Homogeneous Catalysis

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A Versatile Method for Suzuki Cross-Coupling Reactions of Nitrogen Heterocycles**

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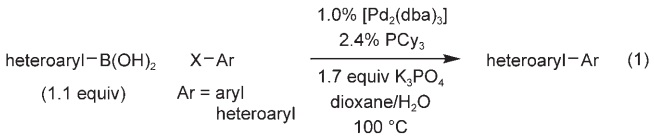
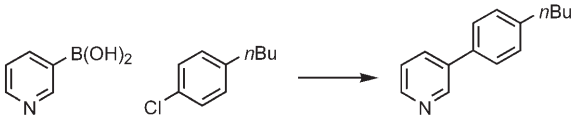
The Suzuki cross-coupling reaction is a powerful method for carbon-carbon bond formation that has been applied in a variety of settings, ranging from natural-products synthesis to materials chemistry, including large-scale production.[1,2] Among the attractive features of the Suzuki reaction are the wide availability, stability to air and moisture, and low toxicity of boronic acids, as well as the facile removal of the boron-containing side products of the coupling process.

In recent years, tremendous progress has been described in the discovery of more active catalysts for the Suzuki reaction. Arguably the most important remaining challenge is the development of a universal method for cross-coupling substrates that include nitrogen heterocycles.[3] The presence of such groups, which are particularly pervasive in medicinal chemistry,[4] can lead to low reactivity in coupling reactions. Herein, we describe an unusually versatile catalyst that achieves Suzuki cross-couplings of an array of nitrogen-containing boronic acids and aryl halides [Eq. (1); dba = dibenzylideneacetone, Cy = cyclohexyl].



Since 1998, we and others have established that trialkylphosphines, including $P(t\mathrm{Bu})_3$ and PCy_3, serve as very effective ligands for a variety of palladium-catalyzed coupling processes.[1,5] In view of the low cost of PCy_3 relative to many of the other ligands that provide highly active cross-coupling catalysts (e.g., $P(t\mathrm{Bu})_3$, aryldialkylphosphines, and carbenes), we decided to examine the possibility of developing a versatile PCy_3-based catalyst for Suzuki reactions of nitrogen heterocycles.

In an earlier study, we employed $Pd/PCy_3/KF/THF$ as a catalyst system for Suzuki cross-couplings of aryl halides.[6,7] Unfortunately, when we applied these conditions to the coupling of 3-pyridineboronic acid with 4-*n*-butylchlorobenzene, we obtained essentially none of the desired biaryl [Eq. (2)]. After considerable exploration of the reaction parameters, we determined that $Pd/PCy_3/K_3PO_4$/dioxane/H_2O achieves the desired cross-coupling in excellent yield [Eq. (2)].[8,9]



1.5% $[Pd_2(dba)_3]$, 4.2% PCy_3, 3.3 equiv KF, THF, 60 °C <2%
1.0% $[Pd_2(dba)_3]$, 2.4% PCy_3, 1.7 equiv K_3PO_4, dioxane/H_2O, 100 °C 92%

We were pleased to find that this standard protocol can be applied directly to Suzuki reactions of an array of nitrogen heterocycles. As illustrated in Table 1, a variety of heteroarylboronic acids can even be coupled with challenging aryl halides. Thus, 3-pyridineboronic acid reacts with a range of chlorobenzenes, including *ortho*-substituted and electronically deactivated substrates, in good yield (Table 1, entries 1–4). As might be anticipated, the corresponding aryl bromides and iodides also couple under these conditions (Table 1, entries 5 and 6). In addition, substituted 3-pyridineboronic acids are suitable cross-coupling partners (Table 1, entries 7–9). The method is effective not only for 3-pyridineboronic acids, but also for an array of other heteroarylboronic acids (e.g., 4-pyridine, 5-pyrimidine, and indole; Table 1, entries 10–13).

