DOI: 10.1002/ejoc.200700654

New Pyrimidylboronic Acids and Functionalized Heteroarylpyrimidines by Suzuki Cross-Coupling Reactions

Kate M. Clapham,[a] Amy E. Smith,[a,b] Andrei S. Batsanov,[a] Laura McIntyre,[a] Adam Pountney,[a] Martin R. Bryce,*[a] and Brian Tarbit[b]

Keywords: Pyrimidine / Lithiation / Boronic acid / Cross-coupling

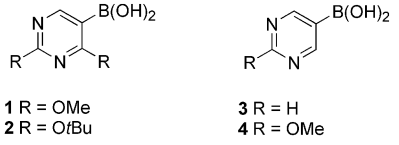
We report the synthesis of 2-chloro-5-pyrimidylboronic acid (**6**) and 2-amino-5-pyrimidylboronic acid (**8**) by lithium–halogen exchange followed by reaction with triisopropylborate. Their reactivity with heteroaryl halides in Suzuki–Miyaura cross-coupling reactions has been evaluated. New highly functionalized 5-heteroarylpyrimidine derivatives **24**–**33** (heteroaryl = quinoline, pyridine, pyrimidine, pyrazine, thiophene, benzothiazole) have been obtained in synthetically useful yields. The X-ray structure of **6** reveals extensive intermolecular O–H···N hydrogen bonding in the crystal.

Introduction

For the contemporary synthesis of functionalized biaryl and heterobiaryl systems, transition-metal-catalyzed reactions have had a major impact.[1] Notably, the Kumada–Corriu, Negishi, Suzuki–Miyaura and Stille cross-coupling protocols have been widely exploited to obtain various targets in such diverse areas as new pharmaceutical products[2] and fluorophores for materials chemistry applications.[3]

This cross-coupling chemistry is considerably more challenging and is less well-developed where both partners are heteroaromatic.[4] Difficulties with preparation and purification have limited the range of borylated heterocycles which are readily available.[5] Arylboronic acids and their ester derivatives generally have the advantage of air-stability (in contrast to zinc, magnesium, copper and tin analogues, etc.), although protodeboronation can impose a significant limitation with more electron-deficient derivatives,[6] especially when the boronic acid/ester group is adjacent to nitrogen, e.g. 2-pyridylboronic acid. The good functional group compatibility and low toxicity of boronic acids/esters, combined with low-cost starting materials, has led to a recent surge of interest in their synthesis and applications.[7] Lithium–halogen exchange[8] or directed *ortho* metalation (D*o*M)[9] followed by borylation are the usual routes to heterocyclic boronic acid/ester derivatives. By using these protocols, functionalized pyridylboronic acids have been intensively studied in recent years.[10] Iridium-catalyzed C–H coupling between bis(pinacolato)diboron and pyridine derivatives provides an alternative access to pyridylboronic esters.[11]

In contrast to the extensive work on pyridyl derivatives,[10,11] pyrimidylboronic acids have been largely neglected, although derivatives **1** and **2** were synthesized in early work.[12] Recently, the parent 5-pyrimidylboronic acid (**3**) and 2-methoxy-5-pyrimidylboronic acid (**4**) were obtained in synthetically useful quantities by lithium–halogen exchange reactions on 5-bromopyrimidine and 2-methoxy-5-bromopyrimidine, respectively, followed by reaction with triisopropylborate (Figure 1).[13]



1 R = OMe
2 R = O*t*Bu

3 R = H
4 R = OMe

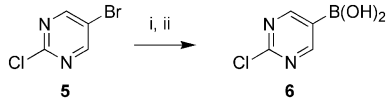
Figure 1. Structures of previous pyrimidylboronic acids.

