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Iridium-Catalyzed C−H Borylation of CF_3-Substituted Pyridines

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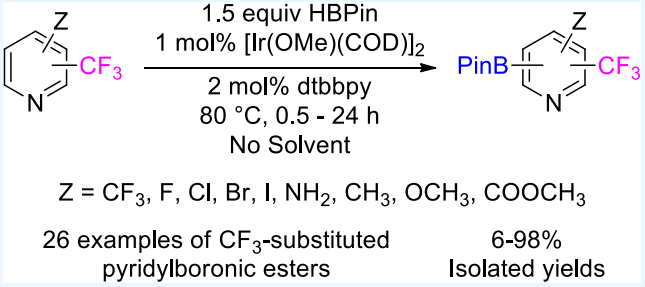
ABSTRACT: Iridium-catalyzed C−H borylation of CF_3-substituted pyridines is described in this paper. The boronic ester group can be installed on the α, β, or γ position of pyridine by an appropriate substitution pattern. Sterically governed regioselectivity provides convenient access to a variety of CF_3-substituted pyridylboronic esters. These catalytic C−H borylation reactions were carried out neatly without the use of any solvent. Several functional groups, such as halo, ester, alkoxy, amino, etc., are compatible with this methodology. These pyridylboronic esters are amenable to column chromatography and the products were isolated in good to excellent yields. α-Borylated pyridines, although isolated in good yields, do not have a long shelf life. The boronic ester derivatives of these CF_3-substituted pyridines can serve as useful precursors in the synthesis regime.



INTRODUCTION

Pyridine and its derivatives are among the most prevalent heteroaromatics in organic chemistry. In addition to the dominant structural unit in pharmaceuticals and agrochemicals, they are also used as biological probes, drug candidates, clinically used drugs, functionalized materials, and ligands (Figure 1).[1−4]

Installation of various functional groups on the pyridine core can have a huge impact on its properties. Introduction of fluorinated groups is highly desirable, as it enhances the stability and functional group compatibility.[5,6] Among other fluorine-containing groups, the trifluoromethyl (CF_3) group exhibits enhanced binding selectivity, lipophilicity, and chemical and metabolic stability.[7,8] Hence, development of new methodologies for the incorporation of trifluoromethyl and its related groups on the pyridine is of great synthesis value. Several protocols are available for the trifluoromethylation of pyridine.[9,10] In addition, preparation of boronic ester derivatives of trifluoromethylpyridines can be very useful since the arylboronate esters are highly versatile intermediates that can be readily converted into a wide range of other functional groups.[11−13]

Pyridylboronic esters are generally synthesized by metal-halogen exchange or by Miyaura borylation.[14] Iridium-catalyzed aromatic C−H borylation was introduced by the groups of Smith−Maleczka, and the method proposed by Hartwig−Miyaura is a highly atom-economical green chemistry approach to prepare (hetero)arylboronic esters.[15] Marder has investigated the application of this iridium-catalyzed borylation protocol to various substituted pyridines and quinolines.[16] Recently, Steel and coworkers utilized iridium-catalyzed borylation methodology to derivatize 2-halopyridines.[17]

Our group is interested in the applications of iridium-catalyzed borylation and Suzuki coupling in organic synthesis.[13,18−25] In 2016, we described the application of this methodology to functionalize 2,6-bis(trifluoromethyl)-pyridine.[26] Herein, we describe the application of iridium-catalyzed borylation to various trifluoromethyl-substituted pyridines.

RESULTS AND DISCUSSION

Most of the trifluoromethylpyridines used in this study are liquids at room temperature or have low melting points. Together with the liquid borylating agent, pinacolborane, they both assist in the dissolution of the precatalyst/ligand, and hence there is no need to use any additional solvent. The iridium precatalyst and ligand were weighed in air and were transferred to the Schlenk flask under positive nitrogen pressure, followed by pinacolborane and the trifluoromethylpyridine substrate. The flask was then heated in an oil bath at

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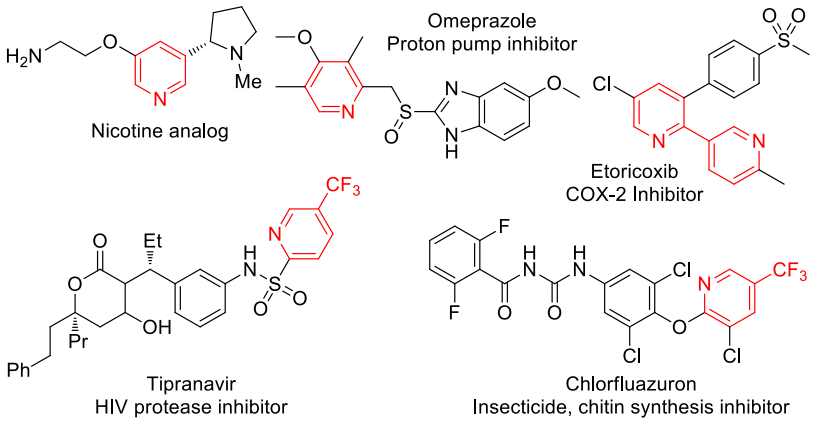


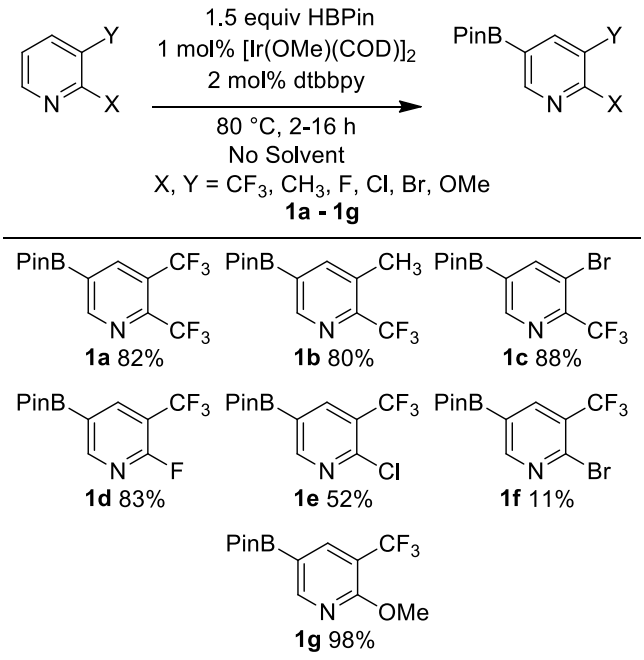
Figure 1. Representation of biologically active pyridines.

80 °C, and the progress of the reaction was monitored by GC−MS.

We started with the borylation of 2,3-bis-trifluoromethyl-substituted pyridine (Scheme 1). A steric bulk of the trifluoromethyl group at 3-position directed the catalytic borylation specifically at the 5-position, and the resulting pyridylboronic ester was isolated in 82% yield (entry **1a**). The 3-methyl and 3-bromo-substituted 2-trifluoromethylpyridines were also selectively borylated at the 5-position (entries **1b** and **1c**). A similar selectivity was again obtained by changing the 2-substituent on pyridine but retaining the trifluoromethyl group at the 3-position (entries **1d**−**1g**). While the 2-methoxy (**1g**) and 2-fluoro (**1d**) derivatives gave a good yield, the presence of a chloro or bromo substituent at the 2-position (**1e** and **1f**) resulted in incomplete conversion and hence reduced isolated yields. In the case of 2-fluoro and 2-chloro (entries **1d** and **1e**) formation, a significant amount (∼7%) of isomeric mono-borylated product was also observed in the crude GC−MS, which is consistent with the literature.[16,27] For 2-bromo-3-trifluoromethylpyridine (entry **1f**), the reaction stopped at 31% conversion. Addition of the catalyst and pinacolborane at this stage was not helpful in in enhancing the conversion.

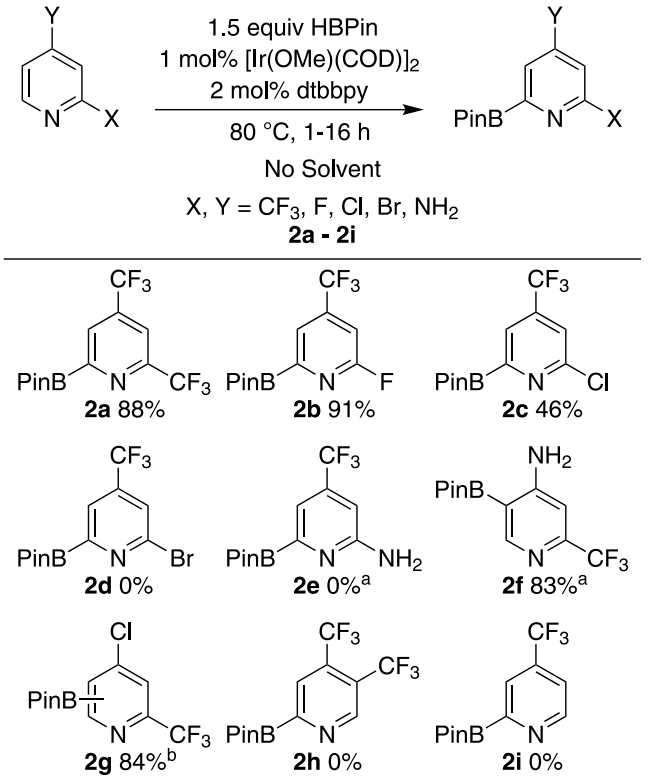
Next, we examined 2,4-disubstituted pyridines (Scheme 2). When the 4-substituent was bulky CF_3, the borylation selectively took place at the 6-position (entries **2a**−**2c**) and the products were isolated in good to excellent yields. For **2b**, the reaction was usually complete in 1−2 h, and prolonged heating for 16 h resulted in the formation of trace amounts

Scheme 1. Iridium-Catalyzed Borylation of 2,3-Disubstituted Trifluoromethylpyridines[a]



[a]Yields are reported for the isolated compounds.

