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Palladium-Catalyzed Suzuki−Miyaura Coupling of Pyridyl-2-boronic Esters with Aryl Halides Using Highly Active and Air-Stable Phosphine Chloride and Oxide Ligands

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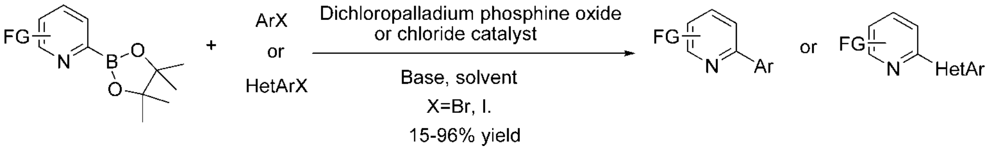
ABSTRACT



The palladium-catalyzed Suzuki−Miyaura coupling of pyridyl-2-boronic esters provided an efficient approach to useful biaryl building blocks containing a 2-pyridyl moiety. The convenient reaction protocol demonstrates its potentially wide applications in medicinal chemistry.

As one of the most powerful C−C bond formation methods, the Suzuki−Miyaura coupling, has been routinely practiced in medicinal and processs chemistry, leading to a wide range of drugs and clinical candidates.[1] Despite the tremendous progress in this arena, Suzuki−Miyaura coupling reactions of 2-substituted nitrogen-containing heteroaryl boronic acids or esters with aryl or heteroaryl halides are extremely challenging. The most prevalent side reactions are protodeboronation and dimerization, thus prohibiting reasonable yields of the desired coupling products. In the literature, aryl iodides have been reported to couple with 2-pyridinyl boronic acids/esters only leading to low yields of coupling products.[2] Efforts to circumvent this problem have focused on utilizing alternate C−B precursors, including the use of 2-pyridyl *N*,*N*-diethanolamine boronate esters,[3] cyclic triolborates,[4] and lithium triisopropyl 2-pyridylborates[5] as nucleophiles to construct biaryl systems containing a 2-pyridyl moiety. These methods however are limited in terms of reaction scope and/or the accessibility of the boron-containing reagent since they must first be prepared from either the boronic acid or halopyridine precursors, and in the case of halopyridine

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(1) For reviews, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev* **1995**, *95*, 2457. (b) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11. (c) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, *15*, 2419. (d) Tyrell, E.; Brookes, P. *Synthesis* **2004**, *4*, 469. (e) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.

(2) For selected examples, see: (a) Shinozuka, T.; Shimada, K.; Matsui, S.; Tamane, T.; Ama, M.; Fukuda, T.; Taki, M.; Takeda, Y.; Otsuka, E.; Yaato, M.; Naito, S. *Bioorg. Med. Chem.* **2006**, *14*, 6807. (b) Bouillon, A.; Lancelot, J.-C.; Sopkova de Oliveira Santos, J.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2003**, *59*, 10043. (c) Mandolesi, S. D.; Vaillard, S. E.; Podestá, J. C.; Rossi, R. A. *Organometallics* **2002**, *21*, 4886. (d) Sindkhedkar, M. D.; Mulla, H. R.; Wirth, M. A.; Cammers-Goodwin, A. *Tetrahedron* **2001**, *57*, 2991. (e) Deshayes, K.; Broene, R. D.; Chao, I.; Knobler, C. B.; Diederich, F. *J. Org. Chem.* **1991**, *56*, 6787.

(3) (a) Hodgson, P. B.; Salingue, F. H. *Tetrahedron Lett.* **2004**, *45*, 685. (b) Gros, P.; Doudouh, A.; Fort, Y. *Tetrahedron Lett.* **2004**, *45*, 6239.

(4) Yamamoto, Y.; Takiawa, M.; Yu, X.-Q.; Miyaura, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 928.

(5) Billinsley, K. L.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 4695.

