Cross-Coupling Reactions

DOI: 10.1002/ange.200801465

A General and Efficient Method for the Suzuki–Miyaura Coupling of 2-Pyridyl Nucleophiles**

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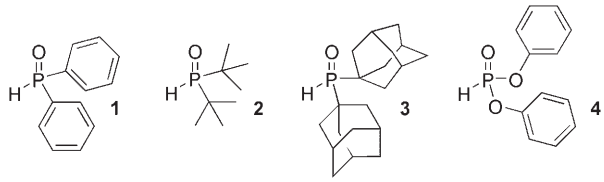
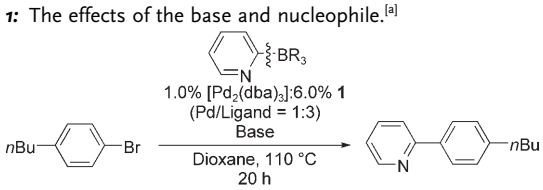
The Suzuki–Miyaura reaction has become one of the most valuable synthetic processes for the construction of carbon–carbon bonds,[1] and our laboratory has developed many highly active catalyst systems that efficiently process challenging combinations of aryl halides and boronic acids.[2] Recently, we have been able to extend our methodology to the cross-coupling of heteroaryl boronic acids and esters, which serve as important building blocks for the assembly of biologically active molecules.[3,4] However, 2-substituted nitrogen-containing heteroaryl organoboranes, which are of importance for the construction of numerous natural products and pharmaceutically interesting compounds,[5] were not effectively transformed by using our standard conditions. Further examination of the literature indicated that only a few reports of the Suzuki–Miyaura reaction of 2-pyridyl nucleophiles with aryl halides have appeared, and in these examples, only aryl iodides have been demonstrated as suitable coupling partners.[3,6–10] The difficulty can be attributed to several factors: 1) Electron-deficient heteroaryl boron derivatives undergo transmetalation at a relatively slow rate, and 2) these reagents rapidly decompose by a protodeboronation pathway. The lack of an efficient method to process this class of nucleophiles led us to develop a technique specifically designed to accomplish this transformation.

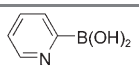
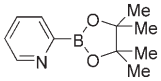
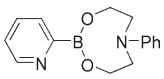
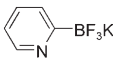
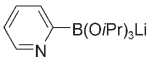
We found that catalysts based upon phosphite or phosphine oxide ligands (**1**–**4**) were highly active for the Suzuki–Miyaura reaction of 2-pyridyl boron derivatives with 1-bromo-4-butylbenzene (Scheme 1). The use of these has been pioneered by the work of Li, and elegant applications by Ackermann and Wolf have appeared more recently.[11] However, the reaction remained sensitive to the nature of the nucleophile and base. For example, the reaction of commercially-available reagents, such as 2-pyridyl boronic acid,[6] pinacol boronate ester,[7] or *N*-phenyl diethanolamine boronate ester,[8] with 4-*n*-butylbromobenzene produced low yields of the desired biaryl product (Table 1, entries 1–3). Similarly, attempts to use organotrifluoroborates resulted in a low conversion of the aryl bromide (Table 1, entry 4).[9] Although 2-pyridylborates have been used in Suzuki–Miyaura reactions, the cross-coupling processes result in only poor to modest yields of the desired biaryl product.[12] However, when lithium triisopropyl 2-pyridylborate (**A**) was employed as the nucleophile, the desired product could be obtained in 85% yield with 100% conversion of the aryl halide (Table 1, entry 5). Although **A** is not yet commercially available, it is stable under an argon atmosphere for up to a month, and it can be prepared in near quantitative yield from 2-bromopyridine by lithium–halogen exchange and immediate in situ quenching of the resulting anion with triisopropylborate.[13] In addition, **A** can be prepared in multigram quantities in excellent yield (Scheme 2). Lithium triisopropyl 2-(6-methoxypyridyl)borate (**B**) and lithium triisopropyl 2-(5-fluoropyridyl)borate (**C**) were also prepared by employing this protocol in 90% and 96% yield, respectively. Similarly, under these conditions, 2-bromopyridines possessing a pro-



Scheme 1. Effective phosphite and phosphine oxide ligands.

Table 1: The effects of the base and nucleophile.[a]



Entry	Ar–BR_3	Base	GC Yield [%]	Conversion [%]
1		KF	0	< 10
		NaO*t*Bu	8	36
2		KF	0	< 10
		NaO*t*Bu	49	73
3		KF	6	43
		NaO*t*Bu	15	100
4		KF	0	< 10
		NaO*t*Bu	10	37
5		KF	85	100
		NaO*t*Bu	68	100

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[**] We thank the National Institutes of Health (GM 46059) for support of this work. We are grateful to Merck, Amgen, and Boehringer Ingelheim for additional support. The Varian NMR instruments used in this work were purchased with funding from the NSF (CHE 9808061 and DBI 9729592).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200801465.

