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Functionalized Heteroarylpyridazines and Pyridazin-3(2*H*)-one Derivatives via Palladium-Catalyzed Cross-Coupling Methodology

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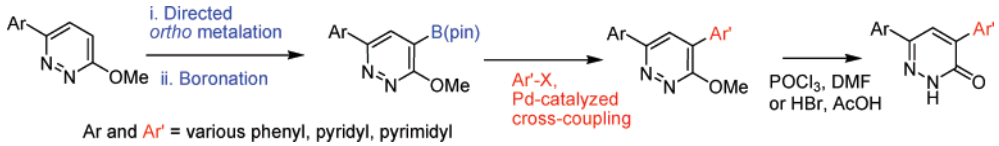
Received November 9, 2007



A general method for the synthesis of functionalized pyridazinylboronic acids/esters is described involving a directed *ortho* metalation (D*o*M)−boronation protocol (Schemes 1 and 2). A comprehensive study of the reactivity of the C−B bond in palladium-catalyzed cross-couplings with aryl/heteroaryl halides is presented. Aryl-/heteroarylpyridazines are thereby obtained in synthetically viable yields (typically 40−75%) although in some cases competing protodeboronation has been observed. A series of pyridazin-3(2*H*)-one derivatives, including 4,6-diaryl/heteroaryl derivatives, have been obtained from the corresponding 3-methoxypyridazines in straightforward procedures (Schemes 3 and 4). Several X-ray crystal structures of aryl-/heteroarylpyridazines and derived pyridazin-3(2*H*)-one derivatives are reported. These multi-ring systems are of considerable interest in contemporary N-heterocyclic chemistry.

Introduction

The pyridazine nucleus and derived 3-oxo derivatives [pyridazin-3(2*H*)-ones] are versatile pharmacophores in many biologically active molecules of contemporary interest.[1] For example, aryl-/heteroarylpyridazine derivatives have been used in the treatment of dementia, and others are selective $GABA_A$ antagonists.[2] Pyridazinone derivatives are cyclooxygenase-2 inhibitors, thereby acting as anti-inflammatory drugs,[1c,d] and show strong affinity for α_1-adrenergic receptors.[3] Several 6-arylpyridazin-3(2*H*)-ones are active cardiotonic agents and platelet aggregation inhibitors, notably 6-(3,4-dialkoxyphenyl)-pyridazin-3(2*H*)-ones, such as zardaverine.[1a] Structures are shown in Chart 1.

Examples of the pyridazine moiety in palladium-catalyzed cross-coupling reactions are restricted to the use of halopyridazines.[4] An organozinc pyridazine has been prepared and reacted in situ to synthesize heteroarylpyridazine derivatives in good yields.[5] Recently, Harrity et al. reported the preparation of substituted pyridazinylboronic esters through the [4 + 2] cycloaddition reaction of an alkynylboronic ester with disub-

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(1) (a) Sotelo, E.; Raviña, E. *Synlett* **2003**, *8*, 1113 and references cited therein. (b) Barbaro, R.; Betti, L.; Botta, M.; Corelli, F.; Giannaccini, G.; Maccari, L.; Manetti, F.; Strappaghetti, G.; Corsano, S. *J. Med. Chem.* **2001**, *44*, 2118. (c) Chintakunta, V. K.; Akella, V.; Vedula, M. S.; Mamnoor, P. K.; Mishra, P.; Casturi, S. R.; Vangoori, A.; Rajagopalan, R. *Eur. J. Med. Chem.* **2002**, *37*, 339. (d) Li, C. S.; Brideau, C.; Chan, C. C.; Savoie, C.; Claveau, D.; Charleson, S.; Gordon, R.; Greig, G.; Gauthier, J. Y.; Lau, C. K.; Riendeau, D.; Thérien, M.; Wong, E.; Prasit, P. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 597. (e) Betti, L.; Corelli, F.; Floridi, M.; Giannaccini, G.; Maccari, L.; Manetti, F.; Strappaghetti, G.; Botta, M. *J. Med. Chem.* **2003**, *46*, 3555. (f) Coelho, A.; Sotelo, E.; Novoa, H.; Peeters, O. M.; Blaton, N.; Ravina, E. *Tetrahedron Lett.* **2004**, *45*, 3459. (g) Tamayo, N.; Liao, L.; Goldberg, M.; Powers, D.; Tudor, Y.-Y.; Yu, V.; Wong, L. M.; Henkle, B.; Middleton, S.; Syed, R.; Harvey, T.; Jang, G.; Hungate, R.; Dominguez, C. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2409. (h) Pu, Y.-M.; Ku, Y.-Y.; Grieme, T.; Henry, R.; Bhatia, A. V. *Tetrahedron Lett.* **2006**, *47*, 149.

(2) Maes, B. U. W.; Lemière, G. L. F.; Dommisse, R.; Augustyns, K.; Haemers, A. *Tetrahedron* **2000**, *56*, 1777 and references cited therein.