Scheme 2. Iridium-Catalyzed Borylation of 2,4-Disubstituted Trifluoromethylpyridines[a,b,c]



[a]3,4,7,8-Tetramethyl-1,10-phenanthroline ligand was used along with 3.0 equiv of HBPin. [b]Mixture of 5- and 6-borylated isomers in 1:3 ratio. [c]Yields are reported for isolated compounds.

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ACS Omega 2022, 7, 11460−11472

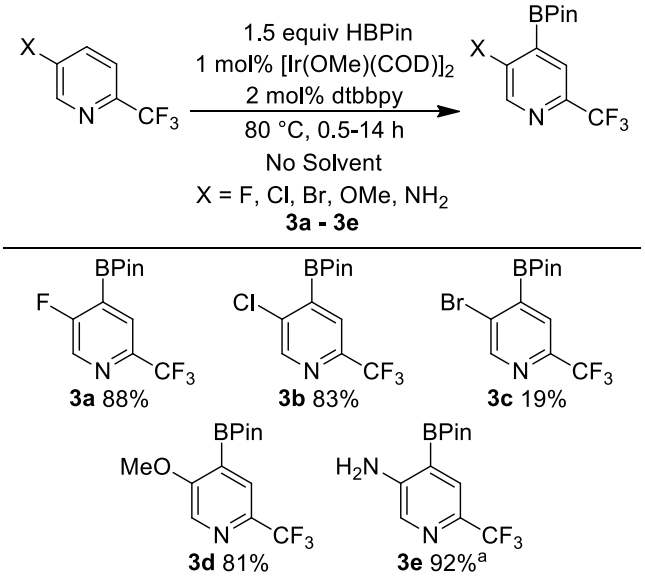
(~1.7%) of the side product with mass = 328 (see Figure S58). A GC−MS library search matched this mass with a compound of formula $C_{12}H_4N_2F_8$, which could potentially arise from the homo-coupling of **2b**. In contrast, catalytic borylation of **2c** never proceeded to full conversion, resulting in a lower isolated yield. For **2c**, 56 mg (31%) starting pyridine was also recovered. When the 4-substituent was of small size, such as Cl, a mixture of 5- and 6-borylated products was obtained in 1:3 ratio, respectively (entry **2g**). These α- or 6-borylated pyridines (**2a**, **2b**, **2c**, and major isomer of **2g**) are not shelf stable and are found to be decomposed upon standing at ambient temperatures in closed vials for 6 months. The instability of α-borylated pyridine derivatives is well known in literature.[28] Access to these 6-borylated (or α-borylated) pyridines by Miyaura borylation has been reported to be problematic due to in situ Suzuki coupling.[14] Very recently, Leonori has reported an alternate radical-based approach to prepare α-borylated pyridines using BH_3−NMe_3.[29]

When the 4-substitent was amino, the traceless borylation protocol developed by Smith III and Maleczka Jr.[30] yielded a 5-borylated product as a single isomer (entry **2f**). No catalytic borylation was observed with 2-bromo- and 2-amino-substituted 4-trifluoromethylpyridines (entries **2d** and **2e**). The C−Br bond in the case of **2d** is probably highly activated, which might be leading to catalyst deactivation. For the borylation of 2-amino pyridines, such as **2e**, the presence of an additional substituent at the pyridine 6-position is critical as per literature.[30] In contrast to **2e**, the isomeric substrate, 2-trifluoromethyl-4-aminopyridine, easily underwent traceless borylation, and the product **2f** was isolated in 83% yield. The presence of any substituent (other than amino or bromo) at the 2-position is essential for borylation at 6-position, as in the case of 4-trifluoromethylpyridine (**2i**) and 3,4-bis-(trifluoromethyl)pyridine (**2h**) formation of a borylated product was not detected by the GC−MS analysis of the crude reaction mixture. Interestingly, 4-trifluoromethylpyridine has been used as a ligand for iridium-catalyzed *ortho*-selective borylation of benzoate esters.[31]

Catalytic borylation of 5-substituted 2-trifluromethylpyridines was also examined (Scheme 3). In this case, borylation selectively took place *ortho* to the smaller 5-substituent, and the resulting 4-borylated pyridines were isolated in excellent yields, except for the 5-bromo case (entry **3c**), where the reaction did not go beyond 49% conversion.

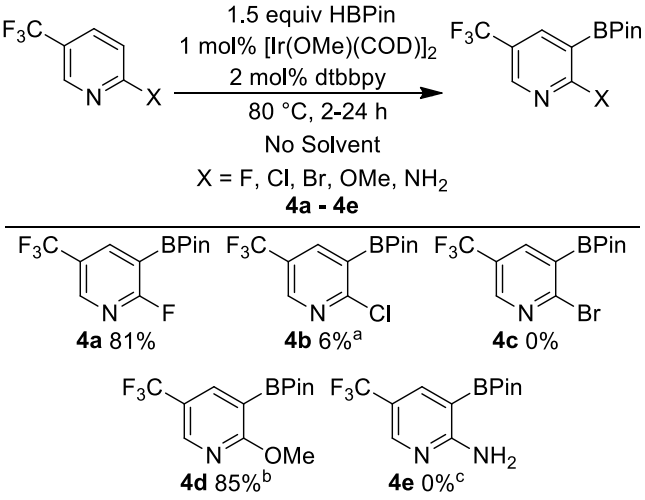
In the case of 2-substituted 5-trifluoromethylpyridines, borylation took place selectively *ortho* to the smaller 2-substituent at the 3-position (Scheme 4). Catalytic borylation in the case of **4d** was accompanied by the ~9% unidentified side product. In contrast to successful borylation for **3b** and **3c**, attempted borylation in case of **4b** and **4c** was not successful. A similar behavior has been reported for the cyanopyridines, where 2-cyano-5-bromopyridine was easily borylated but no borylation was observed for its isomer, i.e., 2-bromo-5-cyanopyridine.[32] Although **4b** was isolated in only 6% yield, 438 mg of the starting material was also recovered, making the isolated yield almost quantitative. The C−X bond in 2-halopyridines is highly activated and may result in catalyst deactivation. Attempted traceless borylation in case of **4e** was also not successful. In their original paper on aminopyridine borylation, Smith III and coworkers have indicated that the presence of any substituent at the α position of the pyridine is critical for the success of these reactions.[30]

Scheme 3. Iridium-Catalyzed Borylation of 5-Substituted 2-Trifluoromethylpyridines[a,b]



[a]3,4,7,8-Tetramethyl-1,10-phenanthroline ligand was used along with 3.0 equiv of HBPin. [b]Yields are reported for isolated compounds.

Scheme 4. Iridium-Catalyzed Borylation of 2-Substituted 5-Trifluoromethylpyridines[a,b,c,d]



[a]Isolated yield is 99% based on the recovered starting material. [b]Isolated product contains ~9% of the unidentified side product. [c]3,4,7,8-Tetramethyl-1,10-phenanthroline ligand was used along with 3.0 equiv of HBPin. [d]Yields are reported for isolated compounds.

For 2-substituted-6-trifluoromethylpyridines, borylation took place selectively at the 4-position (Scheme 5). Besides the 2-chloro and 2-bromo substituents (entries **5a** and **5b**), the 2-iodo group was also tolerable (entry **5c**) although the product was isolated in a low 25% yield (along with 52% recovered starting iodopyridine). For the 2-amino case (entry **5f**), formation of ~4% of a minor borylated isomer was also observed along with the major 4-borylated product. This traceless borylation was carried out neatly in the absence of any solvent, which resulted in slight deviation from the 99% selectivity as reported in the literature.[30]

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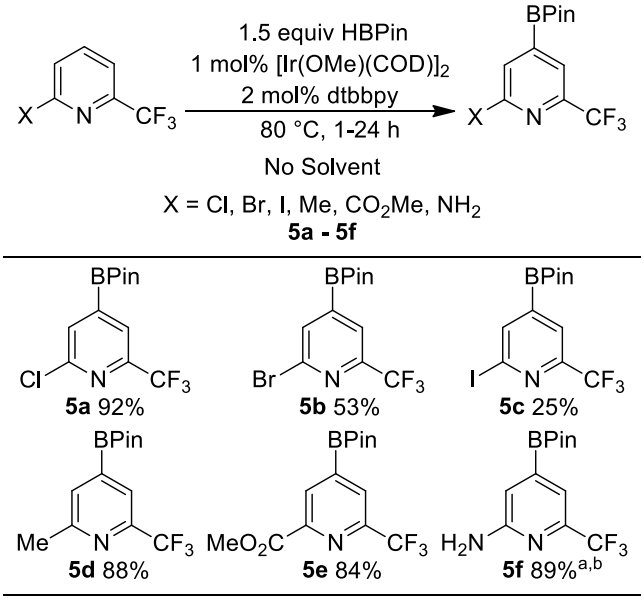
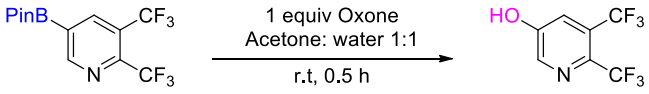
Scheme 5. Iridium-Catalyzed Borylation of 6-Substituted 2-Trifluoromethylpyridines[a,b]



[a]Mixture of 4- and 3-borylated isomers in 24:1 ratio. [b]3,4,7,8-Tetramethyl-1,10-phenanthroline ligand was used along with 3.0 equiv of HBPin. Yields are reported for isolated compounds.

The synthetic utility of the synthesized boronic esters was demonstrated by employing oxidation and Suzuki coupling reactions (Schemes 6 and 7).

