Ligand-free Pd/C-catalyzed Suzuki–Miyaura coupling reaction for the synthesis of heterobiaryl derivatives†

Yoshiaki Kitamura, Satoko Sako, Takahiro Udzu, Azusa Tsutsui, Tomohiro Maegawa, Yasunari Monguchi and Hironao Sajiki*

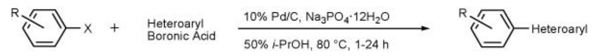
Received (in Cambridge, UK) 8th August 2007, Accepted 17th September 2007
First published as an Advance Article on the web 2nd October 2007
DOI: 10.1039/b712207a

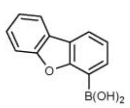
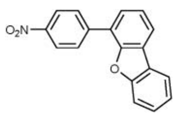
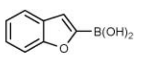
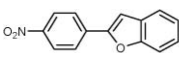
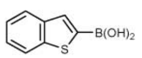
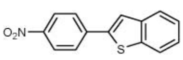
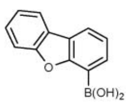
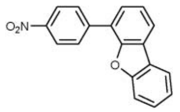
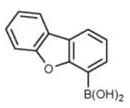
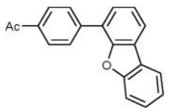
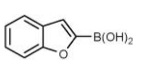
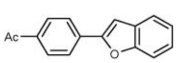
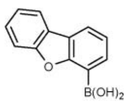
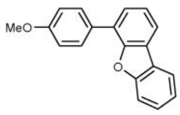
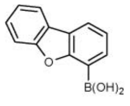
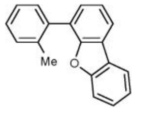
We have developed a mild and efficient protocol for the ligand-free and heterogeneous Pd/C-catalyzed hetero Suzuki–Miyaura coupling reaction that allows for the synthesis of both heteroaryl–aryl and heteroaryl–heteroaryl derivatives in good to excellent yields.

The Suzuki–Miyaura coupling reaction is one of the most useful methods for selective C–C bond formation during the construction of biaryl skeletons,[1] which are often included as partial structures in pharmaceuticals, natural products and functional materials. Significant efforts have focused on the development of efficient systems for the Suzuki–Miyaura reaction, but most developed protocols are mainly limited to the construction of the simple non-hetero aryl–aryl unit, and are usually difficult to apply to the synthesis of heterocyclic biaryl derivatives. Only Buchwald,[2] Fu,[3] Molander,[4] and Doucet/Santelli[5] offered pioneering access to the cross-coupling between heteroaryl halides and heteroaryl boronic acids or heteroaryl trifluoroborates. However, these methods utilized homogeneous palladium catalysts in the presence of phosphine ligands. A ligand-free Suzuki–Miyaura coupling of heterocycle-containing substrates catalyzed by homogeneous palladium catalyst was recently reported,[6] but the reaction required the use of a strong base such as NaOMe, and the coupling between heteroaryl halides and heteroaryl boronic acids is not very efficient. Furthermore, a homogeneous catalyst could be difficult to recover and reuse, and the residual Pd metal in the product could induce serious problems. Several heterogeneous Pd/C-catalyzed Suzuki–Miyaura coupling reactions of heteroaryl compounds including ligand-free fashion were also reported,[7] but they have low availability of substrates and only a single example of heteroaryl–heteroaryl coupling was reported.[8] We now report a heterogeneous Pd/C-catalyzed ligand-free Suzuki–Miyaura coupling reaction that is compatible with a wide range of heteroaryl substrates.

We recently reported a Pd/C–Na_3PO_4–50% *i*-PrOH system that worked efficiently for the Suzuki–Miyaura coupling of non-heteroaryl substrates at room temperature,[9] but the system was not easily applicable to the coupling of heteroaryl boronic acid and non-heteroaryl bromide, such as 4-dibenzofuranboronic acid and 4-bromonitrobenzene. After considerable exploration of the reaction parameters, we found that the application of heat (80 °C) was the most important variable to enhance the reaction progress among the key factors that led to the discovery of the present Pd/C-catalyzed hetero-Suzuki–Miyaura coupling. Most strikingly, the reaction of 4-bromonitrobenzene with 4-dibenzofuranboronic acid (1.5 equiv.) in the presence of 10% Pd/C (3.5 mol% as Pd metal) and $Na_3PO_4{\cdot}12H_2O$ (3.5 equiv.) in 50% *i*-PrOH at 80 °C was completed within 1 h with 98% yield (eqn (1) and Table 1, entry 1).

