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Synthesis of novel halopyridinylboronic acids and esters. Part 1: 6-Halopyridin-3-yl-boronic acids and esters

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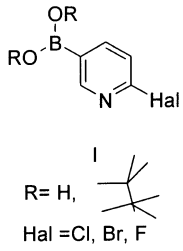
Abstract—This paper describes a general method for the synthesis and isolation of novel 6-halo-pyridin-3-yl-boronic acids and esters **2**–**5**. These compounds are prepared taking in account a regioselective halogen–metal exchange with a trialkylborate starting from 2,5-dihalopyridines. All substrates 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. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

There are many examples of the Suzuki coupling, where the pyridine motive is employed as electrophile in the form of halopyridine but much less where it is used as nucleophile in the form of a pyridinylboron reagent[1–5] and this for two reasons: the pyridinylboronic acids are considered not very stable and also because the number of available pyridinylboronic acids remains very weak compared to that of the aromatic series.[6]

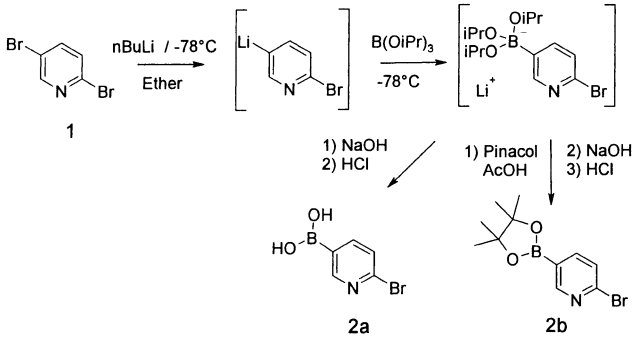
Considering the growth of Suzuki type cross-coupling reaction applications and in order to build new pyridines libraries, we focused on a general method for the synthesis of new pyridinylboronic acids usable in combinatorial approaches. With this aim, we particularly studied the synthesis of new halopyridinylboronic acids likely to offer a double reactivity, via their boronic moiety and their halogen atom. In this first publication, we present the synthesis and the reactivity of 6-halopyridin-3-yl-boronic acids and esters of type **I**.



2. Results and discussion

At the beginning of this work, no halopyridyl boronic acids were described. However, during the course of a study concerning the synthesis of terpyridines, Lehmann[7] recently described the synthesis of 2-[3-(6-bromo)pyridine]-4,4′,5,5′-tetramethyl-1,3-dioxaborolane **2b** obtained from a crude 2-bromo-5-pyridylboronic acid **2a**. He used the classical preparation of boronic acids which requires the reaction of an organolithium intermediate, generated by deprotonation or halogen–metal exchange, with a trialkylborate.[8–10]

On the same basis, our first attempts were carried out in a



Scheme 1.

Keywords: dihalopyridines; cross-coupling; pyridinium salts.

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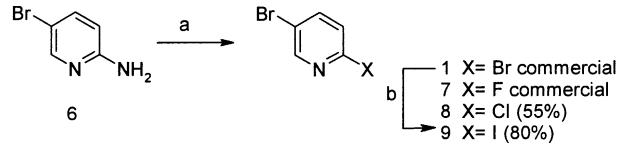
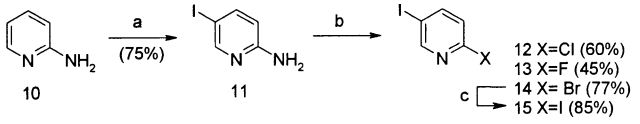


Scheme 2. *Reagents*: (a) HCl, $NaNO_2$, CuCl; (b) AcOCl, NaI.



Scheme 3. *Reagents*: (a) HIO_4, I_2, AcOH, H_2O, H_2SO_4; (b) HCl, $NaNO_2$, CuCl, or HBF_4, $NaNO_2$ or HBr, $NaNO_2$, Br_2; (c) AcOCl, NaI.

similar manner starting from commercially available 2,5-dibromopyridine **1** (Acros Organics) chosen because of the well-known difference in reactivity between its two halogen atoms[11–13] (Scheme 1).