Although substrates that bear an indole NH group undergo Suzuki cross-coupling smoothly with this procedure (Table 1, entry 13), the catalyst appears to be sensitive to pyrazole NH groups (Table 1, entries 14 and 16). However, simple protection of the nitrogen atom leads to coupling with useful efficiency (Table 1, entries 15 and 17).[10]

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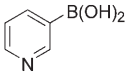
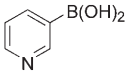
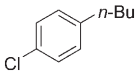
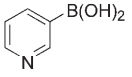
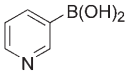
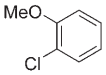
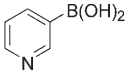
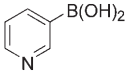
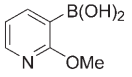
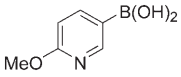
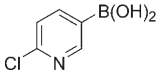
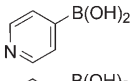
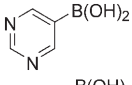
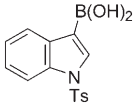
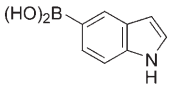
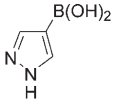
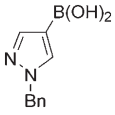
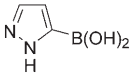
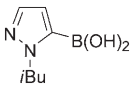
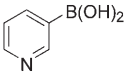
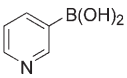
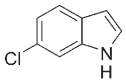
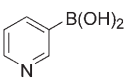
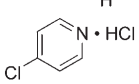
Table 1: Suzuki cross-couplings of heteroarylboronic acids with unactivated aryl halides [for the reaction conditions, see Eq. (1)].

Entry	Heteroarylboronic acid	Aryl halide	Yield [%][a]
1			92
2			92
3			95
4			88
5			90
6			91
7			83
8			87
9			85[b]
10			92
11			72
12			85
13			78
14			8
15			64
16			21
17			92

[a] Yield of isolated product (average of two experiments). [b] The product that results from the cross-coupling of the chloride was isolated in 10% yield.

Table 2: Suzuki cross-couplings of heteroarylboronic acids with heteroaryl chlorides and bromides [for the reaction conditions, see Eq. (1)].

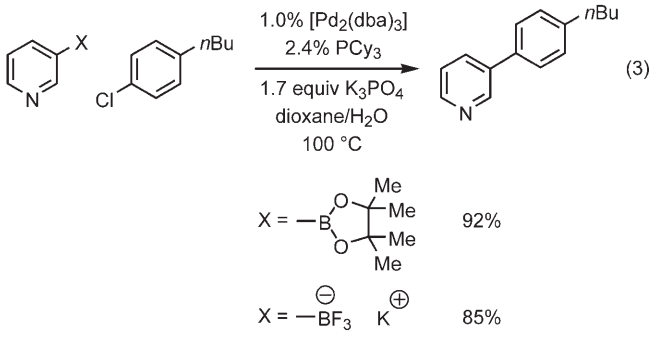
Entry	Heteroarylboronic acid	Heteroaryl halide	Yield [%][a]
1			97
2			93
3			98
4			98[b]
5			75
6			87
7			88
8			97
9			95
10			97
11			77
12			89
13			69[c]
14			30[c]
15			< 2
16			73

[a] Yield of isolated product (average of two experiments). [b] Double Suzuki cross-coupling (2.2 equiv of the boronic acid, 2.0% $[Pd_2(dba)_3]$, 4.8% PCy_3, and 3.4 equiv of K_3PO_4 were used). [c] The Boc protecting group was removed during the Suzuki reaction.

This catalyst system is also effective for Suzuki cross-couplings in which both of the reaction partners are nitrogen heterocycles, thus providing the desired products in generally good yield (Table 2). Consistent with the example illustrated in entry 13 of Table 1, the method tolerates indole NH groups (Table 2, entries 2 and 12). In addition, pyridines that bear hydroxy (Table 2, entry 6) and NH_2 (Table 2, entries 8 and 9) substituents are suitable substrates. *tert*-Butyloxycarbonyl (Boc) protecting groups at pyrrole and indole nitrogen atoms are cleaved under the cross-coupling conditions

(entries 13 and 14, respectively).[11] Protection of the pyrazole NH group is necessary for the coupling of a 4-bromopyrazole with 3-pyridineboronic acid (entry 15 vs. 16; see also Table 1, entries 14–17).