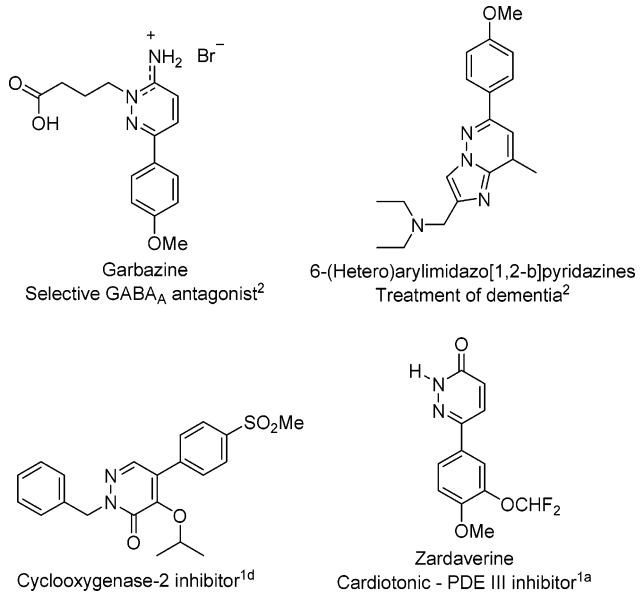
(3) (a) Review: Manetti, F.; Corelli, F.; Strappaghetti, F.; Botta, M. *Curr. Med. Chem.* **2002**, *9*, 1303. (b) For references to the biological activity of arylpyridazinones see: Salives, R.; Dupas, G.; Plé, N.; Quéguiner, G.; Turck, A.; George, P.; Servin, M.; Frost, J.; Almario, A.; Li, A. *J. Comb. Chem.* **2005**, *7*, 414.

(4) For reactions of halopyridazines with arylboronates see: (a) Aldous, D. J.; Bowe, S.; Moorcroft, N.; Todd, M. *Synlett* **2001**, 150. (b) Parrot, I.; Rival, Y.; Wermuth, C. G. *Synthesis* **1999**, 1163. (c) Sotelo, E.; Raviña, E. *Synlett* **2002**, 223. (d) Parrot, I.; Ritter, G.; Wermuth, C. G.; Hibert, M. *Synlett* **2002**, 1123. With aryl/vinylstannanes see: (e) Draper, T. L.; Bailey, T. R. *J. Org. Chem.* **1995**, *60*, 748. (f) Reference 2.

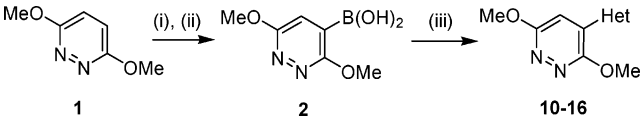
(5) Turck, A.; Plé, N.; Laprêtre, A.; Quéguiner, G. *Heterocycles* **1998**, *49*, 205.

10.1021/jo702420q CCC: $40.75
Published on Web 02/23/2008

CHART 1. Examples of Biologically Active Arylpyridazines and Arylpyridazinones



SCHEME 1. General Route to 10−16[a]



[a] Reagents and conditions: (i) *n*-BuLi, HN*i*-Pr$_2$, −78 °C, THF; (ii) B(O*i*-Pr)$_3$, −78 °C then H$_2$O/HBr; (iii) Het-Br, Pd(OAc)$_2$/D-*t*-BPF, 1,4-dioxane, Na$_2$CO$_3$ (1 M), reflux.

stituted 1,2,4,5-tetrazines.[6] Further transformations of the pyridazinylboronic esters provided access to extensively functionalized pyridazine derivatives.

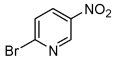
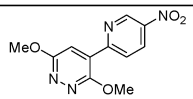
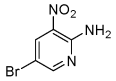
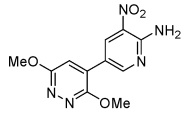
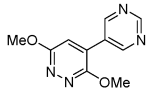
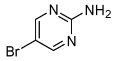
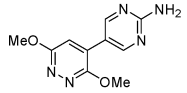
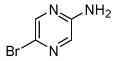
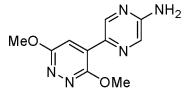
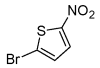
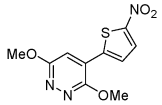
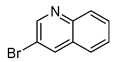
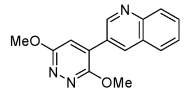
In this paper we present a route to heteroaryl-substituted pyridazines using Suzuki−Miyaura palladium-catalyzed cross-coupling reactions and describe the synthesis of derived pyridazinones. In particular, there are two key aspects to our methodology. (i) We report a series of pyridazinylboronic acids prepared via lithiation/boronation techniques[7] and (ii) we report the facile conversion of substituted 3-methoxypyridazines into the corresponding pyridazin-3(2*H*)-ones with good functional group tolerance: this constitutes an attractive route to substituted pyridazin-3(2*H*)-ones.

Results and Discussion

Directed *ortho*-lithiation of 3,6-dimethoxypyridazine **1**[8] with LDA in THF at −78 °C followed by addition of triisopropylborate and aqueous workup afforded the boronic acid derivative **2** as an air-stable solid in 88% yield (Scheme 1). Suzuki−Miyaura cross-coupling reactions[9] of **2** were carried out with a range of heteroaryl halides **3**−**9** under standard conditions [Pd(OAc)$_2$/1,1′-bis(di-*tert*-butylphosphino)ferrocene (D-*t*-BPF) as the catalyst system,[10] 1,4-dioxane, Na$_2$CO$_3$, reflux][11] to yield products **10**−**16**, respectively, thereby providing expedient access to highly functionalized heteroarylpyridazine derivatives, which would be very difficult to obtain by alternative methodology. The results are collated in Table 1. The reactions proceeded in moderate to high yields with a variety of heteroaryl bromides as coupling partners (viz. pyridyl, pyrimidyl, pyrazyl, thienyl, and quinolyl derivatives) including those bearing nitro (entries 1, 2, and 8) and primary amine substituents (entries 2, 4, and 5). The efficient reactions in the presence of a primary amine

