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Environmentally friendly synthesis of biaryls: Suzuki reaction of aryl bromides in water at low catalyst loadings

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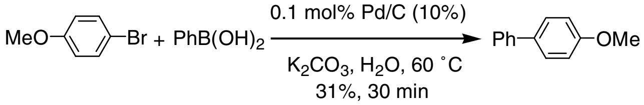
Abstract—Pd(DPPF)Cl_2 is shown to be an extremely active catalyst for the Suzuki reaction of aryl bromides in water. This green procedure provides biaryls in excellent yields and high turnover numbers (TONs) (TONs up to 870,000 for the reaction of 1-bromo-4-nitrobenzene and phenylboronic acid). A small amount of PEG-2000 also allows the recycling of the palladium catalyst for three times without any significant loss of catalytic activity.

Transition-metal-catalyzed cross-coupling reactions are extremely useful synthetic tools for carbon–carbon bond formation.[1] The Suzuki reaction,[2] palladium-catalyzed cross-coupling of aryl boronic acids and aryl halides, has become an attractive standard process for the synthesis of biaryls, which have a diverse spectrum of applications, ranging from pharmaceuticals to materials science.[3] Consequently, much attention has been directed toward improving the Suzuki reaction by designing various new ligands and palladium-precursors, such as bulky electron-rich phosphine ligands,[4] *N*-heterocyclic carbenes,[5] and palladacycles,[6] to accomplish efficient coupling of inexpensive and unreactive aryl bromides and chlorides. However, most of these ligands and palladium precursors are expensive, which significantly limits their industrial applications. Therefore, the development of efficient catalytic systems consisting of economical catalysts, bases, and solvents remains a highly desirable goal.

In addition, intensive efforts have been directed to reduce or eliminate the use of flammable, hazardous, and nonrenewable organic solvents in the Green chemistry focus area.[7] While a variety of environmentally benign media, such as ionic liquids, fluorous solvents,



Scheme 1.

Table 1. Optimizing the reaction conditions for Suzuki coupling of $PhB(OH)_2$ and 4-bromoanisole in water[a]

Entry	Pd (mol %)	T (°C)[b]	Time (h)	Convn[c]/ yield[d] (%)
1	10% Pd/C (0.1)	60	0.5	40/31
2	$Pd(OAc)_2$ (0.1)	60	0.5	19/—
3	$Pd(MeCN)_2Cl_2$ (0.1)	60	0.5	12/—
4	$Pd(PPh_3)_2Cl_2$ (0.1)	60	0.5	62/50
5	Pd(DPPE)Cl_2 (0.1)	60	0.5	74/61
6	Pd(DPPF)Cl_2 (0.1)	60	0.5	88/85
7	Pd(DPPF)Cl_2 (0.1)	80	0.5	100/98
8[e]	Pd(DPPF)Cl_2 (0.1)	80	0.5+0.5	100/95
9[f]	Pd(DPPF)Cl_2 (0.01)	110	3	98/96
10[f]	Pd(DPPF)Cl_2 (0.001)	110	48	82/78

[a] 5 mmol 4-Bromoanisole, 5.5 mmol $PhB(OH)_2$, 10 mmol K_2CO_3, 2 mL H_2O, Pd catalyst, DPPE = 1,2-bis(diphenylphosphino)ethane, and DPPF = 1,1′-bis(diphenylphosphino)ferrocene.
[b] Oil bath temperature.
[c] Determined by ^1H NMR of the crude product mixture.
[d] Isolated yield by flash chromatography.
[e] 5 mmol 4-Bromoanisole, 5.5 mmol $PhB(OH)_2$, and 10 mmol K_2CO_3 were added after 0.5 h stirring for the initial run.
[f] 5 mmol 4-Bromoanisole, 7 mmol $PhB(OH)_2$, and 10 mmol K_2CO_3 were used.

Keywords: Suzuki reaction; Biaryls; Turnover number; Green chemistry.