Scheme 6. Oxidation of 5-(4,4,5,5-Tetramethyl-1,3,2-Dioxaborolan-2-yl)-2,3-Bis(Trifluoromethyl)-Pyridine



In conclusion, iridium-catalyzed C−H borylation of trifluoromethyl-substituted pyridines has been successfully carried out. Various substitution patterns were evaluated and excellent regioselectivities based on sterics were obtained. These trifluoromethyl-substituted pyridylboronic esters are amenable to column chromatography, and most of the synthesized compounds have been isolated in pure form for the first time. However, the α-(2-position) borylated pyridylboronic acid pinacol esters do not have a long shelf life and were decomposed in closed vials at ambient temperatures within 6 months. These trifluoromethyl-substituted pyridylboronic esters can potentially be very useful synthesis intermediates.

EXPERIMENTAL DETAILS

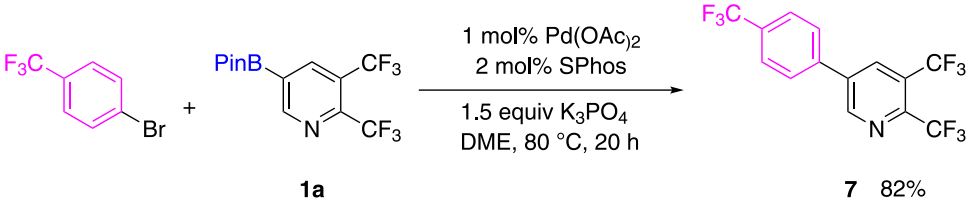
Commercially available reagents, substrates, and other chemicals were used without any purification. Solvents for column chromatography were distilled before use. All reactions were carried out in air-free 25-mL Schlenk flasks that were closed under nitrogen. Catalytic borylation reactions were done neatly without the use of any solvent. Thin-layer chromatography (TLC) was carried out using 250-μm-thick TLC plates, and visualization was achieved under a 254 nm UV lamp. Purification by column chromatography was carried out using silica gel (particle size: 40−63 μm, 230−400 mesh). The yields are reported for the isolated materials. Each borylation reaction was run at least twice, and the approximate reaction times have been indicated.

IR spectra were recorded neatly by employing a compact ATR FT-IR spectrometer. All reported melting points are uncorrected. The reactions were monitored by a single-quadrupole GC−MS system operating in EI mode. ^{1}H NMR and ^{13}C NMR spectra were recorded at 600.19 and 150.93 MHz, respectively. The chemical shifts in the ^{1}H NMR spectra are referenced with the residual proton resonances of the corresponding deuterated solvent ($CDCl_3$: δ = 7.26). The chemical shifts in the ^{13}C NMR spectra are reported relative to the central peak of $CDCl_3$ (δ = 77.0).The carbon atom attached to the boron atom in boronic esters is typically not observed in the ^{13}C NMR spectra due to broadening from and coupling with boron. Regiochemical assignments of the pyridylboronic esters are based on NMR spectroscopy (^{1}H and ^{13}C NMR). The abbreviations used are as follows: HBPin for 4,4,5,5-tetramethyl-1,3,2-dioxaborolane; dtbbpy for 4,4′-di-tert-butyl-2,2′-bipyridyl; and tmphen for 3,4,7,8-tetramethyl-1,10-phenanthroline.

PROCEDURES

General Procedure for Borylation of Trifluoromethyl-Substituted Pyridines. The $[Ir(OMe)(COD)]_2$ precatalyst and dtbbpy ligand were weighed in air. In a fume hood, a Schlenk flask, equipped with a magnetic stirring bar, was filled with nitrogen and evacuated (at least three cycles). Under positive nitrogen pressure, the $[Ir(OMe)(COD)]_2$ precatalyst (1 mol %, 0.01 mmol, 6.6 mg) and 4,4-di-*tert*-butyl bipyridine ligand (2 mol %, 0.02 mmol, 5.4 mg) were added to the Schlenk flask. Pinacolborane (HBPin) (1.5 equiv, 1.5 mmol, 192 mg, 218 μL) and trifluoromethylpyridine substrate (1 equiv, 1 mmol) were added using a micropipette. The Schlenk flask was closed and the reaction mixture was heated at 80 °C using an oil bath. The progress of the catalytic reactions was monitored by TLC and/or GC−MS. Once the reaction was judged to be complete by GC−MS (or when no further conversion was observed), the reaction flask was brought out of the oil bath, cooled to room temperature, and opened to air. The crude reaction mixture was taken out of the flask by

Scheme 7. Suzuki Coupling of 5-(4,4,5,5-Tetramethyl-1,3,2-Dioxaborolan-2-yl)-2,3-Bis(Trifluoromethyl)Pyridine



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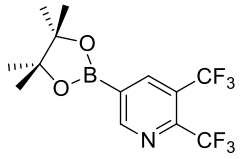
dissolving in the solvent (dichloromethane), and the volatiles were removed under vacuum using a rotary evaporator. The crude product thus obtained was purified by column chromatography using silica gel as the stationary phase.

General Procedure for Traceless Borylation of Amino-Substituted Pyridines. The $[Ir(OMe)(COD)]_2$ precatalyst and tmphen ligand were weighed in air. In a fume hood, a Schlenk flask, equipped with a magnetic stirring bar, was filled with nitrogen and evacuated (at least three cycles). Under positive nitrogen pressure, pinacolborane (HBPin) (1.5 equiv, 1.5 mmol, 192 mg, 218 μL) and trifluoromethylpyridine substrate (1 equiv, 1 mmol) were added using a micropipette and the mixture was stirred at room temperature for 1 h in a closed Schlenk flask. Under nitrogen flow, the $[Ir(OMe)(COD)]_2$ precatalyst (1 mol %, 0.01 mmol, 6.6 mg), 3,4,7,8-tetramethyl-1,10-phenanthroline ligand (2 mol %, 0.02 mmol, 4.7 mg), and additional pinacolborane (HBPin) (1.5 equiv, 1.5 mmol, 192 mg, 218 μL) were added to the Schlenk flask. The Schlenk flask was closed again and the reaction mixture was heated at 80 °C in an oil bath. The progress of the traceless borylation reaction was monitored by TLC and/or GC−MS. Once the reaction was judged to be complete by GC−MS, the reaction flask was brought out of the oil bath, cooled to room temperature, and opened to air. The crude reaction mixture was taken out of the flask by dissolving in the solvent (dichloromethane), and the volatiles were removed under vacuum using a rotary evaporator. The crude product thus obtained was purified by column chromatography using silica gel as the stationary phase.

Experimental Details. *5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-bis(trifluoromethyl)pyridine (**1a**).*



The general borylation procedure was applied to 2,3-bis(trifluoromethyl)pyridine (107.5 mg, 0.5 mmol, 1 equiv) for 16 h.

Colorless liquid; yield: 139 mg (82%); R_f = 0.3 (CH_2Cl_2).

FT-IR (ATR): 2984, 2936, 1605, 1372, 1318, 1293, 1257, 1227, 1140, 1043, 963, 848, 796, 688, 652 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 9.15 (s, 1H), 8.53 (s, 1H), 1.38 (br s, 12H, $4CH_3$ of BPin).

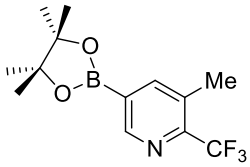
^{13}C NMR $\{^1H\}^2$ (151 MHz, $CDCl_3$): δ = 156.9 (CH), 146.9 (q, $^2J_{C-F}$ = 37.4 Hz, C), 142.3 (q, $^3J_{C-F}$ = 5.4 Hz, CH), 124.4 (q, $^2J_{C-F}$ = 34.7 Hz, C), 122.3 (q, $^1J_{C-F}$ = 274.0 Hz, CF_3), 120.6 (q, $^1J_{C-F}$ = 275.1 Hz, CF_3), 85.3 (2C), 24.8 ($4CH_3$ of BPin).

^{19}F $\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ = −59.7 (q, $^5J_{F-F}$ = 12.0 Hz, CF_3), −64.7 (q, $^5J_{F-F}$ = 12.0 Hz, CF_3).

^{11}B NMR (192 MHz, $CDCl_3$): δ = 30.0.

GC−MS (EI): m/z (%) = 341 (12) $(M)^+$, 326 (100), 284 (31), 242 (15), 222 (19), 172 (38), 113 (12), 85 (14), 69 (48).

*3-Methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyridine (**1b**).*



The general borylation procedure was applied to 3-methyl-2-(trifluoromethyl)pyridine (161 mg, 01 mmol, 1 equiv) for 16 h.

Colorless solid; yield: 230 mg (80%); mp 61−63 °C; R_f = 0.65 (CH_2Cl_2/hexanes 1: 1).

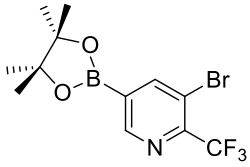
FT-IR (ATR): 2982, 2935, 1603, 1474, 1435, 1392, 1361, 1317, 1190, 1116, 1059, 967, 915, 850, 777, 677, 660 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.79 (s, 1H), 8.01 (s, 1H), 2.47 (d, J = 1.4 Hz, 3H), 1.34 (br s, 12H, $4CH_3$ of BPin).

^{13}C NMR $\{^1H\}$ (151 MHz, $CDCl_3$): δ = 151.8 (CH), 147.8 (q, $^2J_{C-F}$ = 32.6 Hz, C), 146.6 (CH), 131.3 (C), 122.3 (q, $^1J_{C-F}$ = 275.3 Hz, CF_3), 84.6 (2C), 24.8 ($4CH_3$ of BPin), 17.7 (q, $^4J_{C-F}$ = 2.0 Hz, CH_3).

GC−MS (EI): m/z (%) = 287 (56) $(M)^+$, 272 (49), 244 (16), 230 (92), 201 (68), 188 (100).

