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# Synthesis of novel halopyridinylboronic acids and esters. Part 3: 2, or 3-Halopyridin-4-yl-boronic acids and esters☆

Alexandre Bouillon,[a] Jean-Charles Lancelot,[a] Valérie Collot,[a] Philippe R. Bovy[b] and Sylvain Rault[a,*]

[a]*Centre d'Etudes et de Recherche sur le Médicament de Normandie, UFR des Sciences Pharmaceutiques, 5, rue Vaubénard, 14032 Caen Cedex, France*

[b]*Sanofi-Synthélabo Recherche, 10, rue des Carrières, 92500 Rueil-Malmaison, France*

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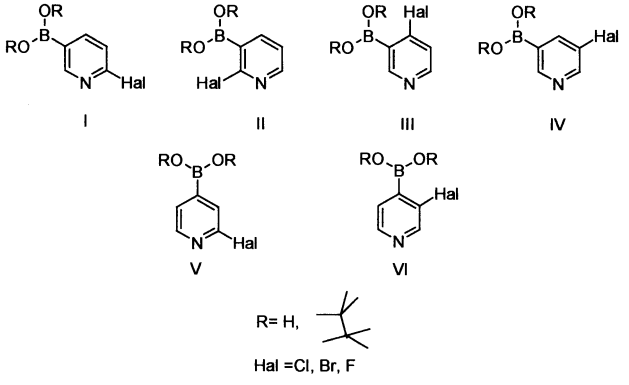
**Abstract**—This paper describes a general method for the synthesis and the isolation of novel 2, or 3-halopyridin-4-yl-boronic acids and esters **12**–**14**, **18**–**20**. These compounds are prepared taking in account a regioselective halogen–metal exchange using *n*BuLi or directed *ortho*-metalation using LDA and subsequent quenching with triisopropylborate starting from appropriate mono or dihalopyridines. All substrates studied to date provided a single regioisomeric boronic acid or ester product. Additionally, these compounds have been found to undergo Pd-catalysed coupling with a range of arylhalides and authorise a strategy to produce new pyridines libraries. 

## 1. Introduction

Within the framework of our research, aiming at continuing the study of new mild and flexible strategies to design new pyridine libraries, we focused on a general method for the synthesis of new pyridinylboronic acids usable in combinatorial approaches. For this reason, we particularly studied the synthesis of new halopyridinylboronic acids likely to offer a double reactivity, via their boronic moiety and their halogen atom. In a first part, we published the synthesis and the isolation of novel 6-halo-pyridin-3-yl-boronic acids and esters **I**[1] and in a second part 2, 4, or 5-halopyridin-3-yl-boronic acids and esters **II**–**IV**.[2] We demonstrated that these compounds were stable, easy to purify and to handle. Now, in the third part of this work, we report the synthesis, the isolation and the reactivity of new 2, or 3-halopyridin-4-yl-boronic acids and esters **V** and **VI**.




## 2. Results and discussion

The successful methods for preparation of halo-pyridin-3-yl-boronic acids and esters **I**–**IV** prompted us to apply them to the synthesis of the new isomers **V** and **VI** bearing halogen atom in a 2, or 3 position and a boronic acid or ester in the 4 position.

### 2.1. 2-Halopyridin-4-yl-boronic acids and esters

Our first concern was the preparation of our precursors 2,4-dihalopyridines, which can undergo halogen–metal exchange (HMe). We chose 2-halo-4-bromopyridines both for their relative ease of preparation and for the great reactivity of bromine toward HMe. Following classical procedures for *N*-oxide preparation,[3] regioselective nitration, reduction and Sandmeyer reaction,[4,5] we were able to prepare **9** and **10**, respectively, in 36 and 32% overall yields. This sequence was problematic for **11**. A more recent method[6] using the ability of bromine to 'dance' during metalation[7,8] was thus used for the preparation of **10** and **11** in satisfactory yields (Scheme 1).

Thus, bromine–lithium exchange was carried out in ether at

☆ For Part 1 see Ref. 1, for Part 2, see Ref. 2.

*Keywords*: halopyridin; boronic acid; boronic ester.