Thus, bromine–lithium exchange was carried out in ether at −78°C with *n*BuLi followed by the reaction with a trialkylborate, $B(OMe)_3$,[14] or better $B(OiPr)_3$.

In order to obtain either the boronic acid or the corresponding pinacolate ester we studied adapted works-up. At the end of the reaction, the boronic acid derivative **2a** was obtained with 75% yield after a work-up avoiding the formation of pyridinium salts. The mixture was quenched by slow addition of 5% aqueous NaOH solution and the resulting aqueous layer neutralised by careful addition of concentrated HCl to prevent protodeboronation.

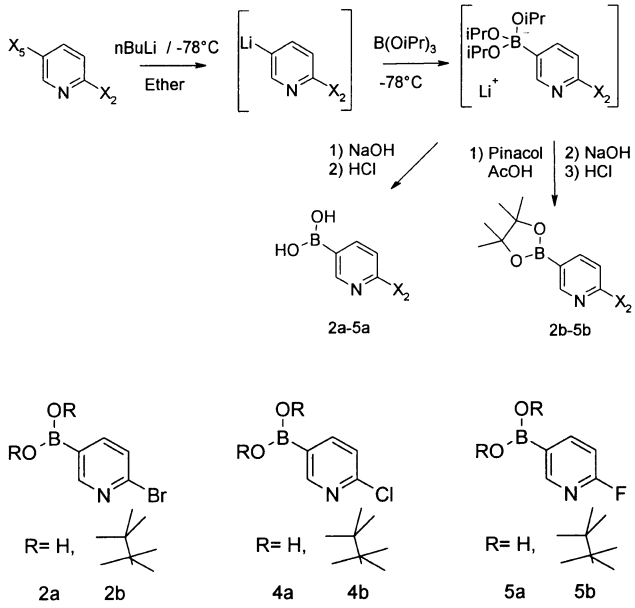
On one hand, our results demonstrated that the boronic acid **2a** was a stable boronic acid easy to purify as a white solid, to handle, and to crystallize.[15]

On the other hand, considering the amphoteric character of this acid, we studied the direct formation of its pinacol ester adapting the method of Coudret[16] who described the synthesis of 4-pyridylboronic pinacol ester in 74% yield starting from 4-iodopyridine. These same conditions applied to **1** gave 78% of the corresponding pinacol ester **2b** in a one pot procedure (Scheme 1).

In order to generalize this method and considering that the nature of halogen atoms should not considerably modify the reactivity of the system, we decided to prepare new boronic species from the other 2,5-dihalopyridines **7**–**9** and **12**–**15**.

5-Bromo-2-fluoropyridine **7** was purchased from Aldrich. 2,5-Dihalopyridines **8** and **9** (Scheme 2) were prepared from commercially available 2-amino-5-bromopyridine **6**. 5-Bromo-2-chloropyridine **8**[17] was obtained via a diazonium salt followed by a treatment with copper(I) chloride. Moreover, we obtained 5-bromo-2-iodopyridine **9**[18] with 80% yield from **1** by halogen–halogen exchange according to the method described by Corcoran et al.[19] using 3 equiv.

Table 1. Synthesis of 6-halopyridin-3-yl-boronic acids and esters **2**–**5**



Compounds	X_2	X_5	Boronic acid	Yield (%)	Boronic ester	Yield (%)
1	Br	Br	**2a**	75	**2b**	78
14	Br	I	**2a**	10	**2b**	10
15	I	I	**3a**	0	**3b**	0
9	I	Br	**3a**	0	**3b**	0
12	Cl	I	**4a**	55	**4b**	20
8	Cl	Br	**4a**	87	**4b**	71
16	Cl	Cl	**4a**	25	**4b**	20
13	F	I	**5a**	25	**5b**	15
7	F	Br	**5a**	76	**5b**	65

of anhydrous sodium iodide and 2 equiv. of acetyl chloride in refluxing acetonitrile.

