Controlled Monoarylation of Dibromoarenes in Water with a Polymeric Palladium Catalyst

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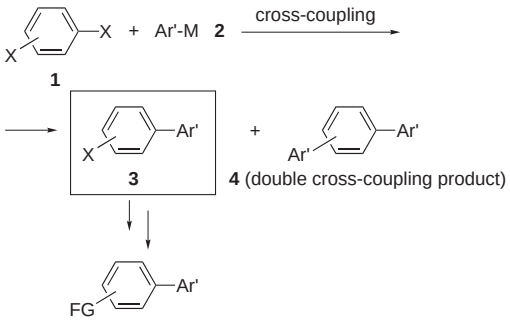
Abstract: A highly selective monoarylation of dibromoarenes was performed via the Suzuki–Miyaura cross-coupling with arylboronic acids with an amphiphilic polystyrene-poly(ethylene glycol) (PS-PEG) resin-supported phosphine–palladium complex in water under heterogeneous conditions to give bromobiaryls in high yields. Introduction of two different aryl groups on a aromatic moiety was achieved in a one-pot reaction by successive addition of two kinds of arylboronic acids under similar conditions. The polymeric palladium catalyst can be readily recovered and recycled.

Key words: Suzuki–Miyaura coupling, cross-coupling, biaryl formation, dibromoarenes

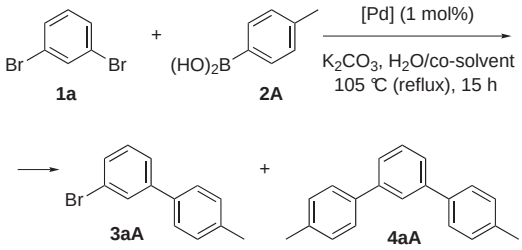


Scheme 1

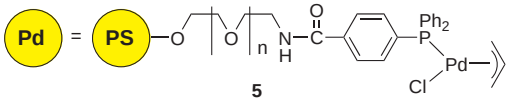
Biaryls have sparked considerable interest due to their presence in a number of biologically active compounds and stereoselective agents, and in the field of materials science, where they have been recognized as the parent unit of dendritic or polycyclic oligoaryl compounds.[2] Among biaryl formations, the transition metal-catalyzed cross-coupling arylation of halobenzenes (or pseudo-halobenzenes) is one of the most versatile and efficient methods to produce biaryl compounds.[3] Consequently, a vast amount of research has been devoted to the catalytic cross-coupling of a variety of haloarenes. However, surprisingly, only scattered attention has been paid to the highly controlled monoarylation of arenes having equally reactive mutiple halogeno groups to provide monohalobiaryls **3**[4,5] as potentially useful synthetic intermediates (Scheme 1).

Moreover, we have recently developed amphiphilic polystyrene-poly(ethylene glycol) (PS-PEG) resin-supported transition metal catalysts which promote various catalytic transformations including the cross-coupling of haloarenes with arylboronic acids (the so-called Suzuki–Miyaura coupling)[6] smoothly in water under heterogeneous conditions.[7] We wish to report here a new practical protocol for the palladium-catalyzed controlled monoarylation of dibromoarenes with arylboronic acids to give bromobiaryls with excellent selectivity which was achieved under heterogeneous aqueous conditions by use of a PS-PEG resin-supported palladium–phosphine complex.

Preliminary studies on the cross-coupling of dihaloarenes were carried out using standard methods. The results showed nearly statistical ratios of the non-/mono-/bis-arylated products, even though in principle the reactivity of the halogeno group of the halobiaryl **3** toward a successive second cross-coupling reaction should be lowered by the electron-donating property[8] of the aromatic substituent (Ar′ in Scheme 1). Thus, the cross-coupling of dibromobenzene **1a** and *p*-tolylboronic acid **2A** in aqueous toluene and in aqueous THF with $Pd(PPh_3)_4$ (1 mol%) as a catalyst provided the desired monoarylation product **3aA**; however, the yields for both were 40% at best and the selectivities were only 59% and 76%, respectively (Scheme 2).