* Corresponding author. Tel.: +33-2-31-93-41-69; fax: +33-2-31-93-11-88; e-mail: rault@pharmacie.unicaen.fr

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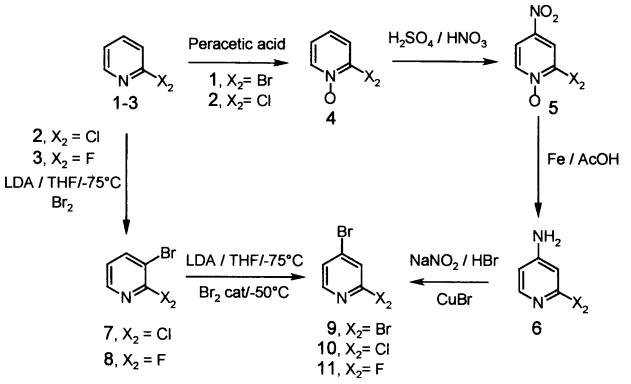
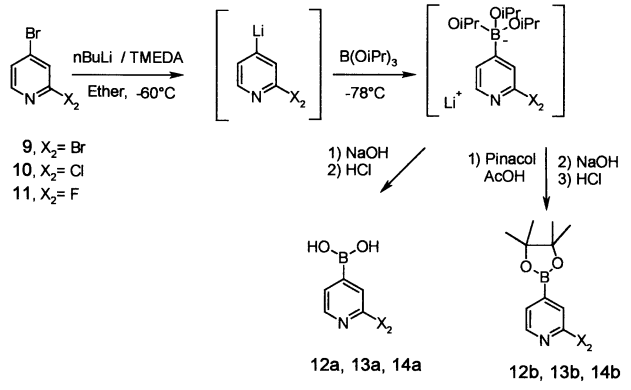



**Scheme 1.** Preparation of 2,4-dihalopyridines **9**–**11**.

−60°C with the *n*BuLi/TMEDA chelate already described by Marsais et al.[6] as a good method for the preparation of C(4)-substituted pyridines. The resulting lithiopyridine was trapped by triisopropylborate, known to give better results than other borates[9] (Scheme 2).

Both boronic acids and the corresponding pinacol esters were isolated using the method already described for halopyridin-3-yl-boronic acids and esters.[1,2] Namely, the boronic acids **12a**, **13a**, and **14a** were obtained within 62–68% yield after a work-up avoiding the formation of pyridinium salts: the mixture was quenched by slow addition of 4% aqueous NaOH solution and the resulting aqueous layer neutralised by careful addition of diluted (2.5N) aqueous HCl to prevent protodeboronation.[10] The boronic acids **12a**, **13a**, and **14a** are stable, easy to purify and to handle as white solids.

On the other hand, we released from the amphoteric character of the free pyridinylboronic acid by the one-pot formation of its pinacol ester, using Coudret's procedure.[12] These protected boronic acids can undergo specific




**Scheme 2.** Obtention of boronic acids **12a**, **13a**, **14a** and esters **12b**, **13b**, **14b** via HMe.

**Table 1.**

| Compound | 2-X | Boronic acid | Yield (%) | Boronic ester | Yield (%) |
|---|---|---|---|---|---|
| **9** | Br | **12a** | 68 | **12b** | 66 |
| **10** | Cl | **13a** | 64 | **13b** | 60 |
| **11** | F | **14a** | 64 | **14b** | 62 |

**Table 2.**

| Compound | 3-X | Boronic acid | Yield (%) | Boronic ester | Yield (%) |
|---|---|---|---|---|---|
| **15** | F | **18a** | 46 | **18b** | 55 |
| **16** | Cl | **19a** | 38 | **19b** | 51 |
| **17** | Br | **20a** | 32 | **20b** | 48 |

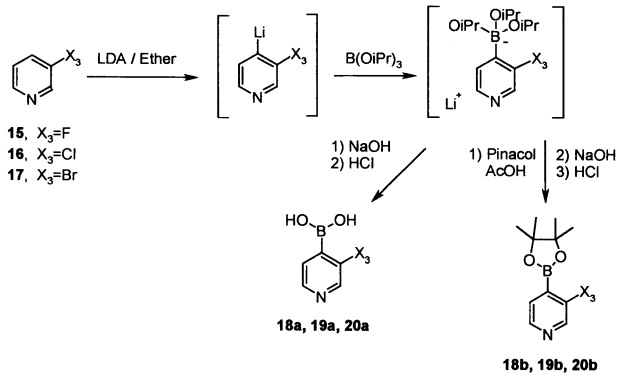
reactions[9,11] that are currently investigated by us. Coudret's conditions (pinacol and acetic acid to adjust pH down to 7) applied to **9**–**11** yielded 60–66% of the corresponding pinacol esters **12b**, **13b**, and **14b**. These relative low yields compared to those obtained with the other isomers are probably due to lesser stability of the former towards hydrolysis (giving partly the corresponding boronic acid) during the work-up (Scheme 2, Table 1).