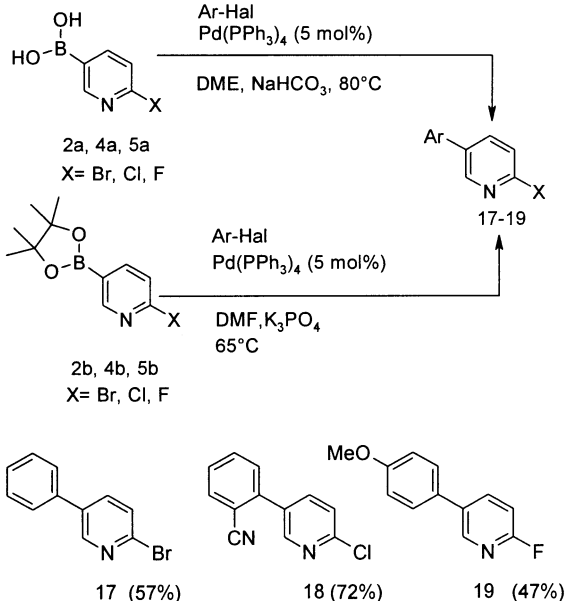
2,5-Dihalopyridines **12**–**15** (Scheme 3) were prepared with the same strategy from commercially available 2-aminopyridine **10** which gave selectively, by treatment with periodic acid and iodine, 2-amino-5-iodopyridine **11**.[20] We adapted and optimised the access to 2-chloro-5-iodopyridine **12**,[21] 2-fluoro-5-iodopyridine **13**[22] and 2-bromo-5-iodopyridine **14**[20] which were obtained via a diazonium salt and its appropriate treatment. We obtained 2,5-diiodopyridine **15** with 80% yield from **5** by halogen–halogen exchange.[19]

All these dihalopyridines **7**–**9**, **12**–**15** were engaged in the same reaction conditions as for 2,5-dibromopyridine **1** in order to compare their ability to produce corresponding boronic acids and pinacol esters. The results are depicted in Table 1. All these reactions were fruitful except for 2,5-diiodopyridine **15** and 5-bromo-2-iodopyridine **9** from which we could not obtain the boronic species because these starting materials were not sufficiently soluble in the ethereal reaction mixture. It must be pointed out that the best results were obtained starting from compounds possessing a bromine atom in position 5, using 1.20 equiv. of *n*BuLi and 1.20 equiv. of $B(OiPr)_3$ in ether at −78°C.

The boronic acids **2a**, **4a** and **5a** and the esters **2b**, **4b** and **5b** conveniently isolated as their 4,4,5,5,-tetramethyl-1,3,2-dioxaborolane esters were obtained in high yields. These optimised conditions allowed a very efficient synthesis of **2a**, **4a**–**5a** and **2b**, **4b**–**5b** on a multigram scale.

All these boronic species were stable, non-hygroscopic and easy to characterize. The reactions were generally very clean, since the crude products obtained after aqueous work-up could be used as reagents without further purification. Moreover, this exhaustive study outlined the regioselectivity of the reaction as the same boronic species could be obtained starting from different 2,5-dihalopyridines (for example see results starting from **12**, **8** and **16**). The boronic compounds in position 2 were not observed even when we applied the peculiar conditions of Wang which permitted a selective lithiation of 2,5-dibromopyridine (toluene, −78°C)[23] in position 2 and this certainly because of the instability of pyridin-2-yl boronic acid derivatives as reported by Fischer.[24]

Table 2. Suzuki cross-couplings of pyridylboronic acid **2a**, **4a**, **5a** or ester **2b**, **4b**, **5b**



As illustrated in Table 2, the acid **2a**, **4a**, **5a** and the ester **2b**, **4b**, **5b** were efficiently coupled with sterically hindered, electron-rich, or electron-poor halides under standard Suzuki-type conditions,[25,26] furnishing a range of unknown or otherwise biaryls not easily accessible, as for example **17**–**19**.

