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Microwave-Promoted Suzuki Reactions of Aryl Chlorides in Aqueous Media

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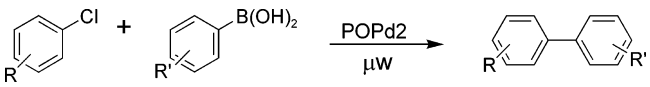
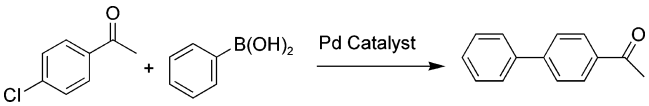


The microwave-promoted Suzuki coupling reaction of aryl chlorides with boronic acids performed in an aqueous media was studied using the air- and moisture-stable catalyst POPd2 (dihydrogen di-μ-chlorodichlorobis(di-*tert*-butylphosphinito-κP)dipalladate (2−)). This catalyst system under microwave conditions (150 °C, 15 min) provided coupled products with yields ranging from 64% to 99%. This method tolerated a variety of substituents and sterically hindered substrates.

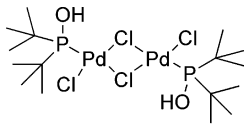
The palladium-catalyzed cross-coupling reaction of aryl halides and triflates has been shown to be a powerful and frequently employed method for the formation of carbon−carbon bonds.[1,2] The use of aryl chlorides in this reaction is now of great interest to synthetic chemists due to the availability of a broad range of inexpensive materials in this class.[2] A number of authors have published on the cross coupling of aryl chlorides with boronic acids using various palladium catalyst systems, which have provided chemists access to several versatile methods across a variety of aryl chlorides.[3] However, these methods all require inert conditions, which represent obstacles for the utility of this chemistry in parallel synthesis.

Recently, Li reported an air-stable palladium complex POPd2 **1** (dihydrogen di-μ-chlorodichlorobis(di-*tert*-butylphosphinito-κP) dipalladate that could be used as an efficient catalyst in the cross-coupling reaction of aryl chlorides with boronic acids.[4] In our initial attempt to apply this catalyst system to parallel synthesis, we found that the reaction usually gave 10−30% yield of desired product with a major side product identified as the homocoupling of the boronic acids.

SCHEME 1[a]



[a] Optimal conditions: 1 equiv of aryl chloride, 1.5 equiv of phenylboronic acid, 3 mol % of POPd2, 4 equiv of Cs_2CO_3, 12 mol % of TBAI, DMF/H_2O, microwave, 150 °C, 15 min.



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To improve the reaction yields, we turned to microwave conditions as part of our ongoing efforts to apply microwave chemistry to parallel synthesis.[5] Microwave irradiation has been reported to promote metal-mediated reactions such as the Suzuki cross coupling.[6] Recently, Leadbeater and co-workers reported the microwave-promoted Suzuki cross-coupling reaction in aqueous media without ligands.[7] However, the yields related to chlorides were poor to moderate compared to those of bromides.

We chose an aqueous solvent system (DMF/H_2O, 5:1) to start our experiments based on Leadbeater's work, the documented advantages of employing a polar and ionically conducting solvent for microwave heating,[8] and the ability to dissolve cesium carbonate, the base of choice for this chemistry. In fact, this solvent system gave better results than other neat solvents such as DMF, THF, or dioxane. We also found that the use of *tert*-butylammonium iodide (TBAI) as an additive was beneficial in this mixed solvent system, similar to previous reports employing neat water as the solvent.[9]

Based on these results, we undertook the optimization of the initial reaction conditions by varying temperature, ratio of reactants, and percentage of catalysts using 4-Cl-acetophenone and phenyl boronic acid as a model reaction (Scheme 1). The reactions were evaluated by monitoring the consumption of the starting materials and the appearance of either the desired product or the homocoupling side product by HPLC. First, temperature variation was tested, which appeared to be crucial to the reaction. Below 120 °C, the homocoupling side product was ob-

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(4) (a) $POPd_2$ catalyst is commercially available exclusively from CombiPhos Catalysts, Inc. Website: www.combiphos.com. (b) Li, G. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1513−1516. (c) Li, G. Y.; Zheng, G.; Noonan, A. F. *J. Org. Chem*. **2001**, *66* (25), 8677−8688. (d) Li, G. Y. *J. Org. Chem.* **2002**, *67* (11), 3643−3650.