## 2.2. 3-Halopyridin-4-yl-boronic acids and esters

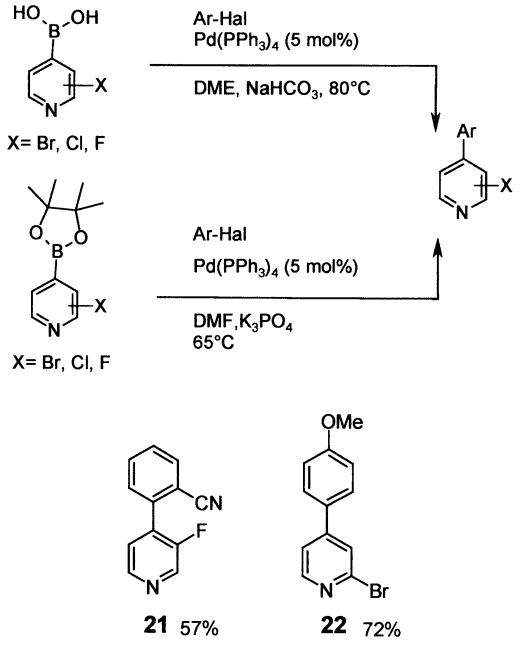
The strategy concerning the synthesis of 3-halopyridin-4-yl-boronic acids and esters was driven by the *ortho* position of the expected boronic moiety and the halogen atom. We were thus able to utilize the halogen as an *ortho*-directing group taking into account the fact that *ortho* lithiation of π-deficient heterocycles is now fully described.[13–15]

The lithiation of 3-fluoropyridine **15** has been described as a C-(4)-regioselective reaction occurring with great yields[16] in standard conditions (LDA, THF, −78°C). As for us, the lithiation of 3-fluoropyridine at −60°C in ether (to make the lithiopyridine precipitate and make easier further treatment) with one equivalent of lithium diisopropylamide (LDA prepared in situ by the action of *n*BuLi on diisopropylamine) took place regioselectively at the more acidic position 4. Quenching this anion at −60°C with triisopropylborate $B(OiPr)_3$ followed by classical work-up avoided the formation of pyridinium salts and gave the expected boronic acid **18a**, which was not very stable. Performing the in situ transesterification with pinacol gave the more stable and easier to handle corresponding ester **18b** in better yield (Table 2).

In the case of 3-chloropyridine **16**, *ortho*-directed lithiation (LDA, THF, −78°C) has been studied by Gribble et al.[17] In our case, we performed the metalation in ether at −60°C by 1 equiv. of lithium diisopropylamide (LDA). These




**Scheme 3.** Obtention of boronic acids **18a**, **19a**, **20a** and esters **18b**, **19b**, **20b** via DoM.




**Scheme 4.** Suzuki cross-couplings of pyridylboronic acids **a** or esters **b**.

conditions resulted in the regioselective lithiation of the C-4 position due to the relative acidity of C-(4) vs C-(2), affording the 3-chloro-4-lithiopyridine. Quenching this anion at low temperature with triisopropylborate $B(OiPr)_3$ gave the expected boronic acid **19a**. Performing the in situ transesterification with pinacol gave the corresponding ester **19b** in 51% yield (Scheme 3, Table 2).

The directed and regioselective deprotonation of 3-bromopyridine is much more difficult because of the ability of bromine to undergo HMe. This has been described by Karig et al.[18] for aryl zinc preparation using LDA in THF at −95°C followed by transmetalation.

We adapted similar conditions (LDA, ether, −95°C) to allow regioselective lithiation; quenching with $B(OiPr)_3$ gave cleanly **20a** in 32% yield and **20b** in 48% yield.

### 2.3. Suzuki couplings

As illustrated in Scheme 4, the boronic acids **a** and the esters **b** were efficiently coupled with sterically hindered, electron-rich, or electron-poor aryl halides under standard Suzuki-type conditions[19,20] furnishing a range of unknown biaryls not easily accessible or recently described,[18] as for example **21** and **22**.

