Homocoupling Reaction of Aryl Boronic Acids Catalyzed by $Pd(OAc)_2/K_2CO_3$ in Water under Air Atmosphere

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Abstract: Moderate to good yields of symmetrical biaryls were obtained under environmental friendly conditions *via* homocoupling reaction of aryl boronic acids catalyzed by $Pd(OAc)_2/K_2CO_3$ in water. Our method explores the synthetic utility of the homocoupling reaction of aryl boronic acids which may provide a simple and general alternative to the Suzuki reaction to achieve symmetrical biaryls.

Keywords: Aryl boronic acids, symmetrical biaryls, homocoupling reaction, environmental friendly reaction, water.

The synthesis of biaryls has been widely studied beginning with the Ullmann coupling reaction [1-3]. Lots of methods have been developed to obtain biaryls since then [4-10]. Among those methods, the Suzuki reaction is an important one. However, in this reaction the molar ratio of aryl boronic acids to aryl halides is always high in order to consume aryl halides completely which is hard to separate from products. Nowadays, the syntheses of boronic acids by using aryl chlorides as starting materials is becoming much easier [11]. Therefore, it is of particular interest to explore the synthetic utility of the homocoupling of boronic acids which may provide a simple and general alternative to the Suzuki reaction. Furthermore, using water as reaction solvent has gained a lot of attention in recent years because of its friendliness to environment. Several articles have reported this homocoupling reaction of boronic acids catalyzed by Pd(OAc)₂ [12-16]. Recently, Au-catalyzed homocoupling reaction was reported [17, 18]. The mechanism of this reaction has also been reported [19]. In addition, some reports have also disclosed the role of copper species in the oxidative demerization of aryl boronic acids [20]. To the best of our knowledge, only one paper reported the homocoupling reaction of aryl boronic acids in water, which had to use PTC (phase tranfer catalyst) and the reaction had to be performed under an oxygen atmosphere [21]. Herein, we report a simple method to prepare symmetrical aryl biphenyls in water without PTC at room temperature and under air condition.

Initially, we carried out the reaction of phenyl boronic acid in water with K_2CO_3 by using different sources of Pd (6.0 mol%), including Pd(dpa)₂, PdCl₂ and Pd(OAc)₂ as the catalyst under air atmosphere. As can be seen from Table **1**, Pd(OAc)₂ gave the best results with 91% yield (Table **1**, entries 1-3). Therefore, we chose Pd(OAc)₂ as the catalyst. Then, we investigated the influence of the loading of Pd(OAc)₂ on the catalytic reactions (Table **1**, entries 3-5). The results showed that 6.0 mol% of Pd(OAc)₂ is suitable for the desired conversion (Table 1, entry 3). When the amount of Pd(OAc)₂ drops from 6.0 mol% to 2.0 mol %, the yield decreases from 91% to 42%. However, the yield does not increase when the amounts of Pd(OAc)₂ increased to 10.0 mol% (Table 1, entries 3-5). Next, we added some phase transfer catalyst to the system, such as TEBA, TBAB and 15-Crown-5, hoping to enhance the yield, but none of them improved the results (Table 1, entries 6-8). It is well known that the base could activate any boronic acid [22]. Thus, we tested different bases, including NaOAc, KOH and K₂CO₃ (Table 1, entries 3, 9-10). It can be seen from the Table 1 that by using NaOAc as the base gave the lowest yield (25%). When the base was changed to KOH, biphenyl was obtained with moderate yield (72%). The highest yield (91%) was achieved by using K_2CO_3 as the base (Table 1, entry 3).

Under the optimized condition, the scope of the reaction was checked. Table 2 shows the experimental results. It seems that the yields of products have no significant relationship to the substituted groups on aryl and may have closed relationship to the solubility of the starting materials in water. Sterical hindrance may be another factor influencing the yields (Table 2, entry 1 and 8). The catalyst system that we developed is suitable for non-sterically hindered boronic acids (Table 2, entries 1-7) and then applied to sterically-hindered substrates with the yield of 47% (Table 2, entry 8). Furthermore, we found that when using 3-formylphenylboronic acid as the substrate, biphenyl-3,3'-dicarbaldehyde was found to be the only product with good yield (Table 2, entry 5), while a complexed mixture was detected when the reaction was performed in acetone/water (4 mL, V:V = 1:1) (Scheme 1). The advantage of our method is significant as compared to the reaction carried out in organic solvent in which by-product is obtained. In contrast to the Suzuki reaction, the advantage of using the methodology described in this paper is that the purification of the product biaryls from any unreacted boronic acid is much more facile than from any unreacted aryl halide. Pure products can be obtained through a short column chromatography by using petroleum ether as eluent.

