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One-Pot Preparation of Unsymmetrical Biaryls via Suzuki Cross-Coupling Reaction of Aryl Halide using Phase-Transfer Catalyst in a Biphasic Solvent System

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Abstract: A one-pot synthetic method of unsymmetrical biaryls was developed via the Suzuki cross-coupling reaction of aryl halide using a phase-transfer catalyst in a biphasic solvent system.

Keywords: biphasic solvent, one-pot reaction, phase-transfer catalyst, Suzuki coupling reaction, tetra(alkoxo)diboron, unsymmetrical biaryls

The one-pot Suzuki cross-coupling reaction is one of the easiest and most efficient methods for the synthesis of unsymmetrical biaryls; however, most methods require air- and moisture-sensitive reagents such as lithium reagents[1a–e] and dialkoxyborane[2a,b] for the preparation of the boronated intermediate.

On the other hand, a method based on the cross-coupling reaction of aryl halides or triflates with commercially available bis(pinacolato)diboron **1** in the presence of a palladium catalyst[3] overcomes these drawbacks

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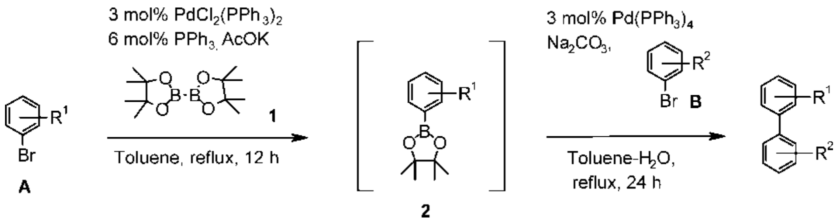
because of the thermal stability and insensitivity to air and moisture of bis(pinacolato)diboron **1**. As in the case of aryl halide, only one method has been reported, by Giroux and coworkers, in which they describe the one-pot unsymmetrical biaryl synthesis using bis(pinacolato)diboron **1** in DMF.[3a] Though their procedure is applicable to several aryl halides, some unsymmetrical biaryls that have electron-withdrawing substituents or heterocyclic rings are not obtained in good yield. Moreover, their method requires 2 equivalents of aryl halide for the second coupling reaction compared to the starting aryl halide for the first borylation reaction.

Recently, we reported the one-pot synthetic procedure for 2,2′-disubstituted biaryls via the Suzuki cross-coupling reaction of aryl triflates in a biphasic solvent system.[4] Results showed that the toluene/H_2O biphasic solvent system was effective in the second coupling reaction in achieving high yields. On this basis, we attempted to apply our biphasic solvent system to aryl halides to the synthesis of unsymmetrical biaryls. That is, the cross-coupling reaction of the aryl halide **A** with bis(pinacolato)diboron **1** in toluene is followed by the next reaction with another aryl halide **B** in toluene/H_2O without isolation of the aryl boronate **2** (Scheme 1). (In our preliminary work, the yield of the cross-coupling reaction of aryl triflate was barely affected by the use of palladium catalysts such as $PdCl_2(PPh_3)_2$ $PdCl_2$(dppf), so we selected $PdCl_2(PPh_3)_2$ with regard to cost. In our preliminary work, the yield substantially decreased without addition of another palladium catalyst for the second cross-coupling reaction.)

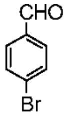
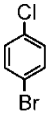
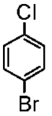
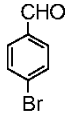
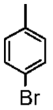
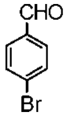
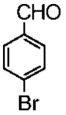
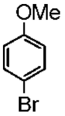
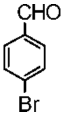
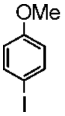
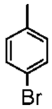
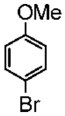
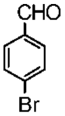
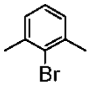
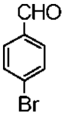
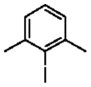
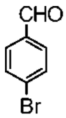
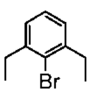
We employed various aryl halides for the one-pot biaryl synthesis (Table 1). A strong influence of the substituents was observed. For example, cross-coupling of electron-withdrawing aryl bromides (**3** and **4**) gave good yields in the corresponding biaryl products (run 1). On the other hand, yields were reduced when the aryl bromides such as 4-bromotoluene **5** or 1-bromo-4-methoxybenzene **6** were employed for the cross-coupling reaction (runs 3 and 4). The sterically demanding aryl bromide **8** reacted more slowly to result in a reduced yield for the corresponding product (run 7). In this case, with corresponding aryl iodide **9**, the desired biaryl was obtained in 54% yield (run 8).