The yields for cross-coupling were generally good, and the resulting 2-bromo-5-substituted pyridines **17**–**19** were isolated following column chromatography. Interestingly, no 'homocoupled' products with 6-halopyridin-3-yl-boronic acid or esters acting as both the aryl boronic and aryl bromide fragments were observed. Recently, an other type of Pd-mediated cross-coupling reaction using Li/Zn transmetalation was described by Karig et al.[27]

Further experiments concerning the double reactivity of these compounds are currently under investigation in order to use these new starting materials in the production of new pyridine libraries. These results will be published elsewhere.

3. Experimental

3.1. General procedures

Commercial reagents were used as received without additional purification. Melting points were determined on a Kofler 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 ionizing 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).

3.1.1. 2,5-Dibromopyridine (1). This compound was purchased from Acros Organics, dissolved in ether, filtered off and concentrated under reduced pressure before use.

3.1.2. 5-Bromo-2-chloropyridine (8). To a stirred solution of 2-amino-5-bromopyridine **6** (7.5 g, 43 mmol) in 65 mL of 37% hydrochloric acid were successively added an aqueous solution of sodium nitrite (7.8 g, 2.6 equiv.) and copper (I) chloride (5.4 g, 1.25 equiv.), the temperature being kept below −5°C during the addition. The reaction

was then continued at room temperature for 4 h and quenched by slow addition of aqueous solution of sodium hydroxide. The mixture was then extracted with ether and the extract washed with brine, dried over magnesium sulfate and concentrated on rotary evaporator yielding 4.5 g of **8** (55%). White solid, mp 72°C (lit.[17] 71°C); IR 3105–3037 (CH), 1556–1445–1359 (CCN); ^{1}H NMR (d_6-DMSO) δ 8.58 (d, J=2.2 Hz, 1 H), 8.11 (dd, J=8.5, 2.2 Hz, 1H), 7.52 (d, J=8.5 Hz, 1H).

3.1.3. 5-Bromo-2-iodopyridine (9). A mixture of 2,5-dibromopyridine (3.5 g, 15 mmol), potassium iodide (12.3 g, 38 mmol, 2.5 equiv.) and acetyl chloride (4.64 g, 30 mmol, 2 equiv.) were refluxed in dry acetonitrile under nitrogen for 24 h. The mixture was neutralised by careful addition of aqueous $NaHCO_3$, extracted twice by chloroform. The organic layer was dried over magnesium sulfate and evaporated to yield 80% of a white solid, mp 118°C (lit.[18] 117°C); IR 3088–3011 (CH), 1541–1433–1353 (CCN); ^{1}H NMR (d_6-DMSO) δ 8.52 (d, J=1.4 Hz, 1H), 7.80 (d, J=8.3 Hz, 1H), 7.75 (dd, J=8.3, 1.4 Hz, 1H); MS m/z 282.9–284.9.

3.1.4. 2-Amino-5-iodopyridine (11). A mixture of 2-aminopyridine **10** (47.2 g, 0.5 mol), periodic acid dihydrate (22.9 g, 0.1 mol, 0.2 equiv.) and iodine (51.1 g, 0.2 mol, 0.4 equiv.) was heated in a mixed solution of 300 mL of acetic acid, 60 mL of water and 9 mL of sulfuric acid at 80°C for 4 h. The mixture was then poured into aqueous diluted sodium thiosulfate to remove unreacted iodine, made alkaline with aqueous diluted sodium hydroxide and extracted with ether. Purification by column chromatography (AcOEt) yielded 82.9 g of compound **11** (75%). White solid, mp 130°C (lit.[20] 132–133°C); IR 3092–3302 (NH_2), 1546–1481–1381 (CCN); ^{1}H NMR (d_6-DMSO) δ 8.02 (d, J=1.6 Hz, 1H), 8.56 (dd J=8.6, 1.6 Hz, 1H), 6.33 (d, J=8.6 Hz, 1H), 6.11 (s, 2H).