Given the considerable interest in specifically functionalized pyrimidine derivatives[14] and azabiaryls in general,[15] it is clearly of value to explore new pyrimidylboronic acids. They offer great potential as versatile reagents for high-throughput library synthesis of druglike compounds. For example, pyrimidine scaffolds have been used recently in the synthesis of kinase inhibitors.[16] We now describe the synthesis of 2-chloro-5-pyrimidylboronic acid (**6**) and 2-amino-5-pyrimidylboronic acid (**8**) and demonstrate their cross-coupling reactions with a range of heteroaryl halides to provide expedient routes to heteroarylpyrimidine derivatives.

[a] Department of Chemistry, Durham University,
Durham DH1 3LE, UK
Fax: +44-191-384-4737
E-mail: m.r.bryce@durham.ac.uk
[b] Vertellus Specialties UK Ltd,
Seal Sands Road, Middlesbrough, TS2 1UB, UK
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

Results and Discussion

Lithium–halogen exchange of **5** (*n*BuLi in THF/toluene) in the presence of triisopropylborate (TPB) followed by an aqueous acid workup gave pure **6** in 85% yield. A sequential addition method (adding the TPB after the lithiation) gave **6** in only 15% yield. It is known that the precise reaction conditions and the order of addition of reagents can be crucial for the successful preparation of certain heteroarylboronic acids (Scheme 1).[10d]



Scheme 1. Reagents and conditions: (i) *n*BuLi (1.2 equiv.), triisopropylborate (1.3 equiv.), –78 °C, toluene/THF; (ii) acidification to pH 5 with 48% aq. HBr.

The structure of **6** was confirmed by X-ray crystallographic analysis (Figure 2). Notably, the free boronic acid and not the anhydride (boroxine) structure was observed, with intermolecular O–H···N hydrogen bonding present in the crystal. The pyrimidine ring and the planar $C(5)BO_2$ moiety are coplanar within 2.5°.

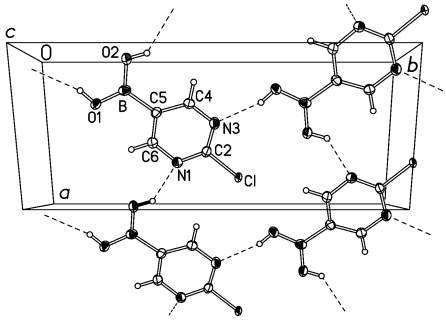
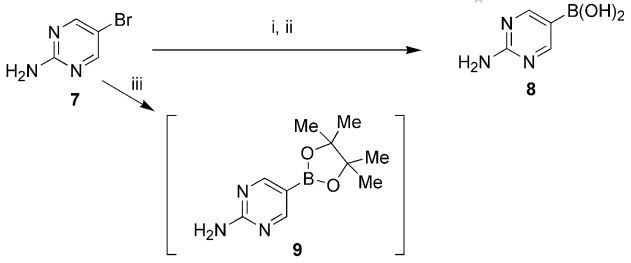


Figure 2. X-ray crystal structure of **6**, showing thermal ellipsoids (50% probability) and hydrogen bonds (dashed lines).

An analogous route to boronic acid **8** from compound **7** by lithium–halogen exchange, notably in the presence of the free 2-amino group,[17] gave 2-amino-5-pyrimidylboronic acid (**8**) in 25–46% yield after purification. Alternatively, boronic ester **9** could be prepared by the palladium-catalyzed reaction of 2-amino-5-bromopyrimidine (**7**) with bis-(pinacolato)diboron and then cross-coupled in situ (Scheme 2).[18] From literature precedents, there is no general rule as to whether the boronic acid or an ester derivative is more suitable for cross-coupling: the systems need to be evaluated on a case-by-case basis.[19]

Suzuki–Miyaura reactions of **6** and **8** with heteroaryl halides were carried out under a variety of standard conditions. Data are given in Table 1; in all cases the yields quoted are for isolated and purified products. For the reactions of boronic acid **6** (entries 1–4), yields were substantially improved by adding tri-*tert*-butylphosphane to the standard reaction mixture {$[Pd(PPh_3)_2Cl_2]$, 1,4-dioxane, reflux} following the protocol of Fu et al.[20]