As previously observed for the Suzuki coupling reaction, the use of a phase-transfer catalyst as promoter increases the reaction rate.[5] On this



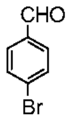
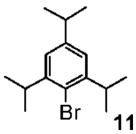
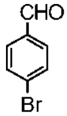
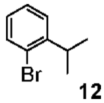
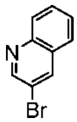
Scheme 1.

Table 1. Effect of a phase-transfer catalyst in a biphasic solvent system on the one-pot cross-coupling reactions of various aryl halides

			Yield (%)	
Run	A	B	None	Bu_4NHSO_4
1	 **3**	 **4**	72 (43)[a]	71
2	 **4**	 **3**	(50)[a]	70
3	 **5**	 **3**	48	73
4	 **3**	 **6**	11	48[b]
5	 **3**	 **7**	NT	53[b]
6	 **5**	 **6**	NT	49[b]
7	 **3**	 **8**	6 (38)[c]	85
8	 **3**	 **9**	54	NT
9	 **3**	 **10**	NT	51

(*continued*)

Table 1. Continued

			Yield (%)	
Run	A	B	None	Bu_4NHSO_4
10	 **3**	 **11**	NT	38
11	 **3**	 **12**	NT	56
12	 **13**	 **14**	$(40)^a$	77

Notes: Yield of isolated product based on the halides used for the second coupling reaction.

[a] Yields reported by Giroux and coworkers are shown in parentheses.

[b] Yields obtained by the $PdCl_2(dppf)/dppf$ system instead of $PdCl_2(PPh_3)_2/PPh_3$.

[c] Yields obtained by us using the Giroux method.

basis, 10 mol% of Bu_4NHSO_4 was tested in the cross-coupling of various aryl halides, as summarized in Table 1.

With this improved method, the phase-transfer catalyst system efficiently promotes the cross-coupling of electronic variation in the aryl halides. (Other phase-transfer catalysts such as Bu_4NBr and $CH_3(CH_2)_{11}SO_3Na$ also promoted the cross-coupling reaction.) For example, when aryl bromide had electron-withdrawing substituents such as CHO and Cl groups, the cross-coupling reaction proceeded smoothly, and the corresponding biaryl was isolated in good yield (runs 1 and 2). The 4-bromotoluene **5** and aryl bromide **3** also gave the corresponding biaryls in 73% yield (run 3). On the other hand, when the aryl bromide **B** for the second cross-coupling reaction had an electron-donating substitutent such as a MeO group, cross-coupling of aryl bromide **3** with **6** occurred in only 33% yield. In this case a substantial amount of by-product, biphenyl-4-carbaldehyde, was isolated. This product was formed by the reaction between a phenyl group from triphenylphosphine with the corresponding aryl bromide **3**.[6] To suppress this unwanted side reaction, we employed a $PdCl_2(dppf)/dppf$ system instead of $PdCl_2(PPh_3)_2/PPh_3$ for the coupling of **3** with **6** and obtained the corresponding biaryl in 48% yield (run 4). (In the case of the cross-coupling of **5** with **3** (Table 1, run 3), a difference in yield was scarcely shown through the use of palladium–ligand system such as $PdCl_2(PPh_3)_2/PPh_3$ and $PdCl_2$(dppf)/dppf). The reaction also tolerates the cross-coupling of **3** with aryl iodide **7** and 4--bromotoluene **5** with **6** (runs 5 and 6). This phase-transfer catalyst efficiently promotes the cross-coupling of sterically demanding substrates. Thus, it is noteworthy that the yield of the cross-coupling reaction of **3** with **8** is remarkably increased from 6% to 85% by the addition of a phase-transfer catalyst (run 7). (No coupled product was isolated when the reaction was done in the reverse order. That is, 2-bromo-1,3-dimethylbenzene **8** was employed for the first borylation reaction and 4-bromobenzaldehyde **3** was employed for the second cross-coupling reaction.) Other sterically demanding aryl bromides also coupled with **3** in moderate yields (runs 9–11).[7] Heteroaromatic bromides (**13** and **14**) were cross-coupled without difficulty (run 10). Compared to the Giroux method, our biphasic phase-transfer catalyst system provides efficient synthesis of biaryls that have electron-withdrawing substituents, sterically demanding substituents, and heterocyclic rings (runs 1, 2, 7, and 12).