3.1.5. 2-Chloro-5-iodopyridine (12). Applying the method described for compound **8**, starting from 2-amino-5-iodopyridine **11** (16 g, 73 mmol), we obtained 9.7 g of pure **12** (56%). White Solid, mp 96°C (lit.[21] 98–99°C); IR 3096–3025 (CH), 1548–1442–1355 (CCN); ^{1}H NMR (d_6-DMSO) δ 8.65 (d, J=1.9 Hz, 1H), 8.20 (dd, J=8.3, 1.9 Hz, 1H), 7.38 (d, J=8.3 Hz, 1H).

3.1.6. 2-Fluoro-5-iodopyridine (13). To a solution of 2-amino-5-iodopyridine **11** (6 g, 27 mmol) in 50 mL of 48% fluoroboric acid was added $NaNO_2$ (4.9 g, 2.6 equiv.) at −5°C. The mixture was stirred at 40–45°C for 1 h and neutralized with concentrated aqueous NaOH. The product was extracted with ether, the organic layers washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure yielding 2.5 g of pure **13** (45%). Yellow Solid; mp <50°C (lit.[22] 33°C); ^{1}H NMR (d_6-DMSO) δ 8.48 (d, J=2 Hz, 1H), 8.31 (dt, J=8.0, 2.4 Hz, 1H), 7.10 (dd, J=8.0, 2.4 Hz, 1H).

3.1.7. 2-Bromo-5-iodopyridine (14). To a stirred solution of 2-amino-5-iodopyridine **11** (18 g, 82 mmol) in 130 mL of 47% hydrobromic acid were successively added an aqueous solution of sodium nitrite (14.65 g, 0.21 mol, 2.6 equiv.) and bromine (13 mL, 0.25 mol, 3.0 equiv.), the temperature being kept below −5°C during the addition. The reaction was then continued at room temperature overnight and quenched by slow addition of aqueous solution of sodium hydroxide. The mixture was then extracted with ether and the extract washed with an aqueous solution of sodium thiosulfate and brine, dried over magnesium sulfate and concentrated on rotary evaporator. Recrystallization from ethanol gave 18 g of pure **14** (77%); white pellets, mp 120°C (lit.[20] 125–126°C); IR 3087–3017 (CH), 1542–1438–1353 (CCN); ^{1}H NMR (d_6-DMSO) δ 8.63 (d, J=2.2 Hz, 1H), 8.09 (dd, J=8.3, 2.2 Hz, 1H), 7.49 (d, J=8.3 Hz, 1H).

3.1.8. 2,5-Diiodopyridine (15). The same procedure as for compound **9** starting from 2-bromo-5-iodopyridine **14** (yield 85%) was employed; white solid, mp 150°C (lit.[20] 148–149°C); IR 3074–3004 (CH), 1530–1435–1348 (CCN); ^{1}H NMR (d_6-DMSO) δ 8.60 (d, J=2.3 Hz, 1H), 7.84 (dd, J=8.2, 2.3 Hz, 1H), 7.66 (d, J=8.2 Hz, 1H); MS m/z 330.9.

3.1.9. 2,5-Dichloropyridine (16). 2,5-Dichloropyridine (**16**) was purchased from Aldrich and used without any purification.

3.2. General procedure for the synthesis of 2-halogeno-5-pyridylboronic acid (2a–5a)

To a slurry of 2.5 M solution of *n*BuLi (9.4 mL, 24 mmol, 1.2 equiv.) in anhydrous ether, cooled to −78°C, was added a solution of 2,5-dihalopyridine (1 equiv.) in ether. The resulting dark red mixture was allowed to react at this temperature for over 45 min. A solution of triisopropylborate (4.42 g, 24 mmol, 1.2 equiv.) was then added and the mixture allowed to warm to room temperature and left to react for an additional hour. The mixture was quenched by slow addition of 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 ethyl acetate, evaporation of the organic layer and recrystallization from ether gave **2a**, **4a**, **5a**.

