

A Highly Active Suzuki Catalyst for the Synthesis of Sterically Hindered Biaryls: Novel Ligand Coordination

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The Suzuki cross-coupling is among the most powerful C–C bond-forming transformations available to synthetic organic chemists.¹ This transformation enjoys a broad scope and wide functional group tolerance. In reactions involving sterically hindered substrates, however, limited success has been realized.^{2,3} Thus, a general method for the coupling of two hindered arenes where each reactant possesses two ortho substituents has yet to be realized.^{1c,3,4} Johnson and Foglesong have reported a Suzuki coupling to prepare an unsymmetrical biaryl with tetra-ortho substitution in 12% yield.^{3a} In his elegant work, Fu reported an example of the preparation of a tetra-ortho-substituted biaryl in 76% yield (Negishi coupling); however, the two ortho substituents were smaller than a methyl group.^{4e} As part of our studies of the Suzuki coupling,⁵ we report a general catalyst to prepare tetra-ortho-substituted unsymmetrical biaryls. We also report new ligands for such processes and crystallographic evidence for an unusual π -coordination mode we previously postulated as important to catalytic efficiency.⁶ In initial studies with biphenyl-based ligands **1a–c**, significant amounts of aryl bromide reduction were observed (Table 1, entries 1–3).⁷ The use of ligands bearing either diisopropyl or diphenylphosphino groups yielded increased amounts of mesitylene (entries 4, 5). Increasing the size of the phosphine alkyl groups to *tert*-butyl resulted in the production of <1% of the desired biaryl. Doubly ortho-substituted ligand **2** furnished a slightly improved catalyst. Phenanthrene-based ligand **3a** gave superior results (entry 8). The reaction proceeded to completion in less than 24 h with 4 mol % Pd and 8 mol % **3a**, affording the biaryl in 91% yield (GC) with 9% mesitylene. The phenanthrene ring of **3a** is critical since lower conversion and biaryl:arene ratios were observed with naphthyl-based ligand **4** (entry 10). In all cases, <4% homocoupling of either reactant was detected.

Phosphine **3a** and diphenyl analogue **3b** proved in general to be excellent ligands for Suzuki cross-coupling reactions to form sterically hindered tetra-ortho-substituted biaryls in good yields (Table 2). Ortho substituents such as methyl, primary alkyl, phenyl, and alkoxy groups are accommodated. It was necessary to use 2.0 equiv of the boronic acid to effect complete consumption of the aryl bromide in some cases, presumably due to competitive protodeboronation (entries 2, 3, 5–7, 11).² While **1a** was not suitable as a ligand for the synthesis of biaryls with four methyl groups, it could be used to prepare products in which one or two of the four ortho substituents were methoxy groups (entries 8, 9). In several examples, *o*-xylene was superior to toluene as a solvent (entries 2, 3, 5–7). In Pd-catalyzed couplings involving aryl chlorides, electron-rich di- or trialkylphosphines are usually used as ligands.^{2f,4,8} Thus, it was surprising that using **3b**, 9-chloroanthracene was reacted in good yield (entry 7).

Unfortunately, the reaction conditions above were not suitable when the aryl halide possessed an ortho electron-withdrawing group; significant amounts of the phenol, presumably due to water present

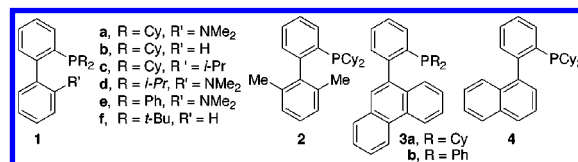


Figure 1. Hindered biarylphosphines.

Table 1. Ligand Effects in the Coupling of Hindered Substrates^a

entry	ligand	conv (%)	biaryl (%) ^b	biaryl/Ar–H
1	1a	47	33	2.3
2	1b	20	10	0.9
3	1c	74	40	1.9
4	1d	68	34	1.6
5	1e	49	25	1.3
6	1f	21	<1	<0.3
7	2	56	48	5.0
8	3a	100	91	10
9	3a^c	57	50	7.4
10	4^c	20	16	4.1

^a Reaction conditions: 1.0 equiv of ArBr, 1.4 equiv of Ar'B(OH)₂, 3.0 equiv of K₃PO₄, toluene, 2 mol % Pd₂(dba)₃, 8 mol % ligand, 110 °C, 17–24 h. ^b GC yield. ^c 0.5 mol % Pd₂(dba)₃, 1.2 mol % ligand used.

