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Note

A simple and efficient protocol for Suzuki coupling reactions of aryl chlorides and aryl bromides in aqueous DMF

Leifang Liu [a,*], Wendi Wang [a], Chuanyong Xiao [b]

[a] Key Laboratory of Coordination Chemistry and Functional Materials in Universities of Shandong, Dezhou University, Dezhou 253023, People's Republic of China
[b] Agricultural Product Quality and Safety Inspection Center, Dezhou 253023, People's Republic of China

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ABSTRACT

A simple, efficient and ligand-free palladium acetate catalyzed protocol was developed in aqueous *N*,*N*-dimethylformamide (DMF) under mild reaction conditions in the presence of Na_2CO_3 in air. This procedure showed good catalytic efficiency towards the Suzuki coupling of aryl bromide and arylboronic acid. Furthermore, under enhanced reaction conditions, various aryl chlorides could smoothly be coupled with arylboronic acids to afford biphenyls without any use of additives and ligands, and good yields were obtained in the Suzuki coupling of activated aryl chlorides.

1. Introduction

Palladium-catalyzed Suzuki coupling reaction of aryl halides and arylboronic acids is one of the most important and powerful synthetic methods for the construction of carbon–carbon bonds, in particular for the formation of unsymmetrical biaryls which are widely found in natural products, herbicides, pharmaceuticals, as well as in conducting polymers and liquid-crystalline materials [1–5]. Water is cheap, nontoxic, and readily available green reaction medium for organic synthesis [6–9]. Recently, many efforts have been paid to develop efficient catalytic systems using pure water as solvent for the Suzuki coupling reaction for the consideration of economy, safety and environment problems. However, the low solubility of substrates, bad reactivity and stability of catalyst in pure water restrict its application in Suzuki reaction. These problems have to some extent been overcome by the use of water-soluble substrate [10,11], phase-transfer catalyst [12–19], and other additives [20].

The mixtures of water–organic solvent (aqueous media), such as aqueous acetonitrile, acetone, toluene, EtOH and DMF, are widely used as solvent in Suzuki reaction. However, almost all attention had been focused on the use of ligands. With the presence of water-soluble and sterically demanding alkylphosphines ligands, palladium acetate could easily catalyzed the Suzuki coupling reaction of aryl bromide and activated aryl chloride in aqueous media [21–26]. Due to the disadvantages of phosphine ligands, a number of phosphine-free *N*-based ligands including *N*,*O*- or *N*,*N*-bidentate ligand, *N*-heterocyclic carbenes, oxime-derived ligands and simple amines have been used in the Suzuki coupling of aryl halides with arylboronic acids in aqueous media [27–32]. Many heterogeneous palladium catalysts were also utilized in aqueous Suzuki coupling reaction, such as Pd/C, Pd-polyoxometalate nanoparticle, Pd-amphiphilic polymer-assembled catalyst and so on [33–39]. Most of them exhibited good catalytic efficiency towards the Suzuki coupling reaction of aryl bromide and aryl iodides.

There is great interest in developing efficient and simple catalytic systems for the Suzuki coupling reaction without any use of ligands. The mixtures of water and organic solvent not only have the advantages of water, which helps with the solvation of mineral bases to promote the Suzuki reaction by activating arylboronic acid, but also have the ability to dissolve organic substrates and corresponding palladium catalysts. These characteristics of water–organic solvent mixtures offer good chances for Suzuki coupling reaction to develop simple and efficient catalytic systems in which only simple palladium salts, such as $Pd(OAc)_2$ or $PdCl_2$, are used without any presence of ligands under mild reaction conditions. To our knowledge, there were only a few reports about such catalytic systems reported in literature. It was reported by Wallow and

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* Corresponding author. No. 566, West of University Road, Dezhou University, Dezhou 253023, People's Republic of China. Tel.: +86 0534 8987866; fax: +86 0534 8985835.
E-mail address: orgllf@163.com (L. Liu).

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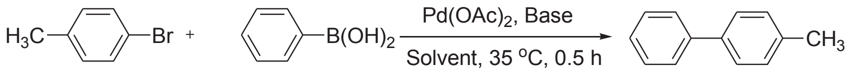
Table 1
Effect of solvent, base on the Suzuki coupling of 4-bromotoluene and phenylboronic acid.[a]



Entry	Solvent	Base	Yield[b] (%)
1	DMF (3 mL)	Na_2CO_3	5
2	H_2O/DMF (0.5/3 mL)	Na_2CO_3	42
3	H_2O/DMF (1/3 mL)	Na_2CO_3	52
4	H_2O/DMF (2/3 mL)	Na_2CO_3	92
5	H_2O/DMF (3/3 mL)	Na_2CO_3	98
6	H_2O/DMF (4/3 mL)	Na_2CO_3	98
7	H_2O/DMF (5/3 mL)	Na_2CO_3	96
8	H_2O/DMF (7/3 mL)	Na_2CO_3	95
9	H_2O/DMF (9/3 mL)	Na_2CO_3	89
10	H_2O (3 mL)	Na_2CO_3	9
11	H_2O/DMF (3.5/3 mL)	K_2CO_3	97
12	H_2O/DMF (3.5/3 mL)	NaOH	96
13	H_2O/DMF (3.5/3 mL)	KOH	96
14	H_2O/DMF (3.5/3 mL)	K_3PO_4	95
15	H_2O/DMF (3.5/3 mL)	K_2HPO_4	68
16	H_2O/DMF (3.5/3 mL)	$NaHCO_3$	72
17	H_2O/DMF (3.5/3 mL)	KF	52
18	H_2O/DMF (3.5/3 mL)	NaOAc	40
19	H_2O/DMF (3.5/3 mL)	NEt_3	63
20	H_2O/DMF (3.5/3 mL)	Pyridine	54

[a] Reaction conditions: 4-bromotoluene (1 mmol), $Ph(OH)_2$ (1.5 mmol), base (2 mmol), $Pd(OAc)_2$ (1 mol%), 35 °C, 0.5 h, in air.
[b] Isolated yields.