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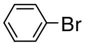
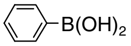
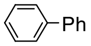
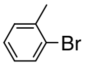
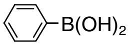
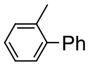
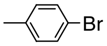
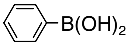
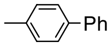
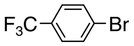
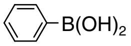
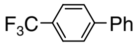
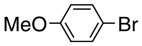
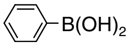
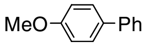
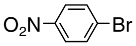
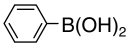
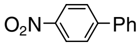
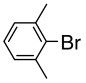
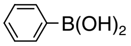
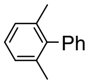
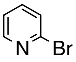
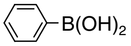
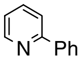
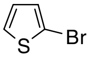
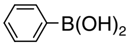
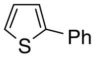
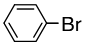
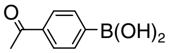
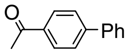
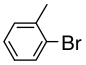
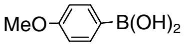
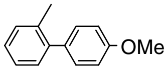
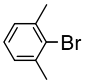
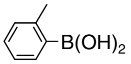
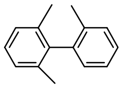
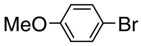
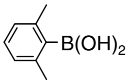
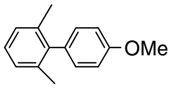
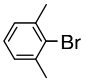
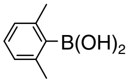
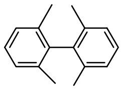
supercritical fluids, and PEGs, have been promoted as replacements to volatile organic compounds (VOCs),[8] water represents one of the most economically and environmentally viable options.[9] The use of water as the reaction solvent has several benefits, including low cost, improved safety, and abundance. Furthermore, phase separation is easier because most organic compounds are lipophilic and can be easily separated from the aqueous phase. To date, aqueous Suzuki coupling reactions have been largely limited to couplings of aryl iodides and activated aryl bromides.[10] In continuation of our interest in minimizing the consumption of depletive resources for sustainable chemistry and environmental benefits, we herein report a highly efficient Suzuki reaction of aryl bromides and arylboronic acids at low catalyst loading in water. Furthermore, we demonstrate that a 20% aqueous PEG-2000 solution can be used as the reaction media for the recycling and reuse of the palladium catalyst.

The initial investigation started with the coupling of phenylboronic acid and 4-bromoanisole, an electron-rich and therefore unreactive aryl bromide, as our test substrate. In the presence of 0.1 mol % palladium charcoal (10%) under nitrogen atmosphere in water at 60 °C, 4-methoxybiphenyl was obtained in 40% conversion and 31% isolated yield after 30 min stirring (Scheme 1).

Further efforts were then focused on screening different palladium catalysts and optimizing the reaction condition. Five other palladium catalysts, $Pd(OAc)_2$, $Pd(MeCN)_2Cl_2$, $Pd(PPh_3)Cl_2$, $Pd(DPPE)Cl_2$, and $Pd(DPPF)Cl_2$ were tested, respectively, and the results are summarized in Table 1. Among the three phosphine-ligand-free palladium catalysts, only Pd/C (10%) gave reasonable conversion. Very low conversions were obtained by $Pd(OAc)_2$ or $Pd(MeCN)_2Cl_2$ (less than 20%, Table 1, entries 2 and 3). The use of $Pd(PPh_3)Cl_2$, $Pd(DPPE)Cl_2$, or $Pd(DPPF)Cl_2$ gave mild to good con-

Table 2. Suzuki coupling of arylbromides and arylboronic acids in water[a]

Entry	Aryl halides	Arylboronic acids	Product	Yield[b] (%)
1				99
2				93
3				97
4				99
5				98
6[c]				87
7[d]				85
8				93
9				89
10				96
11				92
12[d]				81
13[d]				88
14[d]				—

[a] 5 mmol Aryl bromide, 5.5 mmol arylboronic acid, 10 mmol K_2CO_3, 2 mL H_2O, and 0.1 mol% $Pd(DPPF)Cl_2$, oil bath temperature at 80 °C, and 1 h (not optimized).

[b] Isolated yield by flash chromatography.

[c] 5 mmol 4-Bromo-1-nitrobenzene, 7 mmol $PhB(OH)_2$, and 10 mmol K_2CO_3, 2 mL H_2O, and 0.0001 mol % $Pd(DPPF)Cl_2$, 110 °C, 48 h.

[d] Oil bath temperature at 110 °C, 4 h.

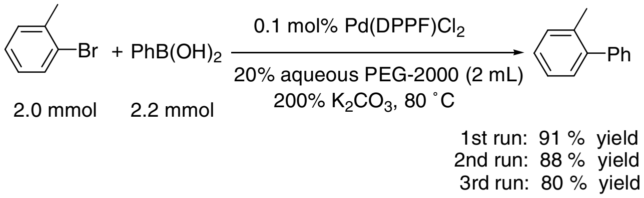
versions, and Pd(DPPF)Cl_2 was found to be optimal,[11] providing 88% conversion and 85% isolated yield (Table 1, entries 4–6). Prolonging reaction times to 12 h, however, failed to improve the reaction conversion due to the product 4-methoxybiphenyl solidifying along with the unreacted 4-bromoanisole.