Cat	Co-solvent	Conversion (%) of **1a**	Yield (%) of **3aA**	Ratio of **3**:**4**
$Pd(PPh_3)_4$	Toluene	75	40	76/24
	THF	68	40	59/41
Pd /PPh_3	Toluene	94	90	98/2



Scheme 2

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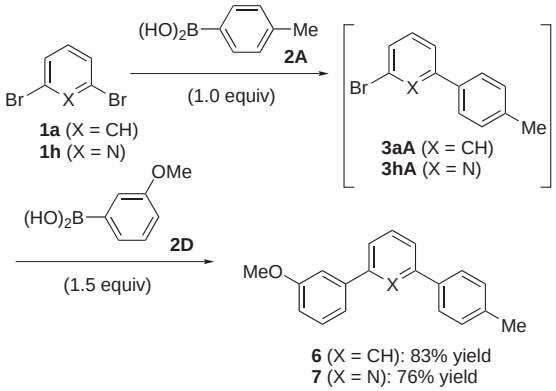
After extensive experimentation, we have found that dibromobenzene **1a** undergoes controlled cross-coupling with **2A** with a PS-PEG resin-supported palladium–phosphine catalyst **5**[7,9] to give the bromobiaryls **3aA** with high monoarylation selectivity under aqueous conditions. Thus, 1,3-dibromobenzene (**1a**) reacted with 1.0 equivalent of *p*-tolylboronic acid (**2A**) with 1 mol% palladium of the polymeric catalyst **5** in the presence of 8 mol% of triphenylphosphine and 1% (v/v) of toluene as the co-solvent in aqueous potassium carbonate (2 M solution) under reflux for 24 hours to give a 90% yield of 3-bromo-4′-methylbiphenyl (**3aA**) along with <1% of the terphenyl **4aA** (GC-MS analysis: **3aA**/**4aA** = >99/<1; Scheme 2).[10] The cross-coupling presumably takes place in the toluene-swollen resin matrix generated in situ to afford the desired monoarylation product. The biphasic system comprised of water and toluene-swollen resin might cause the resulting biaryl **3** to precipitate out from the resin matrix to retard a successive cross-coupling giving the teraryl **4**,[11] in cooperation with electronic deactivation of the bromo group of **3** by an aryl substituent on the bromoarene moiety. Table 1 shows that various combinations of the dibromoarenes **1** and the arylboronic acids **2** undergo cross-coupling to give the halobiaryls **3** with high selectivity using this monoarylation catalyst system.[12–20] Thus, *m*-dibromobenzene (**1a**) reacted with *p*-, *m*-, and *o*-tolylboronic acids (**2A**–**C**) to give the 2-, 3-, and 4-methylbiaryls **3aA**, **3aB**, and **3aC** in 90%, 92%, and 90% yields, respectively, where excellent selectivities were obtained in forming biaryls **3** (entries 1–3). Exclusive monoarylation took place with both electron–rich and electron–deficient arylboronic acids **2D** and **2E** to give 95% and 84% yields of **3aD** and **3aE** (entries 4 and 5). A combination of *o*-dibromobenzene (**1b**) and *o*-tolylboronic acid (**2C**) gave >99% selectivity of monoarylation although the chemical yield of the biaryl **3bC** was relatively low (77% yield), presumably due to steric hindrance of the substrate and/or the reactant (entry 6). Excellent monoarylating selectivities (>98%) were also achieved in the cross-coupling reactions of the *p*-dibromoarenes **1c**, **1d**, and **1e** (entries 7–10) under similar conditions. 1,3-Dibromo-5-fluorobenzene (**1f**) gave an 88% yield of 3-bromo-5-fluoro-4′-methylbiphenyl (**3fA**) where the bromoaryl group of the arylated product **3fA** is activated by the 5-fluoro substituent to result in formation of 12% of the terphenyl **4fA** via successive cross-coupling (entry 11). Cross-coupling of tribromobenzene (**1g**) with *p*-tolylboronic acid (**2A**) gave an 80% yield of the biaryl **3gA** along with 19% of the terphenyl **4gA** where one of two reactive bromides in the desired **3gA** underwent further coupling with **2A** to give **4** (entry 12). The dibromopyridines **1h** and **1i** also underwent cross-coupling with **2A** to give **3hA** and **3iA**, respectively, with exclusive selectivity under similar reaction conditions (entries 13 and 14). It is noteworthy that the polymeric palladium catalyst was readily recovered and reused without any loss of activity and selectivity to meet green chemical requirements. The recycling experiments were examined for the cross-coupling of **1a** and **2A** (entries 15–17). Thus, after being recovered and rinsed, the resin catalyst was subjected to the next series of reactions to give quantitative yields of **3aA** with 98–99% selectivity.