Table 1 Suzuki–Miyaura coupling of aryl bromide with heteroaryl boronic acid[a]

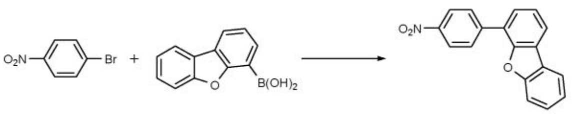


Entry	R	X	Ar–B(OH)$_2$	Product	Time (h)	Yield (%)[b]
1	4-NO_2	Br			1	98
2	4-NO_2	Br			1	98
3	4-NO_2	Br			12	72
4	4-NO_2	I			1	97
5	4-Ac	Br			1	96
6	4-Ac	Br			2	83
7	4-OMe	Br			1	98
8	2-Me	Br			1	85

[a] Reaction conditions: aryl boronic acid (1.5 equiv.), 10% Pd/C (3.5 mol%), $Na_3PO_4{\cdot}12H_2O$ (3.5 equiv.). [b] Isolated yield.

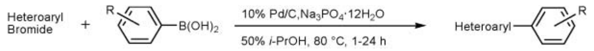
Laboratory of Medicinal Chemistry, Gifu Pharmaceutical University,
5-6-1 Mitahora-higashi, Gifu, 502-8585, Japan.
E-mail: sajiki@gifu-pu.ac.jp; Fax: (+81) 58-237-5979;
Tel: (+81) 58-237-8572

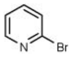
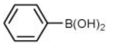
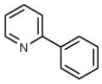
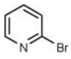
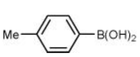
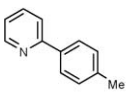
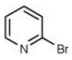
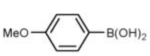
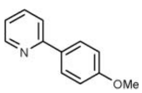
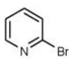
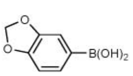
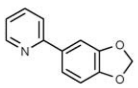
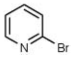
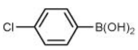
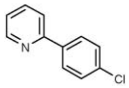
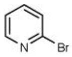
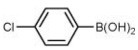
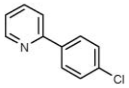
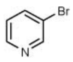
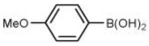
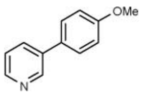
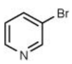
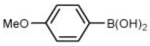
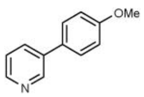
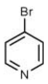
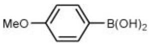
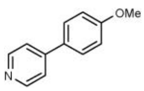
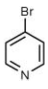
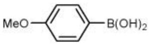
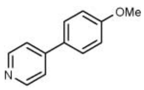
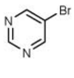
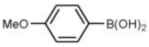
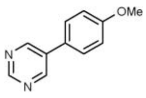
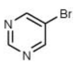
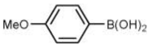
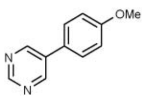
† Electronic supplementary information (ESI) available: Experimental procedures and characterization data for all unknown compounds. See DOI: 10.1039/b712207a



10% Pd/C, 3.5 equiv $Na_3PO_4\cdot12H_2O$, 50% *i*-PrOH, rt 0%
10% Pd/C, 3.5 equiv $Na_3PO_4\cdot12H_2O$, 50% *i*-PrOH, 80 °C 98%

Table 2 Suzuki–Miyaura coupling of heteroaryl bromide with arylboronic acid[a]



Entry	Ar–Br	Ar–B(OH)$_2$	Product	Time (h)	Yield (%)[b]
1				24	94
2				5	97
3				5	97
4				5	96
5				24	42
6[c]				24	95
7				6	27
8[c]				6	98
9[d]				24	58
10[c,d]				3	97
11				6	79
12[c]				1	98