Yields of the cross-coupled products **24**–**26** were limited to ca. 45% because of the concurrent formation of byproducts (i.e. the bipyrimidine derivative and higher oligomers – TLC and mass spectroscopic evidence; products not purified) derived from competitive self-coupling of **6**, as observed previously for bromopyridylboronic acids.[10e]

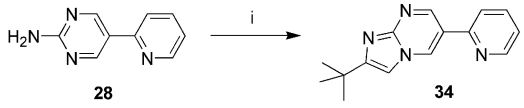


Scheme 2. Reagents and conditions: (i) *n*BuLi (2.5 equiv.), triisopropylborate (1.2 equiv.), –78 °C, THF; (ii) acidification to pH 5 with 48% aq. HBr; (iii) $Pd(OAc)_2$, KOAc, 1,4-dioxane, 80 °C.

For reactions of **8**, iodoheterocycles were generally required to give high yields of products by using conditions (b) {$[Pd(PPh_3)_2Cl_2]$, tBu_3P, 1,4-dioxane, Na_2CO_3, reflux} (entries 8, 11, 14, 18); under these conditions the corresponding bromoheterocycles gave consistently lower yields. However, for the electron-deficient coupling partners using bromo derivatives and different conditions {conditions (e): $[Pd_2(dba)_3]/PCy_3$, 1,4-dioxane, K_3PO_4, reflux}[21] resulted in viable yields of cross-coupling products (43–75%; entries 10, 22 and 24). Chloropyrazine gave **29** in a synthetically useful yield of 61% (entry 13), (cf. 72% yield of **29** from iodopyrazine, entry 12). Protodeboronation of **8** to give 2-aminopyrimidine was a competing side-reaction. The overall yield of cross-coupled product could be further improved by a second addition of **8** (1.1 equiv.) to the reaction mixture after 24 h reflux (entries 9 and 15) to overcome the loss of **8** by protodeboronation and maintain a viable amount of **8** in the reaction mixture. However, for practical purposes the advantage of higher product yield is offset by the use of more of compound **8**.

The halogenated substrates were chosen to demonstrate the versatility of reagents **6** and **8** to provide new 5-heteroarylpyrimidine derivatives (Table 1). A selection of heterocycles (quinoline, pyridine, pyrimidine, pyrazine, thiophene, benzothiazole[22]) were shown to be applicable. One phenyl derivative (entries 23 and 24) was included. Functional groups shown to be compatible with the reaction conditions were: primary amine,[23] ester, bromo and nitro.

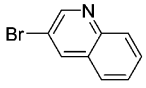
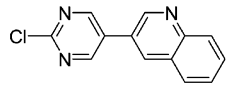
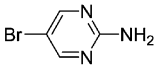
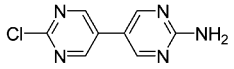
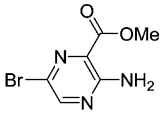
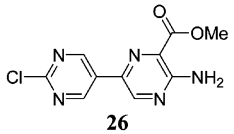
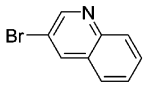
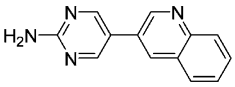
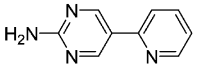
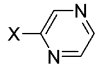
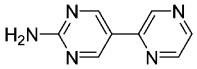
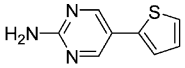
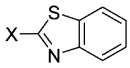
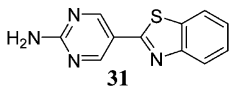
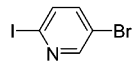
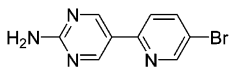
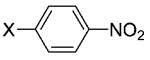
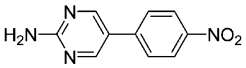
A further transformation of **28** has been achieved by reaction of the aminopyrimidine functionality with 1-bromopinacolone[24] to afford the cyclized derivative **34** in 81% yield (Scheme 3). The structure of **34** was confirmed by 2D NMR techniques (see Supporting Information).



