); yellow oil.

^{1}H {^{19}F} NMR (300 MHz, $CDCl_3$): δ = 7.19 (m, 1 H), 6.97 (m, 2 H), 0.96 (s, 4 H), 0.19 (s, 6 H), 0.09 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.1 (d, $J_{C–F}$ = 245.1 Hz), 136.0, 132.1 (d, $J_{C–F}$ = 16.2 Hz), 125.5 (d, $J_{C–F}$ = 3.3 Hz), 124.3 (d, $J_{C–F}$ = 9.1 Hz), 114.5 (d, $J_{C–F}$ = 23.2 Hz), 8.7, 0.5, –0.4.

^{19}F {^{1}H} NMR (282 MHz, $CDCl_3$): δ = –115.8.

1-(2,6-Difluorophenyl)-2,2,5,5-tetramethyl-1,2,5-azadisilolidine (4e)

Following the typical procedure, **1e** (5.00 g, 38.8 mmol) was converted into **4e**.

Yield: 10.2 g (96%); colorless oil.

^{1}H {^{19}F} NMR (300 MHz, $CDCl_3$): δ = 6.97 (t, J = 8.2 Hz, 1 H), 6.97 (d, J = 8.2 Hz, 2 H), 0.93 (s, 4 H), 0.05 (s, 12 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.2 (dd, $J_{C–F}$ = 245.2, 5.1 Hz), 123.7 (t, $J_{C–F}$ = 9.2 Hz), 122.4 (t, $J_{C–F}$ = 17.4 Hz), 111.5 (dd, $J_{C–F}$ = 17.2, 9.1 Hz), 8.5, –0.5.

^{19}F {^{1}H} NMR (282 MHz, $CDCl_3$): δ = –119.3.

1-(2-Fluoro-6-methylphenyl)-2,2,5,5-tetramethyl-1,2,5-azadisilolidine (4f)

Following the typical procedure, **1f** (49.9 g, 0.399 mol) was converted into **4f**.

Yield: 107 g (100%); colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.98–6.84 (m, 3 H), 2.23 (s, 3 H), 0.93 (s, 4 H), 0.05 (s, 12 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.5 (d, $J_{C–F}$ = 241.6 Hz), 139.6, 131.7 (d, $J_{C–F}$ = 13.7 Hz), 125.8 (d, $J_{C–F}$ = 2.9 Hz), 123.8 (d, $J_{C–F}$ =

8.9 Hz), 113.3 (d, J_{C-F} = 23.0 Hz), 18.4 (d, J_{C-F} = 3.1 Hz), 8.7, 0.6, –0.5.

^{19}F {^{1}H} NMR (282 MHz, $CDCl_3$): δ = –118.9.

Neopentyl Glycol Boronates: 3-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-2-fluoroaniline (7a); Typical Procedure

LTMP was prepared by treating a solution of 2,2,6,6-tetramethylpiperidine (9.0 mL, 7.56 g, 53.6 mmol) in THF (50 mL) with *n*-BuLi (2.5 M in hexanes, 20 mL, 50 mmol) at –10 to –5 °C and then stirring the mixture for 15 min at that temperature.

The resulting LTMP solution was cooled to –75 °C and **4a** (8.72 g, 34.4 mmol) was added dropwise at –75 to –65 °C followed by triisopropylborate (16 mL, 13.0 g, 69.4 mmol). The reaction mixture was slowly warmed to 0 °C over 2 h, quenched with 25% NH_4Cl (15 mL, 72 mmol) and stirred at r.t. for 30 min. The resulting suspension was filtered, and the filter cake was washed with THF (3 × 10 mL). The organic layer of the filtrate was separated and evaporated at 30 °C under reduced pressure.

The residue containing **5a** was mixed with methyl *tert*-butyl ether (MTBE; 35 mL) and a degassed (N_2 sparging) solution of KOH (86% assay, 6.10 g, 93 mmol) in H_2O (50 mL). The resulting emulsion was stirred vigorously for 2 h (more KOH can be added if the deprotection stalls). The aqueous layer containing **6a** was separated, treated with neopentyl glycol (7.78 g, 74.8 mmol) and stirred until a clear solution formed. AcOH was then added dropwise until pH 7.6. The precipitated product was filtered, washed with ice-cold H_2O (3 × 10 mL) and dried overnight under vacuum at 45 °C to afford **7a** (5.56 g, 72%). After standing overnight, a second crop of **7a** (0.26 g, 3%) precipitated and was filtered. Combining the two crops gave **7a**.

