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Synthesis of novel halopyridinylboronic acids and esters. Part 2: 2,4, or 5-Halopyridin-3-yl-boronic acids and esters☆

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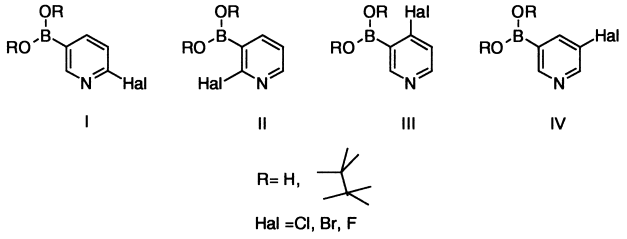
Abstract—This paper describes a general method for the synthesis and the isolation of novel 2,4, or 5-halopyridin-3-yl-boronic acids and esters **4**, **7**, **10**, **13**, **15**. These compounds are prepared taking into account a regioselective halogen–metal exchange using *n*BuLi or a regioselective *ortho*-lithiation using lithium diisopropylamide 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-catalyzed coupling with a range of arylhalides and authorize a strategy to produce new pyridines libraries.

1. Introduction

Aiming at studying mild and flexible strategies to design new pyridines 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. We recently published the synthesis and the isolation of novel 6-halopyridin-3-yl-boronic acids and esters **I**[1] and demonstrated that these compounds were stable, easy to purify and to handle. In the second part of this work, we now report the synthesis, the isolation and the reactivity of new 2,4, or 5-halopyridin-3-yl-boronic acids and esters **II**, **III** and **IV**.



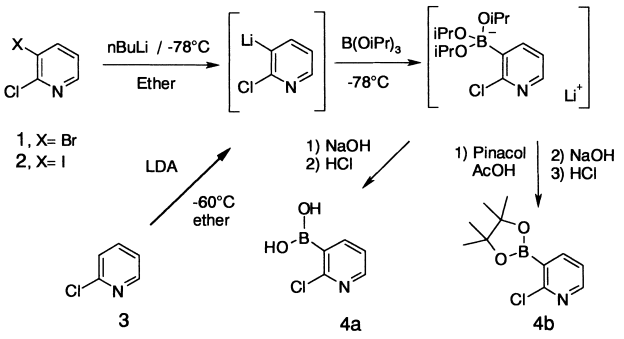
2. Results and discussion

The successful methods of preparation of 6-halopyridin-3-yl-boronic acids and esters **I** prompted us to apply them to the synthesis of various different isomers **II**, **III** and **IV** bearing an halogen atom in 2, 4 or 5 position.

2.1. 2-Halopyridin-3-yl-boronic acids and esters

On these bases our first attempts were carried out starting from 2-chloro-3-bromopyridine **1** and 2-chloro-3-iodopyridine **2** prepared according to reported procedures[2,3] from 3-amino-2-chloropyridine.

Thus, bromine–lithium exchange and iodine–lithium exchange[4,5] were carried out in ether at −78°C with



Scheme 1. Obtention of boronic acid **4a** and ester **4b** via HMe or via DoM.

☆ For Part 1, see Ref. 1.

Keywords: halopyridinylboronic acids; halogen–metal exchange; directed *ortho*-metalation.

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Table 1. Yields of halopyridinylboronic acids and esters, 4, 7 and 10

Compounds	2-X	3-X	Boronic acid	Yield (%)	Boronic ester	Yield (%)
1	Cl	Br	**4a**	66	**4b**	70
2	Cl	I	**4a**	62	**4b**	68
3	Cl	H	**4a**	63	**4b**	65
5	Br	Br	**7a**	60	**7b**	56
6	Br	H	**7a**	45	**7b**	53
9	F	H	**10a**	63	**10b**	58

*n*BuLi followed by the reaction with triisopropylborate, known to give better results than other borates[6] (Scheme 1).

