

(Dimethoxy- and Dihalopyridyl)boronic Acids and Highly Functionalized Heteroarylpyridines by Suzuki Cross-Coupling Reactions

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We report the synthesis of (2,6-dimethoxy-3-pyridyl)boronic acid (**2**), (2,3-dimethoxy-4-pyridyl)boronic acid (**4**), (2,6-difluoro-3-pyridyl)boronic acid (**6**), (2,6-dichloro-3-pyridyl)boronic acid (**8**) and (2,3-dichloro-4-pyridyl)boronic acid (**10**) by directed *ortho*-metalation reactions on the corresponding disubstituted pyridine precursor, followed by the reaction with triisopropyl borate (TPB) or trimethyl borate. The reactivity of the pyridylboronic acids with heteroaryl halides in Suzuki–Miyaura cross-coupling reactions has been evalu-

ated. New highly functionalized heteroarylpyridine derivatives have thereby been obtained in moderate to high yields. The reaction of **8** and 3-amino-2-chloropyridine yielded the rare 5*H*-pyrrolo[2,3-*b*:4,5-*b'*]dipyridine (i.e. 1,5-diazacarbazole) ring system by sequential cross-coupling and intramolecular cyclisation reactions. The X-ray crystal structures are reported for the pyridylboronic acids **2**, **4**, **8** and **10**.

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Introduction

Transition-metal-catalyzed cross-coupling reactions have had a major impact on the construction of C–C bonds in functionalized biaryl and heterobiaryl systems^[1] although this methodology is generally less well developed, and reactions can be less efficient when both partners are heteroaromatic.^[2] In such diverse fields as drug discovery^[3] and fluorophores for materials chemistry applications^[4] the Kumada–Corriu, Negishi, Suzuki–Miyaura and Stille cross-coupling protocols have been widely exploited to link aryl/heteroaryl units in synthetic strategies.

Arylboronic acids and their ester derivatives generally have the benefit of increased air stability compared to analogous zinc, magnesium, copper and tin species. However, for heteroarylboronic acids with a basic nitrogen atom (pyridyl, pyrimidyl, etc.) the usual acidic workup conditions can result in unwanted protonation of the heterocycle leading to difficulties in isolation and purification.^[5] Also protodeboronation is sometimes encountered with more electron-deficient derivatives,^[6] especially when the boronic acid group is adjacent to a nitrogen atom, e.g. 2-pyridylboronic acid is notoriously unstable,^[7] although certain ester derivatives are isolable and can be used effectively in cross-coupling reactions.^[8] An appeal of boronic acid/ester derivatives

is their good functional-group compatibility and their low toxicity.^[9] They are usually synthesized by lithium/halogen exchange^[10] or directed *ortho*-metalation (DoM)^[11] followed by borylation with trimethyl or triisopropyl borate. These protocols have afforded a growing range of air-stable functionalized pyridylboronic and pyrimidylboronic acids in recent years,^[12] although it is recognized that pyridylboronic acids^[2,12a] and pyrimidylboronic acids^[12p] can require very specific conditions for their syntheses and cross-coupling reactions. Iridium-catalysed C–H coupling between bis(pinacolato)diboron and pyridine derivatives is an alternative route to pyridylboronic esters.^[13]

Our motivation for the present work is the continuing widespread interest in specifically functionalized pyridine derivatives^[14] and azabiaryls in general,^[15] which require dependable routes to new pyridyl synthons. It is clearly of value, therefore, to describe their syntheses in the open literature and to broaden the range of cross-coupling reactions involving pyridylboronic acids. Herein, we describe the synthesis of (dimethoxy- and dihalopyridyl)boronic acid derivatives **2**, **4**, **6**, **8** and **10** using DoM methodology in each case,^[16] and explore their cross-coupling reactions with a range of heteroaryl halides to provide expedient routes to heteroarylpyridine derivatives.