Yield: 5.83 g (75%); white solid; mp 55–56 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.06 (ddd, *J* = 7.2, 5.4, 1.7 Hz, 1 H), 6.92 (t, *J* = 7.4 Hz, 1 H), 6.84 (td, *J* = 7.8, 1.8 Hz, 1 H), 3.79 (s, 4 H), 3.68 (br s, 2 H), 1.04 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.8 (d, J_{C-F} = 242.7 Hz), 134.5 (d, J_{C-F} = 15.1 Hz), 124.7 (d, J_{C-F} = 7.1 Hz), 123.8 (d, J_{C-F} = 3.4 Hz), 119.0–118.5 (br s), 119.3 (d, J_{C-F} = 3.8 Hz), 72.5, 31.8, 21.9.

HRMS: *m*/*z* calcd for $C_{11}H_{15}BFNO_2$ + H: 224.1258; found: 224.1265.

5-Chloro-3-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-2-fluoroaniline (7b)

Following the typical procedure (acidified to pH 7.7 in the last step), **4b** (10.0 g, 34.7 mmol) was converted into **7b**.

Yield: 6.26 g (70%); off-white solid; mp 125–128 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.00 (dd, *J* = 4.3, 2.7 Hz, 1 H), 6.79 (dd, *J* = 7.6, 2.6 Hz, 1 H), 3.78 (s, 4 H), 3.75 (br s, 2 H), 1.03 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.2 (d, J_{C-F} = 242.7 Hz), 135.8 (d, J_{C-F} = 16.9 Hz), 128.9 (d, J_{C-F} = 2.0 Hz), 123.7 (d, J_{C-F} = 7.3 Hz), 122.5–119.2 (br s), 118.5 (d, J_{C-F} = 4.1 Hz), 72.6, 31.9, 21.9.

HRMS: *m*/*z* calcd for $C_{11}H_{14}BClFNO_2$ + H: 258.0868; found: 258.0870.

3-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-2-fluoro-5-methylaniline (7c)

Following the typical procedure (acidified to pH 7.9 in the last step), **4c** (9.21 g, 34.4 mmol) was converted into **7c**.

Yield: 6.82 g (84%); white solid; mp 98–99 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.86 (d, *J* = 3.0 Hz, 1 H), 6.66 (d, *J* = 8.5 Hz, 1 H), 3.79 (s, 4 H), 3.61 (br s, 2 H), 2.22 (s, 3 H), 1.04 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.2 (d, J_{C-F} = 240.2 Hz), 134.0 (d, J_{C-F} = 15.6 Hz), 133.2 (d, J_{C-F} = 3.3 Hz), 125.0 (d, J_{C-F} = 7.3 Hz), 120.1 (d, J_{C-F} = 4.0 Hz), 120.0–117.0 (br s), 72.5, 31.8, 21.9, 20.8.

HRMS: *m*/*z* calcd for $C_{12}H_{17}BFNO_2$ + H: 238.1415; found: 238.1418.

6-Chloro-3-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-2-fluoroaniline (7d)

Following the typical procedure, **4d** (6.60 g, 22.9 mmol) was converted into **5d**. The deprotection of **5d** with KOH was sluggish, and the acidic deprotection (see the preparation of **8f** below) was applied. After reacting with neopentyl glycol (pH 7.5), **7d** was obtained.

Yield: 4.30 g (73%); brown solid; mp 59–61 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.00 (m, 2 H), 4.02 (br s, 2 H), 3.78 (s, 4 H), 1.03 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.6 (d, J_{C-F} = 245.8 Hz), 132.3 (d, J_{C-F} = 17.5 Hz), 124.2 (d, J_{C-F} = 2.9 Hz), 123.5 (d, J_{C-F} = 8.7 Hz), 122.6 (d, J_{C-F} = 4.9 Hz), 117.5–116.5 (br s), 72.5, 31.9, 21.9.

HRMS: *m*/*z* calcd for $C_{11}H_{14}BClFNO_2$ + H: 258.0868; found: 258.0861.

3-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-2,6-difluoroaniline (7e)

Following the typical procedure, **4e** (9.34 g, 34.4 mmol) was converted into **5e**. The deprotection of **5e** was sluggish and required 4 h and a large excess of KOH (7.65 g, 116 mmol). After the solution of **6e** and neopentyl glycol was acidified to pH 7.4, **7e** was obtained.