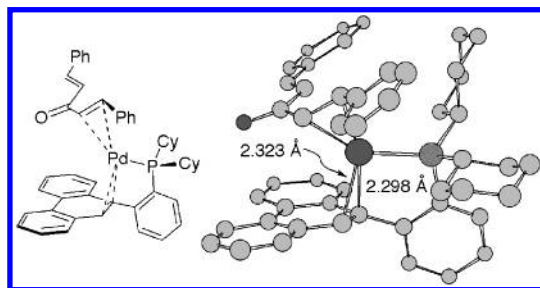


Figure 2. X-ray crystal structure of **3a**/Pd(dba)₃.

in the K₃PO₄ and/or boronic acid, were isolated. The use of DPEPhos as ligand resulted in decreased phenol formation, and further inhibition of this side reaction was realized by the inclusion of freshly activated 4 Å molecular sieves. Thus, a number of hindered aryl bromides with ortho electron-withdrawing groups were efficiently coupled with 2,6-dimethylphenyl boronic acid (Table 3). The DPEPhos-based system could also be used with unactivated aryl bromides (entry 4). The **3b**/Pd catalyst failed to chemoselectively activate the bromo group. In cases directly comparing the **3b**- and DPEPhos-based systems, **3b**/Pd catalyst afforded higher conversions of the aryl halide and higher biaryl:arene ratios.

To determine what features made **3a,b** superior in these challenging cross-couplings, we sought to prepare and characterize a **3a**/Pd complex. Mixing **3a** and Pd₂(dba)₃ in toluene at room temperature followed by chromatographic purification yielded the desired complex. Crystals suitable for X-ray diffraction were grown

Table 2. Hindered Suzuki Couplings Using Biaryl-Based Ligands^a

Entry	ArBr	Ar'B(OH) ₂	Product	L	mol% Pd/L	Yld, %
1				3a	4/8	82
2				3b	4/8	70 ^{b,c,d}
3				3b	2/4	90 ^{b,c}
4				3a	4/8	98
5 (Br)				3a	1/1.2	80 ^{b,c}
6 (Cl)				3a	1/1.2	82 ^{b,c}
7				3b	2/2.4	93 ^{b,c}
8				1a	5/10	78
9				1a	5/10	89
10				3b	10/12	60
11				3a	5/6	58 ^{b,d,e}
12				3a	4/4.8	82

^a Reaction conditions: 1.0 equiv of ArX, 1.5 equiv of Ar'B(OH)₂, 3.0 equiv of K₃PO₄, Pd₂(dba)₃, ligand, toluene, 110 °C. Isolated yields (average of two runs) of compounds estimated to be >95% pure as determined by ¹H NMR and GC or combustion analysis. ^b 2.0 equiv of Ar'B(OH)₂ used. ^c *o*-Xylene as solvent. ^d 120 °C. ^e 1.0 equiv of 2,6-dimethylphenol as additive.

by evaporation of a pentane solution (Figure 2). The key features of this structure are the short C⁹–Pd and C¹⁰–Pd bond distances (2.298 and 2.323 Å, respectively). Similar Pd–aryl interactions have been reported in Pd (II) complexes.⁹ The C⁹–C¹⁰ bond of phenanthrene is likely a better π -donor than a phenyl or naphthyl moiety, as it resides in a less aromatically stabilized ring.¹⁰

In summary, we have described a general catalyst system for the synthesis of tetra-ortho-substituted biaryls via the Suzuki cross-coupling reaction. The most efficient catalyst described is based on the phenanthrene-substituted ligand **3a**. Crystallographic analysis of **3a**/Pd(dba)₃ revealed an unusual π -coordination of the phenanthrene moiety, the first of its type for a Pd (0) complex.

Table 3. Suzuki Couplings of Hindered Electron-Poor Aryl Bromides^a

Entry	ArBr	Ar'B(OH) ₂	Product	mol% Pd	T (°C)/t (h)	Yld, %
1				10	130/48	69
2				5	110/21	87
3				5	110/19	89
4				6	120/24	96

^a Reaction conditions: 1.0 equiv of ArBr, 2.0 equiv of Ar'B(OH)₂, 3.0 equiv of K₃PO₄, Pd₂(dba)₃, DPEPhos (L:Pd = 1.2:1), toluene, activated 4 Å molecular sieves. Isolated yields (average of two runs) of compounds estimated to be >95% pure as determined by ¹H NMR and GC or combustion analysis.

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Supporting Information Available: Experimental procedures, characterization of products, and X-ray crystal structure data for **3a**/Pd(dba)₃ (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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