Novak that $Pd(OAc)_2$ in aqueous acetone could catalyze the Suzuki coupling reaction of aryl bromide and aryl iodide [40,41]. But the complex experimental operations and the tedious measures taken to exclude oxygen at various stages of the reaction restrict its application. In 2006, Zhang et al. reported that $Pd(OAc)_2$ could catalyze smoothly the Suzuki coupling reaction of aryl bromide to prepare biaryls in aqueous acetone and polyaryls in aqueous DMF [42]. Later, aqueous DMF, combined with $Pd(OAc)_2$ and K_3PO_4, was used in the Suzuki coupling of aryl bromide, but the reactions must be carried out under N_2 atmosphere [43]. Very recently, Liu and co-workers have developed a simple and efficient protocol for the Suzuki coupling of aryl bromides and *N*-heteroaryl halides using $PdCl_2$ as catalyst in water–DMF in air [44]. However, the procedures mentioned above focused mainly on the Suzuki coupling of aryl bromide. There is great interest to develop simple and efficient catalytic system using aryl chlorides in Suzuki coupling reaction. We report herein a simple and efficient catalytic system for the Suzuki coupling of aryl halide, especially for the Suzuki coupling of aryl chloride, in aqueous DMF without any presence of ligands and protection of inert gases. This catalytic system, using $Pd(OAc)_2$, Na_2CO_3 and aqueous DMF, was applicable to aryl bromide under milder reaction conditions. With enhanced reaction conditions, this catalytic system could be applied to the Suzuki coupling of aryl chloride, and good yields were obtained for activated aryl chlorides.

2. Results and discussions

To optimize the reaction conditions, the coupling of 4-bromotoluene (1 mmol) and phenylboronic acid (1.5 mmol) was chosen as model reaction. The effect of the amount of water in aqueous DMF was initially investigated. The reaction was carried out in DMF (3 mL) in the presence of $Pd(OAc)_2$ (1 mol%) using Na_2CO_3 (2 mmol) as base at 35 °C for 0.5 h in ambient atmosphere. Using pure DMF as the solvent, only trace amount of product 4-methylbiphenyl was obtained (Table 1, entry 1). However, the additional of incremental amount of water led to a very rapid increase in yield and the highest yield (98%) was achieved when the amount of water used was 3 mL or 4 mL (Table 1, entries 5 and 6). Further addition of water caused a very little decrease in the yield (Table 1, entries 7–9). Using pure water as the solvent under the same reaction condition, only 9% yield was obtained (Table 1, entry 10). These results suggested that the ratio of water and DMF was critical to this catalytic system. In the following optimization process, the mixture of 3 mL DMF and 3.5 mL H_2O was chosen as the solvent for the coupling of 4-bromotoluene.

We further wish to investigate the effect of different common bases on the Suzuki coupling reaction of 4-bromotoluene and phenylboronic acid using $Pd(OAc)_2$ (1 mol%) at 35 °C for 0.5 h. Besides Na_2CO_3, K_2CO_3, NaOH, KOH, and K_3PO_4 had a good effect on the coupling of 4-bromotoluene and desirable yields of product were obtained (Table 1, entries 5 and 6, 11–14). However, other inorganic bases, such as K_2HPO_4, $NaHCO_3$, KF, NaOAc and organic base, such as pyridine, NEt_3 gave much lower yields (Table 1, entries 15–20). With consideration of product yield and economy, Na_2CO_3 was used as the most suitable base in the following Suzuki coupling reaction of aryl bromides and aryl chlorides.

To evaluate the scope and limitations of the procedure, we studied the Suzuki coupling reaction of aryl bromides with arylboronic acid in H_2O–DMF (3.5:3 mL) with $Pd(OAc)_2$ (1 mol%) and Na_2CO_3 (2 mmol) at 35 °C for 0.5 h. The results were presented in Table 2. Good yields were obtained in the reaction of aryl bromide with electron withdrawing and electron donating substituent with phenylboronic acid (Table 2, entries 1–7). Sterically demanding aryl bromide could also be coupled with phenylboronic acid to give excellent yield (Table 2, entry 5). Both the electron-rich and the electron-deficient arylboronic acids gave desirable products in high yields (Table 2, entries 8–10). Good yield was also obtained in the reaction of 4-bromotoluene with sterically demanding *o*-tolylboronic acid (Table 2, entry 9).

The coupling of aryl chlorides was also screened using our methodology (Table 2, entries 11–26). Using $Pd(OAc)_2$ (1 mol%), Na_2CO_3 (2 mmol), and H_2O–DMF (3.5:3 mL) as the reaction conditions, 4-nitrochlorobenzene was coupled with phenylboronic acid at 35 °C for 3 h and the product was achieved only in 32% yield