With this efficient monoarylation protocol to provide bromobiaryls **3** in hand, we were eager to examine the introduction of a second alkyl group via a one-pot monoarylation and a subsequent second cross-coupling reaction (Scheme 3).[21,22]



Scheme 3

When 1.5 equivalents of 3-methoxyphenylboronic acid (**2D**) was added to a reaction mixture of the monoarylation of 1,3-dibromobenzene (**1a**) with *p*-tolylboronic acid (**2A**; 2 mol% Pd of **5**, 16 mol% of PPh_3, 1.0 equiv of **2A**, 105 °C, 24 h), and the resulting mixture was stirred for an additional 15 hours, the successive arylation–arylation product 3-methoxy-3″-methylterphenyl (**6**) was obtained in 83% isolated yield. 2,6-Dibromopyridine (**1h**) reacted with **2A** and **2D** successively under similar conditions to afford 2-(3-anisyl)-6-(4-tolyl)pyridine (**7**) in 76% isolated yield.

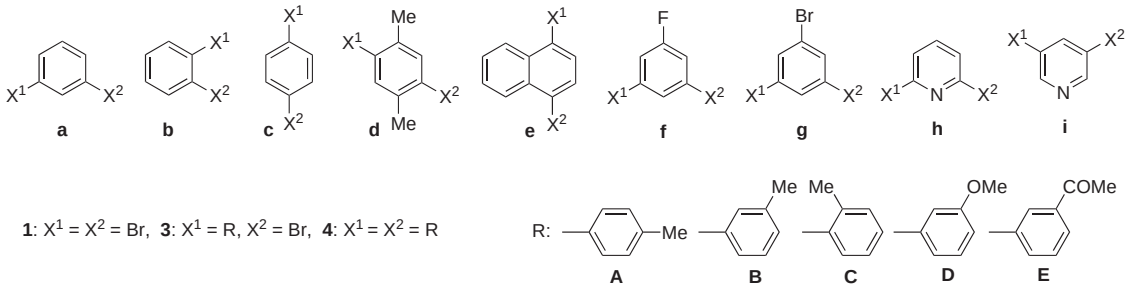


Figure 1

Table 1 Monoarylation of Di- or Trihaloarenes[a]

Entry	1	2	Product	Yield (%) of 3[b]	Ratio of 3:4[c]
1	**1a**	**A**	**3aA**	90	98:2
2	**1a**	**B**	**3aB**	92	98:2
3	**1a**	**C**	**3aC**	90	96:4
4	**1a**	**D**	**3aD**	95	>99:<1
5	**1a**	**E**	**3aE**	84	>99:<1
6	**1b**	**C**	**3bC**	77[d]	>99:<1
7	**1c**	**C**	**3cC**	93	98:2
8	**1c**	**E**	**3cE**	90	>99:<1
9	**1d**	**A**	**3dA**	88	>99:<1
10	**1e**	**A**	**3eA**	81	99:1
11	**1f**	**A**	**3fA**	88	88:12
12	**1g**	**A**	**3gA**	81	81:19
13	**1h**	**A**	**3hA**	75	>99:<1
14	**1i**	**A**	**3iA**	89	>99:<1
Recycle experiments[e]					
	1a	**A**	**3aA**		
15	1st re-use			89	98:2
16	2nd re-use			94	98:2
17	3rd re-use			87	99:1

[a] Reaction conditions: All reactions were carried out with 1.0 equiv of **2**, 1–2 mol% Pd of **5** and 8 mol equiv to Pd of PPh_3 in 2 M aq K_2CO_3 in the presence of 1% (v/v) of toluene at 105 °C (reflux) for 12–24 h, unless otherwise noted: **1** (0.4 mmol), H_2O (0.4 mL).
[b] GC yield (internal standard: biphenyl).
[c] Determined by GC-MS analysis.
[d] 23% (GC) of **1b** was recovered.
[e] Used polymeric catalyst resin was recovered by filtration and washed with EtOAc before re-using. PPh_3 (8 mol equiv to Pd) was added to each re-use run.