Scheme 3. Reagents and conditions: (i) 1-bromopinacolone (1.5 equiv.), EtOH, reflux, 24 h.

Table 1. Suzuki–Miyaura cross-coupling of **6** and **8**.[a]

6 or **8** + R–X $\xrightarrow{\text{conditions a–e}}$ **24–33**

Entry	Boronic Acid	R–X	Product	Conditions	Isolated Yield (%)
1	**6**	 **10**	 **24**	a	21
2				b	47
3	**6**	 **11**	 **25**	b	45
4	**6**	 **12**	 **26**	b	48
5	**8**	 **10**	 **27**	a	22
6				c	45
7				e	72
8	**8**	 **13** X = I **14** X = Br	 **28**	b (from **13**)	56
9				d (from **13**)	96
10				e (from **14**)	75
11	**8**	 **15** X = I **16** X = Cl	 **29**	b (from **15**)	60
12				e (from **15**)	72
13				e (from **16**)	61
14	**8**	 **17** X = I **18** X = Br	 **30**	b (from **17**)	49
15				d (from **17**)	76
16				e (from **17**)	37
17				e (from **18**)	26
18	**8**	 **19** X = I **20** X = Br	 **31**	b (from **19**)	40
19				e (from **19**)	45
20				e (from **20**)	33
21	**8**	 **21**	 **32**	b	27
22				e	49
23	**8**	 **22** X = I **23** X = Br	 **33**	a (from **22**)	42
24				e (from **23**)	43

[a] Reagents and conditions: (a) $[Pd(PPh_3)_2Cl_2]$, 1,4-dioxane, Na_2CO_3 (1 M), reflux, 24 h. (b) $[Pd(PPh_3)_2Cl_2]$, tBu$_3$P, 1,4-dioxane, Na_2CO_3 (1 M), reflux, 24 h. (c) $Pd(OAc)_2$/di-*tert*-butylphosphanylferrocene (DtBPF), 1,4-dioxane, Na_2CO_3 (1 M), reflux, 65 h. (d) conditions (b), with a second addition of boronic acid **8** (1.1 equiv.) after 24 h reflux. (e) $[Pd_2(dba)_3]$/PCy_3, 1,4-dioxane, K_3PO_4 (1.27 M), reflux, 1–30 h.

Conclusions

We have successfully synthesized the new pyrimidylboronic acid derivatives **6** and **8**. They are stable to storage under ambient conditions and should prove to be valuable reagents in pyrimidine chemistry. Suzuki–Miyaura cross-couplings of **6** and **8** with a selection of heteroaryl halides (quinoline, pyridine, pyrimidine, pyrazine, thiophene, benzothiazole) have yielded novel 5-heteroarylpyrimidine scaffolds, which are suitable for further functionalization, as exemplified in the synthesis of **34**.

Experimental Section

General: General details of equipment and techniques used are the same as those we have reported previously.[10j] All synthetic reagents were used as supplied. Solvents were dried and distilled by using standard procedures. Iodobenzothiazole (**19**) was synthesized by adapting the literature preparation for iodination of thiazole.[25] Bromobenzothiazole (**20**) was synthesized by following the literature preparation.[26]

2-Chloro-5-pyrimidylboronic Acid (6): To a solution of 5-bromo-2-chloropyrimidine (**5**) (2.5 g, 13.0 mmol) and triisopropylborate

