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LETTERS

A Convenient Palladium/Ligand Catalyst for Suzuki Cross-Coupling Reactions of Arylboronic Acids and Aryl Chlorides

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Abstract: The Pd/ligand **A** catalyst efficiently catalyzes general Suzuki biaryl cross-coupling reactions of arylboronic acids and aryl chlorides.

Keywords: Arylboronic acid; aryl chloride; catalysis; palladium; phosphine.

The Suzuki cross-coupling reactions of arylboronic acids and aryl halides represent the most versatile, pragmatic, and extensively utilized methods for the synthesis of biaryls,[1] which are an important class of compounds for many applications including pharmaceuticals, polymers, advanced materials, liquid crystals, and ligands. The scope of Suzuki biaryl cross-coupling reactions has been extensively studied for aryl- bromide and iodide substrates. However, the efficient couplings of the comparatively inexpensive and readily available aryl chloride substrates, which represent the most attractive candidates for industrial applications of these reactions, have been generally limited to electron-deficient aryl chlorides or nickel-catalyzed reactions.[2,3] Recently, research groups of Buchwald and Fu, independently, have described Pd/L catalysts for efficient cross-couplings of arylboronic acids and electron-neutral or electron-rich aryl chlorides.[4] Herein, we describe a new, simple, readily accessible, air-stable, and efficient Pd/L catalyst for general Suzuki cross-coupling reactions of arylboronic acids and aryl chlorides.

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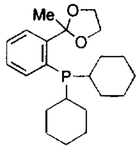
As part of our ongoing efforts to identify, develop, and utilize high throughput methods for rapid discovery of useful materials,[5] we recently reported the discovery of a new, general and efficient homogeneous $Pd(dba)_2$/ligand **A** catalyst for the aminations of aryl chlorides.[6] We have now investigated the utility of this catalyst in catalyzing the cross-coupling reactions of arylboronic acids and aryl chlorides.



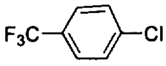
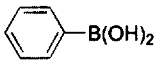
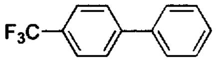
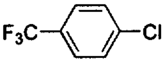
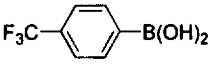
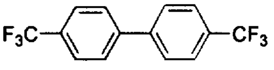
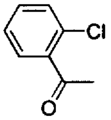
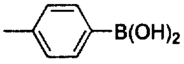
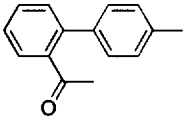
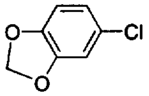
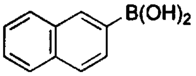
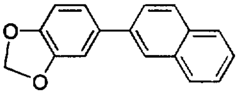
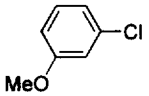
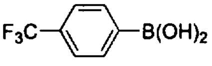
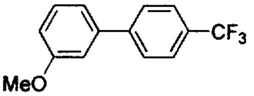
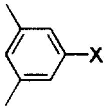
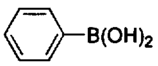
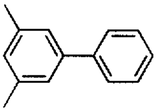
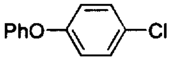
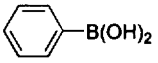
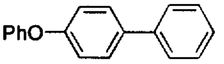
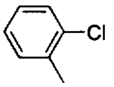
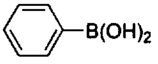
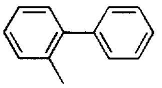
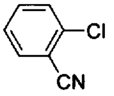
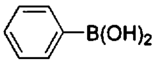
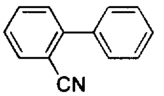
Ligand A

The $Pd(dba)_2$/Ligand **A** catalyst was found to be generally efficient in catalyzing the cross-coupling reaction of arylboronic acids and aryl chlorides (Table 1).[7] A variety of arylboronic acids coupled efficiently with aryl chlorides to afford the desired biaryls in high isolated yields (Table 1). Arylboronic acids and aryl chlorides containing both electron-deficient and electron-rich substituents participated effectively. Aryl chlorides containing *ortho* substituents also reacted effectively. The reaction of *ortho*-chlorotoluene with *ortho*-toluylboronic acid also proceeded to completion to afford the desired sterically demanding biaryl product, 2,2'-dimethyl-1,1'-biphenyl, in quantitative GC yield. Aryl bromides and iodides were also found to be suitable substrates.