TABLE 1. Palladium-Catalyzed Cross-Coupling Reactions of 2[a]

(i) **2** + Het-Br ⟶ **10-16**

Entry	Het-Br	Product	Conditions and isolated yield (%)	
1	 **3**	 **10**	a	90
2	 **4**	 **11**	a b	69 60
3	 **5**	 **12**	a b	74 78
4	 **6**	 **13**	a b	65 19
5	 **7**	 **14**	a b	38 48
6	 **8**	 **15**	a b	77 17
7	 **9**	 **16**	a c	95 72

[a] Reagents and conditions: (a) (i) Pd(OAc)$_2$ (5 mol %)/D-*t*-BPF (5 mol %), 1,4-dioxane, Na$_2$CO$_3$ (1 M), reflux, 65 h. (b) (i) Pd(PhCN)$_2$Cl$_2$ (5 mol %)/*t*-Bu$_3$P (5 mol %), 1,4-dioxane, Na$_2$CO$_3$ (1 M), reflux, 65 h. (c) (i) Pd(PPh$_3$)$_2$Cl$_2$ (5 mol %), 1,4-dioxane, Na$_2$CO$_3$ (1 M), reflux, 65 h.

(6) (a) Helm, M. D.; Moore, J. E.; Plant, A.; Harrity, J. P. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3889. (b) Helm, M. D.; Plant, A.; Harrity, J. P. A. *Org. Biomol. Chem.* **2006**, *4*, 4278. (c) Gomez-Bengoa, E.; Helm, M. D.; Plant, A.; Harrity, J. P. A. *J. Am. Chem. Soc.* **2007**, *129*, 2691.

(7) Review of heterocyclic boronic acids: Tyrrell, E.; Brookes, P. *Synthesis* **2003**, 469.

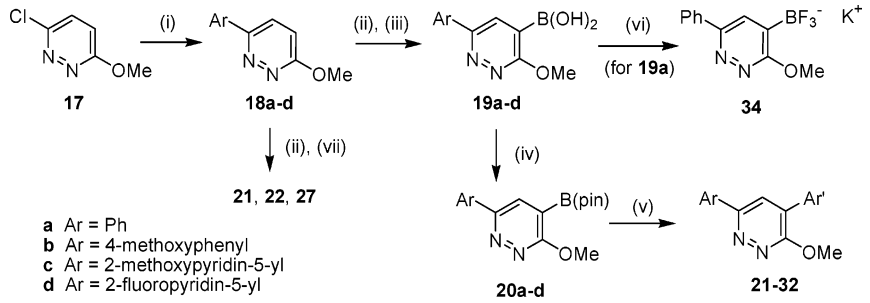
(8) Review of directed metalation of diazines: Turck, A.; Plé, N.; Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4489.

(9) Reviews: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263. (c) Suzuki, A. In *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, Germany, 2005; Chapter 3, pp 123−170.

(10) Itoh, T.; Mase, T. *Tetrahedron Lett.* **2005**, *46*, 3573.

(11) Pd(OAc)$_2$/D-*t*-BPF was selected based on the Suzuki−Miyaura cross-couplings of unprotected amines reported in ref 10. These workers found D-*t*-BPF to be superior to other bidentate ferrocenyl ligands, concluding that this was due to the increased ability of the chelating bis(phosphine) ligand to inhibit the formation of bis(amine) complexes. Other Pd/P catalyst systems were screened [Pd(PPh$_3$)$_2$Cl$_2$/*t*-Bu$_3$P; Pd(PhCN)$_2$/*t*-Bu$_3$P; and Pd(OAc)$_2$/*t*-Bu$_3$P]. In most cases Pd(OAc)$_2$/D-*t*-BPF gave the highest yields.

SCHEME 2. Synthesis of 21−32[a]



[a] Reagents and conditions: (i) $ArB(OH)_2$, $Pd(PPh_3)_2Cl_2$, 1,4-dioxane, Na_2CO_3 (1 M), reflux, 65 h; (ii) *n*-BuLi, HN*i*-Pr_2, −78 °C, THF or Et_2O; (iii) B(O*i*-Pr)$_3$, −78 °C then H_2O/H^+; (iv) pinacol, toluene, rt, 19 h; (v) Ar′Br **4**, **5** or **33**, Pd catalyst, 1,4-dioxane, base, reflux; (vi) KHF_2, H_2O/MeOH, rt, 1 h → 0 °C, 1 h; (vii) $ZnCl_2$, THF, $Pd(PPh_3)_4$, **5** or **33**, reflux.

substituent are notable as new examples of Suzuki reactions where protection of the amino group is not necessary.[12]

When **2** was dissolved in refluxing ethanol, protodeboronation rapidly occurred and X-ray analysis showed that the crystals obtained were a 1:1 molecular complex of **1** and boric acid, **1**·B(OH)$_3$ (see the Supporting Information). Protodeboronation was not observed in Suzuki−Miyaura cross-couplings of **2**.