In order to obtain either the boronic acid or the corresponding pinacol ester we used the same method as for 6-halopyridin-3-yl-boronic acids and esters.[1] At the end of the reaction from **1** or **2**, the boronic acid **4a** was obtained with 62–66% yield after a work-up avoiding the formation of pyridinium salts. Namely, the mixture was quenched by slow addition of 5% aqueous NaOH solution and the resulting aqueous layer neutralized by careful addition of aqueous HCl to prevent protodeboronation.[7] The boronic acid **4a** is stable, easy to purify and to handle as a white solid.

On the other hand, considering the amphoteric character of this acid which could be problematic for further use, we studied the direct formation of its pinacol ester, using Coudret's procedure.[8] These conditions applied to **1** and **2** yielded 70 and 68%, respectively, of the corresponding pinacol ester **4b** (Scheme 1, Table 1).

Using the fact that the expected boronic moiety was in *ortho*-position from the halogen atom, we also tried a more direct method taking into account the fact that *ortho*-lithiation of π-deficient heterocycles is now fully described.[9,10] 2-Chloropyridine **3** was easily and regioselectively deprotonated by lithium diisopropylamide (LDA) at −70°C for 3 h in THF to give corresponding 2,3-disubstituted pyridines.[11]

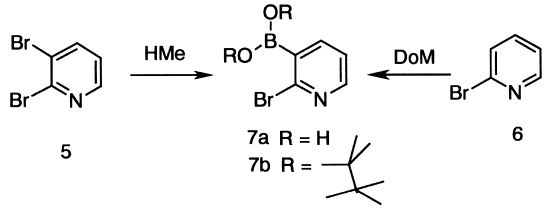
A first attempt of pyridylboronic acid synthesis was already described by Achab et al.[12] starting from 2,6-dichloropyridine deprotonated by LDA in THF at −78°C and quenched by trimethylborate. In our case, commercially available 2-chloropyridine **3** was directly metalated in ether (to make the lithiopyridine precipitate to improve the conversion and make easier further treatment) at −60°C by one equivalent of LDA prepared in situ by the action of *n*BuLi on diisopropylamine (Scheme 1). Lithiation took place regioselectively at position 3 to afford the 2-chloro-3-lithiopyridine. Quenching this anion at low temperature with triisopropylborate $B(OiPr)_3$ gave the expected boronic acid **4a** carrying out the work-up avoiding the formation of pyridinium salts. Performing the in situ transesterification with pinacol gave the corresponding ester **4b** in 65% yield (Table 1).

The same reactions were performed via halogen–metal exchange (HME) with 2,3-dibromopyridine **5**, prepared according to Scheme 2 with 30% overall yield, or from commercial 2-bromopyridine **6** via directed *ortho*-metalation (DoM) (Scheme 3).

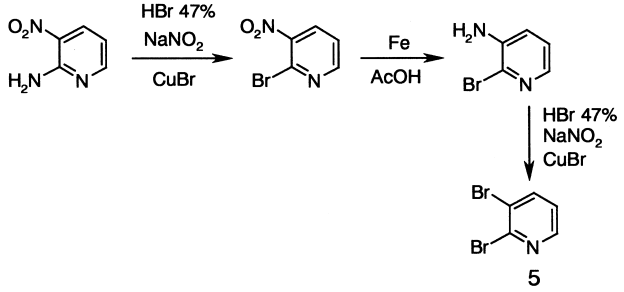
In the case of 2,3-dibromopyridine **5**, conditions of the reaction that are low temperature and slight excess of *n*BuLi had to be strictly monitored in order not to induce halogen dance.[13] With these precautions, we were able to isolate in moderate yields boronic acid **7a** and, after transesterification the corresponding ester **7b** (Scheme 3 and Table 1).

The directed deprotonation of 2-bromopyridine **6** followed by transmetalation has been described by Karig et al. for aryl zinc preparation.[14] The same conditions and further quenching with $B(OiPr)_3$ gave **7a** in 45% yield and **7b** in 53% yield.