(4.2 mL, 18.2 mmol) in anhydrous THF (20 mL) and toluene (5 mL) at –78 °C was added *n*BuLi (2.5 M in hexane, 6.2 mL, 15.6 mmol) dropwise. The reaction mixture was stirred for 4 h at –78 °C; it was then quenched with water (40 mL) and warmed to room temperature with stirring overnight. The organic solvent was evaporated in vacuo, and the remaining aqueous layer was washed with diethyl ether (3 × 10 mL) to remove unreacted starting material. The aqueous layer was then acidified to pH 5 (with 48% aq. HBr) to precipitate **6** as a white solid (1.75 g, 85%); m.p. 200 °C (decomp.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.87 (s, 2 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 165.3, 161.8 ppm. MS (EI): *m*/*z* = 157.8 [M]$^+$. $C_4H_4BClN_2O_2$ (158.4): calcd. C 30.34, H 2.55, N 17.69; found C 30.62, H 1.94, N 17.10.

X-ray Diffraction Measurement: The experiment (from a pseudo-merohedrally twinned crystal) was carried out with a SMART 3-circle diffractometer with a 1 K CCD area detector by using graphite-monochromated Mo-K_α radiation ($\bar{\lambda}$ = 0.71073 Å) and a Cryostream (Oxford Cryosystems) open-flow N_2 cryostat. The structure was solved by direct methods and refined by full-matrix least-squares against F^2 of all reflections by using SHELXTL software (version 6.12, Bruker AXS, Madison WI, USA, 2001). Crystal data: **6**, $C_4H_4BClN_2O_2$, M = 158.35, T = 120 K, monoclinic, space group $P2_1/n$ (no. 14), a = 6.644(2) Å, b = 14.578(4) Å, c = 7.155(2) Å, β = 116.60(1)°, V = 619.7(3) Å^3, Z = 4, D_c = 1.697 g cm^{-3}, μ = 0.54 mm^{-1}, 6468 reflections with $2\theta \leq 55°$, R_{int} = 0.051, R = 0.051 on 1379 data with $I \geq 2\sigma(I)$, $wR(F^2)$ = 0.136 on all 1444 unique data.

CCDC-651541 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

2-Amino-5-pyrimidylboronic Acid (8): To a solution of 2-amino-5-bromopyrimidine (**7**) (1.74 g, 10 mmol) and triisopropylborate (2.9 mL, 12 mmol) in anhydrous THF (50 mL) at –78 °C was added *n*BuLi (2.5 M in hexane, 10 mL, 25 mmol) dropwise over 1 h. The reaction mixture was stirred for 3.5 h at –78 °C, then warmed to –20 °C and quenched with water (50 mL) before being stirred for 30 min. The organic solvent was evaporated in vacuo, and the remaining aqueous layer was filtered to remove inorganic salts. The filtrate was washed with diethyl ether (3 × 50 mL) to remove unreacted starting material, and the aqueous layer was filtered to remove inorganic salts. The filtrate was then acidified to pH 6 (with 48% aq. HBr) to precipitate **8** as a white solid. Yields of pure product from several reactions varied between 25% and 46%; m.p. > 300 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.49 (s, 2 H), 7.96 [br. s, 2 H, B(OH)$_2$] ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 164.1, 163.9 ppm. $C_4H_6BN_3O_2$ (138.9): calcd. C 34.58, H 4.35, N 30.25; found C 34.46, H 4.34, N 30.37.

General Procedure for the Cross-Coupling Reactions

Conditions (a): The boronic acid (1.1 equiv.), the aryl halide (1.0 equiv.) and [Pd(PPh$_3$)$_2$Cl$_2$] (ca. 5 mol-%) were sequentially added to degassed 1,4-dioxane[27] (10 mL), and the mixture was stirred at 20 °C for 30 min. Degassed aqueous Na_2CO_3 solution (1 M, 3.0 equiv.) was added, and the reaction mixture was heated under argon at reflux (typically for 24 h). The solvent was removed in vacuo, then ethyl acetate was added, and the organic layer was washed with brine, separated, and dried with $MgSO_4$. 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) with the addition of tBu$_3$P (ca. 5 mol-%) to the initial mixture.