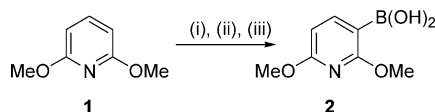
Results and Discussion

A DoM reaction of 2,6-dimethoxypyridine (**1**) using *n*BuLi and the efficient trapping of the 3-lithio intermediate with an electrophile (ClCH₂–OMe) have been reported previously.^[17] Accordingly, **2**^[18] was readily obtained in an op-

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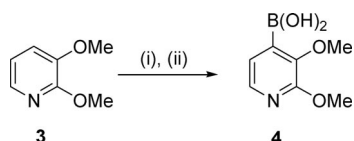
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timised 82% yield by the DoM reaction of **1** (LDA in THF), followed by the addition of triisopropyl borate (TPB) at -78°C and an acidic workup (Scheme 1). Scaled-up reactions gave **2** (>25 g batches) in 70% yield.



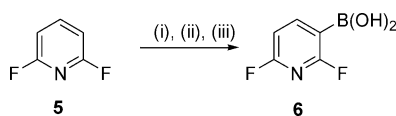
Scheme 1. Reagents and conditions: (i) diisopropylamine (DPA), *n*BuLi, THF, -10°C , 30 min; (ii) **1**, -78°C , 3 h; (iii) TPB, -78°C , 3 h, then 48% aq. HBr.

(2,3-Dimethoxy-3-pyridyl)boronic acid (**4**) was similarly obtained in only 12% yield by a DoM reaction on 2,3-dimethoxypyridine (**3**) [LDA (1 equiv.) in THF]. However, according to literature conditions for the lithiation [*n*BuLi (2.2 equiv.) in THF],^[19] the yield of **4** was improved to 60% (Scheme 2).



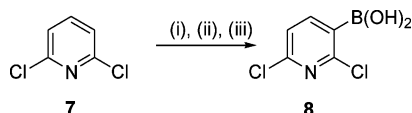
Scheme 2. Reagents and conditions: (i) *n*BuLi (2.2 equiv.), THF, $-78 \rightarrow 0^{\circ}\text{C}$, 1 h; (ii) TPB, -78°C , 2 h, then glacial acetic acid.

(2,6-Difluoro-3-pyridyl)boronic acid (**6**) was obtained in 82% yield (ca. 5 g batches of product) by the DoM protocol from 2,6-difluoropyridine (**5**) (Scheme 3).^[20] The reaction was scaled-up to give **6** (ca. 25 g batch) in 70% yield.



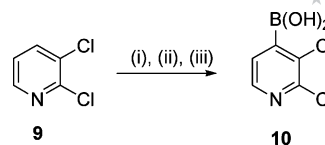
Scheme 3. Reagents and conditions: (i) DPA, *n*BuLi, THF, -10°C , 30 min; (ii) **5**, -78°C , 3 h; (iii) TPB, -78°C , 0.5 h, then 48% aq. HBr.

2,6-Dichloropyridine (**7**) and 2,3-dichloropyridine (**9**) were similarly converted into their boronic acid derivatives **8**^[21] and **10**, in 73% and 56% optimised yields, respectively (Schemes 4 and 5). The syntheses of both **8** and **10** were scaled-up to give ca. 30 g batches of product in similar yields. Scaled-up syntheses of **2**, **6**, **8** and **10** (25–50 g batches) at higher temperatures (e.g. -40 or -20°C) gave significantly lower product yields.



Scheme 4. Reagents and conditions: (i) DPA, *n*BuLi, THF, -10°C , 30 min; (ii) **7**, -78°C , 3 h; (iii) TPB, -78°C , 1 h, then 48% aq. HBr.