The resulting arylpyridines **21** and **22** were isolated following column chromatography. The yields for cross-coupling were generally good. Interestingly, no 'homocoupled' products with halopyridin-4-yl-boronic acids or esters acting as both the aryl boronic and aryl bromide fragments were observed. A detailed study of these Suzuki cross-coupling reactions will be published elsewhere.

Further experiments concerning the double reactivity of these compounds are currently under investigation in order to study the compatibility of the presence of the boronic acid or boronate moiety with for example nucleophilic substitution of the halogen in order to prepare new building blocks.

## 3. Experimental

### 3.1. General procedures

Commercial reagents were used as received without additional purification. Melting points were determined on a Köfler melting point apparatus and are uncorrected. IR spectra were taken with a Genesis Series FTIR spectrometer. $^1H$ NMR (400 MHz) and $^{13}C$ NMR (100 MHz) were recorded on a JEOL Lambda 400 Spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. The mass spectra (MS) were taken on a JEOL JMS GCMate spectrometer at a ionising potential of 70 eV. Thin-layer chromatography (TLC) was performed on 0.2 mm precoated plates of silica gel 60F-264 (Merck). Visualization was made with ultraviolet light. Column chromatography was carried out using silica gel 60 (0.063–0.2 mm) (Merck). Elemental analyses for new compounds were performed at the 'Institut de Recherche en Chimie Organique Fine' (Rouen).

2-Chloropyridine, 3-chloropyridine, 2-fluoropyridine, 3-fluoropyridine, 2-bromopyridine, 3-bromopyridine were purchased from Acros Organics and were used without further purification.

### 3.2. General procedure for the synthesis of 2-halo-4-pyridylboronic acids

To a slurry of freshly distilled tetramethylethylenediamine (1.1 equiv.) in 150 mL of anhydrous ether cooled to −10°C was added dropwise a 2.5 M solution of *n*BuLi (1.2 equiv.). The mixture was allowed to react at this temperature over 20 min, and then cooled to −60°C. A solution of 2,4-dihalopyridine (20 mmol, 1 equiv.) in anhydrous ether (50 mL) was dropwise added, maintaining the temperature at −60°C. The resulting dark coloured (apricot) mixture was allowed to react at this temperature over 30 min. After cooling down to −70°C, a solution of triisopropylborate (1.2 equiv.) in anhydrous ether (50 mL) was added in 10 min. The mixture was mixed at this temperature for 30 min, and allowed to warm to room temperature to react for an additional hour. The mixture was quenched by slow addition of 4% aqueous NaOH solution (150 mL). The resulting aqueous layer was collected and acidified to pH 5–6 by dropwise addition of 3N HCl (≈70 mL), keeping the internal temperature below 5°C. Extraction with ethyl acetate, evaporation of the organic layer and crystallization from $Et_2O$ gave pure **12a**, **13a**, and **14a**.

**3.2.1. 2-Bromo-4-pyridylboronic acid (12a).** White solid, mp 225°C. IR (KBr): 3370, 3088, 1526, 1447, 1418, 1362, 1338, 1202, 1104, 1063, 998, 844, 730, 661 $cm^{-1}$. $^1H$ NMR ($d_6$-DMSO) $\delta$ 8.75 (s, 2H), 8.45 (d, $J$=4.6 Hz, 1H), 7.93 (s, 1H), 7.75 (d, $J$=4.6 Hz, 1H). Anal. calcd for $C_5H_5BBrNO_2$: C, 29.76; H, 2.50; N, 6.94. Found: C, 29.78; H, 2.37; N, 6.76.

**3.2.2. 2-Chloro-4-pyridylboronic acid (13a).** White solid, mp 210°C. IR (KBr): 3357, 3094, 1451, 1422, 1367, 1336, 1209, 1114, 1098, 1070, 1000, 845, 731, 664 $cm^{-1}$. $^1H$ NMR ($d_6$-DMSO) $\delta$ 8.69 (s, 2H), 8.39 (d, $J$=4.7 Hz, 1H), 7.72 (s, 1H), 7.64 (d, $J$=4.7 Hz, 1H). Anal. calcd for $C_5H_5BClNO_2$: C, 38.16; H, 3.20; N, 8.90. Found: C, 38.44; H, 3.41; N, 8.62.