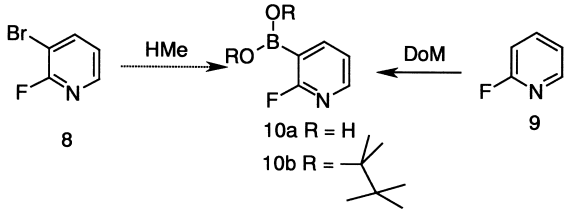
As for fluoro isomers, the most reliable reported procedure[15] for the preparation of 3-bromo-2-fluoropyridine **8** uses directed metalation of 2-fluoropyridine followed by action of bromine. Even if HMe has already been described on 3-bromo-2-fluoropyridine **8** with good yields,[16] we did not



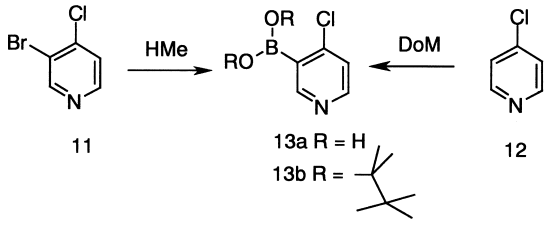
Scheme 3. Obtention of **7a** and **7b** via HMe or DoM.



Scheme 2. Preparation of 2,3-dibromopyridine **5**.



Scheme 4. Obtention of **10a** and **10b** via DoM.



Scheme 5. Obtention of **13a** and **13b**.

The versatility of this functionalization is enhanced by the 4-halogen reactivity toward various nucleophiles.

2.3. 5-Halopyridin-3-yl-boronic acids and esters

As far as 3,5-dihalogenopyridines are concerned, we performed the HMe onto commercial 3,5-dibromopyridine **14** as already described.[24,25] The now usual method gave successfully the boronic acid **15a** and the ester **15b** without changing the conditions for HMe (*n*BuLi, ether, −78°C) (Scheme 6).

Table 2. Yields of halopyridinylboronic acids and esters 13

Compounds	3-X	4-X	Boronic acid	Yield (%)	Boronic ester	Yield (%)
11	Br	Cl	**13a**	25	**13b**	20
12	H	Cl	**13a**	43	**13b**	41

want to multiply reaction steps, so we decided to prepare pyridylboronic acid **10a** and corresponding ester **10b** by action of LDA in ether at −60°C onto commercially available 2-fluoropyridine **9** (Scheme 4).

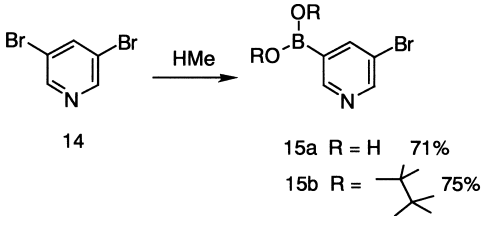
Directed *ortho*-lithiation of 2-fluoropyridine has been described with good yield[17] using LDA. In our case the yields given in Table 1 confirmed that it was not necessary to prepare **8** in order to have better yields. We thus obtained already described[18] **10a** in similar yields, although all the other compounds are, to our knowledge, new ones.

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

Another field of interest concerns the potential effect of halogens on the basic character of pyridine nitrogen. So, we purposed two types of experiment to verify the stability of these new types of pyridyl-boron derivatives. In fact, does the inductive effect of an halogen atom change the p*K*a of the pyridine nitrogen to avoid problems of stability due to interactions between boron and amines?[19]

Thus, experiments were performed with 3-bromo-4-chloropyridine **11** prepared according to reported procedure[20] from 3-bromopyridine.

The boronic acid **13a** and the corresponding ester **13b** were prepared by HMe with limited yields (Scheme 5, Table 2). So, we really preferred to perform a DoM on 4-chloropyridine **12**. Indeed, this has been studied extensively[21–23] and proceed with very great regioselectivity. Carrying out the metalation by LDA in ether at −60°C gave medium yields of stable compounds, proving that the effect of the halogen does not play the role of base moderator.



Scheme 6. Obtention of **15** via HMe.