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Table 1. Initial Screening for Source of Pd, Additives Effects and Base on this Reaction in Water^a

Entry	Pd* (mol %) ^b	Additives ^c	Base	Yield(%) ^d
1	Pd(dpa) ₂ (6.0)	-	K ₂ CO ₃	<10
2	PdCl ₂ (6.0)	-	K ₂ CO ₃	44
3	Pd (OAc) ₂ (6.0)	-	K ₂ CO ₃	91
4	Pd (OAc) ₂ (2.0)	-	K ₂ CO ₃	42
5	Pd (OAc) ₂ (10.0)	-	K ₂ CO ₃	92
6	Pd (OAc) ₂ (6.0)	TEBA	K ₂ CO ₃	90
7	Pd (OAc) ₂ (6.0)	TBAB	K ₂ CO ₃	27
8	Pd (OAc) ₂ (6.0)	15-Crown-5	K ₂ CO ₃	78
9	Pd (OAc) ₂ (6.0)	-	NaOAc	25
10	Pd (OAc) ₂ (6.0)	-	КОН	72

^aReaction conditions: phenyl boronic acid (0.5 mmol, 0.0610g), base (1.25 mmol), 2 mol%-6 mol% Pd(OAc)₂ (0.01 mmol-0.03 mmol), water (2 mL), rt, 18h. ^bThe amount of Pd based on phenyl boronic acid.

"The amount of a dditives was 0.05 mmol. dIsolated yield.



Scheme 1.

Table 2. Homocoupling Reaction of Various Aryl Boronic Acids^a



Entry	ArB(OH) ₂	Product	Isolated Yield ^b
1	B(OH) ₂		93
2	Cl — B(OH) ₂	Cl-	53
3	F B(OH)2	FF	60

(Table 2).	Contd
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Entry	ArB(OH) ₂	Product	Isolated Yield ^b
4	Me B(OH) ₂	Me — Me	61
5	OHC	OHC CHO	87
б	H ₃ CO B(OH) ₂	H ₃ CO OCH ₃	73
7	B(OH) ₂		83
8	B(OH) ₂		47

^aReaction conditions: aryl boronic acid (0.5 mmol), K₂CO₃ (1.25 mmol), 6.0 mol% Pd(OAc)₂ (0.03 mmol), water (2 mL), 10°C and the reactions were carried out for 24h. ^bIsolated yields.

In summary, we have developed a simple, mild and general way for the synthesis of symmetrical biaryls from aryl boronic acids in water under air atmosphere. In contrast to the Suzuki reaction, the advantage of using the methodology described in this paper is that the purification of the product biaryls from any unreacted boronic acid is much more facile than from any unreacted aryl halide. Pure products can be obtained through a short column chromatography using petroleum ether as eluent. Our catalytic system does not need additional oxygen source and allowed very environmentally friendly conditions. Furthermore, by using our protocol, no side product was detected.

EXPERIMENTAL

All the reactions were performed in test tube in air. Flash column chromatography was performed by using silica gel (230-400 mesh). Analytical thin-layer chromatography was performed using glass plates pre-coated with 200-400 mesh silica gel impregnated with a fluorescent indicator (254 nm). ¹H NMR spectra were measured in CDCl₃ on a Bruker-400 spectrometer with TMS as an internal reference. ¹³C NMR spectra were measured in CDCl₃ on a Bruker-400 spectrometer with TMS as an internal reference.

The Representative Procedure for Homocoupling Reaction of Phenyl Boronic Acids

A suspension of phenyl boronic acid (0.5 mmol, 0.0610 g), $Pd(OAc)_2$ (6 mol%, 0.0033 g) and K_2CO_3 (1.25 mmol, 0.08 g) in water (2 mL) was stirred at room temperature for 24h. At the end of the reaction, the product was separated by

extraction with ethyl acetate $(3 \times 10 \text{ mL})$. The extracts were dried over Na₂SO₄, evaporated under reduced pressure. The residue was chromatographed *via* a short column of silica gel to give the pure product.