On the other hand, elevating reaction temperature to 80 °C afforded a 100% conversion and 98% isolated yield (Table 1, entry 7). It is noteworthy that the palladium catalyst was still active at the end of the coupling reaction. For example, after 30 min stirring for the first run, addition of one more equivalent of starting substrates to the reaction mixture led to its total conversion in another 30 min (Table 1, entry 8). Elevating the reaction temperature to 110 °C and reducing the catalyst loading to 0.01 mol % provided a near quantitative yield of 4-methoxybiphenyl after 3 h stirring (Table 1, entry 9). Further reducing the catalyst loading to 0.001 mol % led to a lower conversion with a 78% isolated yield (TON = 78,000) after 48 h stirring (Table 1, entry 10). It should be noted that the choice of Pd(DPPF)Cl_2 as the catalyst precursor was not arbitrary, as the weakly electron-donating bidentate triarylphosphine ligand DPPF stabilizes the catalytic center due to the rigid and blocked conformation of the ferrocenyl backbone.[12]

This catalysis[13] was then applied to various aryl bromides and arylboronic acids, as summarized in Table 2. The desired biaryls were obtained in excellent yields (81–99%).[14] Thus, aryl bromides, which are electron-poor, electron-rich, or very sterically hindered, coupled cleanly with phenylboronic acid (Table 2, entries 1–9). It is important to stress that the cross-coupling of 1-bromo-4-nitrobenzene and phenylboronic acid by 0.0001 mol % Pd(DPPF)Cl_2 afforded 87% isolated yield with a TON of 870,000, which, to the best of our knowledge, is the highest TON for Suzuki coupling of aryl bromides achieved in water (Table 2, entry 6).

The catalysis is also tolerant of electronic variation in the arylboronic acid component, and arylbromides coupled cleanly with electron-poor, electron-rich, or sterically hindered arylboronic acids (Table 2, entries 9–13). Particularly noteworthy is the reaction of very sterically hindered 2-bromo-*m*-xylene coupling with 2-tolylboronic acid (Table 2, entry 12), which proceeded to completion in 4 h and afforded the desired product in 81% isolated yield. However, the coupling reaction of 2-bromo-*m*-xylene coupling and 2,6-dimethylphenylboronic acid failed to provide the target product (Table 2, entry 14). It has to been mentioned that the cross-coupling of aryl chlorides were unsuccessful for this catalysis, and even in the presence of 1 mol % Pd(DPPF)-Cl_2 the coupling of activated 1-chloro-4-nitrobenzene and phenylboronic acid only afforded 24% isolated yield after 24 h stirring at 110 °C.

Encouraged by these overall results, we next examined the recyclability of the catalytic system for Suzuki coupling reaction. It is well known that PEG, poly(ethylene glycol), are nontoxic, recoverable, and inexpensive phase-transfer catalysts.[15] Thus, a 20% aqueous PEG-2000 solution was tested as the reaction media for the cross-coupling of 2-bromotoluene with phenylboronic acid. After stirring for 1 h, 2-methylbiphenyl was extracted from the reaction mixture with *n*-pentane (3 × 5 mL) and the catalyst was reused for another run by adding fresh 2-bromotoluene, phenylboronic acid and potassium carbonate to the reaction media. It is important to stress that this system was shown to be readily recyclable for three runs, and the isolated yields were almost consistent (Scheme 2).



Scheme 2.

In conclusion, a highly efficient Suzuki coupling reaction of aryl bromides in water has been achieved. This green procedure is simple and can be used to generate a wide range of biphenyls with low palladium loadings. Furthermore, a 20% aqueous PEG-2000 solution as the reaction media allows this catalytic system to be readily recyclable for three runs without a significant loss of catalytic activity.

Acknowledgements

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13. It has to be pointed out that many biaryls are solid at room temperature, thus the products can be easily separated in excellent purity by simple filtration, which could allow a VOCs-free process for this extremely useful coupling reaction.
14. A general procedure for the cross-coupling reaction follows: to a solution of 4-bromoanisole (935 mg, 5 mmol), phenylboronic acid (667 mg, 5.5 mmol), K_2CO_3 (1.38 g, 10 mmol), and [1,1′-bis(diphenylphosphino)ferrocene]dichloro-palladium(II) complex, $Pd(DPPF)Cl_2$ (4.0 mg, 0.1 mol %) in 2 mL water was flushed with nitrogen and capped. The reaction mixture was heated and stirred in the oil bath at 80 °C for 30 min, and the reaction mixture was extracted with *n*-pentane (3 × 5 mL). The combined *n*-pentane phase was dried with anhydrous $MgSO_4$. Evaporation of *n*-pentane gave a crude mixture for ^1H NMR analysis, and then was purified by flash chromatography (*n*-pentane–ethyl ether = 10:1) to yield 4-methoxybiphenyl (902 mg, 98%).
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