Synthesis of Bis(diaryl)sulfones by Site-Selective Suzuki–Miyaura Reactions of 2,4′-Bis(trifluoromethylsulfonyloxy)diphenylsulfone

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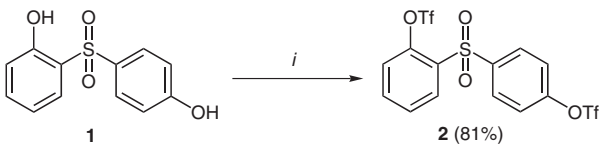
Abstract: The Suzuki–Miyaura reaction of the bis(triflate) of 2,4′-bis(hydroxy)diphenylsulfone with two equivalents of boronic acids gave 2,4′-bis(aryl)diphenylsulfones. The reaction with one equivalent of arylboronic acids resulted in site-selective attack onto carbon atom C-4′.

Key words: catalysis, palladium, Suzuki–Miyaura reaction, site selectivity, sulfones

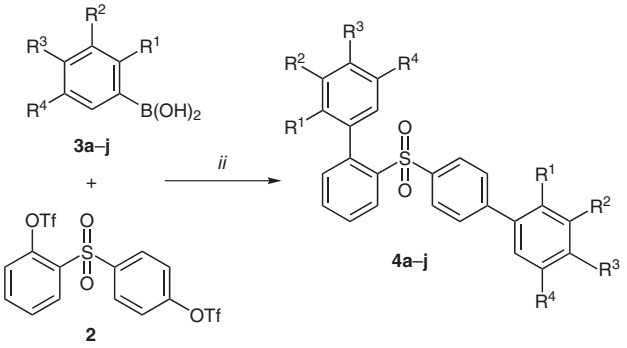
Diarylsulfones are of considerable pharmacological relevance.[1] Diaryl sulfones have been prepared by oxidation of diaryl sulfides,[2] by Friedel–Crafts-type acylation of anisole with phenylsulfonic acid chloride,[3] and by reaction of phenol with benzenesulfonic acid.[4] These methods suffer from low yields, harsh reaction conditions, and low regioselectivities. Transition-metal-mediated syntheses of diaryl sulfones include the CuI/proline-mediated reaction of aryl iodides with sodium benzenesulfinate,[5] Suzuki reactions of 4-methoxybenzeneboronic acid with phenylsulfonic acid chloride,[6] and $Cu(OAc)_2$-catalyzed reaction of 4-methoxybenzeneboronic acid with sodium benzenesulfinate.[7] Diaryl sulfones have also been prepared by cyclization reactions of sulfone-containing building blocks.[8] Herein, we report the synthesis of bis(diaryl)sulfones by site-selective[9,10] Suzuki–Miyaura reactions of the bis(triflate) of 2,4′-bis(dihydroxy)diphenylsulfone.

Commercially available 2,4′-bis(hydroxy)diphenylsulfone (**1**) was transformed into its bis(triflate) **2** in 81% yield (Scheme 1).[11]



Scheme 1 Synthesis of **2**. *Reagents and conditions*: *i*, CH_2Cl_2, **1** (1.0 equiv), –78 °C, pyridine (4.0 equiv), Tf_2O (2.4 equiv), –78 °C to 0 °C, 4 h.

The Suzuki reaction of **2** with arylboronic acids **3a–j** (2.6 equiv) afforded the novel 2,4′-bis(aryl)diphenylsulfones **4a–j** in good yields (Scheme 2, Table 1). The reactions were carried out using $Pd(PPh_3)_4$ (6 mol%) as the catalyst. The employment of other catalysts, such as $PdOAc)_2$/XPhos, resulted in a decreased yield. A slight excess (2.6 equiv) of the boronic acid was used. Potassium phosphate (K_3PO_4) was used as the base. 1,4-Dioxane (110 °C, 4 h) was used as the solvent.[12,13]



Scheme 2 Synthesis of **4a–j**. *Reagents and conditions*: *i*, **2** (1.0 equiv), **3a–j** (2.6 equiv), K_3PO_4 (3.0 equiv), $Pd(PPh_3)_4$ (6 mol%), 1,4-dioxane (5 mL per 1 mmol of **2**), 110 °C, 4 h.