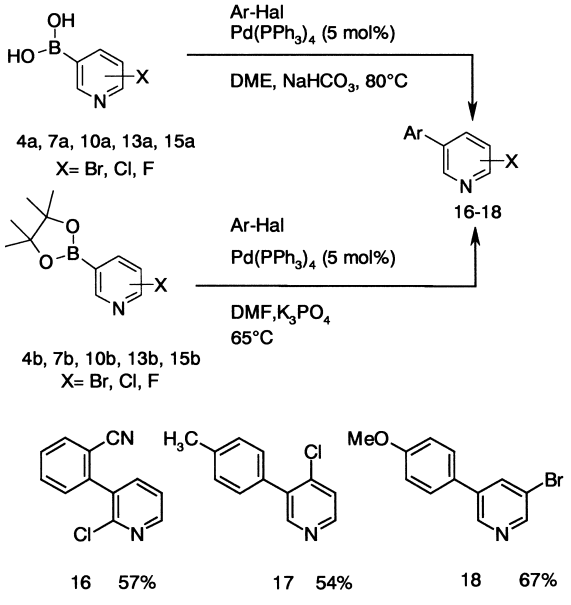
The yields were good as illustrated in Scheme 6, and no disubstituted product was observed even with increased proportions of *n*BuLi (2 equiv.) or longer reaction time for HMe (2 h).

This tends to prove that boronic acid and ester are fully compatible with pyridine without the uncertainty caused by the use of corresponding salts.[26]

2.4. Suzuki couplings

As illustrated in Scheme 7, 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,[27,28] furnishing a range of unknown biaryls not easily accessible, as for example **16–18**.

The yields for cross-coupling were generally good, and the resulting arylpyridines **16–18** were isolated following column chromatography. Interestingly, no 'homocoupled' products with halopyridin-3-yl-boronic acid or esters acting as both the aryl boronic and aryl bromide fragments were



Scheme 7. Suzuki cross-couplings of pyridylboronic acids **a** or esters **b**.

observed. A detailed study of these Suzuki cross-coupling reactions will be published elsewhere.

A discussion concerning the choice between the two different approaches either HMe or DoM starting from mono or polyhalogenated pyridines will be discussed at the end of this general study.

It will be very important to recognize the dual role of such compounds. 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. ^{1}H 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-Bromo-2-chloropyridine, 2-chloro-5-iodopyridine and 3-bromo-4-chloropyridine were prepared according to reported procedures.[2,3,20] 2-Fluoropyridine and 2-chloropyridine were purchased from Acros Organics and were used without further purification. 4-Chloropyridine hydrochloride was purchased from Acros Organics, dissolved in sodium hydroxide and extracted with CH_2Cl_2. Drying the organic phase with $MgSO_4$, filtering and concentrating under reduced pressure gave pure 4-chloropyridine which was used immediately.

3.2. General procedure for the synthesis of pyridylboronic acids via a HMe

To a slurry of 2.5 M solution of *n*BuLi (1.2 equiv.) in anhydrous ether (150 mL), cooled to −78°C, was added to a solution of dihalopyridine (1 equiv.) in anhydrous ether (100 mL). The resulting dark colored mixture was allowed to react at this temperature over 1 h. A solution of triisopropylborate (1.2 equiv.) in anhydrous ether was then added in 10 min 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 (150 mL). The resulting aqueous layer was collected and acidified to pH 6–7 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 recrystallization from Et_2O gave pure **4a**, **7a**, **15a**.

3.2.1. 2-Chloro-3-pyridylboronic acid (4a). White solid; mp 160°C. IR(KBr): 2979, 2930, 1582, 1562, 1451, 1387, 1255, 1101, 1041, 839, 799, 749, 659 cm^{-1}. ^{1}H NMR (d6-DMSO) δ 8.53 (s, 2H), 8.33 (dd, J=2.1, 4.8 Hz, 1H), 7.81 (dd, J=2.1, 7.3 Hz, 1H), 7.33 (dd, J=4.8, 7.3 Hz, 1H). ^{13}C NMR (d6-DMSO) δ 152.4, 149.7, 143.1, 122.3. Anal. calcd for $C_5H_5BClNO_2$: C, 38.16; H, 3.20; N, 8.90. Found: C, 38.25; H, 3.12; N, 8.80.