**3.2.3. 2-Fluoro-4-pyridylboronic acid (14a).** White solid, mp 200°C. IR (KBr): 3357, 1493, 1458, 1397, 1347, 1152, 1127, 1067, 1004, 897, 846, 733, 681, 755 $cm^{-1}$. $^1H$ NMR ($d_6$-DMSO) $\delta$ 8.66 (s, 2H), 8.22 (d, $J$=4.7 Hz, 1H), 7.59 (t, $J$=4.0 Hz, 1H), 7.37 (s, 1H). $^{13}C$ NMR ($d_6$-DMSO) $\delta$ 163.1 (d, $J$=236.1 Hz), 146.8 (d, $J$=13.2 Hz), 126.3 (d, $J$=4.1 Hz), 113.7 (d, $J$=33.7 Hz). Anal. calcd for $C_5H_5BFNO_2$: C, 42.62; H, 3.58; N, 9.94. Found: C, 42.22; H, 3.26; N, 9.62.

### 3.3. General procedure for the synthesis of 3-halo-4-pyridylboronic acids

To a slurry of freshly distilled diisopropylamine (1.2 equiv.) in 150 mL of anhydrous ether cooled to −10°C was added dropwise a 2.5 M solution of *n*BuLi (1.25 equiv.). The mixture was allowed to react at −10°C during 30 min, and then cooled to −60°C (−95°C for **17**). A solution of 3-halopyridine (20 mmol, 1 equiv.) in 50 mL of anhydrous ether was then added dropwise in order to keep the internal temperature at −60°C (−95°C for **17**). The resulting coloured mixture was allowed to react at this temperature over 0.75 h. A solution of triisopropylborate (1.25 equiv.) in 50 mL of anhydrous ether was then dropwise added, keeping the internal temperature at −60°C (−95°C for **17**). The mixture was allowed to warm to room temperature and left to react for an additional hour. The resulting solution was quenched by slow addition of 4% aqueous NaOH solution (150 mL). The resulting aqueous layer was collected and acidified to pH 5–6 by dropwise addition of 3N HCl (≈70 mL), keeping the internal temperature below 5°C. Extraction with ethyl acetate, evaporation of the organic layer and crystallization from $Et_2O$ gave pure **18a**, **19a**, and **20a**.

**3.3.1. 3-Fluoro-4-pyridylboronic acid (18a).** White solid, dec 220°C. IR (KBr): 3220, 1479, 1431, 1379, 1265, 1228, 1187, 1071, 837, 789 $cm^{-1}$. $^1H$ NMR ($d_6$-DMSO) $\delta$ 8.69 (s, 2H), 8.58 (s, 1H), 8.38 (bs, 1H), 7.49 (bs, 1H). Anal. calcd for $C_5H_5BFNO_2$: C, 42.62; H, 3.58; N, 9.94. Found: C, 42.51; H, 3.38; N, 9.72.

**3.3.2. 3-Chloro-4-pyridylboronic acid (19a).** White solid, mp >250°C. IR (KBr): 3105, 1411, 1371, 1298, 1262, 1182, 1163, 1077, 774, 695 $cm^{-1}$. $^1H$ NMR ($d_6$-DMSO) $\delta$ 8.67 (s, 2H), 8.52 (s, 1H), 8.43 (d, $J$=4.1 Hz, 1H), 7.39 (d, $J$=4.1 Hz, 1H). Anal. calcd for $C_5H_5BClNO_2$: C, 38.16; H, 3.20; N, 8.90. Found: C, 38.44; H, 3.41; N, 8.62.

**3.3.3. 3-Bromo-4-pyridylboronic acid (20a).** White solid, mp >250°C. IR (KBr): 3195, 1448, 1411, 1362, 1336, 1207, 1103, 1058, 840, 732, 661 $cm^{-1}$. $^1H$ NMR ($d_6$-DMSO) $\delta$ 8.68 (s, 2H), 8.61 (s, 1H), 8.46 (d, $J$=4.6 Hz, 1H), 7.34 (d, $J$=4.6 Hz, 1H). Anal. calcd for $C_5H_5BBrNO_2$: C, 29.76; H, 2.50; N, 6.94. Found: C, 29.82; H, 2.37; N, 6.76.