Yield: 6.94 g (84%); off-white solid; mp 58–60 °C.

^{1}H {^{19}F} NMR (300 MHz, $CDCl_3$): δ = 7.04 (d, *J* = 8.4 Hz, 1 H), 6.79 (d, *J* = 8.4 Hz, 1 H), 3.78 (s, 4 H), 3.67 (br s, 2 H), 1.03 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.5 (dd, J_{C-F} = 244.1, 7.6 Hz), 154.2 (dd, J_{C-F} = 243.2, 7.0 Hz), 123.7 (dd, J_{C-F} = 18.5, 15.8 Hz), 123.4 (t, J_{C-F} = 9.3 Hz), 115.9–113.6 (br s), 110.7 (dd, J_{C-F} = 18.1, 3.0 Hz), 72.6, 32.0, 22.0.

HRMS: *m*/*z* calcd for $C_{11}H_{14}BF_2NO_2$ + H: 242.1164; found: 242.1168.

2,6-Difluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (8e)

Following the typical procedure above, **4e** (6.77 g, 24.9 mmol) was converted into **6e**. Then, instead of adding neopentyl glycol, pinacol (6.50 g, 54.9 mmol) was added to the aqueous layer. The solution was stirred for 2 h, cooled to 0 °C and neutralized to pH 7 with 1 M aq HCl. The product was filtered, washed with H_2O (3 × 7 mL) and dried to afford **8e**.

Yield: 4.80 g (84%); off-white solid; mp 50–51 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.05 (m, 1 H), 6.81 (m, 1 H), 3.70 (br s, 2 H), 1.35 (s, 12 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.5 (dd, J_{C-F} = 245.3, 7.8 Hz), 154.4 (dd, J_{C-F} = 244.3, 7.1 Hz), 123.9 (t, J_{C-F} = 9.1 Hz), 123.8 (dd, J_{C-F} = 17.5, 15.5 Hz), 111.8–111.0 (br s), 110.9 (dd, J_{C-F} = 18.1, 2.9 Hz), 83.9, 24.9.

MS (ESI+): *m*/*z* = 256.2 [M + H].

HRMS: *m*/*z* calcd for $C_{12}H_{16}BF_2NO_2$ + H: 256.1320; found: 256.1331.

2-Fluoro-6-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (8f)

Following the typical procedure, **4f** (24.7 g, 92.5 mmol) was converted into **5f**. The organic layer obtained after NH_4Cl quench and subsequent filtration was mixed with hexanes (500 mL), 2 M aq HCl (500 mL) and H_2O (100 mL), and vigorously stirred at r.t. for 18 h. Completion of the reaction was monitored by disappearance of the product from the organic layer. The aq layer was separated, neutralized with NH_4OH to pH 8.0 and concentrated under reduced pressure to approximately 200 mL of a semi-solid residue. This residue was shaken with EtOAc (500 mL) and the suspension was filtered. The filter cake was washed with EtOAc (2 × 100 mL), and the organic layer of the filtrate was separated, dried over sodium sulfate for 3 d and filtered. Pinacol (71.0 g, 601 mmol) and -350 mesh $CaSO_4$ (109 g, 801 mmol) were added and the suspension was heated at reflux for 2 h. After filtering the solids and concentrating, the reaction mixture was purified by flash chromatography on silica (EtOAc–hexanes, 10%) to afford **8f**.

Yield: 80% (80.7 g); white solid; mp 41–42 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.02 (t, J = 6.6 Hz, 1 H), 6.84 (d, J = 7.5 Hz, 1 H), 3.62 (s, 2 H), 2.20 (s, 3 H), 1.35 (s, 12 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.7 (d, $J_{C–F}$ = 242.7 Hz), 132.7 (d, $J_{C–F}$ = 14.7 Hz), 128.4 (d, $J_{C–F}$ = 3.7 Hz), 125.3 (d, $J_{C–F}$ = 2.3 Hz), 124.5 (d, $J_{C–F}$ = 8.1 Hz), 114.3–111.7 (br s), 83.7, 24.9, 17.3 (d, $J_{C–F}$ = 3.3 Hz).

HRMS: *m*/*z* calcd for $C_{13}H_{19}BFNO_2$ + H: 252.1571; found: 252.1575.

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