3.2.2. 2-Bromo-3-pyridylboronic acid (7a). White solid; dec 210°C. IR(KBr): 3096, 1585, 1552, 1415, 1380, 1340, 1130, 1083, 1024, 802, 738, 642 cm^{-1}. ^{1}H NMR (d6-DMSO) δ 8.63 (d, J=2.0 Hz, 1H), 8.47 (s, 2H), 7.98 (dd, J=8.0, 2.0 Hz, 1H), 7.62 (d, J=8 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.

3.2.3. 5-Bromo-3-pyridylboronic acid (15a). White solid; dec 210°C. IR(KBr): 3083, 2958, 1578, 1545, 1433, 1410, 1355, 1318, 1286, 1185, 1096, 1037, 1011, 859, 758, 714 cm^{-1}. ^{1}H NMR (d6-DMSO) δ 8.81 (s, 1H), 8.70 (s, 1H), 8.56 (s, 2H), 8.26 (s, 1H). Anal. calcd for $C_5H_5BBrNO_2$: C, 29.76; H, 2.50; N, 6.94. Found: C, 29.92; H, 2.22; N, 7.11.

3.3. General procedure for the synthesis of pyridylboronic acids via a DoM

To a slurry of freshly distilled diisopropylamine (1.2 equiv.) in 150 mL of anhydrous ether cooled to 0°C was added dropwise to a 2.5 M solution of *n*BuLi (1.25 equiv.). The mixture was allowed to react at 0°C during 30 min, and then cooled to −60°C. A solution of halopyridine (1 equiv.) in 50 mL of anhydrous ether was then added dropwise in order to keep the internal temperature at −60°C. The resulting colored 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 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 (150 mL). The resulting aqueous layer was collected and acidified to pH 6–7 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 recrystallization from Et_2O gave pure **4a**, **7a**, **10a** and **13a**.

3.3.1. 2-Fluoro-3-pyridylboronic acid (10a). White solid; mp 172°C. IR(KBr): 3390, 3100, 1602, 1570, 1405, 1309, 1163, 1066, 829, 755 cm^{-1}. ^{1}H NMR (d6-DMSO) δ 8.44 (s, 2H), 8.22 (dd, J=4.4, 2.1 Hz, 1H), 8.06 (dq, J=9.2, 7.2, 2.1 Hz, 1H), 7.29 (dq, J=7.2, 4.4, 2.9 Hz, 1H). ^{13}C NMR (d6-DMSO) δ 165.5 (d, J=229.6 Hz), 148.8 (d, J=14.8 Hz), 147.0 (d, J=9.0 Hz), 121.4 (d, J=4.1 Hz). 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. 4-Chloro-3-pyridylboronic acid (13a). White solid; mp 160°C. IR(KBr): 3390, 3100, 1602, 1570, 1405, 1309,

1163, 1066, 829, 755 cm^{-1}. ^1H NMR (d6-DMSO) δ 8.59 (s, 2H), 8.52 (s, 1H), 8.46 (d, J=5.4 Hz, 1H), 7.44 (d, J=5.4 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.

3.4. General procedure for the synthesis of pyridylboronic esters via a HMe

To a slurry of 2.5 M solution of *n*BuLi (1.2 equiv.) in 150 mL of anhydrous ether, cooled to −78°C, was added a solution of dihalopyridine (1 equiv.) in anhydrous ether (100 mL). The resulting dark colored mixture was allowed to react at this temperature over 1 h. A solution of triisopropylborate (1.2 equiv.) in 50 mL of anhydrous ether was then added dropwise and the mixture was allowed to warm to room temperature and left to react for an additional hour. A solution of anhydrous pinacol (1.35 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 2 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 Et_2O, evaporation of the ethereal layer and purification by column chromatography on silica gel for oils or recrystallization for solids gave **4b**, **7b** and **15b**.