Conditions (c): The boronic acid (1.1 equiv.) the aryl halide (1.0 equiv.) Pd(OAc)$_2$ (ca. 5 mol-%) and DtBPF (ca. 5 mol-%) were sequentially added to degassed 1,4-dioxane (10 mL) and the mixture stirred at 20 °C for 30 min. Degassed aqueous Na_2CO_3 solution (1 M, 3.0 equiv.) was added and the reaction mixture was heated under argon at reflux (typically for 65 h). The solvent was removed in vacuo then ethyl acetate was added and the organic layer was washed with brine, separated, and dried with $MgSO_4$. The mixture was purified by chromatography on a silica gel column. On some occasions an additional recrystallization was necessary.

Conditions (d): As for conditions (b), with a second addition of boronic acid **8** (1.1 equiv.) after 24 h reflux.

Conditions (e): The boronic acid (1.1 equiv.) the aryl halide (1.0 equiv.) [Pd$_2$(dba)$_3$] (ca. 1 mol-%) and PCy$_3$ (ca. 2.4 mol-%) were sequentially added to degassed 1,4-dioxane (2.7 mL), and the mixture was stirred at 20 °C for 30 min. Degassed aqueous K_3PO_4 solution (1.27 M, 1.7 equiv.) was added, and the reaction mixture was heated under argon at reflux (typically between 1–30 h). The solvent was removed in vacuo, then ethyl acetate was added, and the organic layer was washed with brine, separated, and dried with $MgSO_4$. The mixture was purified by chromatography on a silica gel column or by recrystallization.

Supporting Information (see footnote on the first page of this article): Synthetic details and characterization data for compounds **24**–**34**. Copies of NMR spectra of compound **34**.

Acknowledgments

We thank Vertellus Specialties UK Ltd. for funding this work.

[1] Reviews of cross-coupling methodology: a) B. U. W. Maes, *Top. Heterocycl. Chem.* **2006**, *1*, 155–211; b) A. de Meijere, F. Diederich (Eds.), *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH, Weinheim, **2004**; c) J. Hassan, M. Sévignon, C. Gozzi, E. Schultz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359–1470; d) A. Zapf, M. Beller, *Chem. Commun.* **2005**, 431–440; e) S. P. Stanforth, *Tetrahedron* **1998**, *54*, 263–303.

[2] a) A. M. Rouhi, *Chem. & Eng. News* **2004**, *82*, 4958; b) J. S. Carey, D. Laffan, C. Thomson, M. T. Williams, *Org. Biomol. Chem.* **2006**, *4*, 2337–2347.

[3] Reviews: a) G. Hughes, M. R. Bryce, *J. Mater. Chem.* **2005**, *15*, 94–107; b) U. Mitsche, P. Bauerle, *J. Mater. Chem.* **2000**, *10*, 1471–1507.

[4] a) J.-P. Leclerc, K. Fagnou, *Angew. Chem. Int. Ed.* **2006**, *45*, 7781–7786; b) K. Billingsley, K. W. Anderson, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 3358–3366.

[5] For a review of heterocyclic boronic acids: E. Tyrrell, P. Brookes, *Synthesis* **2003**, 469–483.

[6] a) T. Watanabe, N. Miyaura, A. Suzuki, *Synlett* **1991**, 207–440; b) F. C. Fischer, E. Havinger, *Recl. Trav. Chim. Pays-Bas* **1965**, *84*, 439–440; c) A. A. Fuller, H. R. Hester, E. V. Salo, E. P. Stevens, *Tetrahedron Lett.* **2003**, *44*, 2935–2938; d) M. D. Helm, J. E. Moore, A. Plant, J. P. A. Harrity, *Angew. Chem. Int. Ed.* **2005**, *44*, 3889–3892.