In summary, we have developed a selective monoarylation of dibromoarenes with arylboronic acids using a PS-PEG resin-supported palladium catalyst to give various bromobiaryls. One-pot successive double cross-coupling provided a practical protocol for preparing unsymmetrically substituted teraryls. Simple starting materials, a readily recyclable catalyst, and aqueous conditions should make the present method very useful from a synthetic viewpoint.

Acknowledgment

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(8) The σ/σ^+ value of bromo and phenyl groups: σ_μ/σ_μ^+ (Br) = +0.391/+0.405; σ_π/σ_π^+ (Br) = +0.232/+0.150; σ_μ/σ_μ^+ (Ph) = +0.06/+0.109; σ_π/σ_π^+ (Ph) = +0.01/–0.179.
(9) Argo Gel NH_2 (Φ = 130 mm, loading value = 0.3 mmol/g) was used as a polymer support.
(10) **General Procedure for Monoarylation of Dibromoarenes.**
A mixture of the dibromoarene **1** (0.4 mmol), the arylboronic acid **2** (0.4 mmol), 1 mol% palladium of **5** (4 μmol Pd), 8.4 mg of PPh_3 (32 μmol), and 40 μL of toluene in 4 mL of 2 M aqueous solution of K_2CO_3 was refluxed for 24 h. After being cooled, the mixture was filtered and collected resin beads were extracted with EtOAc. The GC yield and the

ratio of **3**:**4** were determined by GC-MS analysis (internal standard: biphenyl) of the organic extract, and an analytically pure product was isolated by silica gel chromatography.

(11) During the reaction, generation of precipitates on the resin surface was observed microscopically.

(12) CAS Registry numbers of biaryl products: **3aA**, 844856-52-6; **3aB**, 844856-54-8; **3aD**, 337535-27-0; **3bC**, 251320-87-3; **3cC**, 106475-19-8; **3iA**, 675590-28-0.

(13) **3-Bromo-2′-methylbiphenyl (3aC).**
Compound **3aC** was not isolated as an analytically pure sample. Characterization of **3aC** was performed by GC-MS analysis: MS: *m/z* = 248, 246 [M^+], 167 [M – Br] (base peak), 152, 139, 115, 82.

(14) **1-(3′-Bromobiphen-3-yl)ethanone (3aE).**
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (s, 1 H), 7.94 (d, *J* = 6.8 Hz, 1 H), 7.73 (d, *J* = 8.0 Hz, 2 H), 7.48–7.55 (m, 3 H), 7.31 (t, *J* = 8.0 Hz, 1 H), 2.65 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.4, 142.0, 139.9, 137.4, 131.4, 130.5, 130.2, 130.0, 129.0, 127.6, 126.6, 125.6, 122.8, 26.8. MS: 274, 259, 231, 152, 76.

(15) **1-(4′-Bromobiphen-3-yl)ethanone (3cE).**
Compund **3cE** was not isolated as an analytically pure sample. Characterization of **3cE** was performed by GC-MS analysis: MS: *m/z* = 276, 274 [M^+], 261, 259 [M – CH_3], 233, 231 [M – $COCH_3$], 152 [M – $COCH_3$-Br] (base peak), 126, 76.

(16) **4-Bromo-2,5,4′-trimethylbiphenyl (3dA).**
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (s, 1 H), 7.20 (d, *J* = 8.0 Hz, 2 H), 7.15 (d, *J* = 8.0 Hz, 2 H), 7.06 (s, 1H), 2.38 (s, 3 H), 2.36 (s, 3 H), 2.19 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.8, 137.7, 136.5, 134.7, 134.5, 133.5, 133.4, 131.9 (2 C), 128.7 (2 C), 123.1, 22.4, 21.3, 19.8. MS: *m/z* = 274, 195, 180, 165, 89.