3.4.1. 2-[3-(2-Chloro)pyridine]-4,4′,5,5′-tetramethyl-1,3-dioxaborolane (4b). Amber solid; mp <50°C. IR(KBr): 2979, 2933, 1578, 1553, 1455, 1393, 1358, 1317, 1131, 1061, 1042, 857, 827, 755, 731, 668 cm^{-1}. ^1H NMR (d6-DMSO) δ 8.46 (dd, J=2.1, 4.8 Hz, 1H), 8.01 (dd, J=2.1, 7.4 Hz, 1H), 7.41 (dd, J=4.8, 7.4 Hz, 1H), 1.30 (s, 12H). ^{13}C NMR (d6-DMSO) δ 154.3, 151.8, 145.8, 122.5, 84.4, 24.5. Anal. calcd for $C_{11}H_{15}BClNO_2$: C, 55.16; H, 6.31; N, 5.85. Found: C, 55.32; H, 6.41; N, 6.03.

3.4.2. 2-[3-(2-Bromo)pyridine]-4,4′,5,5′-tetramethyl-1,3-dioxaborolane (7b). Yellow oil; IR(KBr): 2979, 2932, 1578, 1550, 1450, 1384, 1354, 1125, 1037, 962, 855, 824, 802, 747, 714, 667 cm^{-1}. ^1H NMR (d6-DMSO) δ 8.40 (dd, J=2.1, 4.8 Hz, 1H), 7.89 (dd, J=2.1, 7.4 Hz, 1H), 7.42 (dd, J=4.8, 7.4 Hz, 1H), 1.29 (s, 12H). ^{13}C NMR (d6-DMSO) δ 152.2, 146.2, 145.3, 123.0, 84.8, 24.7. 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.

3.4.3. 2-[3-(5-Bromo)pyridine]-4,4′,5,5′-tetramethyl-1,3-dioxaborolane (15b). White solid; mp 60°C; IR(KBr): 3084, 3038, 2975, 2927, 1578, 1435, 1409, 1354, 1318, 1286, 1184, 1106, 1037, 860, 735, 714 cm^{-1}. ^1H NMR (d6-DMSO) δ 8.79 (s, 1H), 8.70 (s, 1H), 8.09 (s, 1H), 1.30 (s, 12H). ^{13}C NMR (d6-DMSO) δ 152.6, 152.5, 143.6, 120.4, 84.4, 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.

3.5. General procedure for the synthesis of pyridylboronic esters via a DoM

To a slurry of freshly distilled diisopropylamine (1.2 equiv.) in 150 mL of anhydrous ether cooled to 0°C was added dropwise to a 2.5 M solution of *n*BuLi (1.25 equiv.). The mixture was allowed to react at 0°C during 30 min, and then cooled to −60°C. At this time, a solution of halopyridine (1 equiv.) in 50 mL of anhydrous ether was added dropwise in order to keep the internal temperature at −60°C. The resulting colored 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 then added and the mixture was allowed to warm to room temperature and left to react for an additional hour. A solution of anhydrous pinacol (1.35 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 2 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 purification by column chromatography on silica gel for oils or recrystallization for solids gave **4b**, **7b**, **15b**, **10b** and **13b**.

3.5.1. 2-[3-(2-Fluoro)pyridine]-4,4′,5,5′-tetramethyl-1,3-dioxaborolane (10b). Amber solid; mp <50°C. IR(KBr): 2981, 2935, 1602, 1565, 1423, 1361, 1323, 1212, 1146, 1128, 1046, 850, 817, 774, 665 cm^{-1}. ^1H NMR (d6-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 (d6-DMSO) δ 166.1 (d, J=240.2 Hz), 151.0 (d, J=14.8 Hz), 148.5 (d, J=6.6 Hz), 121.8 (d, J=4.1 Hz), 84.2, 24.6. 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-[3-(4-Chloro)pyridine]-4,4′,5,5′-tetramethyl-1,3-dioxaborolane (13b). White solid; mp 120°C. IR(KBr): 2969, 2925, 1597, 1553, 1450, 1397, 1156, 1034, 876, 826, 764, 660 cm^{-1}. ^1H NMR (d6-DMSO) δ 8.69 (s, 1H), 8.57 (d, J=5.4 Hz, 1H), 7.51 (d, J=5.4 Hz, 1H), 1.30 (s, 12H). ^{13}C NMR (d6-DMSO) δ 156.1, 152.9, 148.4, 124.8, 84.4, 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.

