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# Amide as an efficient ligand in the palladium-catalyzed Suzuki coupling reaction in water/ethanol under aerobic conditions

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#### Abstract

Amide, which is derived from proline and is inexpensive and air-stable, has been synthesized and characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR, and MS. It was found to be an efficient ligand in the palladium-catalyzed Suzuki cross-coupling reaction. In the Pd/amide catalytic system, aryl bromides can be coupled with phenylboronic acid in ethanol/water (1:2; v/v) in excellent yields even with a low Pd loading of 0.01 mol%. Moreover, the scope of the reaction is broad, and a wide variety of functional groups are tolerant. © 2011 Hua Chen. Published by Elsevier B.V. on behalf of Chinese Chemical Society. All rights reserved.

Keywords: Suzuki cross-coupling; Palladium catalyst; Aryl bromides; Amide; Water

In the past two decades, the palladium-catalyzed Suzuki cross-coupling reaction of aryl halides with arylboronic acids has evolved into one of the most valuable synthetic processes to form biaryls [1–4]. Phosphine-based ligands have been widely used for the palladium-catalyzed coupling reaction [5–8]. However, most of these phosphines are sensitive to air and moisture and they are also expensive and toxic. Therefore, a few phosphine-free ligands, such as*N*-heterocylic carbenes [9–12], diimines [13], diaminos [14], *N*,*N*,*N*-ligands [15], *O*,*N*,*N*,*O*-ligands [16] and *N*,*N*,*O*-ligands [17] have been studied for the Suzuki reaction. To the best of our knowledge, there are few papers about using amide as ligands for the Suzuki cross-coupling reaction. Herein, we report a new kind of ligands, which is derived from proline (compound 1), for Suzuki cross-coupling reaction in water and ethanol under aerobic conditions. Our synthetic route can be clearly seen in Scheme 1 [18,19]. The new ligand (compound 3) has been elucidated by <sup>1</sup>H NMR, <sup>13</sup>C NMR and MS [20].

## 1. Experimental

<sup>1</sup>H and <sup>13</sup>C 400 MHz spectra were recorded on a Bruker spectrometer using CDCl<sub>3</sub> as solvent and tetramethylsilane [TMS] as internal standard in all cases. Melting points were determined on a Thomas–Hoover capillary melting point apparatus. High-resolution mass spectra were recorded on a Q-TOF mass spectrometry (Waters) equipped with Z-spray ionization source. The isolation of pure products was carried out *via* Silica gel column (Silica gel 300–400 mesh). Aryl halides were used directly as obtained commercially without any process.

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Scheme 1. Reagents and conditions (a) (1) MeOH,  $K_2CO_3$ , RT, 0.5 h; (2) CICOOEt, 0 °C, 12 h; (b) DMF, BuOK, 3-NH<sub>2</sub>-C<sub>6</sub>H<sub>4</sub>OMe, 140 °C, 30 min (75–80%).

All reactions were performed under aerobic conditions. In the first step, the referred solution  $(C_{Pd} = 1.0 \times 10^{-4} \text{ mmol/mL}, C_{Ligand} = 2.0 \times 10^{-4} \text{ mmol/mL}$ , water as solvent) was prepared. A single-necked ground tube  $(r_{inner} = 1.2 \text{ cm}, L = 17.5 \text{ cm})$  equipped with a magnetic stir bar was charged with 1.0 mmol of aryl halides, 1.5 mmol of phenylboronic acid and 2 mmol base under aerobic conditions. Then, 1.0 mL referred solution and 2.0 mL water and 1.5 mL ethanol was added into the tube. The reaction mixture was stirred in oil bath with pre-arranged temperature for appropriate reaction time. After the reaction was completed, 3 mL water was added, and the aqueous phase was extracted with EtOAc (8 mL × 3). The organic phase was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure after filtered. The residue was then purified by column chromatography on silica gel column.

#### 2. Results and discussion

We initially tested the reaction of phenylboronic acid with 4-bromoanisole as a model reaction in EtOH/H<sub>2</sub>O (1:2; v/v) in the presence of ligand and PdCl<sub>2</sub> (Scheme 2). The effects of various inorganic and organic bases on the Suzuki cross-coupling reaction were investigated. Among them, K<sub>3</sub>PO<sub>4</sub> and Cs<sub>2</sub>CO<sub>3</sub> are effective for the reaction. Considering the high-cost of Cs<sub>2</sub>CO<sub>3</sub>, we chose the mild base K<sub>3</sub>PO<sub>4</sub> in all the subsequent reaction.

The temperature ranging from 25 °C to 90 °C was screened for the suitable reaction temperature in the presence of 0.01 mol % PdCl<sub>2</sub> and 0.02 mol% ligand. The GC yield of 4-MeOC<sub>6</sub>H<sub>4</sub>-Ph was only 7% in 10 h at room temperature, and increased significantly with the temperature rising. When the temperature rose up to 80 °C, the GC yield was increased to 99% while only 26% yield can be obtained in the absence of ligand in 1 h.

Under the optimized condition with  $PdCl_2$  (0.01 mol%), ligand (0.02 mol%),  $K_3PO_4$  (2 equiv) in 4.5 mL EtOH/  $H_2O$  mixture, we examined the cross-coupling reaction of a wide range of phenylboronic acid with various aryl halides, and the results were summarized in Table 1.