Compounds **2**, **4**, **8** and **10** were characterised by single-crystal X-ray diffraction, proving in each case the structure of a free boronic acid, rather than the anhydride (boroxine). Structure **2** contains two independent molecules (Fig-



Scheme 5. Reagents and conditions: (i) DPA (2.0 equiv.), *n*BuLi (2.0 equiv.), THF, -10°C , 30 min; (ii) **9**, -78°C , 3 h; (iii) TPB, -78°C , 1 h, then 48% aq. HBr.

ure 1a); both have practically planar conformations and are related by a pseudo-inversion centre (0.158, 0.615, 0.389). They are bound by a pair of hydrogen bonds into a dimer (again practically planar), which motif is typical for boronic acids and closely related to those of carboxylic acids and amides.^[22] The second OH group of each molecule participates in an intramolecular O–H...O bond, while the nitrogen atom, masked by two *cisoid* methyl groups, is excluded from hydrogen bonding. Thus, the dimers are not hydrogen-bonded into any extended pattern. Molecule **4** has a similar intramolecular O–H...O bond (Figure 1b); the B(OH)₂ and 2-methoxy groups are practically coplanar with the pyridine ring, while the torsion angle C(4)–C(3)–O(3)–C(8) is $115.3(1)^{\circ}$. The other OH group forms intermolecular O–H...N bonds, linking into an infinite chain the molecules related by the *n* glide plane.

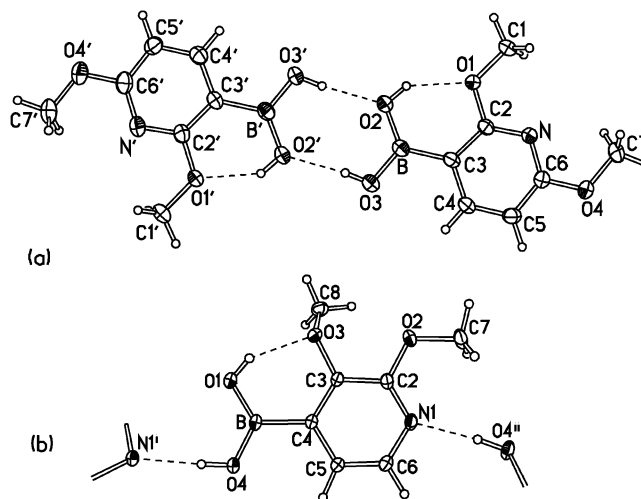


Figure 1. Two independent molecules of **2** (a) and molecule **4** (b) in crystals, showing hydrogen bonds (dashed lines). Thermal ellipsoids are drawn at the 50% probability level.

The asymmetric unit of **8** (Figure 2a) also comprises two molecules (*A* and *B*), together with one water molecule of crystallisation, hydrogen-bonded into a 3-dimensional network (see Supporting Information). Due to steric repulsion from the adjacent chlorine substituent, the boronic acid group is not coplanar with the pyridine ring. In molecule *A* they form a dihedral angle of 38° ; in molecule *B* the boronic group is disordered in a 3:1 ratio between two orientations, for which the corresponding angles are 69° and 89° , respectively. The nitrogen atoms accept hydrogen bonds: that of molecule *A* with the boronic group, in molecule *B* from the water molecule. Structure **10** contains only one independent

molecule (Figure 2b), with the boronic acid group almost normal to the ring plane (dihedral angle 76°). This structure contains no dimeric units but a continuous network of hydrogen bonds (see Supporting Information), involving the

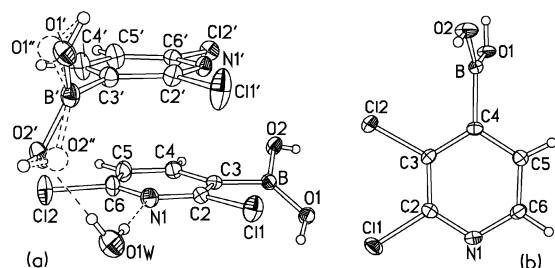
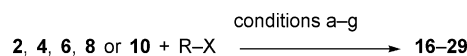


Figure 2. (a) Asymmetric unit of **8**·0.5H₂O (showing the disorder); (b) molecular structure of **10**. Thermal ellipsoids are drawn at the 50% probability level.

nitrogen atom as an acceptor. In both **8** and **10** the chlorine atoms play no part in hydrogen bonding.