### 3.4. General procedure for the synthesis of 2-halo-4-pyridylboronic esters

To a slurry of freshly distilled tetramethylethylenediamine (1.1 equiv.) in 150 mL of anhydrous ether cooled to −10°C was added dropwise a 2.5 M solution of *n*BuLi (1.2 equiv.). The mixture was allowed to react at this temperature over 20 min, and then cooled to −60°C. A solution of 2,4-dihalopyridine (20 mmol, 1 equiv.) in anhydrous ether (50 mL) was dropwise added, maintaining the temperature at −60°C. The resulting dark coloured (apricot) mixture was allowed to react at this temperature over 30 min. After cooling down to −70°C, a solution of triisopropylborate (1.2 equiv.) in anhydrous ether (50 mL) was added in 10 min. The mixture was mixed at this temperature for 30 min, and allowed to warm to 10°C (2 h). A solution of anhydrous pinacol (1.3 equiv.) in 75 mL of anhydrous ether was added and, after 10 min, a solution of glacial acetic acid (1.05 equiv.) in anhydrous ether (50 mL). The mixture was allowed to react for 4 h, then filtered through Celite, and extracted by 4% aqueous NaOH solution (200 mL). The resulting aqueous layer was collected and acidified down to pH 6 by dropwise addition of 3N HCl (≈90 mL), keeping the internal temperature below 5°C. Extraction with $Et_2O$, evaporation of the ethereal layer and recrystallization gave **12b**, **13b**, and **14b**.

**3.4.1. 2-[4-(2-Bromo)pyridine]-4,4,5,5-tetramethyl-1,3-dioxaborolane (12b).** White solid, mp 120°C (acetonitrile). IR (KBr): 2976, 2929, 1519, 1469, 1357, 1326, 1267, 1142, 1082, 964, 859, 718, 670 $cm^{-1}$. $^1H$ NMR ($d_6$-DMSO) $\delta$ 8.43 (d, $J$=4.6 Hz, 1H), 7.68 (s, 1H), 7.58 (d, $J$=4.6 Hz, 1H), 1.29 (s, 12H). $^{13}C$ NMR ($d_6$-DMSO) $\delta$ 150.5, 146.2, 132.4, 127.6, 84.8, 24.67. Anal. calcd for $C_{11}H_{15}BBrNO_2$: C, 46.53; H, 5.32; N, 4.93. Found: C, 46.65; H, 5.47; N, 4.88.

**3.4.2. 2-[4-(2-Chloro)pyridine]-4,4,5,5-tetramethyl-1,3-dioxaborolane (13b).** White solid, mp 68°C (acetonitrile). IR (KBr): 2976, 2926, 1472, 1371, 1329, 1267, 1143, 1088, 964, 864, 738, 674 $cm^{-1}$. $^1H$ NMR ($d_6$-DMSO) $\delta$ 8.44 (d, $J$=4.6 Hz, 1H), 7.54 (bs, 2H), 1.29 (s, 12H). $^{13}C$ NMR ($d_6$-DMSO) $\delta$ 150.5, 149.9, 128.7, 127.4, 84.8, 24.6. Anal. calcd for $C_{11}H_{15}BClNO_2$: C, 55.16; H, 6.31; N, 5.85. Found: C, 55.29; H, 6.41; N, 5.93.

**3.4.3. 2-[4-(2-Fluoro)pyridine]-4,4,5,5-tetramethyl-1,3-dioxaborolane (14b).** White solid, mp 60°C (anhydrous ether). IR (KBr): 3064, 2983, 2935, 1544, 1487, 1400, 1358, 1269, 1214, 1144, 1089, 966, 912, 850, 793, 689 $cm^{-1}$. $^1H$ NMR ($d_6$-DMSO) $\delta$ 8.25 (d, $J$=4.5 Hz, 1H), 7.46 (bs, 1H), 7.19 (bs, 1H), 1.27 (s, 12H). $^{13}C$ NMR ($d_6$-DMSO) $\delta$ 162.9 (d, $J$=237.0 Hz), 147.5 (d, $J$=14.0 Hz), 126.2 (d, $J$=3.3 Hz), 113.9 (d, $J$=35.4 Hz), 84.7, 24.5. Anal. calcd for $C_{11}H_{15}BFNO_2$: C, 59.23; H, 6.78; N, 6.28. Found: C, 59.35; H, 6.96; N, 6.42.