In conclusion, these results demonstrate that for a wide range of aryl halides the Suzuki coupling can be readily promoted by use of a phase-transfer catalyst in a biphasic solvent system. In particular, this procedure is efficient for the cross-coupling of aryl halides with electron-withdrawing substituents and sterically demanding substituents. This procedure also allows cross-coupling between heteroaromatic bromides without difficulty.

GENERAL PROCEDURE

Melting points were determined on a Yanaco micromelting apparatus or Büchi melting-point apparatus B-545 and are uncorrected. Proton magnetic resonance (^{1}H NMR) spectra were obtained in $CDCl_3$ or dimethylsulfoxide-d_6 (DMSO-d_6) using a Jeol JNM-EX400, JNM-GX500, or JNM-A500 spectrometer. Chemical shifts are recorded in parts per million (δ), downfield relative to tetramethylsilane as the internal standard. Mass spectra (MS) were recorded on a Jeol JMS-DX300 or a Hitachi M-80 mass spectrometer. Elemental analysis was carried out on a Yanaco MT-3 or MT-5 CHN analyzer and a Yokogawa IC7000S ion chromatoanalyzer. Chromatographic separations were performed using a silica-gel column (Merck Kieselgel 60).

General Procedure for the One-Pot Suzuki Coupling Reaction of Aryl Halides using Phase-Transfer Catalyst in a Biphasic Solvent System

To a stirred solution of the halide **A** (1.1 mmol), bis(pinacolato)diboron (1.2 mmol), PPh_3 (0.06 mmol) and $PdCl_2(PPh_3)_2$ (0.03 mmol) in toluene (10 ml), AcOK (1.5 mmol) was added at room temperature under an argon atmosphere. The mixture was refluxed overnight, and then the halide **B**

(1.0 mmol), $Pd(PPh_3)_4$ (0.03 mmol), Bu_4NHSO_4 (0.1 mmol), and 2 mol dm^{-3} aq. Na_2CO_3 (4 ml) were added to the reaction mixture. The solution was refluxed overnight. The mixture was extracted with AcOEt, and the organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica-gel column chromatography (hexane/AcOEt) to give the target biaryl.

Data

4′-Chlorobiphenyl-4-carbaldehyde (runs 1 and 2): colorless crystals: mp 114–115°C (AcOEt–hexane) (lit.[3a] mp 113–114°C); ^1H NMR (300 MHz, DMSO-d_6) δ: 7.58 (2H, d, $J = 8.4$ Hz), 7.82 (2H, d, $J = 8.4$ Hz), 7.92 (2H, d, $J = 8.2$ Hz), 8.01 (2H, d, $J = 8.2$ Hz), 10.06 (1H, s); FAB-MS (m/z): 217 $(M + H)^+$; anal. calcd. for $C_{13}H_9ClO$: C, 72.07; H, 4.19; Cl, 16.36. Found: C, 71.87; H, 4.29; Cl, 16.49.

4′-Methylbiphenyl-4-carbaldehyde (run 3): colorless crystals: mp 105–107°C (AcOEt–hexane) (lit.[8] mp 107°C); ^1H NMR (300 MHz, DMSO-d_6) δ: 2.38 (3H, s), 7.33 (2H, d, $J = 8.3$ Hz), 7.68 (2H, d, $J = 8.3$ Hz), 7.89 (2H, d, $J = 8.3$ Hz), 7.98 (2H, d, $J = 8.3$ Hz), 10.04 (1H, s); FAB-MS (m/z): 197 $(M + H)^+$; anal. calcd. for $C_{14}H_{12}O$: C, 85.68; H, 6.16. Found: C, 85.48; H, 6.15.