*3-Bromo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyridine (**1c**).*



The general borylation procedure was applied to 3-bromo-2-(trifluoromethyl)pyridine (255 mg, 1 mmol, 1 equiv) for 2 h.

Colorless liquid; yield: 309 mg (88%); R_f = 0.35 (CH_2Cl_2).

FT-IR (ATR): 2978, 2901, 1457, 1359, 1316, 1209, 1167, 1119, 1035, 862, 924, 845, 770 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.87 (s, 1H), 8.39 (s, 1H), 1.35 (br s, 12H, $4CH_3$ of BPin).

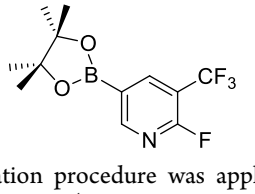
^{13}C NMR $\{^1H\}$ (151 MHz, $CDCl_3$): δ = 152.4 (CH), 148.9 (CH), 147.5 (q, $^2J_{C-F}$ = 34.1 Hz, C), 121.1 (q, $^1J_{C-F}$ = 275.4 Hz, CF_3), 117.8 (C), 85.1 (2C), 24.8 ($4CH_3$ of BPin).

^{19}F $\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ = −66.3 (s, CF_3).

^{11}B NMR (192 MHz, $CDCl_3$): δ = 29.6.

GC−MS (EI): m/z (%) = 351 (11) $(M)^+$, 338 (59), 337 (25), 336 (62), 335 (22), 294 (51), 293 (17), 268 (29), 267 (91), 266 (38), 264 (100), 254 (24), 254 (24), 253 (11), 252 (31), 232 (11), 85 (26), 57 (16).

*2-Fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridine (**1d**).*



The general borylation procedure was applied to 2-fluoro-3-(trifluoromethyl)pyridine (165 mg, 1 mmol, 1 equiv) for 2 h. GC−MS of the crude reaction mixture showed the formation of ∼7% of the minor monoborylated isomer besides the major isomer.

Colorless liquid; yield: 241 mg (83%); R_f = 0.8 (CH_2Cl_2).

FT-IR (ATR): 2977, 2925, 1589, 1365, 1303, 1134, 1062, 963, 851, 776, 676 cm^{-1}.

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^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.73 (s, 1H), 8.39 (d, $^{4}J_{H-F}$ = 9.7 Hz, 1H), 1.36 (br s, 12H, $4CH_3$ of BPin).

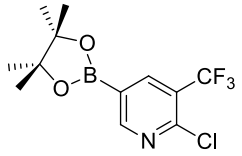
^{13}C NMR {^{1}H} (151 MHz, $CDCl_3$): δ = 161.6 (d, $^{1}J_{C-F}$ = 248.8 Hz, C), 157.7 (d, $^{3}J_{C-F}$ = 15.1 Hz, CH), 144.5 (apparent quintet, CH), 121.9 (qd, $^{1}J_{C-F}$ = 272.2, $^{3}J_{C-F}$ = 6.4 Hz, CF_3), 113.0 (qd, $^{2}J_{C-F}$ = 34.9, $^{2}J_{C-F}$ = 26.8 Hz, C), 84.9 (2C), 24.8 ($4CH_3$ of BPin).

^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$): δ = −62.4 (d, $^{4}J_{F-F}$ = 11.9 Hz, CF_3), −63.4 (q, $^{4}J_{F-F}$ = 11.5 Hz, F).

^{11}B NMR (192 MHz, $CDCl_3$): δ = 30.0.

GC−MS (EI): *m*/*z* (%) = 291 (5) $(M)^+$, 191 (40), 172 (41), 146 (26), 126 (32), 114 (21), 85 (50), 69 (85), 57 (100).

*2-Chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridine (**1e**).*



The general borylation procedure was applied to 2-chloro-3-(trifluoromethyl)pyridine (181 mg, 1 mmol, 1 equiv) for 2 h. GC−MS of the crude reaction mixture showed the formation of ∼2% of the minor monoborylated isomer besides the major isomer.

Pale yellow liquid; yield: 161 mg (52%); R_f = 0.7 (CH_2Cl_2). In addition, 67 mg (37%) of the starting substrate was recovered.

FT-IR (ATR): 2981, 1593, 1556, 1363, 1291, 1236, 1131, 1046, 963, 847, 759, 723 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.84 (s, 1H), 8.35 (s, 1H), 1.35 (br s, 12H, $4CH_3$ of BPin).

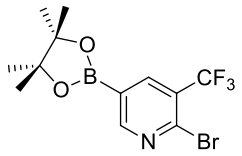
^{13}C NMR {^{1}H} (151 MHz, $CDCl_3$): δ = 157.9 (CH), 151.5 (C), 142.5 (q, $^{3}J_{C-F}$ = 4.5 Hz, CH), 124.8 (q, $^{2}J_{C-F}$ = 33.4 Hz, C), 122.3 (q, $^{1}J_{C-F}$ = 272.8 Hz, C), 85.0 (2C), 24.8 ($4CH_3$ of BPin).

^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$): δ = −63.6 (s, CF_3).

^{11}B NMR (192 MHz, $CDCl_3$): δ = 30.0.

GC−MS (EI): *m*/*z* (%) = 307 (8) $(M)^+$, 294 (31), 293 (21), 292 (100), 291 (36), 252 (23), 251 (14), 250 (73), 249 (24), 223 (13), 222 (26), 221 (38), 210 (10), 208 (28), 207 (8), 85 (26).

*2-Bromo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridine (**1f**).*



The general borylation procedure was applied to 2-bromo-3-(trifluoromethyl)pyridine (226 mg, 1 mmol, 1 equiv) for 16 h. GC−MS at this stage showed 31% conversion.

Yellow semisolid; yield: 40 mg (11%); R_f = 0.7 (CH_2Cl_2/hexanes 2:1).

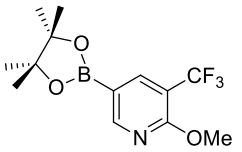
FT-IR (ATR): 2979, 2932, 1592, 1550, 1362, 1291, 1231, 1139, 1040, 963, 847, 685 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.80 (s, 1H), 8.30 (s, 1H), 1.36 (br s, 12H, $4CH_3$ of BPin).

^{13}C NMR {^{1}H} (151 MHz, $CDCl_3$): δ = 157.9 (CH), 142.4 (d, $^{3}J_{C-F}$ = 1.0 Hz, C), 142.1 (q, $^{3}J_{C-F}$ = 5.1 Hz, CH), 127.3 (q, $^{2}J_{C-F}$ = 33.4 Hz, C), 122.4 (q, $^{1}J_{C-F}$ = 273.4 Hz, CF_3), 85.0 (2C), 24.8 ($4CH_3$ of BPin).

GC−MS (EI): *m*/*z* (%) = 351 (16) $(M)^+$, 353 (16) $(M+2)^+$, 336 (100), 296 (30), 252 (10), 172 (10).

*2-Methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridine (**1g**).*



The general borylation procedure was applied to 2-methoxy-3-(trifluoromethyl)pyridine (177 mg, 1 mmol, 1 equiv) for 2 h.

Pale yellow liquid, solidified upon standing; yield: 296 mg (98%); mp 94−96 °C; R_f = 0.9 (CH_2Cl_2).

FT-IR (ATR): 2986, 2953, 1608, 1573, 1495, 1370, 1311, 1124, 1055, 1007, 946, 848, 788, 672, 606 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.65 (s, 1H), 8.19 (s, 1H), 4.06 (s, 3H, OCH_3), 1.34 (br s, 12H, $4CH_3$ of BPin).

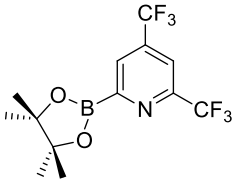
^{13}C NMR {^{1}H} (151 MHz, $CDCl_3$): δ = 162.7 (C), 157.2 (CH), 142.2 (q, $^{3}J_{C-F}$ = 4.4 Hz, CH), 123.1 (q, $^{1}J_{C-F}$ = 271.6 Hz, CF_3), 112.7 (q, $^{2}J_{C-F}$ = 32.8 Hz, C), 84.3 (2C), 54.2 (CH_3), 24.8 ($4CH_3$ of BPin).

^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$): δ = −63.8 (s, CF_3).

^{11}B NMR (192 MHz, $CDCl_3$): δ = 30.2.

GC−MS (EI): *m*/*z* (%) = 303 (84) $(M)^+$, 288 (65), 274 (24), 246 (29), 245 (10), 204 (100), 203 (43).

*2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-4,6-bis-(trifluoromethyl)pyridine (**2a**).*



The general borylation procedure was applied to 2,4-bis(trifluoromethyl)pyridine (107.5 mg, 0.5 mmol, 1 equiv) for 1 h. The isolated compound decomposed on standing at ambient temperature in a closed vial for more than 6 months (see Figure S57).

Pale yellow liquid; yield: 129 mg (88%); R_f = 0.7 (CH_2Cl_2).

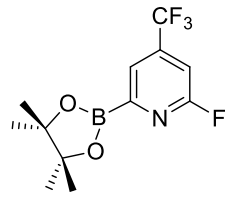
FT-IR (ATR): 3076, 2984, 2935, 1345, 1302, 1276, 1134, 964, 904, 879, 846, 699, 681 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.21 (s, 1H), 7.89 (s, 1H), 1.40 (br s, 12H, $4CH_3$ of BPin).

^{13}C NMR {^{1}H} (151 MHz, $CDCl_3$): δ = 150.0 (q, $^{2}J_{C-F}$ = 35.3 Hz, C), 138.7 (q, $^{2}J_{C-F}$ = 34.9 Hz, C), 128.4 (d, $^{3}J_{C-F}$ = 2.0 Hz, CH), 122.3 (q, $^{1}J_{C-F}$ = 273.6 Hz, CF_3), 121.0 (q, $^{1}J_{C-F}$ = 274.8 Hz, CF_3), 117.3 (q, $^{3}J_{C-F}$ = 3.0 Hz, CH), 85.5 (2C), 24.8 ($4CH_3$ of BPin).