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(7) Leadbeater, N. E.; Marco, M. *Org. Lett.* **2002**, *4*, 2973−2976.

(8) Review: Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225−9283.

(9) Leadbeater, N. E.; Marco, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1407−1409.

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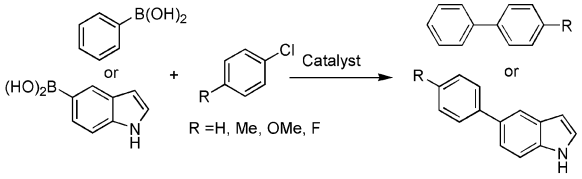
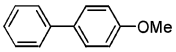
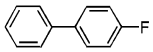
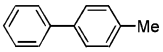
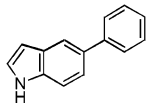
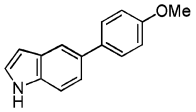
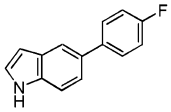
TABLE 1. Suzuki Cross-Coupling Reactions Using Various Pd Catalysts with Microwave and Conventional Heating[a]

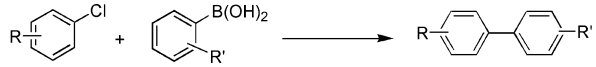


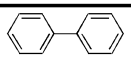
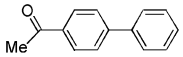
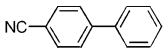
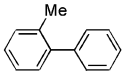
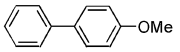
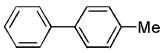
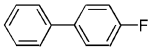
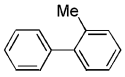
	Product	POPd2	$Pd(OAc)_2$	$Pd(PPh_3)_4$
		Yield[b] (%)		
1		85 (31)	59 (38)	11 (10)
2		76 (39)	66 (42)	21 (36)
3		82 (43)	68 (48)	16 (28)
4		76 (53)	67 (44)	10 (52)
5		77 (28)	63 (30)	<10 (46)
6		78 (39)	48 (41)	<10 (43)

[a] Reaction conditions: 1 equiv of aryl chloride, 1.5 equiv of phenylboronic acid, 3 mol % of Pd catalyst, 4 equiv of Cs_2CO_3, 12 mol % of TBAI, in DMF/H_2O (5/1), either microwave heating (150 °C, 15 min) or thermal heating (150 °C, 2 h). [b] Yields determined by UV quantification based on authentic samples, and the yields for thermal heating experiments are in parentheses.

served as the major component. Temperatures ranging from 180 to 200 °C favored decomposition products derived from the boronic acids. Ultimately, the optimal temperature was determined to be 150 °C on the basis of a number of experiments, and this was then used as a standard for the optimization of other parameters. Second, the ratio of boronic acid to aryl chloride was optimized. An excess of boronic acid is generally required for chloride coupling due to competitive protodeboronation reactions.[9] In our study, it was found that a 50% excess of the boronic acid based on chloride provided the best yield of the cross-coupled product. With a ratio of boronic acid to chloride greater than 1.5, we started to observe formation of homocoupling side products, which complicated the purification of the desired product. Finally, the effect of catalyst loading was examined. A range of 1−5 mol % of the catalyst was evaluated, and it was found that 3 mol % gave the most consistent results. It is noteworthy that in all cases a reaction time of 15 min was sufficient for complete consumption of the starting aryl chloride.

TABLE 2. Suzuki Cross-Coupling of Aryl Chlorides with Aryl Boronic Acids[a]