[7] a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483; b) N. Miyaura, *Top. Curr. Chem.* **2002**, *219*, 11–59; c) N. Miyaura in *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: F. Diederich, A. de Meijere), Wiley-VCH, Weinheim, **2004**, ch. 2; d) D. G. Hall (Ed.), *Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine*, Wiley-VCH, Weinheim, **2005**.

[8] Reviews of lithiation of azines: a) F. Mongin, G. Quéguiner, *Tetrahedron* **2001**, *57*, 4059–4090; b) A. Turck, N. Plé, F. Mongin, G. Quéguiner, *Tetrahedron* **2001**, *57*, 4489–4505.

[9] a) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879–933; b) M. C. Whisler, S. MacNeil, V. Snieckus, P. Beak, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206–2225; c) R. Chinchilla, C. Nájera, M. Yus, *Chem. Rev.* **2004**, *104*, 2667–2722.

[10] a) A. Bouillon, J.-C. Lancelot, V. Collot, P. R. Bovy, S. Rault, *Tetrahedron* **2002**, *58*, 2885–2890; b) A. Bouillon, J.-C. Lancelot, V. Collot, P. R. Bovy, S. Rault, *Tetrahedron* **2002**, *58*, 3323–3328; c) A. Bouillon, J.-C. Lancelot, P. R. Bovy, S. Rault, *Tetrahedron* **2002**, *58*, 4369–4373; d) W. Li, D. P. Nelson, M. S. Jensen, R. S. Hoerrner, D. Cai, R. D. Larsen, P. J. Reider, *J. Org. Chem.* **2002**, *67*, 5394–5397; e) P. R. Parry, C. Wang, A. S. Batsanov, M. R. Bryce, B. Tarbit, *J. Org. Chem.* **2002**, *67*, 7541–7543; f) A. Bouillon, J.-C. Lancelot, J. Sopkova, O. de Santos, V. Collot, P. R. Bovy, S. Rault, *Tetrahedron* **2003**, *59*, 10043–10049; g) A. Bouillon, A. S. Voisin, A. Robic, J.-C. Lancelot, V. Collot, S. Rault, *J. Org. Chem.* **2003**, *68*, 10178–10180; h) P. R. Parry, M. R. Bryce, B. Tarbit, *Synthesis* **2003**, 1035–1038; i) A. Sutherland, T. Gallagher, *J. Org. Chem.* **2003**, *68*, 3352–3355; j) A. E. Thompson, G. Hughes, A. S. Batsanov, M. R. Bryce, P. R. Parry, B. Tarbit, *J. Org. Chem.* **2005**, *70*, 388–390; k) H. M. Hansen, M. Lysén, M. Begtrup, J. Kristensen, *Tetrahedron* **2005**, *61*, 9955–9960; l) A. E. Thompson, A. S. Batsanov, M. R. Bryce, N. Saygili, P. R. Parry, B. Tarbit, *Tetrahedron* **2005**, *61*, 5131–5135; m) T. Cailly, F. Fabis, A. Bouillon, S. Lemaître, J. Sopkova, O. de Santos, S. Rault, *Synlett* **2006**, 53–56; n) A. S. Voisin, A. Bouillon, I. Berenguer, J.-C. Lancelot, A. Lesnard, S. Rault, *Tetrahedron* **2006**, *62*, 11734–11739; o) M. Alessi, A. L. Larkin, K. A. Ogilvie, L. A. Green, S. Lai, S. Lopez, V. Snieckus, *J. Org. Chem.* **2007**, *72*, 1588–1594.

[11] I. A. I. Mkhalid, D. Coventry, D. Albesa-Jove, A. S. Batsanov, J. A. K. Howard, R. N. Perutz, T. B. Marder, *Angew. Chem. Int. Ed.* **2006**, *45*, 489–491.

[12] a) T. K. Liao, E. G. Podrebarac, C. C. Cheng, *J. Am. Chem. Soc.* **1964**, *86*, 1869–1870; b) D. Peters, A.-B. Hornfield, S. Gronowitz, *J. Heterocycl. Chem.* **1990**, *27*, 2165–2173.