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References

1. Bouillon, A.; Lancelot, J. C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 2885–2890.
2. Boucher, E.; Simard, M.; Wuest, J. D. *J. Org. Chem.* **1995**, *60*, 1408–1412.
3. Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1985**, *33*, 4764–4768.
4. Mallet, M.; Quéguiner, G. *Tetrahedron* **1979**, *35*, 1625–1631.
5. Mallet, M.; Quéguiner, G. *Tetrahedron* **1985**, *41*, 3433–3440 and references cited therein.
6. Matteson, D. S. *Tetrahedron* **1989**, *45*, 1859–1885.

7. Matteson, D. S. *J. Organomet. Chem.* **1999**, *581*, 51–65.
8. Coudret, C. *Synth. Commun.* **1996**, *26*, 3543–3547.
9. For a review on Directed Metalation, see: Marsais, F.; Quéguiner, G.; Snieckus, V.; Epsztajn, J. *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic: New York, 1991; Vol. 52, pp. 187–304.
10. Quéguiner, G. *J. Heterocycl. Chem.* **2000**, *37*, 615–621.
11. Trécourt, F.; Marsais, F.; Güngör, T.; Quéguiner, G. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2409–2415.
12. Achab, S.; Guyot, M.; Potier, P. *Tetrahedron Lett.* **1993**, *34*, 2127–2130.
13. Mallet, M.; Quéguiner, G. *Tetrahedron* **1986**, *42*, 2253–2262.
14. Karig, G.; Spencer, J. A.; Gallagher, T. *Org. Lett.* **2001**, *3*, 835–838.
15. Marsais, F.; Pineau, P.; Nivolliers, F.; Turck, A.; Godard, A.; Quéguiner, G. *J. Org. Chem.* **1992**, *52*, 565–573.
16. Marsais, F.; Granger, P.; Quéguiner, G. *J. Org. Chem.* **1981**, *46*, 4494–4497.
17. Güngör, T.; Marsais, F.; Quéguiner, G. *J. Organomet. Chem.* **1981**, *215*, 139.
18. Maetzke, T. European Patent 0 690 061 A1, 1996.
19. Wiskur, S. L.; Lavigne, J. J.; Ait-Haddou, H.; Lynch, V.; Chiu, Y. H.; Canary, J. W.; Anslyn, E. V. *Org. Lett.* **2001**, *3*, 1311–1314.
20. Trécourt, F.; Quéguiner, G. *J. Chem. Res. (M)* **1982**, *3*, 912–942.
21. Gribble, G. W.; Saulnier, M. G. *Heterocycles* **1993**, *35*, 151–169.
22. Gribble, G. W.; Saulnier, M. G. *Tetrahedron Lett.* **1980**, *21*, 4137–4140.
23. Radinov, R.; Haimova, M.; Simova, E. *Synthesis* **1986**, 886–891.
24. Boswell, G.; McNutt, R. W.; Bubacz, D. G.; Davis, A. O.; Chang, K. J. *J. Heterocycl. Chem.* **1995**, *32*, 1801–1818.
25. Verberckmoes, F.; Esmans, E. L.; Balzarini, J.; De Clercq, E. *Nucleosides Nucleotides* **1994**, *13*, 511–526.
26. Black, C.; Hughes, G.; Wang, Z. WO 97/40012, 1997.
27. Collot, V.; Dallemagne, P.; Bovy, P. R.; Rault, S. *Tetrahedron* **1999**, *55*, 6917–6922.
28. Ruhland, B.; Bombrun, A.; Gallop, M. A. *J. Org. Chem.* **1997**, *62*, 7820–7826.