(17) **1-Bromo-4-(4-methylphenyl)naphthalene (3eA).**
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31 (d, *J* = 8.4 Hz, 1 H), 7.89 (d, *J* = 8.4 Hz, 1 H), 7.79 (d, *J* = 7.6 Hz, 1 H), 7.57 (t, *J* = 6.8 Hz, 1 H), 7.44 (t, *J* = 6.8 Hz, 1 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 7.27 (d, *J* = 8.4 Hz, 2 H), 7.22 (d, *J* = 7.6 Hz, 1 H), 2.43 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.2, 137.1, 136.8, 132.8, 131.9, 129.7, 129.3, 128.9, 127.3, 127.0 (2 C), 126.6, 126.5, 121.9, 21.4. MS: *m/z* = 296, 215, 202, 189, 107, 94.

(18) **3-Bromo-5-fluoro-4′-methylbiphenyl (3fA).**
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.50 (m, 1 H), 7.41 (d, *J* = 8.0 Hz, 2 H), 7.24 (d, *J* = 8.0 Hz, 2 H), 7.16–7.21 (m, 2 H), 3.14 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.0, 161.5, 144.7, 144.6, 138.3, 135.6 (2 C), 130.0, 126.8, 125.8, 125.7, 122.8, 122.7, 117.3, 117.1, 112.8, 112.6, 21.2. MS: *m/z* = 264, 183, 165, 91.

(19) **3,5-Dibromo-4′-methylbiphenyl (3gA).**
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.58–7.61 (m, 3 H), 7.38–7.40 (m, 2 H), 7.21–7.24 (m, 2 H), 2.38 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 144.5, 138.2, 135.2, 123.0, 129.5, 128.5, 126.7, 123.0, 21.3. MS: *m/z* = 326, 245, 165, 139, 115, 82.

(20) **2-Bromo-6-(4-methylphenyl)pyridine (3hA).**
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 8.5 Hz, 2 H), 7.64 (d, *J* = 7.0 Hz, 1 H), 7.55 (t, *J* = 7.5 Hz, 1 H), 7.36 (d, *J* = 8.0 Hz, 1 H), 7.26 (d, *J* = 8.5 Hz, 2 H), 2.40 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.4, 141.9, 139.5, 138.6, 134.7, 129.3 (2 C), 126.7 (2 C), 125.7, 118.4, 21.5. MS: *m/z* = 247, 168, 153, 141, 115, 83.

(21) **3-Methoxy-4″-methyl[1,1′:3′,1″]terphenyl(6).**
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.77 (br s, 1 H), 7.51–7.54 (m, 4 H), 7.45 (t, *J* = 7.5 Hz, 1 H), 7.34 (t, *J* = 7.5 Hz, 1 H), 7.20–7.24 (m, 3 H), 7.16 (t, *J* = 2.0 Hz, 1 H), 6.89 (dd, *J* = 7.5, 2.0 Hz, 1 H), 3.81 (s, 3 H), 2.37 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.7, 142.6, 141.4 (2 C), 138.0, 136.9, 129.5, 129.3, 128.9, 126.9 (2 C), 125.8, 125.7, 125.6, 119.6 (2 C), 112.9, 112.6, 55.3, 21.2. MS: *m/z* = 274, 215, 137, 115, 101.

(22) **2-(3-Methoxyphenyl)-6-(4-methylphenyl)pyridine(7).**
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.0 Hz, 2 H), 7.76 (t, *J* = 2.5 Hz, 1 H), 7.70 (t, *J* = 8.0 Hz, 1 H), 7.67 (br d, *J* = 8.0 Hz, 1 H), 7.59 (t, *J* = 7.5 Hz, 2 H), 7.37 (t, *J* = 8.0 Hz, 1 H), 7.26 (d, *J* = 8.0 Hz, 2 H), 6.95 (dd, *J* = 7.5, 2.5 Hz, 1 H), 3.86 (s, 3 H), 2.38 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.7, 156.4, 156.1, 140.8, 138.6, 137.0, 136.4, 129.3, 129.1, 126.6, 119.2, 118.2, 114.4, 112.5, 55.3, 21.4. MS: *m/z* = 274, 245, 137.