GC−MS (EI): *m*/*z* (%) = 341 (19) $(M)^+$, 326 (28), 322 (19), 308 (9), 285 (100), 242 (36), 222 (19), 195 (11), 82 (28), 67 (19).

*2-Fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)pyridine (**2b**).*



The general borylation procedure was applied to 2-fluoro-4-(trifluoromethyl)pyridine (165 mg, 1 mmol, 1 equiv) for 2 h.

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ACS Omega 2022, 7, 11460−11472

The isolated compound decomposed on standing at ambient temperature in a closed vial for more than 6 months.

Light yellow liquid; yield: 264 mg (91%); R_f = 0.3 (CH_2Cl_2).

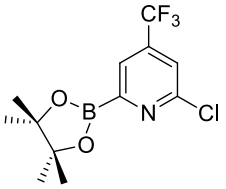
FT-IR (ATR): 2982, 2934, 1458, 1382, 1343, 1294, 1135, 969, 944, 866, 846, 746, 685, 671 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.92 (s, 1H), 7.19 (m, 1H), 1.38 (br s, 12H, $4CH_3$ of BPin).

^{13}C NMR {^1H} (151 MHz, $CDCl_3$): δ = 163.6 (d, $^1J_{C-F}$ = 241.8 Hz, C), 142.4 (qd, $^2J_{C-F}$ = 34.4 Hz, $^3J_{C-F}$ = 7.6 Hz, C), 124.0 (apparent t, $^3J_{C-F}$ = 3.0 Hz, CH), 122.0 (qd, $^1J_{C-F}$ = 273.4 Hz, $^4J_{C-F}$ = 4.1 Hz, CF_3), 108.3 (dq, $^2J_{C-F}$ = 41.4 Hz, $^3J_{C-F}$ = 3.9 Hz, CH), 85.4 (2C), 24.8 ($4CH_3$ of BPin).

GC−MS (EI): m/z (%) = 291 (24) $(M)^+$, 276 (18), 235 (100), 234 (44), 192 (28), 85 (4).

2-Chloro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)pyridine (2c).



The general borylation procedure was applied to 2-chloro-4-(trifluoromethyl)pyridine (181 mg, 1 mmol, 1 equiv) for 16 h. The isolated compound decomposed on standing at ambient temperature in a closed vial for more than 6 months.

Pale yellow liquid; yield: 141 mg (46%); R_f = 0.5 (CH_2Cl_2). In addition, 56 mg (31%) of the starting substrate was recovered.

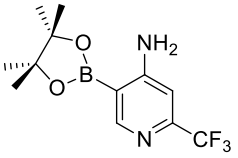
FT-IR (ATR): 2981, 2933, 1561, 1440, 1342, 1292, 1137, 964, 872, 833, 733, 683, 645 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.94 (s, 1H), 7.58 (s, 1H), 1.39 (br s, 12H, $4CH_3$ of BPin).

^{13}C NMR {^1H} (151 MHz, $CDCl_3$): δ = 153.0 (C), 139.8 (q, $^2J_{C-F}$ = 34.2 Hz, C), 124.6 (q, $^3J_{C-F}$ = 3.4 Hz, CH), 122.1 (q, $^1J_{C-F}$ = 273.6 Hz, CF_3), 121.8 (d, $^3J_{C-F}$ = 3.8 Hz, CH), 85.4 (2C), 24.8 ($4CH_3$ of BPin).

GC−MS (EI): m/z (%) = 307 (60) $(M)^+$, 292 (41), 250 (100), 208 (71), 172 (30), 99 (20), 82 (75), 67 (28).

*5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyridin-4-amine (**2f**).*



The general traceless borylation procedure was applied to 2-(trifluoromethyl)pyridin-4-amine (162 mg, 1 mmol, 1 equiv) using 3,4,7,8-tetramethyl-1,10-phenanthroline ligand (4.7 mg, 0.02 mmol, 2 mol %) and 3 equiv of pinacolborane for 2 h.

Yellowish liquid that solidified on standing; yield: 239 mg (83%); mp 139−140 °C; R_f = 0.2 (CH_2Cl_2).

FT-IR (ATR): 3451, 3330, 2982, 1646, 1613, 1392, 1340, 1247, 1137, 1097 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.59 (s, 1H), 6.83 (s, 1H), 5.72 (s, 2H, NH_2), 1.34 (br s, 12H, $4CH_3$ of BPin).

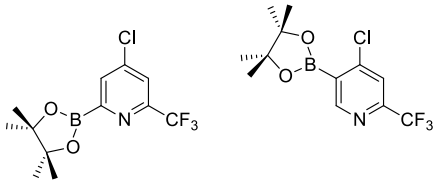
^{13}C NMR {^1H} (151 MHz, $CDCl_3$): δ = 159.9 (C), 157.1 (CH), 149.7 (q, $^2J_{C-F}$ = 34.0 Hz, C), 121.5 (q, $^1J_{C-F}$ = 274.2 Hz, CF_3), 105.9 (q, $^3J_{C-F}$ = 3.7 Hz, CH), 85.4 (2C), 24.8 ($4CH_3$ of BPin).

^{19}F {^1H} NMR (376 MHz, $CDCl_3$): δ = −68.9 (s, CF_3).

^{11}B NMR (192 MHz, $CDCl_3$): δ = 30.6.

GC−MS (EI): m/z (%) = 288 (18) $(M)^+$, 287 (6), 273 (11), 272 (4), 269 (3), 244 (3), 232 (9), 231 (100), 230 (36), 215 (10), 214 (3), 202 (8), 201 (3), 189 (16), 188 (13), 187 (5).

*Mix of 4-chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(trifluoromethyl)pyridine and 4-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyridine (**2g** + **2g′**).*



Major (A) 3 : 1 Minor (B)

The general borylation procedure was applied to 4-chloro-2-(trifluoromethyl)pyridine (181 mg, 1 mmol, 1 equiv) for 3 h. Column chromatography (DCM, R_f = 0.3) furnished the product as a very light yellow sticky solid (227 mg, 84%), which was a mixture of two monoborylated isomers in 3:1 ratio by ^1H NMR. The major isomer A is highly susceptible to deborylation upon standing. Regioisomeric assignment is based on NMR spectroscopy.

FT-IR (ATR): 3068, 2981, 2934, 1368, 1300, 1285, 1133, 1098, 963, 878, 846, 731, 697 cm^{-1}.

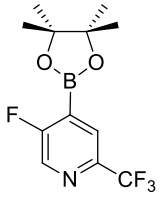
^1H NMR (600 MHz, $CDCl_3$) Isomer A δ: 7.99 (d, J = 1.8 Hz, 1H), 7.69 (d, J = 1.8 Hz, 1H), 1.38 (s, 12H, $4CH_3$ of BPin); Isomer B δ: 8.90 (s, 1H), 7.65 (s, H), 1.38 (s, 12H, $4CH_3$ of BPin).

^{13}C NMR (151 MHz, $CDCl_3$) Isomer A δ: 150.1 (q, $^2J_{C-F}$ = 35.0 Hz, C), 144.9 (C), 133.2 (CH), 122.1 (q, $^3J_{C-F}$ = 3.0 Hz, CH), 121.0 (q, $^1J_{C-F}$ = 274.8 Hz, C), 85.35 (2C), 24.85 ($4CH_3$ of BPin); ^{13}C NMR (151 MHz, $CDCl_3$) Isomer B δ: 156.9 (CH), 151.3 (C), 150.5 (q, $^2J_{C-F}$ = 35.0 Hz, C), 121.5 (q, $^3J_{C-F}$ = 2.4 Hz, C), 120.9 (q, $^1J_{C-F}$ = 274.8 Hz, C), 85.0 (2C), 24.8 ($4CH_3$ of BPin).

GC−MS (EI) major isomer: m/z (%) = 307 (26) $(M)^+$, 292 (21), 288 (15), 274 (15), 264 (17), 251 (100), 208 (72), 188 (42), 181 (14), 85 (29), 82 (53), 67 (25). GC−MS retention time 9.11 min.

GC−MS (EI) minor isomer: m/z (%) = 307 (10) $(M)^+$, 292 (100), 272 (87), 264 (14), 250 (47), 230 (92), 223 (21), 208 (42), 85 (12).

*5-Fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyridine (**3a**).*



The general borylation procedure was applied to 5-fluoro-2-(trifluoromethyl)pyridine (165 mg, 1 mmol, 1 equiv) for 2 h. Besides a single monoborylated product, a small amount (∼1 to 2%) of a diborylated product was also observed by GC−MS at the end of the reaction.

Pale yellow liquid; yield: 255 mg (88%); R_f = 0.3 (CH_2Cl_2).

FT-IR (ATR): 2983, 2936, 1423, 1352, 1308, 1268, 1212, 1135, 1101, 1072, 963, 913, 888, 848, 701, 674, 633, 602 cm^{-1}.

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ACS Omega 2022, 7, 11460−11472

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.54 (s, 1H), 8.00 (d, J = 4.2 Hz, 1H), 1.38 (br s, 12H, $4CH_3$ of BPin).

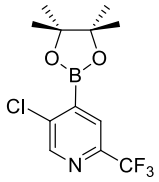
^{13}C NMR {^{1}H} (151 MHz, $CDCl_3$): δ = 164.0 (d, $^1J_{C-F}$ = 265.9 Hz, C), 143.6 (qd, $^2J_{C-F}$ = 35.3 Hz, $^4J_{C-F}$ = 4.2 Hz, C), 138.8 (d, $^2J_{C-F}$ = 28.7 Hz, CH), 127.4 (dq, $^3J_{C-F}$ = 6.0 Hz, $^3J_{C-F}$ = 3.0 Hz, CH), 121.4 (q, $^1J_{C-F}$ = 273.4 Hz, CF_3), 85.3 (2C), 24.8 ($4CH_3$ of BPin).