Table 1 Synthesis of **4a–j**

3, 4	R^1	R^2	R^3	R^4	Yield of **4** (%)[a]
a	H	H	H	H	75
b	H	H	Me	H	70
c	H	CF_3	H	H	60
d	OMe	H	H	H	62
e	H	H	CF_3	H	65
f	H	H	*t*-Bu	H	70
g	H	H	F	H	55
h	H	H	vinyl	H	65
i	H	Me	H	Me	60
j	H	OMe	H	OMe	72

[a] Yields of isolated products.

The Suzuki–Miyaura reaction of **2** with boronic acids **3b**,**f**,**k–m** (1.1 equiv), in the presence of $Pd(PPh_3)_4$ (3 mol%), proceeded with very good site selectivity (attack at carbon atom C-4′) to give the 2-trifluoromethylsulfonyl-

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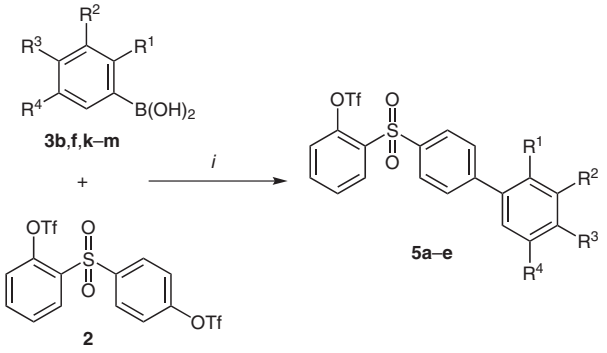
oxy-4′-(aryl)diphenylsulfones **5a–e** (Scheme 3, Table 2).[12,14] All products were isolated in pure form by chromatographic purification. In most cases, a small amount of the biscoupled product could be detected in the crude product before chromatography (by ^{1}H NMR and GC-MS). The reaction of **5e** with arylboronic acids **3a**,**k**,**l** (1.1 equiv) gave the unsymmetrical 2,4′-bis(aryl)diphenylsulfones **6a–c** containing two different aryl groups (Scheme 4, Table 3).[12,15] The structures of the products were proved by 2D NMR experiments (NOESY, HMBC).

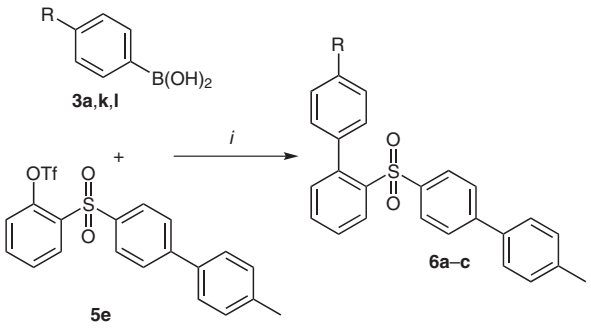


Scheme 3 Synthesis of **5a–e**. *Reagents and conditions*: *i*, **2** (1.0 equiv), **3b**,**f**,**k–m** (1.1 equiv), K_3PO_4 (1.5 equiv), $Pd(PPh_3)_4$ (3 mol%), 1,4-dioxane (5 mL per 1 mmol of **2**), 110 °C, 4 h.

Table 2 Synthesis of **5a–e**

3	5	R^1	R^2	R^3	R^4	Yield of **5** (%)[a]
k	**a**	H	H	Et	H	75
l	**b**	H	H	OMe	H	76
f	**c**	H	H	*t*-Bu	H	70
m	**d**	OMe	OMe	H	H	55
b	**e**	H	H	Me	H	62

[a] Yields of isolated products.



Scheme 4 Synthesis of **6a–c**. *Reagents and conditions*: *ii*, **5e** (1.0 equiv), **3a**,**k**,**l** (1.1 equiv), K_3PO_4 (1.5 equiv), $Pd(PPh_3)_4$ (3 mol%), 1,4-dioxane, 110 °C, 4 h.

The oxidative addition of palladium usually occurs first at the most electron-deficient carbon atom.[9] Carbon atoms C-2 and C-4′ of bis(triflate) **2** are expected to be equally electron deficient. The site-selective formation of **5a–e** can be explained by the fact that carbon atom C-4′ is less sterically hindered.

Table 3 Synthesis of **6a–c**

3	6	R	Yield of **6** (%)[a]
k	**a**	Et	60
a	**b**	H	57
l	**c**	OMe	50

[a] Yields of isolated products.

