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A Convenient and General Method for Pd-Catalyzed Suzuki Cross-Couplings of Aryl Chlorides and Arylboronic Acids[**]

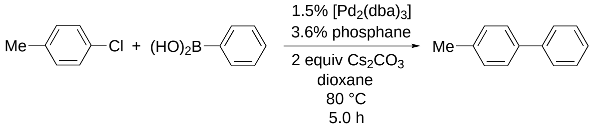
Adam F. Littke and Gregory C. Fu[*]

In memory of George Büchi

The Suzuki reaction has emerged as an extremely powerful method for the cross-coupling of aryl bromides, iodides, and triflates with arylboronic acids.[1] As compared with the Stille cross-coupling,[2] the Suzuki reaction possesses the practical advantages that the boron-containing by-products, unlike the tin-containing by-products of the Stille process, are nontoxic and are easily separated from the desired product.[3] One current limitation in the scope of the Suzuki reaction is its inefficiency when aryl chlorides are employed as substrates. Although there have been several accounts of Suzuki reactions of electron-poor aryl chlorides,[4–6] to the best of our knowledge there has been only one report of a coupling of an electron-neutral or an electron-rich aryl chloride (41% yield).[5i] In view of the increased availability and decreased expense of aryl chlorides relative to aryl bromides and iodides,[4a] this methodological gap becomes all the more significant. Herein we describe a solution to this problem: specifically, the development of conditions under which Suzuki cross-couplings of an array of electronically and sterically different aryl chlorides and arylboronic acids proceed in excellent yield with commercially available reagents (see Table 3).

In early experiments we established that 4-chlorotoluene and phenylboronic acid are efficiently cross-coupled in the presence of 1.5% $[Pd_2(dba)_3]$ (dba = dibenzylideneacetone), 3.6% $PtBu_3$, and two equivalents of Cs_2CO_3 (dioxane, 80 °C; 86% yield by GC after 5.0 h; Table 1, entry 9). We observe little or no coupling in the absence of phosphane (entry 1) or in the presence of triarylphosphanes (entries 2–5) and chelating phosphanes (entries 6 and 7). Of the ligands that we have examined to date, only PCy_3 approaches $PtBu_3$ in effectiveness (entries 8 and 9). , The use of a phosphane:Pd ratio between 1 and 1.5 appears to be optimal with $PtBu_3$ as the ligand, an observation that suggests that the active palladium catalyst bears a single $PtBu_3$ group. Thus, we believe that the steric bulk and the electron-richness of $PtBu_3$ are critical for this unprecedented reactivity.[4, 7]

Table 1. Effect of phosphane on the palladium-catalyzed Suzuki cross-coupling of aryl chlorides.



Entry	Phosphane	Yield [%] (GC)
1	–	0
2	PPh_3	0
3	BINAP[a]	0
4	dppf[b]	0
5	$P(o\text{-tol})_3$	10
6	$Ph_2P(CH_2)_3PPh_2$	0
7	$Cy_2P(CH_2)_2PCy_2$	0
8	PCy_3	75
9	$PtBu_3$	86

[a] BINAP = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl. [b] dppf = 1,1-bis(diphenylphosphanyl)ferrocene.

Among the bases listed in Table 2, Cs_2CO_3 has proved to be the base of choice (entry 6).[8, 9] In the absence of base (entry 1) or in the presence of other bases commonly used in Suzuki reactions (entries 2–5), cross-coupling proceeds with diminished efficiency. In contrast to most Suzuki cross-couplings,[1] only one equivalent of base is required for our process (95% GC yield after five hours with 1.2 equiv Cs_2CO_3). We have found $[Pd_2(dba)_3]$ and dioxane to be best among the palladium sources (for example, $Pd(OAc)_2$) and solvents (for example, THF) that we have surveyed thus far.