As stated recently,^[2] a primary problem associated with Suzuki–Miyaura reactions of pyridylboronic acids is their slow rate of transmetalation which is attributed to the electron deficiency of the heteroaromatic ring. Suzuki–Miyaura reactions of **2**, **4**, **6**, **8** and **10** with the heteroaryl halides **11**–**15** were carried out under a variety of standard conditions (Scheme 6). The halogenated substrates were chosen to demonstrate the versatility of the boronic acid reagents to provide new highly functionalized heteroarylpuridine derivatives. A selection of heterocycles (quinoline, pyridine, pyr-

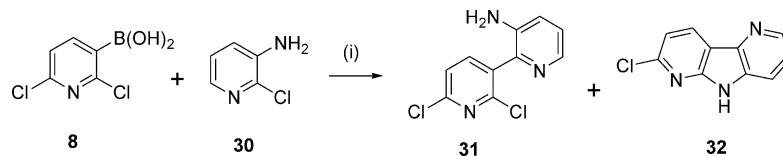


Scheme 6. For conditions a–g, see Table 1.

Table 1. Suzuki–Miyaura cross-couplings of **2**, **4**, **6**, **8** and **10**.

Entry	Boronic acid	R-X	Product	Isolated yield (%)	Entry	Boronic acid	R-X	Product	Isolated yield (%)
1	2			83 ^[a]	8	6			82 ^[a]
2	2			74 ^[a]	9	6			69 ^[a]
3	2			75 ^[a]	10	8			38 ^[a] 54 ^[b] 56 ^[c] 57 ^[d] 55 ^[e] 24 ^[f] 30 ^[g]
4	4			96 ^[a]	11	8			46 ^[b]
5	4			86 ^[a]	12	10			57 ^[a] 48 ^[b] 54 ^[c] 54 ^[d] 56 ^[e]
6	4			80 ^[a]	13	10			42 ^[b]
7	6			81 ^[a] 84 ^[b]	14	10			41 ^[b] (from 14) 50 ^[b] (from 15)

[a] Reagents and conditions: Pd(PPh₃)₂Cl₂, 1,4-dioxane, Na₂CO₃ (1 M), reflux, 1–24 h (for reactions of **12**, 15 min). [b] Pd(PPh₃)₂Cl₂, *t*Bu₃P, 1,4-dioxane, Na₂CO₃ (1 M), reflux, 24 h. [c] Pd(PPh₃)₂Cl₂, *t*Bu₃P, 1,4-dioxane, Cs₂CO₃ (1 M), reflux, 24 h. [d] Pd(OAc)₂, *t*Bu₃P, 1,4-dioxane, Na₂CO₃ (1 M), reflux, 24 h. [e] Pd(OAc)₂, *t*Bu₃P, 1,4-dioxane, Cs₂CO₃ (1 M), reflux, 24 h. [f] Pd(PPh₃)₂Cl₂, 1,4-dioxane, Na₂CO₃ (1 M), 150 °C, 5 min at 150 W. [g] Pd(PPh₃)₂Cl₂, 1,4-dioxane, Na₂CO₃ (1 M), 150 °C, 20 min at 150 W.



Scheme 7. Reagents and conditions: (i) $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, $t\text{Bu}_3\text{P}$, 1,4-dioxane, Na_2CO_3 (1 M), reflux, 24 h.

imidine, pyrazine) were shown to be applicable. The data are given in Table 1; in all cases the yields quoted are for isolated and purified products.