In a further development that has led to more highly functionalized systems, we explored an alternative cross-coupling protocol. Reaction of commercial 3-chloro-6-methoxypyridazine **17** with the readily available benzene-, 4-methoxybenzene-, 2-methoxy-5-pyridyl-,[13] and 2-fluoro-5-pyridylboronic acids[14] [$Pd(PPh_3)_2Cl_2$, 1,4-dioxane, Na_2CO_3, reflux] gave products **18a**−**d**, respectively, in high yields, providing the first example of the 3-(pyridin-5-yl)pyridazine system.[15] Treatment of pyridazines **18a**−**d** with the standard lithiation−boronation technique used for the preparation of boronic acid **2** yielded boronic acids **19a**−**d** in 61−96% yields (Scheme 2). Electron-deficient heterocyclic boronic acids are known to be susceptible to protodeboronation both during their synthesis (where careful neutralization is required) and during their subsequent reactions.[6a,16] Initial cross-couplings of **19a** with 2-bromopyridine, **33**, showed protodeboronation occurring under a variety of Suzuki−Miyaura conditions. In some cases boronic esters are regarded as being more stable than their boronic acid derivatives,[17] consequently we converted boronic acids **19a**−**d** into their pinacol ester derivatives **20a**−**d** in good yields after stirring with pinacol and magnesium sulfate in toluene at room temperature (Scheme 2).[18]

It is pleasing to note that despite the presence of a second directing metalation group (DMG) in **18b**−**d** lithiation occurred regioselectively on the more electron-deficient pyridazine ring. Compounds **18b** and **18c** are of particular interest in this regard. To our knowledge there are no literature reports which compare the effect of the same DMG (i.e., methoxy for **18b** and **18c**) on different rings in a biaryl/heteroaryl system.[19] The substitution pattern in the boronated products was confirmed unequivocally by X-ray crystal structure determinations of **20b** and **20d** (see the Supporting Information).

Suzuki−Miyaura cross-coupling reactions of **19a**,**b** and **20a**−**d** were carried out with heteroaryl bromides **4**, **5**, and **33** under standard conditions [$Pd_2(dba)_3/PCy_3$, 1,4-dioxane, K_3PO_4 (1.27 M), reflux][20] to yield products **21**−**32**; the results are collated in Table 2. In every case competing protodeboronation occurred yielding pyridazines **18a**−**d** as byproducts, and in some cases as the major isolated product. In attempts to overcome the protodeboronation reaction solid K_3PO_4 was used;[21] however, this led to decreased yields of the coupling products (Table 2, conditions b, entries 1 and 3). The catalyst system was changed to $Pd_2(dba)_3$/[*t*-Bu_3PH]BF_4 (entry 1, conditions c), which had been used by Harrity et al. for reactions of their pyridazinylboronic esters.[6a] However, this gave no improvement (cf. entry 1, conditions a). Microwave conditions (entry 10, conditions d) did increase the yield of cross-coupling product **25**; however, protodeboronation was again obtained. In some cases the reactivity of trifluoroborates in coupling reactions is superior to that of the corresponding boronic acids.[22] **19a** was converted to the potassium trifluoroborate derivative **34** in 97% yield by using the established protocol with KHF_2 in aqueous methanol. However, **34** was less efficient than **19** in cross-

(12) Thompson, A. E.; Hughes, G.; Batsanov, A. S.; Bryce, M. R.; Parry, P. R.; Tarbit, B. *J. Org. Chem.* **2005**, *70*, 388.

(13) Parry, P. R.; Wang, C.; Batsanov, A. S.; Bryce, M. R.; Tarbit, B. *J. Org. Chem.* **2002**, *67*, 7541.

(14) Parry, P. R.; Bryce, M. R.; Tarbit, B. *Synthesis* **2003**, 1035.

(15) For previous Suzuki arylation reactions on halopyridazines see: (a) Reference 2. (b) Reference 3b. (c) Goodman, A. J.; Stanforth, S. P.; Tarbit, B. *Tetrahedron* **1999**, *55*, 15067. (d) Maes, B. U. W.; Kosmrlj, J.; Lemière, G. L. F. *J. Heterocycl. Chem.* **2002**, *39*, 535.

(16) (a) Gronowitz, S.; Bobosik, V.; Lawitz, K. *Chem. Scr.* **1984**, *23*, 120. (b) Coudret, C.; Mazenc, V. *Tetrahedron Lett.* **1997**, *38*, 5293. (c) Alessi, M.; Larkin, A. L.; Ogilvie, K. A.; Green, L. A.; Lai, S.; Lopez, S.; Snieckus, V. *J. Org. Chem.* **2007**, *72*, 1588.

(17) Cailly, T.; Fabis, F.; Bouillon, A.; Lemaître, S.; Sopkova, J.; de Santos, O.; Rault, R. *Synlett* **2006**, 53.

(18) The direct preparation of pinacol esters **20c**,**d** by trapping the lithiated species from **18c**,**d** with 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was less efficient than the two-step route via **19c**,**d**.

(19) (a) Regioselectivity of DMG on 3- and 3,6-disubstituted pyridazines: Turck, A.; Plé, N.; Ndzi, B.; Quéguiner, G. *Tetrahedron* **1993**, *49*, 599. (b) Relative *ortho* directing power of DMG in the diazine series: Turck, A.; Plé, N.; Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4489. Toudic, F.; Turck, A.; Plé, N.; Quéguiner, G.; Darabantu, M.; Lequeux, T.; Pommelet, J. C. *J. Heterocycl. Chem.* **2003**, *40*, 855. (c) Examples of regioselective DoM on DMG-substituted pyridines: Mallet, M. *J. Organomet. Chem.* **1991**, *406*, 49. Comins, D. L.; Baevsky, M. F.; Hong, H. *J. Am. Chem. Soc.* **1992**, *114*, 10971.