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precursors conditions are required that are not compatible with base-sensitive functional groups. In an attempt to develop a convenient protocol that utilizes commercially readily available 2-hetereoaryl boronic esters for the Suzuki–Miyaura reaction, we were interested in exploring the use of highly active and air-stable palladium phosphine oxide and chloride complexes developed originally by Dupont and currently commercially available from Combiphos (Figure 1).[6]

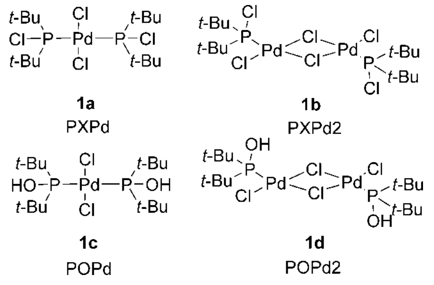
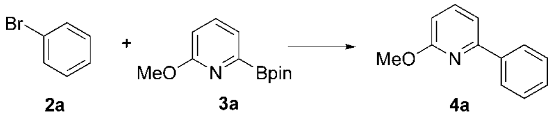


Figure 1. Palladium phosphine chloride and oxide catalysts.

Utilizing bromobenzene **2a** and 6-methoxypyridyl-2-boronic ester **3a** as substrates, only poor yields of the desired coupling product **4a** were obtained after a limited survey of catalysts and bases that are commonly used in the Suzuki–Miyaura reaction (Table 1, entries 1–4). The palladium phosphine oxide and chloride complexes were also tested because of their air-stability, good activity, and utility in various C–C, C–N, and C–S bond-forming reactions.[6] Using dioxane as the solvent, these catalysts were found to give moderate yields of **4a** (Table 1, entries 5–8). As advantageous water could be detrimental by facilitating protodeboronation, aqueous base solutions were therefore avoided for this type of reaction. The use of *i*-PrOH to replace dioxane dramatically improved the yield (Table 1, entry 9 vs entry 5) and turned out to be the best solvent for this system in comparison with methanol, *tert*-butanol, toluene, DME, or dioxane (data not shown). Although KF, K_2CO_3, and K_3PO_4 all gave moderate yields, CsF and Cs_2CO_3 are the best bases for this transformation (Table 1, entries 9–13). In contrast, the use of $NaHCO_3$ or Na_2CO_3 led to only trace amounts of product **4a** (Table 1, entries 14 and 15). It should be noted that solvents were used directly from commercial sources without drying or degassing. All reagents were weighed in air, and there is no need to degass the reaction mixture. Typically a nitrogen-flushed reaction tube is employed as the reaction vessel. Thus this appears to be a very convenient procedure for the Suzuki–Miyaura coupling of this type of 2-pyridyl nucleophiles.

Table 1. Effects of Catalyst, Base, and Solvent[a]



entry	catalyst	base	solvent	yield[b] (%)
1	$Pd(PPh_3)_4$	K_2CO_3	dioxane	11
2	Pd_2dba_3	Cs_2CO_3	dioxane	5
3	$Pd(OAc)_2$, S-Phos[c]	K_3PO_4	*n*-BuOH	27
4	$Pd(OAc)_2$, S-Phos	CsF	*i*-PrOH	17
5	**1a**	Cs_2CO_3	dioxane	30
6	**1b**	Cs_2CO_3	dioxane	25
7	**1c**	Cs_2CO_3	dioxane	29
8	**1d**	Cs_2CO_3	dioxane	27
9	**1a**	Cs_2CO_3	*i*-PrOH	62
10	**1a**	CsF	*i*-PrOH	**64**
11	**1a**	KF	*i*-PrOH	47
12	**1a**	K_3PO_4	*i*-PrOH	48
13	**1a**	K_2CO_3	*i*-PrOH	22
14	**1a**	Na_2CO_3	*i*-PrOH	<5
15	**1a**	$NaHCO_3$	*i*-PrOH	<5

[a] General procedure unless otherwise noted: To a resealable tube were added aryl bromide (1 equiv), boronic ester (1.2 equiv), base (2 equiv), solvent, and catalyst (3 mol %). The resealable tube was then heated at 90 °C over 18 h. [b] Isolated yield. [c] S-phos = 2-dicyclohexyl phosphino-2′,6′-dimethoxybiphenyl.

With optimized reaction conditions in hand for boronic ester **3a**, we then explored the scope of this reaction by using a variety of aryl halides (Table 2).[7] Reactions of both electron-rich and electron-poor aryl halides proceeded smoothly. More significantly, heteroaryl halides also participated in the coupling reactions and gave moderate yields of biheteroaryl products (Table 2, entries 5–7).