The high efficiency of the $Pd(dba)_2$/ligand **A** catalyst can be ascribed to both the overall structure of ligand **A** and the presence of the PCy_2 unit. The rigid phenyl backbone-derived structure most likely favors the generation and stability of the chelating "(P,O)-Pd" intermediates which appear to be most suitable for catalysis,[8] while the PCy_2 unit makes the Pd-center sufficiently electron-rich to promote oxidative addition of the usually unreactive aryl chlorides.

In summary, we have shown that the $Pd(dba)_2$/Ligand **A** catalyst efficiently catalyzes the cross-coupling reactions of arylboronic acids and aryl chlorides. The simplicity, ready accessibility, low cost, and air-stability of ligand **A** makes $Pd(dba)_2$/ligand **A** catalyst a more convenient candidate for general Pd/L-catalyzed Suzuki cross-coupling reactions of arylboronic acids and aryl chlorides.[9]

Table 1. Pd/Ligand A-Catalyzed Suzuki Cross-Coupling of Arylboronic Acids and Aryl Chlorides.[a]

Entry	Aryl Chloride	Arylboronic acid	Product	Yield%
A[b]				92
B				97
C				83
D				96
E				93
				
F	X = Cl			94
G	X = Br			88
H	X = I			96
I[c]				94
J[d]				95
K				91

[a] General reaction conditions: 1.0 equiv of aryl halide, 1.5 equiv of boronic acid, 3.0 equiv of CsF, 0.5 - 1 mol % $Pd(dba)_2$, 1.5 - 3 mol % ligand **A**, 1,4-dioxane or toluene (4 ml), 100-110 °C. Yields correspond to isolated material of > 95 % purity by GC & NMR. Reaction time = 5 - 20 h unoptimized, complete conversion of aryl chloride. [b] 80 °C. [c] *o*-Xylene as solvent, 130 °C, 2 mol% $Pd(dba)_2$. [d] 2 mol% $Pd(dba)_2$.

References and Notes

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1 For a review of metal-catalyzed Suzuki biaryl cross-couplings, see (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483. (b) Suzuki, A. *In Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Chapter 2. For a review of general metal-catalyzed biaryl cross-couplings, see (c) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263-303.

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6 Bei, X.; Guram, A. S.; Turner, H. W.; Weinberg, W. H. *Tetrahedron Lett.* **1999**, *40*, 1237–1241.

7 *Representative Experimental Procedure:* A mixture of aryl chloride (1.0 mmol), aryl boronic acid (1.5 mmol), CsF (3 mmol), $Pd(dba)_2$ (0.005 – 0.02 mmol), ligand **A** (0.015 – 0.06 mmol) in 1,4-dioxane or toluene (4 mL) was heated at 100 - 110 °C. The reaction was cooled to room temperature, taken up in diethyl ether (125 mL), washed with water (2 X 30 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel to afford desired biaryl product, after drying under vacuum.

8 Bei, X.; Uno, T. Norris, J.; Turner, H. W.; Weinberg, W. H.; Guram, A. S.; Petersen, J. L. *Organometallics*, **1999**, in press.

9 Ligand **A** is available in two synthetic steps as a white air-stable solid in 90 % overall yield from inexpensive, commercially available materials (see ref. 6 and 8). In comparison, the binaphyl-based (P,N)-ligand (ref. 4a) requires a 3-4 step synthetic sequence involving relatively expensive materials and lower yields, while the $P(^tBu)_3$ ligand (ref. 4b), although commercially available, is not convenient to use due to its potentially pyrophoric nature.