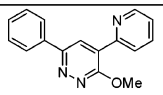
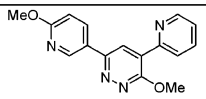
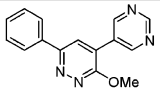
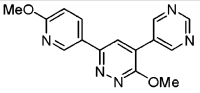
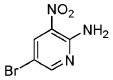
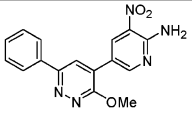
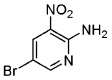
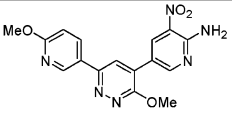
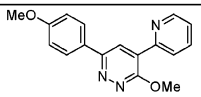
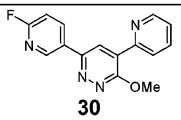
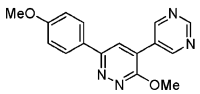
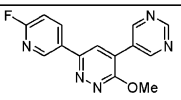
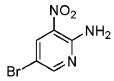
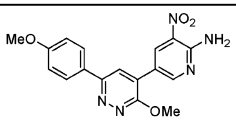
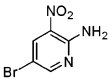
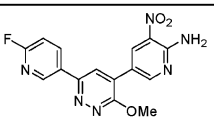
(20) Palladium catalyst and phosphine ligand systems were initially screened with the reaction between **19a** or **20a** and **33**; $Pd_2(dba)_3/PCy_3$ gave the highest yields and was subsequently used as the standard catalyst system. Kudo, N.; Perseghini, M.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1282.

(21) Protodeboronation is partially base promoted and can be strongly dependent on the base used. In our case other bases were not tried as the thermal instability of the boronic acids was established; when **19a** was heated in 1,4-dioxane (in the absence of base and palladium catalyst), protodeboronation was observed through TLC monitoring at temperatures >50 °C. Other workers have found, for example, dicyclohexylamine to be an excellent base for the Suzuki cross-coupling of a 2-boronic acid derivative of indole, at the same time preventing protodeboronation: Payack, J. F.; Vazquez, E.; Matty, L.; Kress, M. H.; McNamara, J. *J. Org. Chem.* **2005**, *70*, 175.

(22) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302.

TABLE 2. Cross-Coupling Reactions[a]

19a, b, 20a-d + Het-Br —(Conditions a-f)→ **21-32**

Entry	Boronic acid or ester	Het-Br	Product	Conditions and isolated yield (%)	Entry	Boronic acid or ester	Het-Br	Product	Conditions and isolated yield (%)
1	**20a**	 **33**	 **21**	a 76 b 47 c 73	13	**20c**	 **33**	 **27**	a 58
2	**19a**			a 67					
3	**20a**	 **5**	 **22**	a 47 b 46	14	**20c**	 **5**	 **28**	a 37
4	**19a**			a 34					
5	**20a**	 **4**	 **23**	a 59	15	**20c**	 **4**	 **29**	a 42
6	**19a**			a 40					
7	**20b**	 **33**	 **24**	a 77	16	**20d**	 **33**	 **30**	a 67
8	**19b**			a 62					
9	**20b**	 **5**	 **25**	a 28	17	**20d**	 **5**	 **31**	a 29
10	**19b**			a 27 d 43 e 14					
11	**20b**	 **4**	 **26**	a 46	18	**20d**	 **4**	 **32**	a 18 f 52
12	**19b**			a 39					

[a] Reagents and conditions: (a) $Pd_2(dba)_3$ (1 mol %)/PCy_3 (2.4 mol %), 1,4-dioxane, K_3PO_4 (1.27 M), reflux, 24 h. (b) $Pd_2(dba)_3$ (1 mol %)/PCy_3 (2.4 mol %), 1,4-dioxane, $K_3PO_{4(s)}$, reflux, 24 h. (c) $Pd_2(dba)_3$ (5 mol %)/(*t*-$Bu_3PH)BF_4$ (12 mol %),MeCN, $K_3PO_{4(s)}$, 85 °C, 1 h. (d) $Pd_2(dba)_3$ (1 mol %)/PCy_3 (2.4 mol %), 1,4-dioxane, K_3PO_4 (1.27 M), μW 120 °C, 1 h. (e) $Pd_2(dba)_3$ (1 mol %)/PCy_3(2.4 mol %), DMF, $K_3PO_4 \cdot 2H_2O$, μW 160 °C, 5 min. (f) $Pd(OAc)_2$ (5 mol %)/D-*t*-BPF (5 mol %), 1,4-dioxane, Na_2CO_3 (1 M), reflux, 5 h.

coupling reactions.[23] This may be anticipated as the formation of such an "ate" complex polarizes the C−B bond leading to facile protodeboronation in some α-heteroaryltrifluoroborates.[22] As can be observed in Table 2, we have successfully prepared novel highly functionalized (hetero)arylpyridazine derivatives in synthetically useful yields. Protodeboronation of these pyridazinylboronic species dominates Suzuki−Miyuara cross-coupling especially when less reactive coupling partners are applied. In general the overall yields of the cross-coupled products from the two-step protocol via the pyridazinylboronic esters are comparable to the one-step procedure from the boronic acid derivatives. X-ray diffraction studies confirmed the structures of compounds **22** and **24** (see the Supporting Information).