Spectral Data

Biphenyl

¹H NMR (300 MHz, CDCl₃) (δ , ppm): 7.60 (t, J = 7.8 Hz, 4H, ArH), 7.45 (t, J = 7.8 Hz, 4H, ArH), 7.36 (d, J = 7.8 Hz, 2H, ArH); ¹³C NMR (75 MHz, CDCl₃) (δ , ppm): 127.64, 127.72, 129.22, 141.67.

4,4'-Dimethylbiphenyl

¹H NMR (300 MHz, CDCl₃) (δ , ppm): 7.46 (d, J = 8.1 Hz, 4H, ArH), 7.22 (d, J = 7.8 Hz, 4H, ArH), 2.38 (s, 6H, CH₃); ¹³C NMR (75 MHz, CDCl₃) (δ , ppm): 21.48, 127.22, 129.85, 137.11, 138.73.

4,4'-Dichlorobiphenyl

¹H NMR (300 MHz, CDCl₃) (δ , ppm): 7.40 (d, *J* = 8.1 Hz, 4H, ArH), 7.33 (d, *J* = 8.4 Hz, 4H, ArH); ¹³C NMR (75 MHz, CDCl₃) (δ , ppm): 128.70, 129.52, 134.02, 138.88.

4,4'-Difluorobiphenyl

¹H NMR (300 MHz, CDCl₃) (δ , ppm): 7.51-7.46 (m, 4H, ArH), 7.12 (t, J = 8.4 Hz, 4H, ArH); ¹³C NMR (75 MHz, CDCl₃) (δ , ppm): 116.02 (d, $J_{C,F} = 21.0$ Hz), 129.10 (d, $J_{C,F} = 8.2$ Hz), 136.88 (d, $J_{C,F} = 3.0$ Hz), 164.52 (d, $J_{C,F} = 2.2$ Hz).

3,3'-Dimethoxybiphenyl

¹H NMR (300 MHz, CDCl₃) (δ , ppm): 7.34 (t, J = 7.8 Hz, 2H, ArH), 7.20 (d, J = 7.8 Hz, 2H, ArH), 7.08 (s, 2H,

ArH), 6.89 (d, *J* = 7.8 Hz, 2H, ArH), 3.85 (s, 6H, CH₃O); ¹³C NMR (75 MHz, CDCl₃) (*δ*, ppm): 55.69, 108.21, 113.27, 120.18, 130.20, 143.07, 160.30.

Bipheny-3,3'-dicarbaldehyde

¹H NMR (300 MHz, CDCl₃) (δ , ppm): 10.12 (s, 2H, CHO), 8.16 (s, 2H, ArH), 7.92 (d, J = 7.5 Hz, 4H, ArH), 7.67 (t, J = 7.5 Hz, 2H, ArH); ¹³C NMR (75 MHz, CDCl₃) (δ , ppm): 128.50, 129.99, 130.30, 133.52, 137.52, 141.16, 192.60.

Binaphthyl

¹H NMR (300 MHz, CDCl₃) (δ , ppm): 7.94 (d, J = 8.4 Hz, 4H, ArH), 7.59 (t, J = 7.8 Hz, 2H, ArH), 7.49 (d, J = 7.6 Hz, 4H, ArH), 7.39 (d, J = 8.4 Hz, 2H, ArH), 7.28 (t, J = 8.4 Hz, 4H, ArH); ¹³C NMR (75 MHz, CDCl₃) (δ , ppm): 125.87, 126.30, 126.46, 127.04, 128.31, 128.38, 128.63, 133.31, 133.98, 138.93.

2,2'-Dimethylbiphenyl

¹H NMR (300 MHz, CDCl₃) (δ , ppm): 7.19-7.14 (m, 6H, ArH), 7.02 (d, J = 6.9 Hz, 2H, ArH), 1.98 (s, 6H, CH₃); ¹³C NMR (75 MHz, CDCl₃) (δ , ppm): 20.26, 125.97, 127.59, 129.73, 130.25, 136.26, 142.03.

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