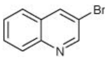
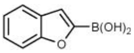
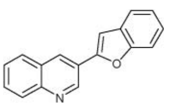
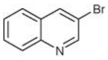
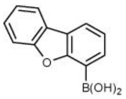
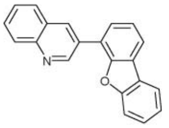
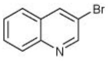
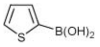
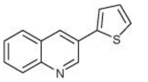
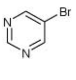
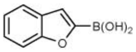
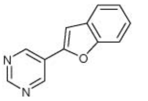
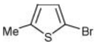
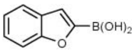
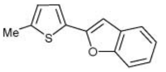
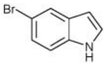
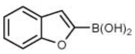
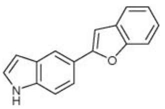
[a] Reaction conditions: arylboronic acid (1.5 equiv.), 10% Pd/C (3.5 mol%), $Na_3PO_4\cdot12H_2O$ (3.5 equiv.). [b] Isolated yield. [c] *i*-PrOH was used as the solvent. [d] 4-Bromopyridine hydrogen chloride was used as a substrate and 4.5 equiv. of $Na_3PO_4\cdot12H_2O$ were added to buffer the hydrogen chloride.

As shown in Table 1, a wide range of aryl bromides and an iodide bearing an electron-withdrawing group (Table 1, entries 1–6) and an electron-donating group (Table 1, entries 7 and 8) clearly reacted with 4-dibenzofuranboronic acid, 2-benzofuranboronic acid and 2-benzothiopheneboronic acid within 1–2 h except for entry 3 (thiophene derivatives, 12 h).

The scope of the reactions using a range of heteroaryl bromides and non-heteroaryl boronic acids is summarized in Table 2. The reactions of 2-bromopyridine with a series of electron-neutral to electron-rich phenylboronic acids formed the desired heterobiaryl products with > 94% yields (Table 2, entries 1–4). The coupling with 4-chloroboronic acid was incomplete even after 24 h (Table 2, entry 5) while the use of *i*-PrOH in place of 50% *i*-PrOH as the solvent dramatically improved the reaction progress and provided the product in 95% yield (Table 2, entry 6). In contrast to 2-bromopyridine, 3- and 4-bromopyridine and 5-bromopyrimidine reacted in low to moderate yields (Table 2, entries 7, 9 and 11) because of the incomplete reaction. Remarkably, in the case of 2-bromopyridine, the coordination of the nitrogen lone pair of 2-bromopyridine to the Pd metal facilitated the approach of Pd to the adjacent C–Br

Table 3 Suzuki–Miyaura coupling of heteroaryl bromide with heteroaryl boronic acid[a]

$$\text{Heteroaryl Bromide} + \text{Heteroaryl Boronic Acid} \xrightarrow[i\text{-PrOH, 80 °C}]{10\%\ \text{Pd/C, Na}_3\text{PO}_4\cdot12\text{H}_2\text{O}} \text{Heteroaryl} - \text{Heteroaryl}$$

Entry	Ar–Br	Ar–B(OH)$_2$	Product	Time (h)	Yield (%)[b]
1				0.5	100
2				12	75
3				24	91
4				3	95
5				24	94
6				24	70

[a] Reaction conditions: aryl boronic acid (1.5 equiv.), 10% Pd/C (1.0 mol%), $Na_3PO_4\cdot12H_2O$ (1.0 equiv.). [b] Isolated yield.

bond at the *ortho*-position, and the subsequent oxidative addition of the Pd to the aryl bromide easily took place. This coordination effect cannot be expected in the case of the other heteroaryl bromides listed in Table 2. Interestingly, the use of *i*-PrOH instead of 50% *i*-PrOH as the solvent for the coupling reactions led to excellent results and the desired products were obtained in nearly quantitative yields (Table 2, entries 8, 10 and 12).