As an alternative route in the preparation of heteroarylpyridazines we have explored the formation and reactions of organozincate derivatives from **18a** and **18c** (Scheme 2).[24] The overall yields of the cross-coupling products **21**, **22**, and **27** (based on the starting pyridazines **18a** and **18c**) were improved to 77%, 44%, and 73%, respectively, compared to the overall yields of 64%, 33%, and 32% via the boronic acid **19a** or ester **20c**. Nevertheless, the boronic acid/ester route may be more practical due to the isolation and stability of boronic acids/esters compared to organozincate derivatives.

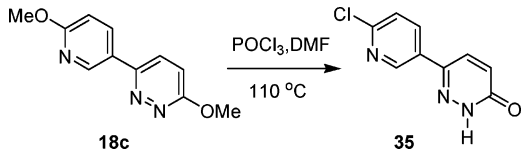
To increase the structural diversity of heteroarylpyridazines, the reaction of **18c** with phosphorus oxychloride/DMF under standard Vilsmeier−Haack conditions did not give the dichlorobiheteroaryl product: instead compound **35** was obtained in 60% yield, representing a new route into the pharmacologically important 6-substituted-pyridazin-3(2*H*)-one motif (Scheme 3).[1,3] While the standard methoxy → chloro transformation occurred at the pyridine ring of **18c**,[25] this was not the case at the pyridazine ring where demethylation of the methoxy group occurred in preference to chlorination. One explanation is that

(23) Cross-couplings of **34** with 2-bromopyridine **33** to yield **21** were attempted under different reaction conditions. In each case **34** was found to be highly insoluble at reflux temperature and no cross-coupling was observed by TLC analysis. On the addition of water to make the reaction mixture homogeneous, protodeboronation occurred yielding **18a** as the major product: $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, Et_3N, EtOH, reflux gave **21** in 47% yield; $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, Et_3N, MeCN, reflux gave predominantly deboronated species **18a**; $Pd_2(dba)_3/PCy_3$, Et_3N, 1,4-dioxane, reflux gave **21** in 33% yield; $Pd_2(dba)_3/PCy_3$, $K_3PO_{4\ (s)}$, DMF, 110 °C gave (by LCMS analysis) deboronated boronic species 70%, **21** 26% LCMS yield.

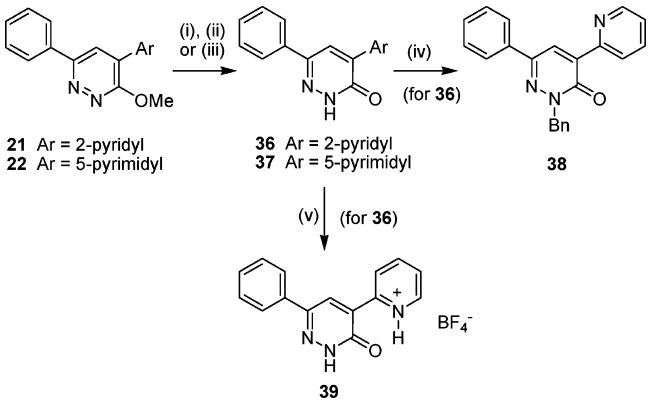
(24) (a) Transmetalation of the lithio derivative of 3,6-dimethoxypyridazine **1** to the zincate species, followed by Negishi coupling has been reported: see ref 5. (b) Seggio, A.; Chevallier, F.; Vaultier, M.; Mongin, F. *J. Org. Chem.* **2007**, *72*, 6602.

(25) For the conversion of 2-methoxypyridine to 2-chloropyridine under Vilsmeier−Haack conditions see: Lai, L.-L.; Lin, P.-Y.; Hwu, J.-R.; Shiao, M.-J.; Tsay, S.-C. *J. Chem. Res.* (*S*) **1996**, 194.

SCHEME 3. Synthesis of 35



SCHEME 4. Synthesis of 36−39[a]



[a] Reagents and conditions: (i) $POCl_3$/DMF, 110 °C, 19 h; (ii) BBr_3, DCM, reflux, 4 h; (iii) HBr (48% aq soln), AcOH, 80 °C, 3.5 h; (iv) **36**, BnBr, K_2CO_3, Bu_4NCl, MeCN, reflux, 1 h; (v) **36**, HBF_4, MeOH.

the Vilsmeier−Haack reagent is acting as an acylating agent, forming the pyridazinone, which is more stable than the pyridazinol tautomer[26] and consequently is not susceptible to nucleophilic attack from chloride ions. Alternatively, the 3-chloropyridazine derivative may be formed and hydrolyzed to **35** during aqueous workup. The 2-chloropyridine function would be relatively more hydrolytically stable.

To investigate the expedient conversion of methoxypyridazines to their pyridazin-3(2*H*)-one derivatives we developed the demethylation protocol further (Scheme 4). Compound **21** was treated with $POCl_3$/DMF to give pyridazinone derivative **36** in 55% yield. An improved yield of 84% was obtained when **21** was treated with BBr_3 in DCM at reflux. The attempted conversion of **22** to **37** with use of BBr_3 was unsuccessful; however, using HBr (48% aq soln) in acetic acid at 80 °C gave **37** in 77% yield. Compound **36** was *N*-benzylated to yield **38** (93% yield) and **36** was converted into its pyridinium salt **39**. X-ray diffraction studies confirmed the structures of **38** and **39** (see the Supporting Information).

In conclusion, we have reported that lithiation/boronation of pyridazines provides an efficient entry into a series of new pyridazinylboronic acid/ester derivatives which are stable to storage under ambient conditions. We have shown that these species undergo palladium-catalyzed cross-coupling reactions to provide aryl/heteroarylpyridazines in synthetically viable yields, although in some cases competing protodeboronation has been observed. Substituted 3-methoxypyridazines have been converted into the corresponding pyridazin-3(2*H*)-ones with good functional group tolerance. These functionalized heterocycles are attractive candidates as new pharmacophores and scaffolds for drug discovery. Moreover, they offer scope for further synthetic transformations.