In preliminary experiments, we determined that this Pd/PCy_3/K_3PO_4/dioxane/H_2O-based method is effective not only for Suzuki cross-couplings of heteroarylboronic acids, but also for boronate esters and trifluoroborates [Eq. (3)]. Finally, we



(3)

established that the procedure can be conducted on a multigram scale (18 mmol of 4-*n*-butylchlorobenzenechloride + 20 mmol of 3-pyridineboronic acid, yield = 3.4 g (88%) of product).

To the best of our knowledge, this is the most wide-ranging study that has been described for Suzuki reactions of nitrogen-containing cross-coupling partners. Attractive features of this method include its versatility (a single procedure was employed for all of the examples, including boronate esters and trifluoroborates), its compatibility with a variety of unprotected functionalities (e.g., NH_2- and OH-substituted pyridines and unprotected indoles), its convenience (commercially available components), and its efficiency even with inexpensive, unactivated aryl chlorides. We anticipate that this catalyst system will find application in academia and, in particular, in industry.

Experimental Section

General procedure: The heteroarylboronic acid (1.10 mmol), [Pd_2(dba)$_3$] (9.2 mg, 0.010 mmol), and PCy_3 (6.7 mg, 0.024 mmol) were added to a 25-mL Schlenk flask equipped with a stir bar in air. The flask was evacuated and refilled with argon five times. Dioxane (2.67 mL), the (hetero)aryl halide (1.00 mmol; if the halide was a solid, it was added prior to the evacuation/refill cycle), and aqueous K_3PO_4 (1.27 M, 1.33 mL, 1.70 mmol) were added by syringe. The Schlenk flask was sealed and heated in an oil bath at 100 °C for 18 h with vigorous stirring. The mixture was then filtered through a pad of silica gel (washing with EtOAc), the filtrate concentrated under reduced pressure, and the aqueous residue extracted three times with EtOAc. The combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was then purified by column chromatography on silica gel.

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[2] For an overview, see: A. M. Rouhi, *Chem. Eng. News* **2004**, *82*, 49–58.
[3] For recent reports that include Suzuki reactions of nitrogen heterocycles, see: a) T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696; b) T. E. Barder, S. L. Buchwald, *Org. Lett.* **2004**, *6*, 2649–2652; c) I. Kondolff, H. Doucet, M. Santelli, *Synlett* **2005**, 2057–2061; d) A. E. Thompson, G. Hughes, A. S. Batsanov, M. R. Bryce, P. R. Parry, B. Tarbit, *J. Org. Chem.* **2005**, *70*, 388–390, and references therein.
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[5] For an overview, see: J. Tsuji, *Palladium Reagents and Catalysts*, Wiley, New York, **2004**.
[6] A. F. Littke, C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028; see, also: A. F. Littke, G. C. Fu, *Angew. Chem.* **1998**, *110*, 3586–3587; *Angew. Chem. Int. Ed.* **1998**, *37*, 3387–3388.
[7] For an early report of the use of Pd/PCy_3 for palladium-catalyzed Suzuki reactions, see: W. Shen, *Tetrahedron Lett.* **1997**, *38*, 5575–5578.
[8] For an overview of the use of water as a (co)solvent for Suzuki reactions, see: N. E. Leadbeater, *Chem. Commun.* **2005**, 2881–2902.
[9] For the application of a related system to the cross-coupling of cyclopropylboronic acid with (hetero)aryl bromides, see: D. J. Wallace, C.-y. Chen, *Tetrahedron Lett.* **2002**, *43*, 6987–6990.
[10] For the Suzuki cross-coupling illustrated in entry 15 of Table 1, deboronation is a significant side reaction.
[11] For a previous example, see: C. N. Johnson, G. Stemp, N. Anand, S. C. Stephen, T. Gallagher, *Synlett* **1998**, 1025–1027.