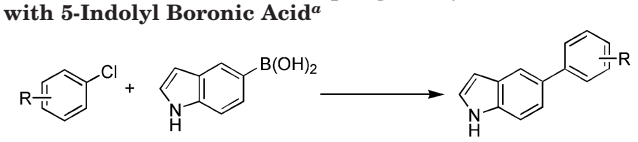


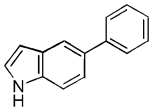
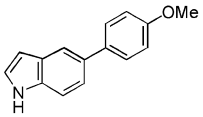
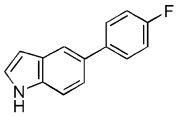
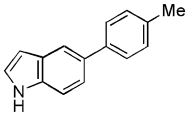
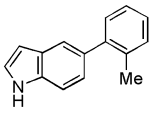
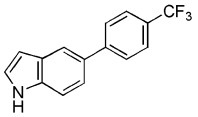
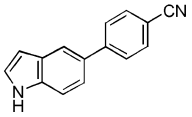
	R	R'	Product	Yield[b] (%)
1	H	H		68
2	4-C(O)Me	H		85
3	4-CN	H		84
4	2-Me	H		69
5	H	4-OMe		88
6	H	4-Me		75
7	H	4-F		82
8	H	2-Me		89

[a] Reaction conditions: 1 equiv of aryl chloride, 1.5 equiv of phenylboronic acid, 3 mol % of POPd2, 4 equiv of Cs_2CO_3, 12 mol % of TBAI, microwave, 150 °C, 15 min in DMF/H_2O (5/1). [b] Yields determined by UV quantification based on authentic samples.

To optimize the catalyst system further and the microwave conditions for this reaction, we performed the chemistry in the presence of various catalysts, with both microwave irradiation and conventional heating (Table 1). It was found that microwave heating did not improve the yields when $Pd(PPh_3)_4$ was employed as the catalyst and, in fact, in most cases actually reduced the yield of the desired product. However, the microwave conditions did provide consistent improvement in the chemistry with both $Pd(OAc)_2$ and $POPd_2$. Palladium acetate resulted in moderate yields with microwave irradiation as expected from Leadbeater's report.[7] On the other hand, the catalyst $POPd_2$ clearly outperformed the other catalysts

TABLE 3. Suzuki Cross-Coupling of Aryl Chlorides with 5-Indolyl Boronic Acid[a]



Entry	R	Product	Yield[b] (%)
1	H		61
2	4-OMe		72
3	4-F		76
4	4-Me		71
5	2-Me		68
6	4-CF_3		64
7	4-CN		75

[a] Reaction conditions: 1 equiv of aryl chloride, 1.5 equiv of phenylboronic acid, 3 mol % of POPd2, 4 equiv of Cs_2CO_3, 12 mol % of TBAI, microwave, 150 °C, 15 min in DMF/H_2O (5/1). [b] Isolated yield.

under the microwave conditions affording improved yields in all cases.

To further understand the scope of this chemistry, we tested a variety of boronic acids and aryl chlorides under the optimized conditions. From Table 2, it is clear that this is a general method that tolerates both electron-rich and electron-deficient substituents. This trend held true for both the boronic acids and the aryl chlorides. In addition, even an ortho-substituted boronic acid provided a very good yield of the corresponding biphenyl product (entry 8). On the basis of these results, the chemistry was now well suited for utilization in the parallel synthesis of diverse screening libraries.

Finally, we chose to apply this method to the synthesis of 5-arylindoles, a biologically relevant class of heterocycles. 5-Arylindoles have been reported to be agonists of the CNS neurotransmitter serotonin,[10] and Yang first reported the preparation of this class of compounds via the Suzuki cross-coupling of 5-indolylboronic acid with aryl bromides.[11] Our synthesis was initiated by preparing solutions of eight aryl chlorides, the catalyst $POPd_2$, Cs_2CO_3, and 5-indolylboronic acid in the appropriate solvents (Table 3). These reagent solutions were added to 2-dram vials mixed well and then transferred to microwave vials using a liquid handler (Tecan). The reaction mixtures were then subjected to microwave irradiation, which provided the 5-substituted indoles in good isolated yields, shown in Table 3.

In summary, we have developed a novel, general, and effective method for the Suzuki cross-coupling reaction of aryl chlorides by utilizing microwave irradiation and the POPd2 catalyst system in aqueous media. This method provides a convenient and versatile approach relative to existing methods that frequently require more rigorous conditions due to the air-sensitive nature of other catalysts. Hence, our synthetic strategy is quite adaptable to the automated parallel synthesis of small molecule libraries as illustrated in this report.

Supporting Information Available: Experimental procedures and ^1H and ^{13}C NMR spectra for compounds listed in Table 3. This material is available free of charge via the Internet at http://pubs.acs.org.

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