[13] N. Saygili, A. S. Batsanov, M. R. Bryce, *Org. Biomol. Chem.* **2004**, *2*, 852–857. For earlier syntheses of 5-pyrimidylboronic acid see: S. Gronowitz, A.-B. Hornfeldt, V. Kristjansson, T. Musil, *Chem. Scr.* **1986**, *26*, 305–309 and ref.[10d]

[14] Functionalized pyrimidines: a) V. Bonnet, F. Mongin, F. Trecourt, G. Queguiner, P. Knochel, *Tetrahedron* **2002**, *58*, 4429–4438; b) B. Gong, F. Hong, C. Kohm, S. Jenkins, J. Tulinsky, R. Bhatt, P. de Vries, J. W. Singer, P. Klein, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2303–2308; c) C. G. Hartung, A. C. Backes, B. Felber, A. Missio, A. Philipp, *Tetrahedron* **2006**, *62*, 10055–10064; d) R. T. Wheelhouse, S. A. Jennings, V. A. Phillips, D. Pletsas, P. M. Murphy, N. C. Garbett, J. B. Chaires, T. C. Jenkins, *J. Med. Chem.* **2006**, *49*, 5187–5198.

[15] For biologically significant azabiaryls: a) T. T. Denton, X. Zhang, J. R. Cashman, *J. Med. Chem.* **2005**, *48*, 224–239; b) R. A. Smith, D. L. Hertzog, M. H. Osterhout, G. H. Ladouceur, M. Korpusik, M. A. Bobko, J. H. Jones, K. Phelan, R. H. Romero, T. Hundertmark, M. L. MacDougall, J. N. Livingston, W. R. Shoen, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1303–1306.

[16] S. Ding, N. S. Gray, X. Wu, Q. Ding, P. G. Schultz, *J. Am. Chem. Soc.* **2002**, *124*, 1594–1596.

[17] Analogous lithiation/borylation procedures on 2-amino-5-bromopyridine and 1-amino-4-bromobenzene gave complex product mixtures; the corresponding boronic acid/ester derivatives could not be isolated.

[18] The isolated yields of cross-coupled products from in situ trapping of ester **9** were lower (based on **7**) than from reactions via the purified acid **8**.

[19] For example, *o*-cyanopyridylboronic esters are more suitable than the corresponding boronic acids: T. Cailly, F. Fabis, A. Bouillon, S. Lemaître, J. Sopkova, O. de Santos, S. Rault, *Synlett* **2006**, 53–56.

[20] a) A. F. Littke, G. C. Fu, *Angew. Chem. Int. Ed.* **1998**, *37*, 3387–3388; b) A. F. Littke, C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028.

[21] N. Kudo, M. Perseghini, G. C. Fu, *Angew. Chem. Int. Ed.* **2006**, *45*, 1282–1284.

[22] For examples of 2-arylbenzothiazoles for biomedical applications see: V. J. Majo, J. Prabhakaran, J. J. Mann, J. S. D. Kumar, *Tetrahedron Lett.* **2003**, *44*, 8535–8537.

[23] For other successful Suzuki reactions with halogenated substrates containing a primary amino group see: a) ref.;[10j] b) F. Bracher, J. Daab, *Eur. J. Org. Chem.* **2002**, 2288–2291.

[24] For a related cyclization see: E. F. DiMauro, J. R. Vitullo, *J. Org. Chem.* **2006**, *71*, 3959–3962.

[25] B. G. Van den Hoven, H. Alper, *J. Am. Chem. Soc.* **2001**, *123*, 1017–1022.

[26] C. Boga, E. Del Vecchio, L. Forlani, P. E. Todesco, *J. Organomet. Chem.* **2000**, *601*, 233–236.

[27] As noted by a referee, the degassing procedure does not ensure that the solvent is free of peroxide.

Received: July 16, 2007
Published Online: October 1, 2007

