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Water-soluble 2-arylnaphthoxazole-derived palladium (II) complexes as phosphine-free catalysts for the Suzuki reaction in aqueous solvent

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Two water-soluble palladium (II) complexes 2 and 4 have been synthesized from easily available 2-arylnaphthoxazole derivatives. They were successfully applied to the Suzuki coupling of aryl bromides with phenylboronic acid in water at 100 °C under phosphine-free conditions.

Keywords: Suzuki; palladium; 2-arylnaphthoxazole; phosphine-free; water

Introduction

The palladium-catalyzed Suzuki reaction is one of the most important methods for the selective formation of carbon–carbon bonds, especially for the formation of biaryls.[1–3] As the biaryl motif is found in a range of pharmaceuticals, herbicides and natural products, as well as in conducting polymers and liquid crystalline materials, the development of improved conditions for the Suzuki reaction has received much attention recently.[4–7] One area of research interest has been in the use of water as a solvent for the Suzuki reaction, because water is a readily available, safe and environmentally benign solvent.[8–10] Many efficient Suzuki coupling reactions in aqueous solution using different catalyst systems, such as Pd/C/TBAB,[11,12] $Pd(OAc)_2$ or $PdCl_2$/μw,[13–16] palladium salt/alkylphosohine[17–20] and palladium/NHC[21–24] have been reported.

To date, there are relatively few examples of water-soluble palladium catalysts used in Suzuki coupling. Nájera and co-workers reported several hydrophilic oxime-derived palladacycles which were successfully applied to the Suzuki reaction in water with TBAB as an additive.[25,26] Shaughnessy *et al*. recently showed that water-soluble palladacycles in combination with a hydrophilic alkylphosphine give active catalysts for the Suzuki coupling of aryl bromides.[27] However, both of these reactions need additives, especially the latter involving phosphine ligands, which are air-sensitive, expensive and toxic. Herein, we prepare two new water-soluble palladium (II) complexes (**2** and **4**), and find that they are effective catalysts for the Suzuki reaction of aryl bromides in water under phosphine-free conditions.

Results and Discussion

Synthesis and characterization of palladium complexes

Cyclopalladation of 2-arylnaphthoxazole derivative **1** readily occurred using $Pd(OAc)_2$ in acetic acid at 100 °C under nitrogen to give the dark yellow cyclopalladated complex **2** in moderate yield (Scheme 1). Complex **2** was fully characterized by elemental analysis, IR, ^{1}H and ^{13}C NMR. The IR spectra of **1** shows a sharp band at about 1650 cm^{-1},[28] while for complex **2**, this band shifted to 1598 cm^{-1}, indicating that the nitrogen atom was coordinated to palladium through its lone electron pair. The appearance of the signal at about δ 2.2 ppm in the ^{1}H NMR spectrum and the signal at δ 180.7 ppm in the ^{13}C NMR spectrum suggested the presence of an acetate group.

The reaction of 2-arylnaphthoxazole derivative **3** with Li_2PdCl_4 in MeOH in the presence of NaOAc as a proton scavenger at room temperature afforded quantitatively the brown solid **4** (Scheme 2), which was fully characterized by elemental analysis, IR and ^{1}H and ^{13}C NMR. The $\upsilon_{C=N}$ at 1603 cm^{-1} in the IR spectrum of **4** was lower than that of **3** (1627 cm^{-1}),[28] due to the intramolecular coordination of nitrogen to palladium. Moreover the signal at δ 9.5 ppm in the ^{1}H NMR spectrum of **4** shifted to lower field than that of **3** (δ 8.5 ppm)[14] for the formation of coordinated complex.