3.2.1. 2-Bromo-5-pyridylboronic acid (2a). White solid, mp 198°C. ^{1}H NMR (d_6-DMSO) δ 8.63 (d, J=2.0 Hz, 1H), 8.47 (s, 2H), 7.98 (d, J=8.0 Hz, J=2.0 Hz, 1H), 7.62 (d, J=8 Hz, 1H). ^{13}C NMR (d_6-DMSO) δ 155.7, 144.8, 143.7, 127.4. Anal. Calcd for $C_5H_5BBrNO_2$: C, 29.76; H, 2.50; N, 6.94. Found: C, 29.83; H, 2.43; N, 6.87.

3.2.2. 2-Chloro-5-pyridylboronic acid (4a). White solid, mp 190°C. ^{1}H NMR (d_6-DMSO) δ 8.67 (s, 1H), 8.49 (s, 2H), 8.11 (d, J=8.0 Hz, 1H), 7.47 (d, J=8.0 Hz, 1H). ^{13}C NMR (d_6-DMSO) δ 155.2, 152.1, 145.1, 123.6. Anal. Calcd for $C_5H_5BClNO_2$: C, 38.16; H, 3.20; N, 8.90. Found: C, 38.07; H, 3.23; N, 8.94.

3.2.3. 2-Fluoro-5-pyridylboronic acid (5a). White solid, mp 172°C. ^{1}H NMR (d_6-DMSO) δ 8.54 (d, J=2.2 Hz, 1H), 8.40 (s, 2H), 8.25 (dt, J=8.6, 2.2 Hz, 1H), 7.12 (dd, J=8.0, 2.2 Hz, 1H). ^{13}C NMR (d_6-DMSO) δ 164.5 (d, J=236 Hz), 153.5 (d, J=14 Hz), 147.7 (d, J=7 Hz), 108.8 (d, J=35 Hz). Anal. Calcd for $C_5H_5BFNO_2$: C, 42.62; H, 3.58; N, 9.94. Found: C, 42.69; H, 3.63; N, 9.89.

3.3. General procedure for the synthesis of 2-[3-(6-halogeno)pyridine]-4,4′,5,5′-tetramethyl-1,3-dioxaborolane (2b–5b)

To a slurry of 2.5 M solution of *n*BuLi (17 mL, 43 mmol, 1.2 equiv.) in anhydrous ether cooled to −78°C, was added a solution of 2,5-dihalogenopyridine (1 equiv.) in ether. The resulting dark red mixture was allowed to react at this temperature for over 45 min. A solution of triisopropylborate (8.0 g, 43 mmol, 1.2 equiv.) was then added dropwise and the mixture allowed to warm to room temperature and left to react for an additional hour. A solution of anhydrous pinacol (5.65 g, 48 mmol, 1.35 equiv.) in ether was added and, after 5 min, a solution of glacial acetic acid (2.3 g, 40 mmol, 1.05 equiv.). The mixture was filtered through Celite, and extracted with 5% aqueous NaOH solution (400 mL). The resulting aqueous layer was collected and acidified down to pH 6–7 by dropwise addition of 3N HCl (≈180 mL), keeping the internal temperature below 5°C. Extraction with ether, evaporation of the ethereal layer and washing with acetonitrile gave **2b**, **4b**, **5b**.

3.3.1. 2-[3-(6-Bromo)pyridine]-4,4′,5,5′-tetramethyl-1,3-dioxaborolane (2b). White solid, mp 92°C; ^{1}H NMR (d6-DMSO) δ 8.53 (s, 1H), 7.89 (d, J=7.7 Hz, 1H), 7.66 (d, J=7.7 Hz, 1H), 1.30 (s, 12H); ^{13}C NMR (d_6-DMSO) δ 155.3, 144.9, 144.8, 128.0, 84.4, 24.6; MS *m/z* 282.9–284.9; Anal. Calcd for $C_{11}H_{15}BBrNO_2$: C, 46.53; H, 5.32; N, 4.93. Found: C, 46.62; H, 5.41; N, 4.84.