Next we tested the Suzuki–Miyaura coupling reactions of several pyridyl-2-boronic esters (Table 3). These reactions generally gave moderate to good isolated yields. It is worth noting that excellent conversions (90–100%) were achieved for most reactions on the basis of LC/MS data. Optimal reaction conditions are sometimes substrate-dependent. For example, in the case of boronic esters **3b**, catalyst **1c** afforded a better yield of **4j** than catalyst **1a** (Table 3, entries 1 and 2). A profound additive effect was observed in the reaction of 6-methylpyridine-2-boronic ester **3d** with bromide **2k**, in which the use of 2 equiv of lithium isopropoxide dramatically improved the yield (Table 3 entry 5 vs entry 4).

For boronic ester **3e**, dioxane appeared to be a better solvent than isopropanol (yield <10%) by providing a 5-fold higher yield (Table 3, entry 6). Pyridine boronic esters containing a 6-substituted chloride or bromide underwent chemoselective coupling reactions to give moderate yields

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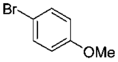
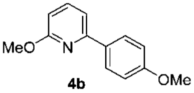
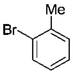
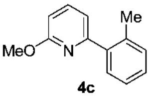
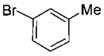
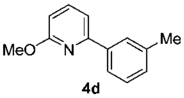
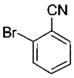
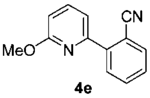
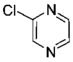
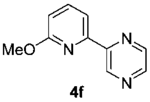
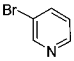
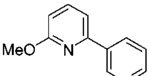
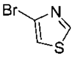
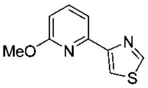
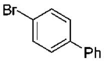
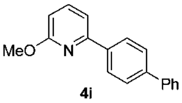
(6) (a) Li, G. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1513. (b) Li, G. Y.; Marshall, W. J. *Organometallics* **2002**, *21*, 590. (c) Wolf, C.; Lerebours, R. *J. Org. Chem.* **2003**, *68*, 7551. (d) Wolf, C.; Lerebours, R. *Org. Lett.* **2004**, *6*, 1147. (e) Ackermann, L.; Born, R.; Spatz, J. H.; Meyer, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 7216. (f) Ackermann, L.; Althammer, A. *Org. Lett.* **2006**, *8*, 3457. (g) Wolf, C.; Ekoue-Kovi, K. *Eur. J. Org. Chem.* **2006**, 1917.

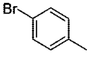
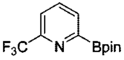
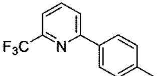
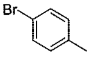
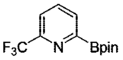
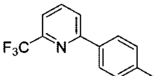
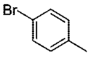
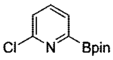
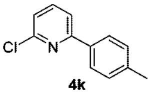
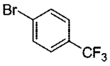
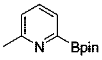
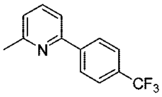
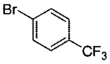
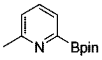
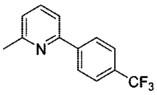
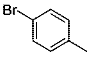
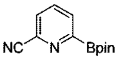
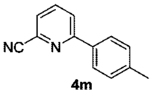
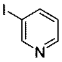
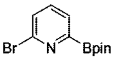
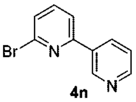
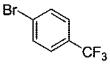
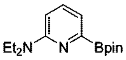
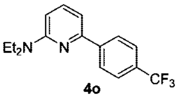
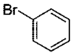
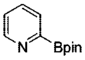
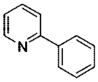
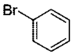
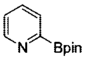
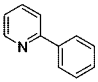
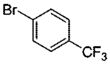
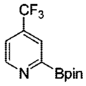
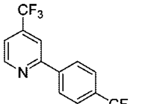
(7) **General Procedure.** To a sealed tube were added aryl bromide (1 equiv), boronic ester (1.2 equiv), base (2 equiv), solvent, and catalyst (3 mol %). The sealed tube was then heated at 90 °C over 18 h. After 1 h, to the mixture were added dichloromethane and water. The organic layer was concentrated and purified by silica gel chromatography eluting with ethyl acetate and hexanes to give the desired product.