Reagents **2**,^[23] **4** and **6** gave cross-coupled products with bromo partners in consistently high yields under standard conditions, [$\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, 1,4-dioxane, Na_2CO_3 at reflux] (Entries 1–7). Predictably, reactions of the (dihalopyridyl)boronic acids **8** and **10** gave lower yields of the desired products. (Halo)pyridylboronic acids (halo = Cl or Br) are prone to self-coupling, competing side-reactions and/or protodeboronation reactions.^[24] Nonetheless, by varying the catalyst and the conditions for reactions of **8** and **10** synthetically viable yields (ca. 40–60%) were obtained for the cross-coupled products (Entries 9–14). In some cases, the addition of tributylphosphane to the standard reaction mixture^[25] increased the product yield for reactions of **8** (Entry 10; cf. conditions a and b) but not for reactions of **10** (Entry 12). The use of a mixture of $\text{Pd}(\text{OAc})_2$ and $t\text{Bu}_3\text{P}$ as the catalyst also consistently gave yields of ca. 55% (Entries 10 and 12; conditions d and e). Changing the base from Na_2CO_3 to Cs_2CO_3 (conditions c and e) had no effect on the yields. The use of microwave heating also did not further improve the product yields (Entry 10; conditions f and g). Entry 14 shows that using 3-iodopyridine increased the yield only slightly compared to the bromo analogue. Entries 3, 5 and 8 show that reagent **12** was unusually reactive as a cross-coupling partner, as noted previously:^[12] these reactions were complete in 15 min. The high level of functionality tolerated in the reactions (methoxy, methoxycarbonyl, primary amine^[26] and halogens) further illustrates their wide applicability. The X-ray crystal structure of compound **19** is described in the Supporting Information.

Two products were isolated from the cross-coupling reaction of (2,6-dichloro-3-pyridyl)boronic acid (**8**) and 3-amino-2-chloropyridine (**30**) (Scheme 7). Alongside the standard cross-coupled product **31** (15% yield) the 5H-pyrrolo[2,3-*b*:4,5-*b'*]dipyridine (i.e. 1,5-diazacarbazole) derivative **32** (32% yield) was obtained, presumably by intramolecular reaction of **31** with the amino group acting as the nucleophile to displace chloride from C(2) of the pyridine ring. The structure of **32** was supported by detailed NMR studies, including gCOSY, ROESY, gHSQC and gHMBC data (see Supporting Information). This two-step tandem route to **32**, which is a very rare ring system,^[27] should be applicable to other polycyclic azaheteroaromatic skeletons.^[28]

Conclusions

We have successfully synthesized the pyridylboronic acid derivatives **2**, **4**, **6**, **8** and **10**. They are stable to storage un-

der ambient conditions, and they should prove to be versatile synthons in pyridine chemistry, for example as scaffolds for use in the high throughput synthesis of libraries of drug-like compounds. For example, arylpyridines are of interest as DNA-targeted cytotoxic agents,^[14f] pyrazinylpyridine derivatives are studied as agents for the reduction of angiogenesis and suppression of tumour growth,^[15c] and azabiaris are being investigated for treatment of Type 2 diabetes.^[15b] The pyridylboronic acids have been shown to undergo Suzuki–Miyaura cross-couplings with a range of heteroaryl bromides to yield new highly-functionalized heteroarylpyridines in good yields (Table 1). These products offer scope for further synthetic transformations. A future development of this work could involve polymer-supported boronic esters.^[29]

Experimental Section

General: Details of equipment and techniques used are the same as those we have reported previously.^[12j] All synthetic reagents were used as supplied. Solvents were dried and distilled using standard procedures.

