

A General Method for the Suzuki–Miyaura Cross-Coupling of Sterically Hindered Aryl Chlorides: Synthesis of Di- and Tri-ortho-substituted Biaryls in 2-Propanol at Room Temperature

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Transition metal-mediated cross-coupling reactions represent an extremely versatile tool in organic synthesis.¹ Reactions leading to C–C bond formation are often key steps in a wide range of organic processes ranging from supramolecular chemistry² to natural product synthesis.³ Among these, the Suzuki–Miyaura reaction, involving the coupling of an aryl chloride with an organoboron reagent, has emerged as a favorite.^{4,5} Palladium–phosphine complexes have been the most commonly employed catalysts for the Suzuki–Miyaura reaction.^{6,7}

Some of the challenges associated with cross-coupling reactions have focused on the use of “unreactive” aryl chlorides as coupling partners in view of their attractive cost and readily available diversity.⁸ Efforts aimed at developing catalytic systems that perform at mild reaction temperatures in short times using low catalyst loadings are an ongoing effort. Some progress has been achieved in this area.^{7–9} A remaining challenge is to achieve cross coupling under these optimum conditions for highly hindered biaryl junctures such as poly-ortho-substituted biaryls.¹⁰

N-Heterocyclic carbenes (NHC)¹¹ and metallacycle scaffolds¹² have been used as alternatives to tertiary phosphines in cross-coupling reactions.^{11–13} The NHC are sterically demanding ligands with better σ -donor ability than tertiary phosphines. The metallacycle framework has shown to be quite robust and capable of high turnover numbers in the Heck reaction.¹² We recently reported a new class of catalysts combining the highly donating and sterically demanding NHC with the stability imparted by the palladacycle framework (Figure 1). These catalysts displayed excellent performance in aryl amination and α -arylation of ketones using low catalyst loading.¹⁴ We now report the activity of one of these catalysts, **1**, in the Suzuki–Miyaura cross-coupling reaction.

During the course of performing experiments on the catalytic dehalogenation of aryl chlorides with **1** using technical grade 2-propanol (1.5 mL) as the solvent and Na^tBu as base (1.2 equiv), we achieved very high yields of dehalogenated product at room temperature in minutes.¹⁵ In view of similarities between both processes,^{7a,16} the activity of this catalyst/solvent system was examined in the Suzuki–Miyaura reaction. To minimize and hopefully eliminate the undesirable dehalogenation of the aryl chloride under catalytic conditions, this substrate was slowly added to the catalytic reaction mixture. In test reactions, using phenylboronic acid as coupling partner, various aryl chlorides (activated and unactivated) afforded the corresponding biaryl products in very short reaction times at room temperature in high yields (Table 1).

The use of anhydrous 2-propanol did not lead to improved yields or shorter reaction times. This is a true testimony to the robustness of the catalytic species. The phosphine congeners of **1** do not afford product under these reaction conditions,¹⁷ highlighting the need for the NHC supporting ligand in this transformation.

The present methodology was also successfully tested in reactions leading to di- and tri-ortho-substituted biaryls. Reactions under these

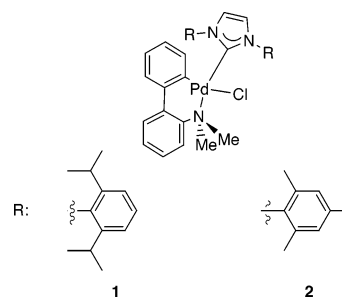


Figure 1. NHC-bearing palladacycles.

Table 1. Suzuki–Miyaura Cross-Coupling of Aryl Chlorides with Phenylboronic Acid

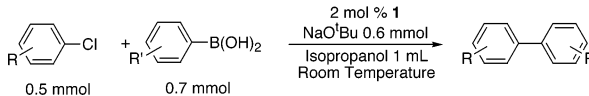
entry	aryl chloride	product	time(min)	%yield ^a
1			75	95(95)
2			45	91(85)
3			90	95(87)
4			60	96(84)
5			90	95(94)
6			90	95(93)
7			120	96(95)

^a GC yield (isolated yield), average of two runs.

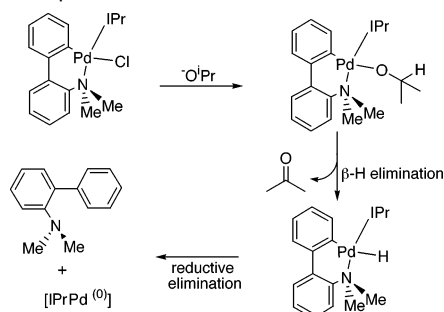
mild conditions afford high yields of desired products in short reaction times (Table 2). A larger-scale experiment (2.5 mmol of aryl chloride) was carried out for the reaction in entry 4 and afforded 428 mg (87%) of the desired product in 75 min.

To gain insight on the exact mechanism at play in this system, the organic fragment liberated in the initial activation step of the catalysis was isolated and fully characterized in reactions involving **1**, Na^tBu and 2-propanol. After flash chromatography, 2-(dimethylamino)-biphenyl was isolated in quantitative yield. When the base was not added, the palladacycle was recovered intact. This suggests an activation pathway involving the formation of a palladacycle hydride species that subsequently undergoes reductive elimination of the biphenyl moiety (Scheme 1). The [(IPr)Pd]

Table 2. Synthesis of Di- and Tri-ortho-substituted Biaryls

					
entry	aryl chloride	boronic acid	product	time(min)	%yield ^a
1				50	85(77)
2				60	96(85)
3				75	98(88)
4				75	88(79)
5				75	95(87)

^a GC yield (isolated yield), average of two runs.

Scheme 1. Proposed Mechanism for the Activation of **1**

species generated then becomes available for oxidative addition of aryl chloride and initiates the catalytic cycle.

In summary, we have described a catalytic system that is general for the Suzuki–Miyaura cross-coupling reaction involving aryl chlorides and boronic acids at room temperature. Reactions reach completion in short reaction times. Sterically hindered unactivated aryl chlorides couple with sterically hindered boronic acids under these conditions and lead to di- and tri-ortho-substituted biaryls in high yields. The use of technical grade 2-propanol as solvent makes this system very attractive in view of its low cost and environmental friendliness. Studies aimed at elucidating the exact mechanistic details involved in this transformation are presently being examined with this and related palladacycles.

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Supporting Information Available: Experimental procedures and characterization of products (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>

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