Letters to the Editor

A $PdCl_2$ complex with isonicotinaldehyde oxime, an efficient catalyst for the Suzuki reaction in aqueous media

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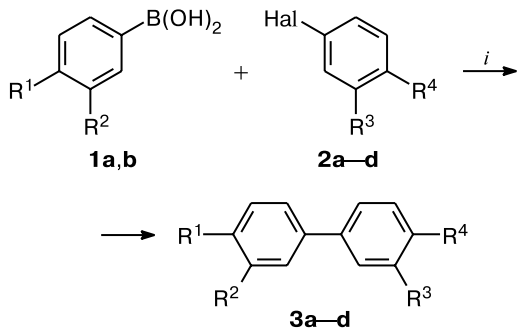
Cross-coupling of arylboronic acids with aryl halides (the Suzuki reaction) is widely employed in modern organic synthesis as a convenient and versatile method for the preparation of biaryls containing virtually any functional groups.[1] The Suzuki reaction is most often carried out in organic or aqueous organic solvents in the presence of an inorganic base and catalyzed by palladium complexes with phosphine ligands. However, most of the efficient phosphine ligands are readily oxidized by atmospheric oxygen and are accessible *via* rather complicated procedures, whereas commercial ligands are usually very expensive. For this reason, a search for effective phosphine-free palladium catalysts is currently one of the most important tasks in the study of the Suzuki reaction.[2] For practical applications, it is also promising to develop methods of conducting the Suzuki reaction in water in the absence of toxic and not easily recoverable organic solvents, because water is the most accessible, inexpensive, and ecologically pure solvent.[3]

Here we showed that a complex of palladium chloride with isonicotinaldehyde oxime $PdCl_2(4\text{-}C_5H_4NCH{=}NOH)_2$ is an efficient catalyst for cross-coupling of arylboronic acids **1** with aryl halides **2** (Scheme 1). The above ligand is accessible and contains two electron-donating N atoms. The catalytic activity of the complex is so high that reactions of water-soluble (in the presence of bases) aryl halides **2a,b** occur in water at 100 °C in the presence of only 0.2 mol.% of the catalyst.

Scheme 1



i. 0.05—0.37 mol.% $PdCl_2(4\text{-}C_5H_4NCH{=}NOH)_2$, K_2CO_3, water or water—EtOH (1 : 1), 80—100 °C.

1: R^1 = OMe, R^2 = H (**a**); R^1 = H, R^2 = OMe (**b**)

2	R^3	R^4	Hal	**3**	R^1	R^2	R^3	R^4
a	CO_2H	H	Br	**a**	OMe	H	CO_2H	H
b	H	CO_2H	I	**b**	OMe	H	H	CO_2H
c	H	C(O)Me	Br	**c**	OMe	H	H	C(O)Me
d	H	NH_2	Br	**d**	H	OMe	H	NH_2

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Reactions of water-insoluble aryl bromides **2c,d** were carried out in aqueous ethanol (EtOH : H_2O = 1 : 1) at 80 °C. However, in contrast to 4′-bromoacetophenone (**2c**) containing a strong electron-withdrawing substituent, which was quantitatively converted in the presence of the Pd catalyst (0.2 mol.%) into cross-coupling product **3c** within 10 min, the conversion of 4-bromoaniline (**2d**) containing the electron-donating amino group over the same period of time was only 26.5% (0.37 mol.% [Pd]; ^{1}H NMR data). The accompanying formation of Pd black caused the reaction to stop. In this case, the formation of Pd black was suppressed by lowering the amount of the catalyst to 0.05 mol.% and by using water as a reaction medium. Under these conditions, the reaction was completed in 1.5 h; the yield of cross-coupling product **3d** was 94%.

It should be noted that the related complex $PdCl_2(4\text{-}C_5H_4NCH{=}NOH)$, which contains one ligand molecule per palladium atom, has been recently proposed as a catalyst for the Suzuki reaction in water under microwave irradiation.[4]

Dichlorobis(4-pyridinaldoxime)palladium(II). Palladium dichloride (0.102 g, 0.564 mmol) and NaCl (0.127 g, 2.17 mmol) were dissolved with heating in methanol (20 mL). The resulting red-brown solution was added to a stirred solution of isonicotinaldehyde oxime (0.140 g, 1.15 mmol) in methanol (5 mL). The yellow precipitate that formed was filtered off, washed with a small amount of water, and dried to give dichlorobis(4-pyridinaldoxime)palladium(II) (0.230 g, 97%), decomp. at 305—310 °C. Found (%): C, 34.28; H, 2.93; N, 13.17. $C_{12}H_{12}Cl_2N_4O_2Pd$. Calculated (%): C, 34.19; H, 2.87; N, 13.29. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 7.66 (d, 2 H, J = 5.3 Hz); 8.21 (s, 1 H); 8.74 (d, 2 H, J = 5.3 Hz); 12.23 (s, 1 H). ^{13}C NMR (DMSO-d_6), δ: 121.86, 143.21, 145.55, 153.20. The ligand, ^{1}H NMR (400 MHz, DMSO-d_6), δ: 7.52 (d, 2 H, J = 6.1 Hz); 8.16 (s, 1 H); 8.57 (d, 2 H, J = 6.1 Hz); 11.83 (s, 1 H). ^{13}C NMR (DMSO-d_6), δ: 120.61, 140.35, 146.64, 150.10.