### 3.5. General procedure for the synthesis of 3-halo-4-pyridylboronic esters

To a slurry of freshly distilled diisopropylamine (1.2 equiv.) in 150 mL of anhydrous ether cooled to −10°C was added dropwise a 2.5 M solution of *n*BuLi (1.25 equiv.). The

mixture was allowed to react at −10°C for 30 min, and then cooled to −60°C (−95°C for **17**). A solution of 3-halopyridine (20 mmol, 1 equiv.) in 50 mL of anhydrous ether was then added dropwise in order to keep the internal temperature at −60°C (−95°C for **17**). The resulting coloured mixture was allowed to react at this temperature over 45 min. A solution of triisopropylborate (1.25 equiv.) in 50 mL of anhydrous ether was added dropwise, keeping the internal temperature at −60°C (−95°C for **17**). The mixture was allowed to warm to 10°C. A solution of anhydrous pinacol (1.3 equiv.) in 75 mL of anhydrous ether was then added and, after 10 min, a solution of glacial acetic acid (1.05 equiv.) in anhydrous ether (50 mL). The mixture was allowed to react for 4 h, then filtered through Celite, and extracted by 5% aqueous NaOH solution (200 mL). The resulting aqueous layer was collected and acidified down to pH 6–7 by dropwise addition of 3N HCl (≈90 mL), keeping the internal temperature below 5°C. Extraction with ether, evaporation of the ethereal layer and recrystallization gave **18b**, **19b**, and **20b**.

**3.5.1. 2-[4-(3-Fluoro)pyridine]-4,4,5,5-tetramethyl-1,3-dioxaborolane (18b).** White solid, mp 126°C (anhydrous ether). IR (KBr): 2986, 2970, 2928, 1476, 1423, 1384, 1362, 1273, 1195, 1145, 1044, 896, 777, 761, 703, 649 $cm^{-1}$. $^1H$ NMR ($d_6$-DMSO) $\delta$ 8.54 (s, 1H), 8.45 (bs, 1H), 7.57 (bs, 1H), 1.30 (s, 12H). $^{13}C$ NMR ($d_6$-DMSO) $\delta$ 162.0 (d, $J$=257.5 Hz), 145.3 (d, $J$=4.2 Hz), 137.9 (d, $J$=25.5 Hz), 129.4 (d, $J$=4.1 Hz), 84.4, 24.5. Anal. calcd for $C_{11}H_{15}BFNO_2$: C, 59.23; H, 6.78; N, 6.28. Found: C, 59.45; H, 6.90; N, 6.37.

**3.5.2. 2-[4-(3-Chloro)pyridine]-4,4,5,5-tetramethyl-1,3-dioxaborolane (19b).** White solid, mp 112°C (anhydrous ether). IR (KBr): 2974, 2926, 1614, 1460, 1405, 1382, 1361, 1190, 1166, 1146, 1104, 1043, 880, 820, 762, 699, 656 $cm^{-1}$. $^1H$ NMR ($d_6$-DMSO) $\delta$ 8.61 (s, 1H), 8.52 (d, $J$=4.2 Hz, 1H), 7.55 (d, $J$=4.2 Hz, 1H), 1.30 (s, 12H). $^{13}C$ NMR ($d_6$-DMSO) $\delta$ 148.6, 147.2, 135.3, 129.6, 84.7, 24.5. Anal. calcd for $C_{11}H_{15}BClNO_2$: C, 55.16; H, 6.31; N, 5.85. Found: C, 55.29; H, 6.41; N, 5.93.

**3.5.3. 2-[4-(3-Bromo)pyridine]-4,4,5,5-tetramethyl-1,3-dioxaborolane (20b).** White solid, mp 102°C (acetonitrile). IR (KBr): 2990, 2971, 2925, 1610, 1460, 1402, 1382, 1361, 1190, 1164, 1142, 1040, 878, 809, 758, 737, 692, 655 $cm^{-1}$. $^1H$ NMR ($d_6$-DMSO) $\delta$ 8.72 (s, 1H), 8.55 (d, $J$=4.5 Hz, 1H), 7.50 (d, $J$=4.5 Hz, 1H), 1.31 (s, 12H). $^{13}C$ NMR ($d_6$-DMSO) $\delta$ 150.8, 147.3, 129.8, 124.7, 84.7, 24.5. Anal. calcd for $C_{11}H_{15}BBrNO_2$: C, 46.53; H, 5.32; N, 4.93. Found: C, 46.71; H, 5.48; N, 5.11.

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