^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$): δ = −67.0 (s, CF_3), −112.1 (s, F).

^{11}B NMR (192 MHz, $CDCl_3$): δ = 29.1.

GC−MS (EI): m/z (%) = 291 (18) $(M)^+$, 276 (100), 232 (19), 207 (21), 187 (20), 58 (7).

*5-Chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyridine (**3b**).*



The general borylation procedure was applied to 5-chloro-2-(trifluoromethyl)pyridine (181 mg, 1 mmol, 1 equiv) for 14 h. Besides a single monoborylated product, a small amount (∼1%) of a diborylated product was also observed by GC−MS at the end of the reaction.

Colorless solid; yield: 256 mg (83%); mp 79−80 °C; R_f = 0.3 (CH_2Cl_2).

FT-IR (ATR): 2984, 1351, 1307, 1257, 1139, 1097, 964, 872, 845, 698, 671 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.66 (s, 1H), 7.92 (s, 1H), 1.39 (br s, 12H, $4CH_3$ of BPin).

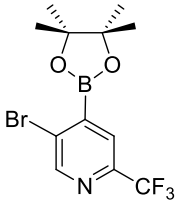
^{13}C NMR {^{1}H} (151 MHz, $CDCl_3$): δ = 149.4 (CH), 145.4 (q, $^2J_{C-F}$ = 35.3 Hz, C), 139.8 (C), 126.6 (q, $^3J_{C-F}$ = 2.5 Hz, CH), 121.5 (q, $^1J_{C-F}$ = 274.5 Hz, CF_3), 85.4 (2C), 24.8 ($4CH_3$ of BPin).

^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$): δ = −67.6 (s, CF_3).

^{11}B NMR (192 MHz, $CDCl_3$): δ = 29.7.

GC−MS (EI): m/z (%) = 307 (10) $(M)^+$, 292 (29), 272 (100), 230 (95), 208 (26), 188 (14), 138 (14), 85 (22), 57 (26).

*5-Bromo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyridine (**3c**).*



The general borylation procedure was applied to 5-bromo-2-(trifluoromethyl)pyridine (225 mg, 1 mmol, 1 equiv) for 4 h. GC−MS at the end of the reaction showed 49% conversion.

Colorless solid; yield: 68 mg (19%); mp 75 °C; R_f = 0.3 (CH_2Cl_2).

FT-IR (ATR): 2983, 2923, 1306, 1256, 1167, 1134, 1094, 1026, 964, 914, 867, 843, 710 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.80 (s, 1H), 7.85 (s, 1H), 1.39 (br s, 12H, $4CH_3$ of BPin).

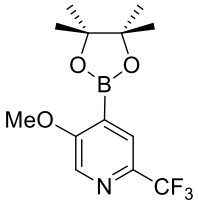
^{13}C NMR {^{1}H} (151 MHz, $CDCl_3$): δ = 151.9 (CH), 145.8 (q, $^2J_{C-F}$ = 35.1 Hz, C), 129.1 (C), 126.8 (q, $^3J_{C-F}$ = 2.2 Hz, CH), 121.5 (q, $^1J_{C-F}$ = 274.5 Hz, CF_3), 85.8 (2C), 24.8 ($4CH_3$ of BPin).

^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$): δ = −67.7 (s, CF_3).

^{11}B NMR (192 MHz, $CDCl_3$): δ = 29.8.

GC−MS (EI): m/z (%) = 351 (4) $(M)^+$, 337 (6), 273 (7), 272 (66), 271 (18), 251 (5), 250 (5), 230 (100), 229 (43), 210 (17), 209 (10), 172 (3), 166 (3), 85 (4), 77 (3).

*5-Methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyridine (**3d**).*



The general borylation procedure was applied to 5-methoxy-2-(trifluoromethyl)pyridine (177 mg, 1 mmol, 1 equiv) for 2 h.

Light yellow solid; yield: 246 mg (81%); mp 73−75 °C; R_f = 0.5 (CH_2Cl_2).

FT-IR (ATR): 2982, 2948, 2849, 1549, 1464, 1335, 1274, 1120, 1018, 963, 903, 882, 848, 698, 674, 614 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.35 (s, 1H), 7.88 (s, 1H), 3.99 (s, 3H), 1.36 (br s, 12H, $4CH_3$ of BPin).

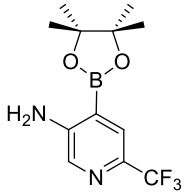
^{13}C NMR {^{1}H} (151 MHz, $CDCl_3$): δ = 160.7 (C), 140.3 (q, $^2J_{C-F}$ = 34.8 Hz, C), 133.4 (CH), 126.8 (q, $^3J_{C-F}$ = 2.5 Hz, CH), 121.9 (q, $^1J_{C-F}$ = 273.0 Hz, CF_3), 84.7 (2C), 56.7 (OCH_3), 24.8 ($4CH_3$ of BPin).

^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$): δ = −66.7 (s, CF_3).

^{11}B NMR (192 MHz, $CDCl_3$): δ = 30.1.

GC−MS (EI): m/z (%) = 303 (5) $(M)^+$, 288 (61), 284 (12), 246 (28), 230 (23), 202 (100), 174 (20), 160 (17).

*4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(trifluoromethyl)pyridin-3-amine (**3e**).*



The general traceless borylation procedure was applied to 6-(trifluoromethyl)pyridin-3-amine (162 mg, 1 mmol, 1 equiv) using 3,4,7,8-tetramethyl-1,10-phenanthroline ligand (4.7 mg, 0.02 mmol, 2 mol %) and 3 equiv of pinacolborane for 0.5 h.

White solid; yield: 265 mg (92%); mp 149−150 °C; R_f = 0.35 (CH_2Cl_2).

FT-IR (ATR): 3459, 3330, 3224, 2983, 1619, 1548, 1373, 1300, 1273, 1247, 1163, 1115, 964, 892, 850, 679, 638 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.07 (s, 1H), 7.77 (s, 1H), 4.47 (s, 2H, NH_2), 1.36 (br s, 12H, $4CH_3$ of BPin).

^{13}C NMR {^{1}H} (151 MHz, $CDCl_3$): δ = 150.6 (C), 137.2 (CH), 135.6 (distorted q, C), 126.9 (CH), 122.4 (q, $^1J_{C-F}$ = 272.2 Hz, CF_3), 84.7 (2C), 24.8 ($4CH_3$ of BPin).

^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$): δ = −66.7 (s, CF_3).

^{11}B NMR (192 MHz, $CDCl_3$): δ = 30.1.

GC−MS (EI): m/z (%) = 288 (26) $(M)^+$, 173 (4), 231 (100), 215 (8), 188 (13), 169 (5), 83 (2), 165 (14), 85 (7).

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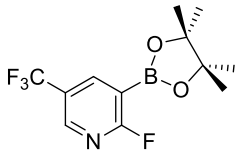
ACS Omega 2022, 7, 11460−11472

*2-Fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)pyridine (**4a**).*



The general borylation procedure was applied to 2-fluoro-5-(trifluoromethyl)pyridine (165 mg, 1 mmol, 1 equiv) for 2 h.

Light brown liquid; yield: 236 mg (81%); R_f = 0.4 (CH_2Cl_2).

FT-IR (ATR): 2982, 2935, 1608, 1447, 1340, 1298, 1130, 1075, 963, 850, 780, 674, 630 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.58 (d, J = 2.0 Hz, 1H), 8.40 (dd, J = 7.3 Hz, J = 2.5 Hz, 1H), 1.37 (br s, 12H, $4CH_3$ of BPin).

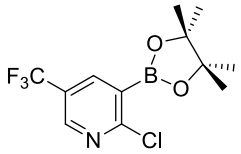
^{13}C NMR {^1H} (151 MHz, $CDCl_3$): δ = 167.3 (d, $^1J_{C-F}$ = 250.0 Hz, C), 147.3 (dq, $^3J_{C-F}$ = 17.3 Hz, $^3J_{C-F}$ = 3.9 Hz, CH), 144.8 (dq, $^3J_{C-F}$ = 8.7 Hz, $^3J_{C-F}$ = 3.0 Hz, CH), 123.7 (qd, $^2J_{C-F}$ = 33.7 Hz, $^4J_{C-F}$ = 4.6 Hz, C), 122.2 (q, $^1J_{C-F}$ = 272.7 Hz, CF_3), 84.0 (2C), 23.7 ($4CH_3$ of BPin).

^{19}F {^1H} NMR (376 MHz, $CDCl_3$): δ = −53.0 (s, F), −61.8 (s, CF_3),.

^{11}B NMR (192 MHz, $CDCl_3$): δ = 29.5.

GC−MS (EI): m/z (%) = 291 (1) $(M)^+$, 276 (39), 232 (52), 218 (54), 191 (46), 172 (65), 146 (54), 126 (43), 99 (25), 75 (36), 69 (100).

*2-Chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)pyridine (**4b**).*



The general borylation procedure was applied to 2-chloro-5-(trifluoromethyl)pyridine (543 mg, 3 mmol, 1 equiv) with $[Ir(OMe)(COD)]_2$ (39.7 mg, 0.02 mmol, 2 mol %) and 4,4′-di-tert-butyl bipyridine (32.2 mg, 0.04 mmol, 4 mol %) for 24 h.

Yellowish liquid; yield: 59 mg (6%); R_f = 0.15 (CH_2Cl_2). In addition, 438 mg of the starting substrate was recovered. Yield based on the recovered starting material 99%.