In conclusion, we have reported the synthesis of 2,4′-bis(aryl)diphenylsulfones based on what are, to the best of our knowledge, the first palladium(0)-catalyzed cross-coupling reactions of bis(triflates) of 2,4′-bis(hydroxy)diphenylsulfone. The reactions proceed with very good site selectivity.

Acknowledgment

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(11) **Synthesis of 2,4′-Bis(trifluoromethylsulfonyloxy)-diphenylsulfone (2)**

To a solution of **1** (1.0 equiv) in CH_2Cl_2 (10 mL per 1 mmol of **1**) was added pyridine (4.0 equiv) at –78 °C under an argon atmosphere. After stirring for 10 min, Tf_2O (2.4 equiv) was added at –78 °C. The mixture was allowed to warm to 0 °C and stirred for 4 h. The reaction mixture was filtered, and the filtrate was concentrated in vacuo. The products of the reaction mixture were isolated by rapid column chromatography (flash silica gel, heptanes–EtOAc). Starting with **1** (250 mg, 1.0 mmol), pyridine (0.32 mL, 4.0 mmol), and Tf_2O (0.40 mL, 2.4 mmol), compound **2** was isolated as a white solid (416 mg, 81%), mp 112 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.39 (m, 3 H, ArH), 7.50–7.56 (m, 1 H, ArH), 7.63–7.69 (m, 1 H, ArH), 7.99–8.04 (m, 2 H, ArH), 8.21–8.24 (m, 1 H, ArH). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –73.2, –73.3 CF. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 114. 5 (q, J_{CF} = 324.2 Hz, CF_3), 121.8 (q, J_{CF} = 324.2 Hz, CF_3), 122.4, 122.5, 128.9, 131.1, 131.4 (CH), 133.3 (C), 136.4 (CH), 140.5, 146.5, 152.9 (C). IR (KBr): ν = 3104 (w), 1594 (w), 1484 (w), 1434 (s), 1404 (w), 1325 (m), 1272 (w), 1203 (s), 1161 (s), 1127 (s), 1089 (m), 1054 (m), 992 (w), 966 (w), 870 (s), 749 (s), 781 (m), 726 (m), 688 (m), 629 (m), 599 (s), 562 (s), 552 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 514 (44) [M]$^+$, 317 (1), 273 (27), 225 (05), 209 (33), 177 (100), 155 (06), 115 (17). HRMS (EI, 70 eV): *m/z* calcd for $C_{14}H_8F_6O_8S_3$: 514.39262; found: 514. 39351.

(12) **General Procedure for the Synthesis of 4a–j, 5a–e, and 6a–c**

A 1,4-dioxane solution of the arylboronic acid, K_3PO_4, $Pd(PPh_3)_4$, and **2** or **5** was stirred at 110 °C for 4 h under argon atmosphere. After cooling to 20 °C, a sat. aq solution of NH_4Cl was added. The organic and the aqueous layer were separated, and the latter was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography.

(13) **2,4′-Bis(4-tolyl)diphenylsulfone (4b)**

Starting with **2** (205 mg, 0.4 mmol), K_3PO_4 (254 mg, 1.2 mmol), $Pd(PPh_3)_4$ (6 mol%), 4-methylphenylboronic acid (136 mg, 1.0 mmol), and 1,4-dioxane (5 mL per 1 mmol of **2**), compound **4b** was isolated as a white solid (112 mg, 70%), mp 131 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.29 (s, 3 H, CH_3), 2.30 (s, 3 H, CH_3), 6.77–6.80 (m, 2 H, ArH), 6.89–6.92 (m, 2 H, ArH), 7.11–7.20 (m, 6 H, ArH), 7.26–7.33 (m, 2 H, ArH), 7.44–7.52 (m, 3 H, ArH), 8.31–8.35 (m, 1 H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2, 21.3 (CH_3), 126.6, 127.1, 127.6, 127.8, 128.2, 128.5, 129.8, 130.0, 132.8, 132.9 (CH), 135.4, 136.5, 137.4, 138.5, 139.3, 140.1, 142.3, 145.3 (C). IR (KBr): ν = 3058 (w), 2921 (w), 2854 (w), 1731 (w), 1613 (m), 1484 (m), 4163 (m), 1404 (m), 1392 (m), 1313 (s), 1247 (w), 1151 (s), 1091 (m), 959 (w), 820 (m), 757 (s), 670 (m), 585 (s), 532 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 398 (100) [M]$^+$, 366 (2), 318 (22),

215 (6), 198 (4), 183 (22), 165 (46), 155 (7), 152 (38), 115 (6). HRMS (EI, 70 eV): *m/z* calcd for $C_{26}H_{22}O_2S$ $[M]^+$: 398.13350; found: 398.133551.