(26) (a) Katrusiak, A.; Katrusiak, A. *J. Mol. Struct.* **2004**, *694*, 85. (b) Jones, R. A.; Whitmore, A. *ARKIVOC*, **2007**, *11*, 114 and references cited therein.

Experimental Section

Preparation of 3,6-Dimethoxy-4-pyridazinylboronic Acid (2). Diisopropylamine (13.4 mL, 0.10 mol) was added to *n*-butyllithium (2.5 M in hexane, 41.0 mL, 0.10 mol) in anhydrous THF (400 mL) at −78 °C under argon. The mixture was warmed to 0 °C and left to stir for 0.5 h. The reaction was then cooled to −78 °C and a solution of 3,6-dimethoxypyridazine **1** (6.73 g, 48 mmol) in anhydrous THF (100 mL) was added over 1 h. The reaction was stirred for a further 0.5 h. Triisopropylborate (33.2 mL, 0.144 mol) was added at −78 °C and the mixture was stirred for 1.5 h. The mixture was warmed to −10 °C and quenched with deionized water (100 mL). The organic solvent and most of the water were removed in vacuo. The resulting slurry was then dissolved in water and filtered. The filtrate was washed with diethyl ether (2 × 150 mL) and acidified to pH 4 with HBr (48% aq solution) to precipitate **2** as a white solid (7.78 g, 88%): mp 152.1−153.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (2H, s), 7.13 (1H, s), 3.95 (6H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.0, 162.5, 125.4, 55.0, 54.8. ^{11}B NMR (128 MHz, DMSO-d_6) δ 28.9. Anal. Calcd for $C_6H_9BN_2O_4$: C, 39.17; H, 4.93; N, 15.23. Found: C, 39.00; H, 4.93; N, 15.11.

Typical Procedure for the Cross-Coupling Reactions in Table 1. The boronic acid **2** (1.0 equiv), the aryl halide (0.9 equiv), and the catalyst (ca. 5 mol %) were sequentially added to degassed 1,4-dioxane (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 for 65 h. Solvent was removed in vacuo, then ethyl acetate was added and the organic layer was washed with brine, separated, and dried over $MgSO_4$. The mixture was purified by chromatography on a silica gel column followed if needed by recrystallization.

Representative Procedure for the Synthesis of 18a−d: 3-Methoxy-6-(4-methoxyphenyl)pyridazine[27] (18b). 4-Methoxyphenylboronic acid (2.38 g, 0.016 mol), 3-chloro-6-methoxypyridazine **17** (2.0 g, 0.014 mol), and $Pd(PPh_3)_2Cl_2$ (0.55 g, 0.78 mmol) were sequentially added to degassed 1,4-dioxane (100 mL) and the mixture was stirred at 20 °C for 30 min. Degassed aqueous Na_2CO_3 solution (1 M, 37 mL) was added and the reaction mixture was heated under argon at reflux for 65 h. Solvent was removed in vacuo then ethyl acetate (50 mL) was added and the organic layer was washed with brine (50 mL), separated, and dried over $MgSO_4$. Recrystallization from toluene yielded **18b** as a white solid (2.59 g, 87%): mp 137.4−139.0 °C (lit. mp[27] 134 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (2H, d, J = 8.8 Hz), 7.71 (1H, d, J = 9.2 Hz), 7.00 (3H, m), 4.16 (3H, s), 3.85 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 160.9, 155.0, 128.9, 127.9, 126.7, 117.8, 114.5, 55.5, 54.9; MS (ES$^+$) m/z 217.1 ([M + 1]$^+$, 100%). Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.75; H, 5.62; N, 13.10.

Representative Procedure for the Synthesis of 19a−d: 3-Methoxy-6-(4-methoxyphenyl)-4-pyridazinylboronic Acid (19b). Diisopropylamine (0.65 mL, 4.6 mmol) was added to *n*-butyllithium (2.5 M in hexane, 1.8 mL, 4.6 mmol) in anhydrous ether (20 mL) at −78 °C under argon. The mixture was warmed to 0 °C and left to stir for 0.5 h. The reaction was then cooled to −78 °C and a solution of 3-methoxy-6-(4-methoxyphenyl)pyridazine **18b** (0.5 g, 2.3 mmol) in anhydrous ether (40 mL) was added over 1 h. (The solid did not completely dissolve in ether at room temperature.) The reaction was stirred for a further 1 h. Triisopropylborate (1.6 mL, 6.9 mmol) was added at −78 °C and the mixture was stirred for 1.5 h. The mixture was warmed to room temperature and stirred for 0.5 h before quenching with deionized water (50 mL) and then left to stir at room temperature for 1 h. The organic solvent was removed in vacuo. The resulting aqueous phase was then washed with diethyl ether (3 × 50 mL) and treated with NaOH to obtain pH 10, then acidified to pH 6 with HBr (48% aq solution) to

(27) Parrot, I.; Rival, Y.; Wermuth, C. G. *Synthesis* **1999**, 1163.

precipitate a white solid. The mixture was stirred overnight at pH 6. On further acidification to pH 2 more precipitate formed; after filtration and drying **19b** was obtained as a white solid (0.53 g, 88%): mp 170.4−171.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (2H, s), 8.05 (1H, s), 8.01 (2H, d, J = 8.4 Hz), 7.07 (2H, d, J = 8.4 Hz), 4.04 (3H, s), 3.82 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.7, 160.2, 153.6, 130.5, 128.6, 127.5, 114.3, 55.2, 54.2; ^{11}B NMR (128 MHz, DMSO-d_6) δ 28.9. Anal. Calcd for $C_{12}H_{13}BN_2O_4$: C, 55.42; H, 5.04; N, 10.77. Found: C, 55.39; H, 5.03; N, 10.56.