(2,6-Dimethoxy-3-pyridyl)boronic Acid (2): To a solution of diisopropylamine (6.5 mL, 46.45 mmol) in anhydrous THF (100 mL) at -10°C , $n\text{BuLi}$ (2.5 M in hexane, 20.0 mL, 50 mmol) was added dropwise. The reaction mixture was stirred at 0°C for 0.5 h and was then cooled to -78°C , before 2,6-dimethoxypyridine (**1**) (56 mL, 42 mmol) was added dropwise. The reaction mixture was stirred at -78°C for 3 h, then triisopropyl borate (6.2 mL, 54 mmol) was added slowly. The reaction mixture was stirred at -78°C for another 1 h, then quenched with water (100 mL) and warmed to room temperature with stirring overnight. The organic solvent was evaporated in vacuo and the residue then filtered. The filtrate was washed with diethyl ether (3×50 mL) to remove unreacted starting material. The aqueous layer was then acidified to pH = 6 (with 48% HBr) to precipitate **2** as white solid (6.3 g, 82%); m.p. 108.2 – 109.1°C . ^1H NMR (400 MHz, $[\text{D}_6]\text{DMSO}$): δ = 7.86 (d, 3J = 8.0 Hz, 1 H), 7.53 (s, 2 H), 6.36 (d, 3J = 8.0 Hz, 1 H), 3.89 (s, 3 H), 3.86 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $[\text{D}_6]\text{DMSO}$): δ = 166.9, 164.6, 148.6, 101.6, 53.7, 53.6 ppm. MS (EI): m/z = 183.0 $[\text{M}^+]$. $\text{C}_7\text{H}_{10}\text{BNO}_4$ (183.0) calcd. C 45.95, H 5.51, N 7.66; found C 45.46, H 5.34, N, 7.79.

(2,3-Dimethoxy-4-pyridyl)boronic Acid (4): To a solution of **3** (0.7 mL, 5.2 mmol) in anhydrous THF (50 mL) at -78°C , $n\text{BuLi}$ (2.5 M in hexane, 4.6 mL, 11.5 mmol) was added dropwise. The reaction mixture was warmed to 0°C and stirred for 1 h. The reaction mixture was then cooled to -78°C , before triisopropyl borate (1.8 mL, 7.8 mmol) was added slowly. The reaction mixture was stirred at -78°C for another 2 h, then quenched with water (30 mL) and warmed to room temperature. The organic solvent was evaporated in vacuo. The aqueous phase was washed with diethyl ether (2×50 mL) to remove unreacted starting material. The aqueous layer was then acidified to pH = 4 (with glacial acetic acid) to

precipitate **4** as white solid, and the aqueous phase was extracted with ethyl acetate (2 × 50 mL). The organic extracts were combined, and the solvent was evaporated in vacuo to yield a yellowish solid which was dissolved in the minimal amount of ethyl acetate, and then the boronic acid **4** was precipitated as a white solid on addition of water (0.57 g, 60%); m.p. 125.8–126.5 °C. ¹H NMR (400 MHz, [D₆]DMSO): δ = 7.85 (d, ³J = 8.0 Hz, 1 H), 7.54 (s, 2 H), 6.35 (d, ³J = 8.0 Hz, 1 H), 3.89 (s, 3 H), 3.85 (s, 3 H) ppm. ¹³C NMR (100 MHz, [D₆]DMSO): δ = 166.5, 164.3, 148.2, 101.3, 53.2, 53.1 ppm. C₇H₁₀BN₂O₄ (183.0): calcd. C 45.95, H 5.51, N 7.66; found C 45.91, H 5.27, N 7.40.

(2,6-Difluoro-3-pyridyl)boronic Acid (6): To a solution of diisopropylamine (6.5 mL, 47.7 mmol) in anhydrous diethyl ether (50 mL) at 0 °C, *n*BuLi (2.5 M in hexane, 20 mL, 52.1 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 0.5 h and then cooled to –78 °C, before 2,6-difluoropyridine (**5**, 5.0 g, 43.4 mmol) was added dropwise. The reaction mixture was stirred at –78 °C for 3 h, then triisopropyl borate (15 mL, 65.0 mmol) was added slowly. The reaction mixture was stirred at –78 °C for another 0.5 h, then quenched with water (50 mL) and warmed to room temperature with stirring overnight. The organic solvent was evaporated in vacuo and the residue washed with diethyl ether (3 × 50 mL) to remove unreacted starting material. The aqueous layer was then acidified to pH = 6 (with 48% HBr) and then extracted with ethyl acetate (3 × 50 mL). The organic layer was concentrated in vacuo and the crude product recrystallized from toluene to give **6** as a white solid (5.6 g, 82%); m.p. 136.7–137.2 °C. ¹H NMR (400 MHz, [D₆]DMSO): δ = 8.28 (q, ³J = 8.4 Hz, 1 H), 7.47 (s, 2 H), 7.03 (d, ³J = 8.4 Hz, 1 H) ppm. ¹³C NMR (100 MHz, [D₆]DMSO): δ = 164.6 (dd, ¹J = 178.4, ³J = 13.6 Hz), 162.1 (dd, ¹J = 178.4, ³J = 13.6 Hz), 153.0, 106.6 (dd, ²J = 32.4, ⁴J = 5.4 Hz) ppm. C₅H₄BF₂NO₂ (159.0): calcd. C 37.79, H 2.54, N 8.81; found C 37.92, H 2.34, N 8.67.