The Suzuki–Miyaura coupling reaction encompassed the coupling between the heteroaryl boronic acids and heteroaryl bromides. 3-Bromoquinoline, 5-bromopyrimidine, 2-bromo-5-methylthiophene and 5-bromoindole possessing the non-protected NH group on the indole ring smoothly reacted with heteroaryl boronic acids under Pd/C–Na_3PO_4–*i*-PrOH–80 °C conditions (Table 3). It is noteworthy that the present protocol is applicable to sulfur containing heterocycles as substrates (Table 3, entries 3 and 5 and also Table 1, entry 3), a reaction which has previously been plagued by several limitations involving protodeboronation[2a,10] and catalyst poisoning of the sulfur atom.[11]

We have developed a mild and efficient protocol for the ligand-free and heterogeneous Pd/C-catalyzed hetero Suzuki–Miyaura coupling reaction. To the best of our knowledge, this methodology is the first to be reported which has widespread application for the synthesis of various heterobiaryl compounds using a *heterogeneous* catalyst under ligand-free conditions. We anticipate that this approach will offer an alternative synthetic strategy for the practical construction of heterobiaryl compounds.

We thank the N. E. Chemcat Corporation for the gift of the 10% Pd/C.

Notes and references

1 For reviews of the palladium-catalyzed Suzuki–Miyaura coupling reactions see: N. Miyaura, *Top. Curr. Chem.*, 2002, **219**, 11–59; A. Suzuki, *J. Organomet. Chem.*, 1999, **576**, 147–168; N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457–2483.

2 K. Billingsley and S. L. Buchwald, *J. Am. Chem. Soc.*, 2007, **129**, 3358–3366; T. E. Barder, S. D. Walker, J. R. Martinelli and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 4685–4696; T. E. Barder and S. L. Buchwald, *Org. Lett.*, 2004, **6**, 2649–2652.

3 N. Kudo, M. Perseghini and G. C. Fu, *Angew. Chem., Int. Ed.*, 2006, **45**, 1282–1284.

4 G. A. Molander and B. Biolatto, *J. Org. Chem.*, 2003, **68**, 4302–4314.

5 I. Kondolff, H. Doucet and M. Santelli, *Synlett*, 2005, 2057–2061.

6 C.-L. Deng, S.-M. Guo, Y.-X. Xie and J.-H. Li, *Eur. J. Org. Chem.*, 2007, 1457–1462.

7 F.-X. Felpin, T. Ayad and S. Mitra, *Eur. J. Org. Chem.*, 2006, 2679–2690; G. Cravotto, M. Beggiato, A. Penoni, G. Palmisano, S. Tollari, J.-M. Lévêque and W. Bonrath, *Tetrahedron Lett.*, 2005, **46**, 2267–2271; T. Tagata and M. Nishida, *J. Org. Chem.*, 2003, **68**, 9412–9415; A. Arcadi, G. Cerichelli, M. Chiarini, M. Correa and D. Zorzan, *Eur. J. Org. Chem.*, 2003, 4080–4086; M. G. Organ and S. Mayer, *J. Comb. Chem.*, 2003, **5**, 118–124; D. A. Conlon, B. Pipik, S. Ferdinand, C. R. LeBlond, J. R. Sowa, Jr., B. Izzo, P. Collins, G.-J. Ho, J. M. Williams, Y.-J. Shi and Y. Sun, *Adv. Synth. Catal.*, 2003, **345**, 931–935.

8 Roschangar *et al.* described the coupling between 2-iodothiophene and 5-(diethoxymethyl)-2-furanboronic acid as the particular case. See: M. S. McClure, F. Roschangar, S. J. Hodson, A. Millar and M. H. Osterhout, *Synthesis*, 2007, 1681–1685.

9 T. Maegawa, Y. Kitamura, S. Sako, T. Udzu, A. Sakurai, A. Tanaka, Y. Kobayashi, K. Endo, U. Bora, T. Kurita, A. Kozaki, Y. Monguchi and H. Sajiki, *Chem.–Eur. J.*, 2007, **13**, 5937–5943.

10 N. Miyaura, in *Metal-Catalyzed Cross-Coupling Reactions*, ed. A. de Meijere and F. Diederich, Wiley-VCH, Weinheim, 2nd edn, 2004, vol. 1, ch. 2, pp. 80–82.

11 A. S. Guram, A. O. King, J. G. Allen, X. Wang, L. B. Schenkel, J. Chan, E. E. Bunel, M. M. Faul, R. D. Larsen, M. J. Martinelli and P. J. Reider, *Org. Lett.*, 2006, **8**, 1787–1789; N. T. S. Phan, J. Khan and P. Styring, *Tetrahedron*, 2005, **61**, 12065–12073.