3-(4-Methoxyphenyl)benzoic acid (3a). A mixture of 3-bromobenzoic acid (**2a**) (0.603 g, 3 mmol), 4-methoxyphenylboronic acid (**1a**) (0.593 g, 3.9 mmol), K_2CO_3 (1.24 g, 9 mmol), and $PdCl_2(4\text{-}C_5H_4NCH{=}NOH)_2$ (20 mg, 0.0047 mmol, 0.16 mol.%) was stirred in water (5 mL) in a 15-mL Schlenk flask at ~20 °C for 5 min. Then the stirred mixture was rapidly heated to boiling and refluxed for 60 min. On cooling, the mixture was poured into water (50 mL), acidified to pH 1, and heated to boiling. The precipitate that formed was filtered off, washed with hot water, and dried in air. The yield was 0.685 g (100%), m.p. 201—202 °C (*cf.* Ref. 5: m.p. 202—203 °C). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 3.79 (s, 3 H); 7.03 (d, 2 H, J = 8.7 Hz); 7.55 (t, 1 H, J = 7.8 Hz); 7.63 (d, 2 H, J = 8.7 Hz); 7.82—7.90 (m, 2 H); 8.13 (s, 1 H); 13.05 (br.s, 1 H).

4-(4-Methoxyphenyl)benzoic acid (3b) was obtained analogously from 4-iodobenzoic acid (**2b**) (0.744 g, 3 mmol), 4-methoxyphenylboronic acid (**1a**) (0.65 g, 3.9 mmol), and K_2CO_3 (1.24 g, 9 mmol); the reaction duration was 40 min. The yield of acid **3b** was 0.68 g (99%), m.p. 252—253 °C (*cf.* Ref. 6: m.p. 248—249 °C). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 3.78 (s, 3 H); 7.02 (d, 2 H, J = 7.8 Hz); 7.65, 7.72 (both d, 2 H each, J = 7.6 Hz); 7.98 (d, 2 H, J = 7.8 Hz); 12.93 (br.s, 1 H).

4-Acetyl-4′-methoxybiphenyl (3c) was obtained analogously from 4′-bromoacetophenone (**2c**) (0.597 g, 3 mmol), 4-methoxyphenylboronic acid (**1a**) (0.55 g, 3.6 mmol), and K_2CO_3 (0.83 g, 6 mmol) in EtOH—water (1 : 1, 4 mL); the reaction duration was 10 min. The yield of compound **3c** was 0.65 g (96%), m.p. 147—148 °C (*cf.* Ref. 7: m.p. 153—154 °C). ^{1}H NMR (400 MHz, acetone-d_6), δ: 2.58, 3.85 (both s, 3 H each); 7.04, 7.67 (both d, 2 H each, J = 8.6 Hz); 7.73, 8.02 (both d, 2 H each, J = 8.1 Hz).

4-Amino-3′-methoxybiphenyl (3d) was obtained analogously from 4-bromoaniline (**2d**) (1.03 g, 6 mmol), 3-methoxyphenylboronic acid (**1b**) (1.00 g, 6.6 mmol), K_2CO_3 (2.0 g, 14 mmol), and $PdCl_2(4\text{-}C_5H_4NCH{=}NOH)_2$ (0.05 mol.%) in water; the catalyst was used as a 0.01 *M* solution in DMF (0.3 mL). The reaction duration was 1.5 h. The yield of compound **3d** was 1.19 g (95%), m.p. 118—119 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 3.78 (br.s, 2 H); 3.89 (s, 3 H); 6.76 (d, 2 H, J = 8.6 Hz); 6.89 (ddd, 1 H, J = 8.3 Hz, J = 2.5 Hz, J = 1.0 Hz); 7.14—7.17 (m, 1 H); 7.20 (ddd, 1 H, J = 7.6 Hz, J = 1.8 Hz, J = 1.0 Hz); 7.37 (t, 1 H, J = 7.8 Hz); 7.47 (d, 2 H, J = 8.6 Hz). The ^{1}H NMR spectrum agreed with the literature data.[8]

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