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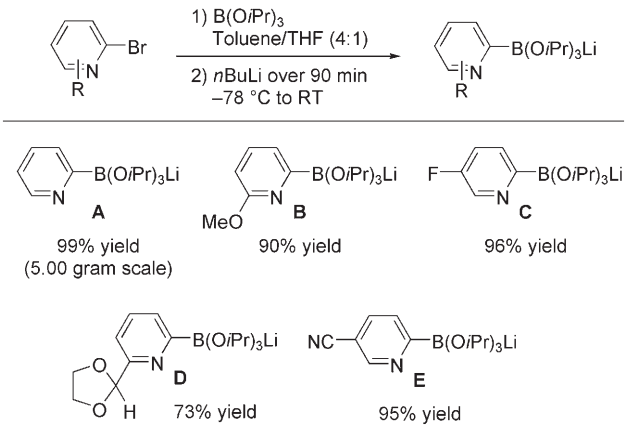


Scheme 2. Synthesis of lithium triisopropyl 2-pyridylborates.

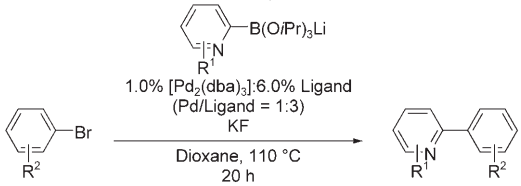
tected aldehyde (**D**) or a nitrile (**E**) could be efficiently transformed to the corresponding borates.[14]

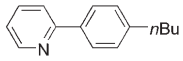
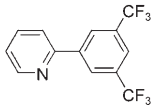
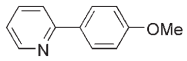
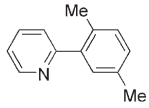
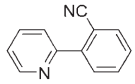
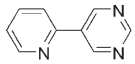
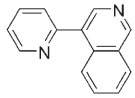
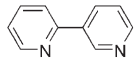
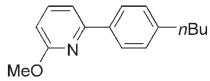
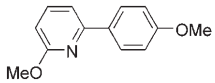
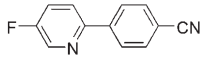
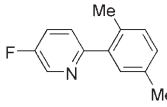
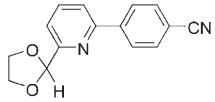
A catalyst based upon $[Pd_2(dba)_3]$/**1** proved to be highly effective for the Suzuki–Miyaura reactions of **A** with aryl and heteroaryl bromides. For example, this system efficiently combined 3,5-(bistrifluoromethyl)bromobenzene (Table 2, entry 2) and 4-bromoanisole (Table 2, entry 3) with **A** to furnish the desired biaryl in 82% and 74% yield, respectively. In addition, *ortho*-substituted aryl bromides were coupled in good to excellent yields (Table 2, entries 4 and 5). Heteroaryl bromides were also suitable coupling partners as seen in the reactions of **A** with 5-bromopyrimidine (Table 2, entry 6) and 4-bromoisoquinoline (Table 2, entry 7) which resulted in a 91% and 82% yield, respectively, of the desired heterobiaryl compound. Utilizing a $[Pd_2(dba)_3]$/**2** catalyst, a range of lithium triisopropyl 2-pyridylborates possessing functional groups were successfully cross-coupled with aryl bromides. Indeed, this catalyst system allowed the reaction of **B** and **C** with a variety of electron-poor, -neutral, -rich, and *ortho*-substituted aryl bromides (Table 2, entries 9–12). In addition, the reaction of 4-bromobenzonitrile and **D** furnished the desired biaryl in 63% yield (Table 2, entry 13). However, the cross-coupling reactions utilizing **E** resulted in incomplete conversion in its reaction with a variety of aryl bromides. We attributed this difficulty to the relatively slow rate of transmetalation of the highly electron-deficient 2-pyridylborate. Overall, however, this protocol still represents the most general available method for the Suzuki–Miyaura reaction of 2-pyridyl nucleophiles with aryl or heteroaryl bromides.

Despite the efficacy of the $[Pd_2(dba)_3]$/**1** catalyst system for the reactions of lithium triisopropyl 2-pyridylborates with aryl bromides, more modest yields of the desired biaryls were obtained in the reactions of the corresponding aryl or heteroaryl chlorides. Employing **2** as the supporting ligand, however, provided a more active catalyst for this transformation. For example, the reaction of **A** with 4-chlorobenzonitrile furnished the desired product in 73% yield (Table 3, entry 1). In addition, unactivated aryl chlorides were efficiently coupled as the reactions of 4-*n*-butylchlorobenzene (Table 3, entry 2) and 4-chloroanisole (Table 3, entry 4) with **A** resulted in a 76% and 78% yield, respectively, of the desired product. Similarly, under these conditions, *ortho*-substituted aryl chlorides were suitable substrates; for example, the reaction of 2-chloro-*p*-xylene and **A** gave the desired product in 70% yield (Table 3, entry 3). In addition, a heteroaryl chloride, 3-chloropyridine, was coupled with **A** in an excellent yield to give *o,m*-bipyridine (Table 3, entry 6).