FT-IR (ATR): 2980, 2930, 1600, 1563, 1336, 1294, 1131, 1087, 1054, 963, 849, 760 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.67 (d, J = 2.4 Hz, 1H), 8.23 (d, J = 2.4 Hz, 1H), 1.38 (br s, 12H, $4CH_3$ of BPin).

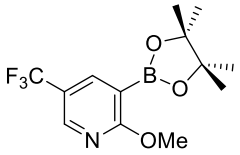
^{13}C NMR {^1H} (151 MHz, $CDCl_3$): δ = 159.3 (C), 148.2 (q, $^3J_{C-F}$ = 3.6 Hz, CH), 142.7 (q, $^3J_{C-F}$ = 3.0 Hz, CH), 125.1 (q, $^2J_{C-F}$ = 33.4 Hz, C), 123.3 (q, $^1J_{C-F}$ = 272.7 Hz, C), 85.2 (2C), 24.8 ($4CH_3$ of BPin).

^{19}F {^1H} NMR (376 MHz, $CDCl_3$): δ = −62.3 (s, CF_3),.

^{11}B NMR (192 MHz, $CDCl_3$): δ = 30.0.

GC−MS (EI): m/z (%) = 307 (14) $(M)^+$, 292 (33), 272 (30), 230 (100), 208 (41), 172 (51), 145 (43), 126 (38), 99 (43), 85 (59), 69 (78), 57 (83).

*2-Methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)pyridine (**4d**).*



The general borylation procedure was applied to 2-methoxy-5-(trifluoromethyl)pyridine (177 mg, 1 mmol, 1 equiv) for 2 h. The isolated product is 91% pure by ^1H NMR and has ∼9% of the unidentified side product.

White solid; yield: 258 mg (85%); mp 79−80 °C; R_f = 0.6 (CH_2Cl_2).

FT-IR (ATR): 2981, 2946, 1608, 1581, 1484, 1329, 1292, 1143, 1110, 1071, 1014, 965, 930, 899, 852, 786, 675, 597 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.48 (d, J = 2.4 Hz, 1H), 8.16 (d, J = 2.4 Hz, 1H), 4.01 (s, 3H), 1.35 (br s, 12H, $4CH_3$ of BPin).

^1H NMR (600 MHz, $CDCl_3$): side product: δ = 8.50 (dd, J = 2.5, 0.7 Hz, 1H), 8.35 (d, J = 2.6 Hz, 1H), 4.08 (s, 3H), 1.35 (br s, 12H, $4CH_3$ of BPin).

^{13}C NMR {^1H} (151 MHz, $CDCl_3$): δ = 169.1 (C), 147.3 (q, $^3J_{C-F}$ = 4.1 Hz, CH), 143.43 (q, $^3J_{C-F}$ = 3.1 Hz, CH), 124.1 (q, $^1J_{C-F}$ = 271.0 Hz, C), 119.6 (q, $^2J_{C-F}$ = 33.2 Hz, C), 84.3 (2C), 54.4 (OCH_3), 24.8 ($4CH_3$ of BPin).

^{13}C NMR {^1H} (151 MHz, $CDCl_3$): side product δ = 169.2 (C), 147.3 (q, $^3J_{C-F}$ = 4.1 Hz, CH), 143.58 (q, $^4J_{C-F}$ = 3.1 Hz, CH), 123.9 (q, $^1J_{C-F}$ = 271.2 Hz, C), 121.0 (q, $^2J_{C-F}$ = 32.9 Hz, C), 84.3 (2C), 54.4 (OCH_3), 24.8 ($4CH_3$ of BPin).

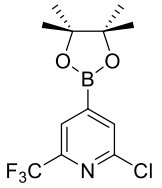
^{19}F {^1H} NMR (376 MHz, $CDCl_3$): δ = −61.5 (s, CF_3).

^{19}F {^1H} NMR (376 MHz, $CDCl_3$): side product δ = −61.7 (s, CF_3).

^{11}B NMR (192 MHz, $CDCl_3$): δ = 30.2.

GC−MS (EI): m/z (%) = 303 (39) $(M)^+$, 288 (64), 245 (48), 217 (100), 202 (83), 174 (92), 160 (47).

*2-Chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6(trifluoromethyl)pyridine (**5a**).*



The general borylation procedure was applied to 2-chloro-6-(trifluoromethyl)pyridine (182 mg, 1 mmol, 1 equiv) for 4 h.

White solid; yield: 283 mg (92%); mp 108−109 °C; R_f = 0.2 (CH_2Cl_2/hexanes 2:3).

FT-IR (ATR): 2984, 1360, 1290, 1134, 965, 835 cm^{-1}.

^1H NMR (700 MHz, $CDCl_3$): δ = 7.93 (s, 1H), 7.87 (s, 1H), 1.37 (br s, 12H, $4CH_3$ of BPin).

^{13}C NMR {^1H} (176 MHz, $CDCl_3$): δ = 151.8 (C), 147.8 (q, $^2J_{C-F}$ = 35.6 Hz, C), 132.9 (CH), 123.7 (d, $^3J_{C-F}$ = 2.4 Hz, CH), 120.8 (q, $^1J_{C-F}$ = 274.6 Hz, CF_3), 85.4 (2C), 24.8 ($4CH_3$ of BPin).

GC−MS (EI): m/z (%) = 307 (26) $(M)^+$, 309 (8) $(M+2)^+$, 294 (35), 292 (100), 265 (15), 221 (45).

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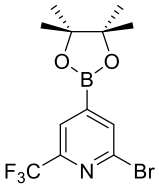
ACS Omega 2022, 7, 11460−11472

*2-Bromo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(trifluoromethyl)pyridine (**5b**).*



The general borylation procedure was applied to 2-bromo-6-(trifluoromethyl)pyridine (226 mg, 1 mmol, 1 equiv) for 24 h.

White solid; yield: 188 mg (53%); mp 126−128 °C; R_f = 0.2 (CH_2Cl_2/hexanes 1:1 → CH_2Cl_2).

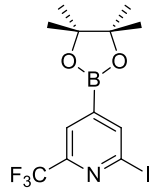
FT-IR (ATR): 2983, 2931, 1360, 1299, 1129, 964, 897, 871, 843, 810 cm^{-1}.

^1H NMR (700 MHz, $CDCl_3$): δ = 8.02 (s, 1H), 7.96 (s, 1H), 1.36 (br s, 12H, $4CH_3$ of BPin).

^{13}C NMR {^1H} (176 MHz, $CDCl_3$): δ = 148.2 (q, $^2J_{C-F}$ = 35.6 Hz, C), 142.3 (C), 136.6 (CH), 124.0 (d, $^3J_{C-F}$ = 2.4 Hz, CH), 120.7 (q, $^1J_{C-F}$ = 274 Hz, CF_3), 85.4 (2C), 24.8 ($4CH_3$ of BPin).

GC−MS (EI): *m*/*z* (%) = 351 (41) $(M)^+$, 353 (41) $(M+2)^+$, 338 (100), 336 (92), 311 (12), 267 (30), 265 (28).

*2-Iodo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(trifluoromethyl)pyridine (**5c**).*



The general borylation procedure was applied to 2-iodo-6-(trifluoromethyl)pyridine (273 mg, 1 mmol, 1 equiv) for 1 h.

Pale yellowish liquid that solidified upon standing; yield: 98 mg (25%); mp 125−127 °C; R_f = 0.5 (CH_2Cl_2). In addition, 144 mg (52%) of the starting substrate was recovered.

FT-IR (ATR): 2986, 1529, 1357, 1287, 1126, 843, 706, 684 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.23 (s, 1H), 7.94 (s, 1H), 1.35 (br s, 12H, $4CH_3$ of BPin).

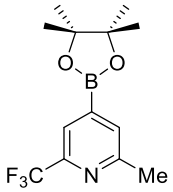
^{13}C NMR {^1H} (151 MHz, $CDCl_3$): δ = 148.7 (q, $^2J_{C-F}$ = 35.0 Hz, C), 143.1 (CH), 124.3 (distorted q, CH), 120.7 (q, $^1J_{C-F}$ = 274.9 Hz, C), 117.8 (C), 85.4 (2C), 24.8 ($4CH_3$ of BPin).

^{19}F {^1H} NMR (376 MHz, $CDCl_3$): δ = −67.9 (s, CF_3).

^{11}B NMR (192 MHz, $CDCl_3$): δ = 29.4.

GC−MS (EI): *m*/*z* (%) = 399 (6) $(M)^+$, 384 (6), 313 (6), 300 (4), 273 (12), 272 (100), 271 (31), 230 (12), 190 (23), 186 (17), 166 (7), 146 (4).

*2-Methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(trifluoromethyl)pyridine (**5d**).*



The general borylation procedure was applied to 2-methyl-6-(trifluoromethyl)pyridine (161 mg, 1 mmol, 1 equiv) for 24 h.

White solid; yield: 254 mg (88%); mp 89−90 °C; R_f = 0.4 (CH_2Cl_2 → CH_2Cl_2/ethyl acetate 2:1).

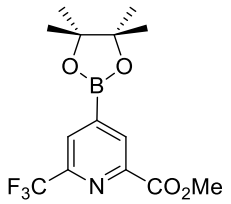
FT-IR (ATR): 2984, 1440, 1371, 1340, 1296, 1134, 965, 867, 844 cm^{-1}.

^1H NMR (700 MHz, $CDCl_3$): δ = 7.82 (s, 1H), 7.70 (s, 1H), 2.64 (s, 3H), 1.36 (br s, 12H, $4CH_3$ of BPin).

^{13}C NMR {^1H} (176 MHz, $CDCl_3$): δ = 158.7 (C), 147.1 (q, $^2J_{C-F}$ = 33.7 Hz, C), 131.6 (CH), 122.2 (d, $^3J_{C-F}$ = 2.5 Hz, CH), 121.7 (q, $^1J_{C-F}$ = 274 Hz, CF_3), 84.9 (2C), 24.8 ($4CH_3$ of BPin), 24.2 (CH_3).

