

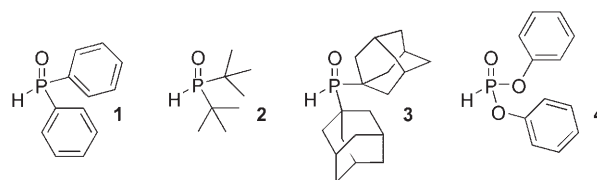
Cross-Coupling Reactions

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



Scheme 1. Effective phosphite and phosphine oxide ligands.

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

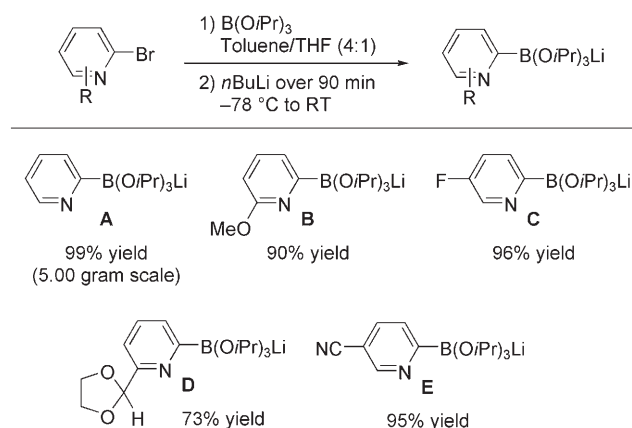
$n\text{Bu}-\text{C}_6\text{H}_4-\text{Br} \xrightarrow[\text{Dioxane, 110 } ^\circ\text{C, 20 h}]{1.0\% [\text{Pd}_2(\text{dba})_3]:6.0\% \text{ 1 (Pd/Ligand = 1:3) Base}} \text{Product}$				
Entry	Ar–BR ₃	Base	GC Yield [%]	Conversion [%]
1		KF	0	< 10
		NaOtBu	8	36
2		KF	0	< 10
		NaOtBu	49	73
3		KF	6	43
		NaOtBu	15	100
4		KF	0	< 10
		NaOtBu	10	37
5		KF	85	100
		NaOtBu	68	100

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-

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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 $[\text{Pd}_2(\text{dba})_3]/\mathbf{1}$ 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 $[\text{Pd}_2(\text{dba})_3]/\mathbf{2}$ 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 $[\text{Pd}_2(\text{dba})_3]/\mathbf{1}$ 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*-

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. $[\text{Pd}_2(\text{dba})_3]$, L: Pd = 3:1. [b] Yield of isolated product based upon an average of two runs. [c] 1.5 % $[\text{Pd}_2(\text{dba})_3]$ used instead of 1.0 %.

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 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. [Pd₂(dba)₃], L: Pd = 3:1. [b] Yield of isolated product based upon an average of two runs. [c] 1.5% [Pd₂(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 [Pd₂(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.

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