In summary, we have developed an efficient method for the Suzuki–Miyaura reaction of lithium triisopropyl 2-pyridylborates. The borates can be readily prepared in one step from the corresponding 2-bromo- or 2-iodopyridine deriva-

Table 2: The reaction of **A**–**D** with aryl bromides.[a]



Entry	Borate	Ligand	Product	Yield [%][b]
1	**A**	**1**		85
2	**A**	**1**		82
3	**A**	**1**		74
4	**A**	**1**		87
5	**A**	**1**		90
6	**A**	**1**		91
7	**A**	**1**		82
8	**A**	**1**		73
9	**B**	**2**		90[c]
10	**B**	**2**		61[c]
11	**C**	**2**		65[c]
12	**C**	**2**		40[c]
13	**D**	**1**		63[c]

[a] Reaction conditions: 1 equiv of aryl or heteroaryl bromide, 1.5 equiv of 2-pyridylborate, 3.0 equiv of KF, dioxane (3 mL mmol^{-1} halide), cat. $[Pd_2(dba)_3]$, L:Pd = 3:1. [b] Yield of isolated product based upon an average of two runs. [c] 1.5% $[Pd_2(dba)_3]$ used instead of 1.0%.

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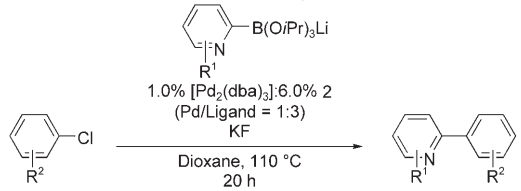
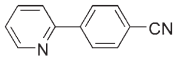
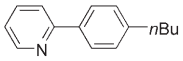
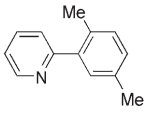
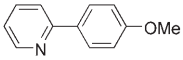
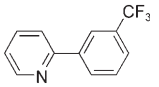
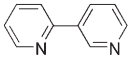
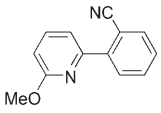
Table 3: The reaction of **A** and **B** with aryl chlorides.[a]



Entry	Borate	Product	Yield [%][b]
1	**A**		73
2	**A**		76
3	**A**		70
4	**A**		78
5	**A**		57
6	**A**		92
7	**B**		76[c]

[a] Reaction conditions: 1 equiv of aryl or heteroaryl chloride, 1.5 equiv of 2-pyridylborate, 3.0 equiv of KF, dioxane (3 mL mmol^{-1} halide), cat. [$Pd_2(dba)_3$], L:Pd = 3:1. [b] Yield of isolated product based upon an average of two runs. [c] 1.5% [$Pd_2(dba)_3$] used instead of 1.0%.

tives. This represents the first relatively general Suzuki–Miyaura cross-coupling reaction of these substrates with aryl and heteroaryl bromides and chlorides.

Experimental Section

General procedure for the Pd-catalyzed Suzuki–Miyaura reaction of lithium triisopropyl 2-pyridylborates with aryl bromides: An oven-dried re-sealable Schlenk tube with a Teflon screw valve was charged with [$Pd_2(dba)_3$] (1.0–1.5%), **1** (6.0–9.0%), lithium triisopropyl 2-pyridylborate (0.375 mmol), and anhydrous KF (43.5 mg, 0.75 mmol). The Schlenk tube was capped with a rubber septum and then evacuated and backfilled with argon (this sequence was carried out an additional time). 1,4-Dioxane (0.75 mL) was added by syringe, through the septum, followed by the addition of the aryl halide (0.25 mmol) in a like manner (aryl halides that were solids were added with the other solid reagents). The septum was then replaced with a Teflon screw valve and the Schlenk tube was sealed. The reaction mixture was heated to 110°C until the aryl halide had been completely consumed (as determined by gas chromatography) and was allowed to cool to room temperature. The reaction solution was then filtered through a thin pad of silica gel (eluting with ethyl acetate) and the eluent was concentrated under reduced pressure. The crude material so obtained was purified by flash chromatography on silica gel.

Received: March 28, 2008
Published online: May 19, 2008

Keywords: C–C coupling · nitrogen heterocycles · palladium · Suzuki–Miyaura coupling

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[7] During the development of this work, we discovered unpublished results from CombiPhos Catalysts, Inc. utilizing 2-pyridyl pinacol boronate esters. Chlorodialkyl phosphines and dialkyl phosphine oxides were used as supporting ligands. However, we found that 2-pyridyl pinacol boronate ester was not effectively coupled under our conditions as seen in Table 1.

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