Table 2. Reactions of Aryl Halides with 6-Methoxypyridyl-2-boronic Ester **3a**[a]

entry	substrate	product	yield[b] (%)
1[c]	 **2b**	 **4b**	72
2[c]	 **2c**	 **4c**	52
3	 **2d**	 **4d**	42
4	 **2e**	 **4e**	56
5[c]	 **2f**	 **4f**	55
6	 **2g**	 **4g**	55
7[c]	 **2h**	 **4h**	18
8	 **2i**	 **4i**	73

[a] General procedure unless otherwise noted: To a resealable tube were added aryl bromide (1 equiv), boronic ester (1.2 equiv), base (2 equiv), solvent, and catalyst **1a** (3 mol %). The sealed tube was then heated at 90 °C over 18 h. [b] Isolated yield. [c] 2 equiv of boronic ester and 3 equiv of base were used.

Table 3. Reactions of Pyridyl-2-boronic Esters[a]

entry	halide	boronic ester	product	yield[b] (%)
1	 **2j**	 **3b**	 **4j**	49
2[c]	 **2j**	 **3b**	 **4j**	80
3	 **2j**	 **3c**	 **4k**	41
4	 **2k**	 **3d**	 **4l**	15
5[d]	 **2k**	 **3d**	 **4l**	56
6[e]	 **2j**	 **3e**	 **4m**	54
7	 **2l**	 **3f**	 **4n**	25
8	 **2k**	 **3g**	 **4o**	42
9[f]	 **2a**	 **3h**	 **4p**	60
10[g]	 **2a**	 **3h**	 **4p**	50
11[d]	 **2k**	 **3i**	 **4q**	52

[a] General procedure unless otherwise noted: To a resealable tube were added aryl bromide (1 equiv), boronic ester (2 equiv), CsF (2 equiv), solvent, and catalyst **1a** (3 mol %). The resealable tube was then heated at 90 °C over 18 h. [b] Isolated yield. [c] **1c** (3 mol %) was used as the catalyst. [d] Reaction was run in dioxane with 2 equiv of *i*-PrOLi and 3 equiv of CsF at 90 °C. [e] Reaction was run with **1c** (3 mol %) in dioxane at 105 °C for 18 h. [f] Reaction was run in dioxane with 2 equiv of *t*-BuOLi, 3 equiv of CsF, and **1c** (3 mol %) at 90 °C for 14 h. The isolated yield of **4p** is 36% using 50 mg of boronic ester and 60% using 1 g of boronic ester. [g] Reaction was run with 1.2 equiv of **3h** in isopropanol with 2 equiv of *t*-BuOLi and POPd-mix (3 mol %) at 90 °C for 12 h.

of desired coupling products with 6-subsituted halides intact (Table 3, entries 3 and 7).

As for the substrate scope of pyridine-2-boronic esters lacking a 6-substituent, the reaction yields were low under the conditions described in Table 1 (<10%). The addition of lithium *tert*-butoxide (Table 3, entries 9 and 10) or lithium isopropoxide (Table 3, entry 11) boosted the reaction yield to a moderate range.[8]

As an example of a medium scale reaction, 1 g of boronic ester **3b** (1.2 equiv) coupled with aryl bromide **2k** with a low loading of catalyst **1c** (0.5 mol %) (Scheme 1). This reaction gave almost quantitative yield of **4r**. To our knowledge, this is the most efficient catalytic system for this type of Suzuki–Miyaura reaction, regarding catalyst loading.

In conclusion, we have developed a method for the challenging cross-coupling reactions of pyridyl-2-boronic esters with aryl halides using palladium phosphine chloride and oxide catalysts (**1a**–**d**). The major advantage of these catalysts is their air- and heat-stability, which make a low catalyst loading possible. Bases and solvents were found to play a profound role in the reaction outcome. Lastly,

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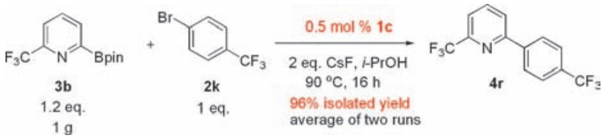
(8) In ref 5, Buchwald and Billinsley utilized lithium triisopropyl 2-pyridylborates. Presumably similar lithium borate species were formed in situ here from boronic esters and lithium alkoxides.

Scheme 1



the convenient benchtop procedures allow access to biaryl systems containing one or two heteroaryl groups, which can be readily incorporated into drug discovery programs.

The full scope and limitation of this chemistry, as well as mechanistic studies, will be elaborated in due course.

Acknowledgment. We thank Dr. Yongkui Sun for helpful discussions.

Supporting Information Available: Representative experimental procedures and spectroscopic data or new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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