(2,3-Dichloro-4-pyridyl)boronic Acid (10): To a solution of diisopropylamine (9.5 mL, 67.6 mmol) in anhydrous THF (50 mL) at 0 °C, *n*BuLi (2.5 M in hexane, 27.0 mL, 67.6 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 0.5 h and then cooled to –78 °C, before 2,3-dichloropyridine (**9**, 5.0 g, 33.8 mmol) in anhydrous THF (25 mL) was added dropwise. The reaction mixture was stirred at –78 °C for 3 h, then triisopropyl borate (9.3 mL, 40.5 mmol) was added slowly. The reaction mixture was stirred at –78 °C for another 1 h, then quenched with water (50 mL) and warmed to room temperature with stirring overnight. The organic solvent was evaporated in vacuo and the residue then filtered. The filtrate was washed with diethyl ether (3 × 25 mL) to remove unreacted starting material. The aqueous layer was then acidified to pH = 6 (with 48% HBr) to precipitate **10** as white solid (3.6 g, 56%); m.p. 140.2–141.0 °C. ¹H NMR (400 MHz, [D₆]DMSO): δ = 8.30 (d, *J* = 4.4 Hz, 1 H), 7.41 (d, *J* = 4.4 Hz, 1 H) ppm. ¹³C NMR (100 MHz, [D₆]DMSO): δ = 147.4, 146.9, 130.9, 126.8 ppm. MS (EI): *m/z* = 190.8 [M⁺]. C₅H₄BCl₂NO₂ (191.8): calcd. C 31.31, H 2.10, N 7.30; found C 30.71, H 1.94, N 6.90.

General Procedures for the Cross-Coupling Reactions. Conditions a: The boronic acid, the aryl halide and Pd(PPh₃)₂Cl₂ (ca. 5 mol-%) were sequentially added to degassed 1,4-dioxane and the mixture stirred at 20 °C for 30 min. Degassed aqueous Na₂CO₃ solution (1 M) was added, and the reaction mixture heated under argon at reflux. The solvent was removed in vacuo, then ethyl acetate was added, and the organic layer was washed with brine, separated, and dried with MgSO₄. The mixture was purified by chromatography on a silica gel column. On some occasions an additional recrystallization was necessary. **Conditions b:** As for conditions a, but with the

addition of *t*Bu₃P (5–10 mol-%) to the initial mixture. **Conditions c:** As for conditions b, but using Cs₂CO₃ instead of Na₂CO₃. **Conditions d:** Pd(OAc)₂, *t*Bu₃P, 1,4-dioxane, Na₂CO₃ (1 M), reflux. **Conditions e:** As for conditions d, but using Cs₂CO₃ instead of Na₂CO₃. **Conditions f:** As for conditions a, but at 150 °C, 5 min in a microwave oven at 150 W. **Conditions g:** As for conditions f, but with heating for 20 min instead of 5 min.

Supporting Information (see footnote on the first page of this article): Detailed procedures and characterization data for compounds **8**, **16–29**, **31** and **32**; X-ray molecular structure of **19**; NMR spectra of compound **32**; X-ray crystallographic data for structures **8**·0.5H₂O and **10**.

Acknowledgments

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