4′-Methoxybiphenyl-4-carbaldehyde (runs 4 and 5): colorless crystals: mp 103–104°C (AcOEt–hexane) (lit.[9] mp 104–105°C); colorless solid: ^1H NMR (300 MHz, DMSO-d_6) δ: 3.82 (3H, s), 7.08 (2H, d, $J = 8.5$ Hz), 7.75 (2H, d, $J = 8.5$ Hz), 7.87 (2H, d, $J = 8.5$ Hz), 7.96 (2H, d, $J = 8.5$ Hz), 10.03 (1H, s); FAB-MS (m/z): 213 $(M + H)^+$; anal. calcd. for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 79.16; H, 5.71.

4-Methoxy-4′-methylbiphenyl (run 6): colorless crystals: mp 109–110°C (AcOEt–hexane) (lit.[10] mp 109–110°C); ^1H NMR (400 MHz, $CDCl_3$) δ: 2.38 (3H, s), 3.84 (3H, s), 6.96 (2H, d, $J = 9.1$ Hz), 7.22 (2H, d, $J = 8.1$ Hz), 7.45 (2H, d, $J = 8.1$ Hz), 7.51 (2H, d, $J = 9.1$ Hz); EI-MS (m/z): 198 $(M)^+$.

2′,6′-Dimethylbiphenyl-4-carbaldehyde (runs 7 and 8): colorless crystals: mp 66–67°C (AcOEt–hexane); ^1H NMR (300 MHz, DMSO-d_6) δ: 1.97 (6H, s), 7.12–7.24 (3H, m), 7.40 (2H, d, $J = 8.1$ Hz), 8.00 (2H, d, $J = 8.1$ Hz), 10.07 (1H, s); EI-MS (m/z): 210 $(M)^+$; anal. calcd. for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.60; H, 6.70.

2′,6′-Diethylbiphenyl-4-carbaldehyde (run 9): colorless crystals: mp 36–38°C (AcOEt–hexane); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.01 (3H, t,

$J = 7.3$ Hz), 2.30 (2H, q, $J = 7.3$ Hz), 7.16 (2H, q, $J = 7.3$ Hz), 7.28–7.66 (1H, m), 7.37 (2H, d, $J = 8.3$ Hz), 7.94 (2H, d, $J = 8.1$ Hz), 10.08 (1H, s); EI-MS (m/z): 238 $(M)^+$.

2′,4′,6′-Triisopropylbiphenyl-4-carbaldehyde (run 10): colorless crystals: mp 152–155°C (AcOEt–hexane); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.08 (12H, d, $J = 6.9$ Hz), 1.31 (6H, d, $J = 7.0$ Hz), 2.43–2.58 (2H, m), 2.89–3.02 (1H, m), 7.07 (2H, s), 7.37 (2H, d, $J = 8.2$ Hz), 7.93 (2H, d, $J = 8.2$ Hz), 10.08 (1H, s); FAB-MS (m/z): 309 $(M + H)^+$; anal. calcd. for $C_{22}H_{28}O$: C, 85.66; H, 9.15. Found: C, 85.56; H, 9.19.

2′-Isopropylbiphenyl-4-carbaldehyde (run 11): colorless crystals: mp 172–174°C (benzene); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.17 (6H, d, $J = 6.9$ Hz), 2.91–3.06 (1H, m), 2.89–3.02 (1H, m), 7.14–7.18 (1H, m), 7.21–7.25 (1H, m), 7.35–7.43 (2H, m), 7.47 (2H, d, $J = 8.2$ Hz), 7.93 (2H, d, $J = 8.2$ Hz), 10.08 (1H, s); EI-MS (m/z): 224 $(M)^+$.

3-(3-Thienyl)quinoline (run 12): colorless crystals: mp 86–87°C (AcOEt–hexane) (lit.[3a] mp 88–89°C); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.50 (1H, dd, $J = 2.9$ Hz, 4.9 Hz), 7.53–7.59 (2H, m), 7.66–7.68 (1H, m), 7.68–7.73 (1H, m), 7.86 (1H, d, $J = 8.1$ Hz), 8.12 (1H, d, $J = 8.1$ Hz), 8.29 (1H, d, $J = 2.2$ Hz), 9.21 (1H, d, $J = 2.2$ Hz); EI-MS (m/z): 211 $(M)^+$; anal. calcd. for $C_{13}H_9NS$: C, 73.90; H, 4.29; N, 6.63; S, 15.18. Found: C, 73.88; H, 4.33; N, 6.53; S, 15.09.

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