Catalytic activity of palladium complexes in Suzuki reactions

The reaction conditions were screened using 4-bromotoluene with phenylboronic acid as the reactants. The results are listed in Table 1. They showed that using 0.1 mol% of **2** as catalyst, the reaction occurred smoothly in neat water at 100 °C to afford the product in excellent yield (entry 1). When the same loading of **4** was

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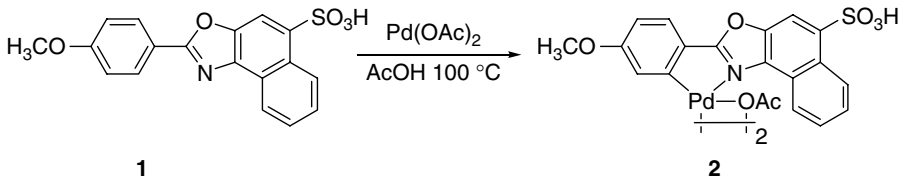
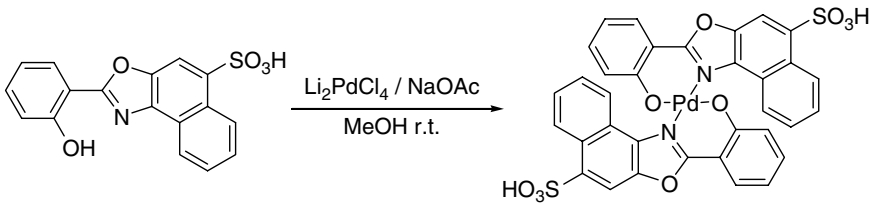


1 2

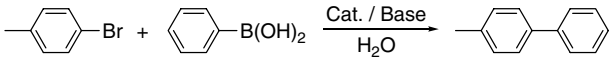
Scheme 1. Synthesis of cyclopalladated complex **2**.



3 4

Scheme 2. Synthesis of palladium complex **4**.

Table 1. Effect of catalysts and bases on the Suzuki coupling of 4-bromotoluene with phenylboronic acid



Entry	Catalyst (mol%)	Base	*T* (°C)	Reaction time (h)	Yield (%)[a]
1	**2** (0.1)	K_2CO_3	100	4	92
2	**4** (0.2)	K_2CO_3	100	4	90
3	**2 (0.1)**	**K_3PO_4**	**100**	**4**	**95**
4	**2** (0.1)	*t*-BuOK	100	4	86
5	**2** (0.1)	KF.2H_2O	100	4	71
6	**2** (0.1)	NaOH	100	4	90
7	**2** (0.1)	KOAc	100	4	31
8	**2** (0.1)	Cs_2CO_3	100	4	93
9	**2** (0.01)	K_3PO_4	100	8	65
10	**2** (0.1)	K_3PO_4	80	4	85
11	**2** (0.1)	K_3PO_4	50	8	70

Reaction conditions: 4-bromoanisole (0.5 mmol), $PhB(OH)_2$ (0.75 mmol), base (1.0 mmol), H_2O (2 ml), in air. [a] Isolated yields based on 4-bromoanisole, average of two runs.

used, the isolated yield was slightly lower, probably because of the presence of electron-donating methoxy group in **2** (entries 1 and 2). After the different bases, catalyst loadings and temperatures were examined, the combination of K_3PO_4 with 0.1 mol% of **2** at 100 °C gave the best result (entry 3).

Under the optimized reaction conditions, the scope of Suzuki reaction was investigated by varying the aryl halides (Table 2). The Suzuki coupling reactions should be tolerant to electronically and structurally diverse aryl bromides, including heteroaryl bromides. The products were isolated in excellent yields for electron-rich, -neutral and -deficient aryl bromide substrates after 4–6 h (entries 1–6). For *ortho*-monosubstituted aryl bromides, 2-methylbromobenzene and 1-bromonaphthalene, high yields were obtained (entries 7 and 9), while for the *ortho*-disubstituted aryl bromides, 2-bromo-*m*-xylene, the isolated yield was decreased to 43% (entry 8). In addition, coupling of phenylboronic acid with heteroaryl bromides, such as 2-bromopyridine, 3-bromopyridine and 2-bromothiophene, were also investigated to provide the products in yields of 62, 88 and 61%, respectively (entries 10–12). Encouraged by these results, we decided to see whether the catalyst system was active for aryl chlorides. Unfortunately, in contrast to corresponding aryl bromides, this catalyst showed almost no activity for the coupling of aryl chlorides (entries 13–15). In the case of 4-chlorotoluene, catalyst **2** was almost inactive (entry 13). Even when the catalyst loading was up to 1 mol%, the yield was only 26% (entry 14). For activated aryl chlorides, such as 4-chloronitrobenzene, the yield could reach to 65% using 1 mol% of **2** (entry 15).