A wide array of electronically and structurally diverse aryl chlorides and arylboronic acids can be cross-coupled very efficiently under these conditions (1.5% $[Pd_2(dba)_3]$, 3.6% $PtBu_3$, 1.2 equiv Cs_2CO_3).[10] Thus, with respect to the aryl chloride, both electron-neutral 4-chlorotoluene and electron-

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[*] Prof. Dr. G. C. Fu, A. F. Littke
Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139 (USA)
Fax: (+1) 617-258-7500
E-mail: gcf@mit.edu

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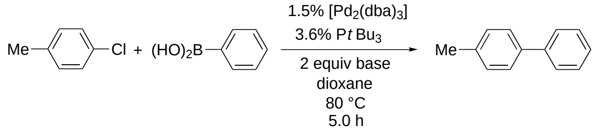
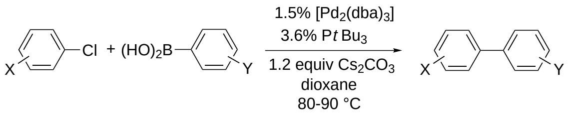
Table 2. Effect of base on the palladium-catalyzed Suzuki cross-coupling of aryl chlorides.



Entry	Base	Yield [%][a]	Entry	Base	Yield [%][a]
1	–	3	4	NEt_3	50
2	Na_2CO_3	23	5	K_3PO_4	83
3	K_2CO_3	29	6	Cs_2CO_3	86

[a] Determined by gas chromatography.

Table 3. Scope of the $[\mathrm{Pd_2(dba)_3}]/\mathrm{P}t\mathrm{Bu_3}/\mathrm{Cs_2CO_3}$-catalyzed Suzuki cross-coupling of aryl chlorides.



Entry	X	Y	Yield [%]
1	4-Me	H	87
2	4-MeCO	H	91
3	4-MeO	H	89
4	4-NH_2	H	92
5	4-Me	4-CF_3	86
6	4-Me	4-OMe	82
7	2-Me	H	90
8	2-Me	2-Me	87

poor 4-chloroacetophenone react with $\mathrm{PhB(OH)_2}$ to provide the biaryl product in excellent yield (Table 3, entries 1 and 2). More remarkable is our observation that even extremely electron-rich aryl chlorides, including 4-chloroanisole and 4-chloroaniline, couple cleanly with $\mathrm{PhB(OH)_2}$ in the presence of this catalyst system (entries 3 and 4).

The cross-coupling also proceeds smoothly regardless of the electronic character of the boronic acid component. More electron-rich boronic acids have been reported to be less reactive partners in other Suzuki reactions.[1] With our catalyst system, trifluoromethyl- and methoxy-substituted benzeneboronic acids couple with 4-chlorotoluene to produce the desired biaryls in excellent yields under comparable reaction conditions (Table 3, entry 5: 5 h at 80 °C; entry 6: 9 h at 80 °C).

Finally, this $[\mathrm{Pd_2(dba)_3}]/\mathrm{P}t\mathrm{Bu_3}$-catalyzed cross-coupling is tolerant of *ortho* substitution in both the aryl halide and the arylboronic acid (Table 3, entries 7 and 8). For example, sterically hindered 2,2′-dimethyl-1,1′-biphenyl is formed in 87% yield after seven hours at 80 °C.

In summary, we have developed a general method for the Suzuki cross-coupling of aryl chlorides with arylboronic acids. Our catalyst system, which employs readily available components (1.5% $[\mathrm{Pd_2(dba)_3}]$, 3.6% $\mathrm{P}t\mathrm{Bu_3}$, 1.2 equiv $\mathrm{Cs_2CO_3}$), couples effectively a broad spectrum of substrates, to provide the desired biaryls in excellent yields. Because of the accessibility of aryl chlorides and the relatively innocuous nature of the boron-containing by-products of Suzuki reactions, we anticipate that this method is likely to find widespread use in synthetic organic chemistry. Future work will be directed at further optimization of this process and on the development of related coupling reactions.[11]

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[10] General experimental conditions: A solution of aryl chloride (0.833 mmol; in dioxane (0.5 – 0.7 mL)) and a solution of $\mathrm{P}t\mathrm{Bu_3}$ (0.030 mmol; in dioxane (0.3 mL)) were added in turn to a Schlenk tube charged with $[\mathrm{Pd_2(dba)_3}]$ (0.0125 mmol), boronic acid (0.875 mmol), $\mathrm{Cs_2CO_3}$ (1.00 mmol), and a magnetic stir bar under an atmosphere of nitrogen. The Schlenk tube was stirred at 80 °C for five hours. The reaction mixture was then cooled to room temperature, diluted with $\mathrm{Et_2O}$, filtered through a pad of Celite, concentrated, and purified by flash chromatography.

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