In the above Pd-catalyzed Suzuki cross-coupling system, the Suzuki reaction was found to afford good to excellent yield for the desired product. For example, in the presence of 0.01 mol% PdCl<sub>2</sub> and 0.02 mol% ligand, an excellent conversion (97%) and high TON (9700) for the substrate 4-BrC<sub>6</sub>H<sub>4</sub>OMe was obtained at 80 °C in 1 h, and a moderate yield (58%) still could be obtained even the Pd-loading was reduced to 0.001 mol%. As can be seen from Table 1 (entries 1–12), various aryl bromides with electron rich or deficient group were converted efficiently to the target products in good to excellent yields within 1 h. In spite of the hindrance of 2-BrC<sub>6</sub>H<sub>4</sub>Me, 2-BrC<sub>6</sub>H<sub>4</sub>NO<sub>2</sub> and 2-bromo-*m*-xylene, a good yield of desired products was still obtained (Table 1, entries 6, 9, and 12). The coupling of phenylboronic acid with heteroaryl bromides, such as 3-bromopyridine, 3-bromoquinoline and 5-bromopyrimidine was also investigated. The target products were also obtained in good yields (Table 1, entries 13–15) and high TONs (8100, 9500 and 9400) were obtained when the reaction temperature was elevated to 90 °C (refluxed temperature) and the time was prolonged to 6 h. The coupling reaction of phenylboronic acid with activated aryl chloride such as 4-ClC<sub>6</sub>H<sub>4</sub>NO<sub>2</sub> and 4-ClC<sub>6</sub>H<sub>4</sub>CF<sub>3</sub> was carried out with 0.5 mol% catalyst loading. But the yield was only 52% and 39% (Table 1, entries 16 and 17) respectively, even though the Pd-loading was raised and the reaction temperature was elevated to 90 °C and the reaction time was prolonged to 20 h.



Scheme 2. The model reaction in EtOH/H2O.

Table 1 The coupling reaction of aryl halides with phenylboronic acid in water/ethanol ArX + Ph  $-B(OH)_{2} \xrightarrow{PdCl_2} Ar - Ph X = Br, Cl.$ 

Entry	Ar–X	Pd loadings (mol%)	Temp. (%)/time (h)	Yield (%) <sup>b</sup>	TON
1	BrC <sub>6</sub> H <sub>5</sub>	0.01	80/1	98	9800
2	4-BrC <sub>6</sub> H <sub>4</sub> OMe	0.01	80/1	97	9700
3	4-BrC <sub>6</sub> H <sub>4</sub> OMe	0.001	80/20	58	58,000
4	3-BrC <sub>6</sub> H <sub>4</sub> OMe	0.01	80/1	97	9700
5	$4-BrC_6H_4Me$	0.01	80/1	98	9800
6	$2-BrC_6H_4Me$	0.01	80/1	94	9400
7	$4-BrC_6H_4CF_3$	0.01	80/1	98	9800
8	$4-BrC_6H_4NO_2$	0.01	80/1	98	9800
9	$2-BrC_6H_4NO_2$	0.01	80/1	92	9200
10	4-BrC <sub>6</sub> H <sub>4</sub> COMe	0.01	80/1	97	9700
11	4-BrC <sub>6</sub> H <sub>4</sub> CHO	0.01	80/1	96	9600
12	2-Bromo-m-xylene	0.01	90/1	89	8900
13	3-Bromopyridine	0.01	90/6	81	8100
14	3-Bromoquinoline	0.01	90/6	95	9500
15	5-Bromopyrimidine	0.01	90/6	94	9400
16	$4-ClC_6H_4NO_2$	0.5	90/20	52	104
17	4-ClC <sub>6</sub> H <sub>4</sub> CF <sub>3</sub>	0.5	90/20	39	78

*Reaction conditions:* n(L)/n(Pd) = 2, aryl halide (1.0 mmol), phenyl boronic (1.5 mmol), K<sub>3</sub>PO<sub>4</sub> (2.0 mmol), H<sub>2</sub>O (3.0 mL), and ethanol (1.5 mL). <sup>b</sup> Isolated yield.

In conclusion, we have successfully synthesized and characterized a novel ligand derived from proline, which has been shown to be highly effective in the Suzuki cross-coupling reaction of phenylboronic acid with different substituted bromobenzenes and heteroaryl bromides under aerobic conditions in EtOH/H<sub>2</sub>O (1:2; v/v).

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- [20] Selected analytical data for amide ligand: mp 178–181 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 3.2 (m, 2H, CH<sub>2</sub>), 1.9 (m, 2H, CH<sub>2</sub>), 2.2 (m, 2H, CH<sub>2</sub>), 4.6 (m, 1H, CH), 3.9 (s, 6H, OCH<sub>3</sub>–OCH<sub>3</sub>), 6.3 (m, 1H, CONH), 9.4 (m, 1H, CONH), 6.8–7.3 (m, 8H, ArH–ArH); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>): δ 169.79, 160.23, 160.07, 155.51, 139.57, 139.53, 129.64, 129.48, 112.39, 112.08, 110.13, 109.31, 106.15, 105.26, 60.96, 55.28, 55.26, 46.68, 27.23, and 25.28; HRMS Calcd. for C<sub>20</sub>H<sub>23</sub>N<sub>3</sub>O<sub>4</sub>: 370.1760 [M]<sup>+</sup>, found: 370.1689.