Conclusions

In conclusion, we have developed a new, simple and environmentally friendly method for Suzuki coupling using the water-soluble catalysts of palladium (II) complexes in neat water. The system is very efficient for the coupling of aryl bromides and moderate to good yields are obtained. The scope of the substrate could be extended to some *ortho*-monoubstituted aryl bromides. Further investigations on the catalytic activity of this kind of palladium complexes are currently underway in our laboratory.

Experimental

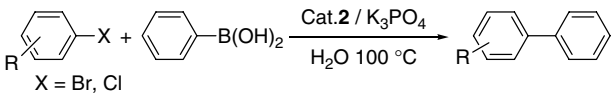
Materials

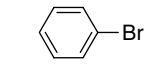
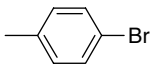
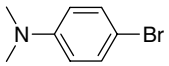
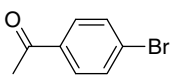
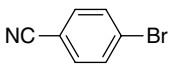
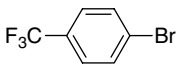
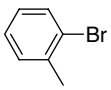
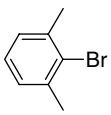
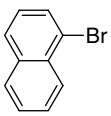
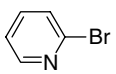
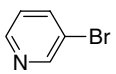
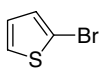
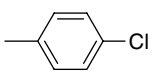
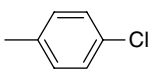
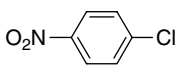
MeOH was purchased from Tianjin No. 1 Chemical Reagent factory and distilled from Mg powder prior to use. 2-Arylnaphthoxazole derivatives **1**,[28] **3**,[28] $Pd(OAc)_2$,[29] Li_2PdCl_4[30] and $PhB(OH)_2$[31] were prepared according to previously reported procedures. AcOH and the bases, such as NaOAc, K_2CO_3 and K_3PO_4, were purchased from Tianjin No. 1 Chemical Reagent factory and used as received. All the aryl halides were purchased from Aldrich and used without further treatment. Reactions were monitored by thin-layer chromatography, which was carried out on silica gel (60 F_{254})-coated glass plates.

Analyses

Melting points were measured on a WC-1 microscopic apparatus and uncorrected. Elemental analyses were conducted with a Carlo

Table 2. Suzuki coupling of aryl halide with phenylboronic acid catalyzed by **2** in water



Entry	ArX	Catalyst **2** (mol%)	Time (h)	Yield (%)[a]
1		**2** (0.1)	4	96
2		**2** (0.1)	4	95
3		**2** (0.1)	6	90
4		**2** (0.1)	4	96
5		**2** (0.1)	4	97
6		**2** (0.1)	4	98
7		**2** (0.1)	4	87
8		**2** (0.1)	12	43
9		**2** (0.1)	4	94
10		**2** (0.1)	8	62
11		**2** (0.1)	8	88
12		**2** (0.1)	8	61
13		**2** (0.1)	24	Trace
14		**2** (1)	24	26
15		**2** (1)	24	65

Reaction conditions: ArX (0.5 mmol), $PhB(OH)_2$ (0.75 mmol), K_3PO_4 (1.0 mmol), H_2O (2 mL), 100 °C, in air. [a] Isolated yields based on 4-bromoanisole, average of two runs.

Erba 1160 elemental analyzer. IR spectra were collected on a Bruker VEC-TOR22 spectrophotometer in KBr pellets.

NMR analyses

All ^1H and ^{13}C NMR spectra were performed in DMSO and recorded on a Bruker DPX 400 instrument using tetramethylsilane as the internal standard. ^1H-NMR spectra were collected at 400.0 MHz using a 8000 Hz spectral width, a relaxation delay of 2.0 s, 32K data points, a pause width of 30° and DMSO (2.54 ppm) as the internal standard. ^{13}C-NMR spectra were collected at 100.0 MHz using a 2500 Hz spectral width, a relaxation delay of 2.0 s, 32K data points, a pause width of 30° and DMSO (40.45 ppm) as the internal standard.