3.3.2. 2-[3-(6-Chloro)pyridine]-4,4′,5,5′-tetramethyl-1,3-dioxaborolane (4b). White solid, mp 98°C; ^{1}H NMR (d_6-DMSO) δ 8.54 (s, 1H), 7.98 (d, J=7.5 Hz, 1H), 7.48 (d, J=7.5 Hz, 1H), 1.27 (s, 12H). ^{13}C NMR (d_6-DMSO) δ 154.9, 153.2, 145.1, 124.1, 84.3, 24.6. MS *m/z* 239–241. Anal. Calcd for $C_{11}H_{15}BClNO_2$: C, 55.16; H, 6.31; N, 5.85. Found: C, 55.28; H, 6.39; N, 5.92.

3.3.3. 2-[3-(6-Fluoro)pyridine]-4,4′,5,5′-tetramethyl-1,3-dioxaborolane (5b). Colourless oil; ^{1}H NMR (d_6-DMSO) δ 8.43 (d, J=2.0 Hz, 1H), 8.16 (dt, J=8.2, 2.1 Hz, 1H), 7.18 (dd, J=8.2, 2.1 Hz, 1H), 1.29 (s, 12H). ^{13}C NMR (d_6-DMSO) δ 164.3 (d, J=238 Hz), 154.1 (d, J=15 Hz), 147.8 (d, J=8 Hz), 109.4 (d, J=36 Hz). MS *m/z* 222.9; Anal. Calcd for $C_{11}H_{15}BFNO_2$: C, 59.23; H, 6.78; N, 6.28. Found: C, 59.43; H, 6.86; N, 6.40.

3.4. General procedure for the palladium-assisted coupling of pyridyl-boronate with halo compounds

A mixture of halopyridylboronate (1.2 equiv.), halo-compound (bromobenzene, 2-bromobenzonitrile or 4-iodoanisole) (1 equiv.), tetrakis-(triphenylphosphine)palladium(0) (6% mol) and 2N aqueous K_3PO_4 solution in DMF was heated at 65°C for 3–12 h. Ethyl acetate and water were then added. The organic layer was separated, dried over $MgSO_4$ and concentrated to dryness. The residue was chromatographied on silica gel.

3.4.1. 2-Bromo-5-phenylpyridine (17). White solid (57%), mp 80°C (lit.[28] 78–79°C); ^{1}H NMR ($CDCl_3$) δ 8.47 (d, J=2.1 Hz, 1H), 7.58 (dd, J=8.1, 2.1 Hz, 1H), 7.30–7.40 (m, 4H), 6.91 (d, J=8.2 Hz, 2H). ^{13}C NMR (d_6-DMSO) δ 150.6, 149.6, 147.9, 143.3, 133.7, 130.2, 126.3, 125.7, 124.2.

3.4.2. 2-(6-Chloropyridin-3-yl)benzonitrile (18). White solid (72%) mp 128°C. IR(KBr): 2220, 1463, 1438, 1112, 835, 761 cm^{-1}. ^{1}H NMR (d_6-DMSO) δ 8.71 (s, 1H), 8.20 (d, J=7.5 Hz, 1H), 8.08 (d, J=7.5 Hz, 1H), 7.92–7.73 (m, 4H). ^{13}C NMR (d_6-DMSO) δ 150.6, 149.4, 140.0, 139.8, 133.9, 133.8, 133.1, 130.4, 129.3, 124.6, 118.1, 110.6.

3.4.3. 2-Fluoro-5-(4-methoxyphenyl)pyridine (19). Orange solid (47%), mp 64°C; IR(KBr): 2967, 2922, 2845, 1590, 1480, 1250, 1043, 1014, 835 cm^{-1}. ^{1}H NMR (d_6-DMSO) δ 8.49 (s, 1H), 8.22 (dt, J=8.3, 2.5 Hz, 1H), 7.65 (d, J=8.5 Hz, 1H), 7.23 (dd, J=8.3, 2.5 Hz, 1H), 7.04 (d, J=8.5 Hz, 2H), 3.79 (s, 3H). ^{13}C NMR (d_6-DMSO) δ 162.1 (d, J=242 Hz), 159.4, 144.8 (d, J=16 Hz), 139.8 (d, J=9 Hz), 133.8, 128.1, 128.0, 114.6, 109.5 (d, J=37 Hz), 55.3.

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