GC−MS (EI): *m*/*z* (%) = 287 (29) $(M)^+$, 272 (93), 230 (12), 201 (100), 188 (52).

*Methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(trifluoromethyl)picolinate (**5e**).*



The general borylation procedure was applied to methyl 6-(trifluoromethyl)picolinate (205 mg, 1 mmol, 1 equiv) for 1 h.

Pale yellowish liquid; yield: 279 mg (84%); R_f = 0.35 (CH_2Cl_2).

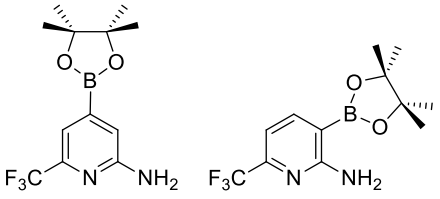
FT-IR (ATR): 2988, 2955, 1752, 1388, 1298, 1253, 1136, 980, 913, 858, 841, 788, 710 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.62 (d, *J* = 2.4 Hz, 1H), 8.18 (d, *J* = 2.4 Hz, 1H), 4.01 (s, 3H), 1.38 (br s, 12H, $4CH_3$ of BPin).

^{13}C NMR {^1H} (151 MHz, $CDCl_3$): δ = 164.8 (CO), 147.9 (q, $^2J_{C-F}$ = 34.7 Hz, C), 147.8 (C), 132.7 (CH), 128.5 (CH), 121.2 (q, $^1J_{C-F}$ = 272.7 Hz, CF_3), 85.4 (2C), 51.2 (CH_3), 24.9 ($4CH_3$ of BPin).

GC−MS (EI): *m*/*z* (%) = 331 (8) $(M)^+$, 316 (19), 288 (43), 287 (15), 273 (100), 272 (89), 271 (24), 256 (17), 246 (32), 245 (11), 232 (41), 231 (18), 230 (33), 229 (20), 200 (23), 191 (10), 190 (10).

4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(trifluoromethyl)pyridin-2-amine.



Major 24 : 1 Minor

The general traceless borylation procedure was applied to 6-(trifluoromethyl)pyridin-2-amine (162 mg, 1 mmol, 1 equiv) using 3,4,7,8-tetramethyl-1,10-phenanthroline ligand (4.7 mg, 0.02 mmol, 2 mol %) and 3 equiv of pinacolborane for 1 h. The ratio of the major to minor monoborylated isomer was 96:4 by GC−MS.

Pale yellowish liquid; yield: 257 mg (89%); R_f = 0.25 (CH_2Cl_2).

FT-IR (ATR): 3322, 3206, 2981, 1640, 1553, 1436, 1317, 1277, 1191, 1129, 966, 862, 845 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): major isomer δ = 7.31 (s, 1H), 7.02 (s, 1H), 4.86 (s, 2H, NH_2), 1.33 (br s, 12H, $4CH_3$ of BPin).

^1H NMR (600 MHz, $CDCl_3$): minor isomer δ = 7.97 (d, *J* = 7.4 Hz, 1H), 6.89 (d, *J* = 7.4 Hz, 1H), 4.86 (s, 2H, NH_2), 1.33 (br s, 12H, $4CH_3$ of BPin).

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^{13}C NMR {^{1}H} (151 MHz, $CDCl_3$): major isomer δ = 158.1 (C), 145.7 (q, $^{2}J_{C-F}$ = 33.8 Hz, C), 121.7 (q, $^{1}J_{C-F}$ = 273.9 Hz, C), 117.9 (CH), 114.4 (distorted q, CH), 84.7 (2C), 24.8 ($4CH_3$ of BPin).

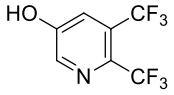
^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$): major isomer δ = −68.4 (s, CF_3).

^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$): minor isomer δ = −69.1 (s, CF_3).

^{11}B NMR (192 MHz, $CDCl_3$): δ = 29.9.

GC−MS (EI): *m*/*z* (%) = 288 (33) $(M)^+$, 287 (12), 231 (100), 230 (32), 215 (19), 211 (10), 189 (12), 188 (12), 187 (5), 169 (9), 168 (4).

*5,6-Bis(trifluoromethyl)pyridin-3-ol (**6**).*



In an oven-dried round-bottom flask, 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-bis(trifluoromethyl)pyridine (341 mg, 1 mmol) and acetone (3 mL) were added. Stirring produced a homogeneous solution. An aqueous solution of oxone (615 mg, 1 mmol, 1 equiv in 3 mL of water) was added dropwise over 2−4 min. After complete addition, the reaction mixture was vigorously stirred for 30 min. After the completion of the reaction, an aqueous solution of $NaHSO_3$ (1 mL) was added. The reaction mixture was extracted with DCM (15 mL × 3). The combined organics were washed with brine. The organic layer was separated and dried using anhydrous sodium sulfate (2 g) and filtered. Volatiles were removed under reduced pressure using a rotary evaporator. The product was isolated by column chromatography.

White solid; yield: 211 mg (91%); mp 64−66 °C; R_f = 0.4 (ethyl acetate/hexanes 1:1).

FT-IR (ATR): 3300 (br), 2997, 1604, 1579, 1462, 1248, 1099, 1038, 901, 750 cm^{-1}.

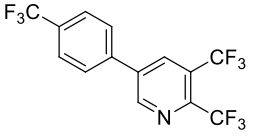
^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 2.4 Hz, 1H), 7.63 (d, *J* = 2.4 Hz, 1H), 2.43 (br s, 1H, OH).

^{13}C NMR {^{1}H} (151 MHz, $CDCl_3$): δ = 154.7 (C), 139.4 (CH), 136.9 (distorted q, C), 126.6 (distorted q, C), 122.6 (distorted q, CH), 120.8 (distorted q, 2 CF_3).

^{19}F NMR (376 MHz, $CDCl_3$): δ = −60.2 (m, CF_3), −63.2 (m, CF_3).

GC−MS (EI): *m*/*z* (%) = 231 (100) $(M)^+$, 230 (7), 229 (3), 213 (4), 212 (30), 183 (2), 182 (5), 181 (45), 163 (4), 162 (60), 160 (2), 114 (11), 106 (3), 69 (3).

*2,3-Bis(trifluoromethyl)-5-(4-(trifluoromethyl)phenyl)-pyridine (**7**).*



An oven-dried Schlenk flask, equipped with a magnetic stirring bar, was filled with nitrogen and evacuated (three cycles). Under nitrogen atmosphere, $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 1 mol %), SPhos (8.2 mg, 0.02 mmol, 2 mol %), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-bis(trifluoromethyl)-pyridine (341 mg, 1 mmol, 1 equiv), K_3PO_4 (318 mg, 1.5 mmol, 1.5 equiv), 1-bromo-4-(trifluoromethyl)benzene (269 mg, 1.2 mmol, 1.2 equiv), and dimethoxyethane (2 mL) were added under nitrogen atmosphere. The Schlenk flask was closed and the reaction mixture was heated at 80 °C in an oil bath for 20 h. The progress of the reaction was monitored by GC−MS and TLC. Upon completion of the reaction, the Schlenk flask was cooled to room temperature and exposed to air. The reaction mixture was taken out by dissolving in dichloromethane and the volatiles were removed under reduced pressure using a rotary evaporator. Water (5 mL) was added into the crude reaction mixture and the product was extracted using ethyl acetate (10 mL × 3). The organic layer was separated and dried using anhydrous sodium sulfate (2 g), and then filtered. Volatiles were removed under reduced pressure using a rotary evaporator. The product was isolated by column chromatography.

Colorless liquid; yield: 296 mg (82%); R_f = 0.4 (CH_2Cl_2/hexanes 1:2).

FT-IR (ATR): 2974, 2901, 1317, 1254, 1138, 1109, 1074, 1034, 930, 845, 790, 762, 728 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.10 (d, *J* = 1.8 Hz, 1H), 8.35 (d, *J* = 1.2 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 1H).

^{13}C NMR {^{1}H} (151 MHz, $CDCl_3$): δ = 149.8 (CH), 144.6 (q, $^{2}J_{C-F}$ = 37.1 Hz, C), 138.3 (s, C), 138.2 (s, C), 134.6 (q, $^{3}J_{C-F}$ = 5.4 Hz, CH), 131.9 (q, $^{2}J_{C-F}$ = 32.9 Hz, C), 127.9 (2 CH), 126.6 (q, $^{3}J_{C-F}$ = 5.4 Hz, 2 CH), 125.6 (q, $^{2}J_{C-F}$ = 35.1 Hz, C), 123.7 (q, $^{1}J_{C-F}$ = 272.4 Hz, CF_3), 122.0 (q, $^{1}J_{C-F}$ = 274.0 Hz, CF_3), 120.6 (q, $^{1}J_{C-F}$ = 275.1 Hz, C).

^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$): δ = −59.8 (q, *J* = 11.9 Hz, CF_3), −62.9 (s, CF_3), −64.2 (q, *J* = 11.9 Hz, CF_3).

GC−MS (EI): *m*/*z* (%) = 359 (100) $(M)^+$, 340 (35), 309 (59), 291 (23), 290 (96), 290 (96), 271 (15), 270 (52), 269 (49), 243 (30), 240 (11), 221 (26), 220 (68), 202 (14), 201 (27), 200 (20), 194 (11), 193 (12).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c00773.

NMR spectra of synthesized compounds; ^{1}H NMR spectrum of decomposed 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4,6-bis(trifluoromethyl)pyridine; GC−MS of crude reaction mixture of iridium-catalyzed borylation of 2-fluoro-4-(trifluoromethyl)pyridine (PDF)

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Notes

The authors declare no competing financial interest.

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