Synthesis of cyclopalladated complex 2

A mixture of 2-arylnaphthoxazole **1** (71 mg, 0.2 mmol) and palladium (II) acetate (55 mg, 0.2 mmol) in 2 ml of acetic acid was heated at 100 °C under nitrogen for 6 h. After cooling to room temperature, the precipatate was filtered off and washed with methanol to give a dark yellow complex **2** (83 mg, 80%).

Characterization data: m.p. >270 °C; $\upsilon_{(CN)} = 1598\ cm^{-1}$. Anal. found: C, 46.13; H, 2.88; N, 2.75%. Calcd for $C_{40}H_{30}N_2O_{14}Pd_2S_2$: C, 46.21; H, 2.91; N, 2.69%. ^1H NMR(400 MHz, DMSO) δ (ppm): 2.24 (s, 6H, CH_3), 3.07 (s, 6H, OCH_3), 5.66 (s, 2H, Ar–H), 5.81 (d, $J = 7.6$ Hz, 2H, Ar–H), 6.84 (d, $J = 8.3$ Hz, 2H, Ar–H), 7.55–7.57 (m, 4H, Ar–H), 8.11 (s, 2H, Ar–H), 8.65 (d, $J = 7.2$ Hz, 2H, Ar–H), 8.97 (d, $J = 7.4$ Hz, 2H, Ar–H). ^{13}C NMR(100 MHz, DMSO) δ (ppm): 25.2(CH_3), 54.3(OCH_3), 108.5(CH), 109.6(C), 116.9(CH), 120.3(CH), 123.0(C), 123.4(C), 125.3(CH), 126.1(CH), 127.6(C), 128.3(CH), 133.7(CH), 143.3(CH), 143.6(C), 144.1(C), 159.1(C), 169.2(C═N), 172.2(C), 180.7(C═ O).

Synthesis of palladium complex 4

To a solution of Li_2PdCl_4 (52 mg, 0.2 mmol) in methanol (2 ml), a methanolic solution (2 ml) of corresponding 2-arylnaphthoxazole **3** (68 mg, 0.2 mmol) and NaOAc (16 mg, 0.2 mmol) was added at room temperature. Then, the solution was stirred for about 10 h and a precipitate was formed. The precipitate was filtered and washed with methanol to give brown palladium complex **4** (71 mg, 90%).

Characterization data: m.p. >270 °C; $\upsilon_{(CN)} = 1603\ cm^{-1}$. Anal. found: C, 51.79; H, 2.63; N, 3.62%. Calcd for $C_{34}H_{20}N_2O_{10}PdS_2$: C, 51.88; H, 2.56; N, 3.56%. ^1H NMR(400 MHz, DMSO) δ (ppm): 6.04 (d, $J = 8.5$ Hz, 2H, Ar–H), 6.62–6.66 (m, 2H, Ar–H), 7.00–7.04 (m, 2H, Ar–H), 7.66–7.70 (m, 2H, Ar–H), 7.71–7.75 (m, 2H, Ar–H), 7.88 (d, $J = 8.0$ Hz, 2H, Ar–H), 8.34 (s, 2H, Ar–H), 9.09 (d, $J = 8.4$ Hz, 2H, Ar–H), 9.45 (d, $J = 8.2$ Hz, 2H, Ar–H). ^{13}C NMR (100 MHz, DMSO) δ (ppm): 109.7(CH), 112.5(C), 116.1(CH), 121.3(C), 123.5(C), 124.6(CH), 125.8(CH), 126.0(CH), 127.8(CH), 128.3(CH), 128.4(CH), 132.4(CH), 134.6(C), 144.4(C), 146.4(C), 161.3(C═N), 167.1(C).

General procedure for the Suzuki reaction

A 5 ml round-bottom flask was charged with aryl halides (0.5 mmol), phenylboronic acid (0.75 mmol), catalyst (0.5 × 0.1% mmol) and base (1 mmol). A 2 mL aliquot of water was added. The reaction mixture was heated and stirred in the oil bath at different temperature in air until the starting aryl halides had been completely consumed, as monitored by thin-layer chromatography. After cooling to room temperature, the mixture was extracted with dichloromethane. Then the combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with acetic ether–petroleum ether (1 : 10 to 1 : 30). (The purified products were identified by comparison of melting points with the literature values or by ^1H NMR.)

Acknowledgments

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