(14) **2-(Trifluoromethylsulfonyloxy)-4′-(4-ethylphenyl)-diphenylsulfone (5a)**

Starting with with **2** (205 mg, 0.4 mmol), K_3PO_4 (127 mg, 0.6 mmol), $Pd(PPh_3)_4$ (3 mol%), 4-ethylphenylboronic acid (66 mg, 0.44 mmol), and 1,4-dioxane (5 mL per 1 mmol of **2**), compound **5a** was isolated as a white solid (141 mg, 75%), mp 78 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (t, *J* = 7.6 Hz, 3 H, CH_3), 2.64 (q, *J* = 7.6 Hz, 2 H, CH_2CH_3), 7.18–7.24 (m, 2 H, ArH), 7.32–7.35 (m, 1 H, ArH), 7.42–7.53 (m, 3 H, ArH), 7.58–7.66 (m, 3 H, ArH), 7.93–7.97 (m, 2 H, ArH), 8.23–8.27 (m, 1 H, ArH). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –73.4. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.4 (CH_3), 28.5 (CH_2), 118.8 (q, J_{CF} = 320.1 Hz, CF_3), 122.2, 127.3, 127.5, 128.5, 128.6, 128.9, 130.9 (CH), 134.4 (C), 135.5 (CH), 136.3, 138.3, 145.1, 146.5, 146.9 (C). IR (KBr): ν = 3108, 3053, 2965, 2852 (w), 1591 (m), 1555, 1520, 1448 (w), 1468 (m), 1433 (s), 1391, 1267 (w), 1247 (m), 1200, 1157, 1128, 1056 (s), 1002 (m), 965 (w), 870, 818, 786 (s), 739, 716, 684 (m), 619, 584, 545 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 470 (100) $[M]^+$, 337 (10), 309 (02), 244 (42), 229 (16), 197 (24), 181 (07), 165 (28), 152 (15), 115 (05). HRMS (EI, 70 eV): *m/z* calcd for $C_{21}H_{17}O_5S_2F_3$ $[M + H]^+$: 471.05423; found: 471.05405.

(15) **2-(4-Ethylphenyl)-4′-(4-methylphenyl)diphenyl-sulfone (6a)**

Starting with **5e** (182 mg, 0.40 mmol), K_3PO_4 (127 mg, 0.60 mmol), $Pd(PPh_3)_4$ (3 mol%), 4-ethylphenylboronic acid (66 mg, 0.44 mmol), and 1,4-dioxane (5 mL per 1 mmol of **5e**), compound **6a** was isolated as a solid (98 mg, 60%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (t, *J* = 7.7 Hz, 3 H, CH_2CH_3), 2.31 (s, 3 H, CH_3), 2.61 (q, *J* = 7.6Hz, 2 H, CH_2CH_3), 6.80–6.82 (m, 2 H, ArH), 6.89–6.93 (m, 2 H, ArH), 7.07–7.20 (m, 5 H, ArH), 7.23–7.36 (m, 4 H, ArH), 7.44–7.48 (m, 2 H, ArH), 8.32–8.36 (m, 1 H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.4, 21.1 (CH_3), 28.5 (CH_2), 127.1 (C), 127.2, 127.3, 127.5, 127.6, 128.6, 128.9, 129.8, 130.9, 135.5, 136.1 (CH), 138.3, 138.8, 139.7, 145.1, 146.5, 146.7, 146.9 (C). IR (KBr): ν = 3104 (w)3058 (w), 2967 (w), 2920 (w), 2873 (w), 1592 (m), 1555 (w), 1484 (w), 1450 (w), 1423 (s), 1406 (w), 1333 (s), 1297 (m), 1228 (m), 1209 (s), 1157 (s), 1128 (s), 1089 (m), 1054 (m), 1003 (m), 958 (w), 884 (s), 781 (m), 717 (m), 685 (m), 622 (m), 595 (s), 560 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 412 (100) $[M]^+$, 348 (12), 333 (22), 318 (26), 197 (26), 165 (50), 152 (32). HRMS (EI, 70 eV): *m/z* calcd for $C_{27}H_{24}O_2S$: 412.14973; found: 412.14882.