Representative Procedure for the Synthesis of 20a−d: 3-Methoxy-6-(4-methoxyphenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridazine (20b). A solution of **19b** (1.0 g, 3.85 mmol), pinacol (0.45 g, 3.85 mmol), and $MgSO_4$ (2.0 g) in toluene (25 mL) was stirred for 20 h at room temperature (TLC monitoring). The suspension was filtered and the resulting solution was washed with brine (3 × 20 mL) and the organic phase dried over $MgSO_4$, filtered, and evaporated to give **20b** as a white solid (1.1 g, 85%): mp 176.4−177.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (1H, s), 7.98 (2H, d, J = 8.8 Hz), 6.97 (2H, d, J = 8.8 Hz), 4.17 (3H, s), 3.82 (3H, s), 1.35 (12H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 160.7, 154.4, 133.2, 128.9, 127.8, 114.3, 84.8, 55.4, 55.2, 24.8; ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.2; MS (ES$^+$) m/z 343.4 ([M + 1]$^+$, 100%). Anal. Calcd for $C_{18}H_{23}BN_2O_4$: C, 63.18; H, 6.77; N, 8.19. Found: C, 63.10; H, 6.82; N, 8.21. Crystals for X-ray diffraction analysis were grown from hexane.

Typical Procedure for the Cross-Coupling Reactions in Table 2. The boronic ester **20a−d** or acid **19a**,**b** (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 for 24 h. Solvent was removed in vacuo then ethyl acetate was added and the organic layer was washed with brine, separated, and dried over $MgSO_4$. The mixture was purified by chromatography on a silica gel column followed if needed by recrystallization.

Representative Procedures for the Synthesis of Pyridazinone Derivatives: 6-(6-Chloropyridin-3-yl)pyridazin-3(2*H*)-one (35). Phosphorus oxychloride (1.86 mL, 20 mmol) was added dropwise to a stirred solution of **18c** (434 mg, 2.0 mmol) in anhydrous DMF (40 mL) at 0 °C. Stirring was continued for 1 h then the mixture was heated at 110 °C for 19 h. The reaction was cooled to 0 °C and quenched with saturated NaOAc solution (60 mL). The mixture was transferred to a separating funnel with the addition of deionized water (25 mL). The mixture was extracted with EtOAc (3 × 200 mL) and washed with deionized water (3 × 150 mL). The organic layer was dried over $MgSO_4$ and evaporated to dryness. The solid was recrystallized from EtOAc to give **35** as a beige solid (249 mg, 60%): mp 262.4−263.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.40 (1H, s), 8.89 (1H, s), 8.29 (1H, dd, J = 8.9 Hz, J = 1.3 Hz), 8.10 (1H, d, J = 10.4 Hz), 7.64 (1H, d, J = 8.3 Hz), 7.05 (1H, d, J = 9.9 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.6, 151.1, 147.6, 141.2, 137.2, 131.8, 130.8, 130.4, 124.9; MS (ES$^+$) m/z 208.1 ([M + 1]$^+$, 100%). Anal. Calcd for $C_9H_6ClN_3O$: C, 52.07; H, 2.91; N, 20.24. Found: C, 52.10; H, 2.95; N, 20.06.

Preparation of 6-Phenyl-4-(pyridin-2-yl)pyridazin-3(2*H*)-one (36). Boron tribromide (1 M in DCM, 3.6 mL, 3.6 mmol) was added dropwise to a solution of **21** (232 mg, 0.89 mmol) in anhydrous DCM (30 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 15 min before warming to room temperature. The reaction mixture was then heated at reflux for 4 h. The reaction was cooled and deionized water (40 mL) added. The mixture was neutralized with a saturated $NaHCO_3$ solution to pH 7, before being extracted with DCM (2 × 50 mL). The combined organic phase was dried over Na_2SO_4, evaporated to dryness, and recrystallized from chloroform/petroleum ether (bp 40−60 °C) to give **36** as a yellow solid (186 mg, 84%): mp 247.6−248.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.57 (1H, s), 8.72 (3H, m), 7.92 (3H, m), 7.51 (4H, m); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.8, 150.2, 149.7, 144.5, 136.7, 135.8, 134.8, 129.2, 129.0, 127.7, 125.6, 124.64, 124.57; MS (ES$^+$) m/z 250.2 ([M + 1]$^+$, 100%). Anal. Calcd for $C_{15}H_{11}N_3O$: C, 72.28; H, 4.45; N, 16.86. Found: C, 71.99; H, 4.38; N, 16.77.

Acknowledgment. We thank Vertellus Specialties UK Ltd. and EPSRC for funding.

Supporting Information Available: Synthetic procedures and characterization data for new compounds and X-ray crystallographic data for compounds **20b**, **20d**, **22**, **24**, **38**, **39**, and **1**·$B(OH)_3$. This material is available free of charge via the Internet at http://pubs.acs.org.

JO702420Q