# Synthesis of 3,4-Diarylbenzophenones by Site-Selective Suzuki–Miyaura Reactions of 3,4-Bis(trifluoromethylsulfonyloxy)benzophenone

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**Abstract:** The Suzuki–Miyaura reaction of the bis(triflate) of 3,4-dihydroxybenzophenone with two equivalents of boronic acids gave 3,4-diarylbenzophenones. The reaction with one equivalent of arylboronic acids resulted in site-selective attack onto carbon atom C-4. 3,4-Diarylbenzophenones containing two different aryl groups were prepared by sequential addition of two different boronic acids.

**Key words:** catalysis, palladium, Suzuki–Miyaura reaction, site-selectivity, benzophenones

Aryl-substituted benzophenones are of pharmacological relevance. Biological properties include, for example, cytotoxic[1a] and antibacterial activity,[1b] inhibition of various enzymes,[2] and activity as selectin antagonists.[3] Structurally related benzoylfluorenones are also of pharmacological interest.[4] The 4-arylbenzophenone core structure occurs in polycyclic frameworks of naturally occurring anthraquinones and tetracyclines.[5] 2-Hydroxy- and 2-aminobenzophenones represent antitubulin agents and are of importance in anticancer therapy.[6] Functionalized benzophenones are also important as UV-filters (e.g., sun screens) and photosensitizers.[7]

Benzophenones are available by reaction of organometallic reagents with aldehydes and subsequent oxidation or by Friedel–Crafts acylation.[6b,8] An alternative strategy relies on the $SmI_2$-mediated reaction of benzaldehydes with benzylhalides and subsequent oxidation.[9] Friedel–Crafts acylations of highly substituted derivatives do not always proceed with good regioselectivity. Recently, we reported the synthesis of 2′,4-diarylbenzophenones based on site-selective[10] Suzuki–Miyaura cross-coupling reactions of bis(triflates) of 2′,4-dihydroxybenzophenones.[11] The selectivity can be explained by steric reasons. Herein, we report what are, to the best of our knowledge, the first site-selective palladium(0)-catalyzed cross-coupling reactions of the bis(triflate) of 3,4-dihydroxybenzophenone which represents a commercially available and inexpensive substrate. The site-selectivity can be explained by electronic reasons. The products reported herein are not readily available by other methods.

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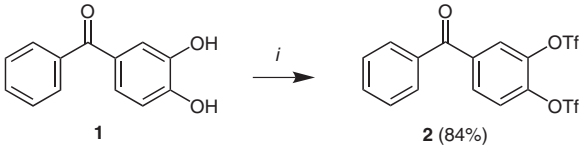
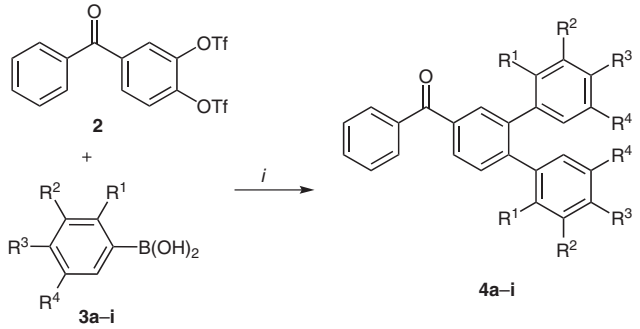
3,4-Dihydroxybenzophenone (**1**) was transformed into its bis(triflate) **2** in 84% yield (Scheme 1).[12]




**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 to 0 °C, 4 h.

The Suzuki reaction of **2** with boronic acids **3a–i** (2.6 equiv) afforded the novel 3,4-diarylbenzophenones **4a–i** in good yields (Scheme 2, Table 1). The best yields were obtained when $Pd(PPh_3)_4$ (6 mol%) was used as the catalyst, when 2.6 equivalents of the boronic acid were employed, and when the reaction was carried out in 1,4-dioxane (reflux, 4 h) using $K_3PO_4$ as the base.[13,14] The structures of all products were established by spectroscopic methods. The structure of **4c** was independently confirmed by X-ray crystal-structure analysis (Figure 1).[15]




**Scheme 2** Synthesis of **4a–i**. *Reagents and conditions*: *i*, **2** (1.0 equiv), **3a–i** (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.

The Suzuki reaction of **2** with boronic acids **3d** and **3j–m** (1.3 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 benzophenones **5a–e** (Scheme 3, Table 2).[13,16] In some cases, a small amount of the biscoupled product could be detected in the crude product (by $^1H$ NMR and GC-MS). The pure monocoupled products were obtained after chromatographic purification. The reaction

**Table 1** Synthesis of **4a–i**

| 4 | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Yield of **4** (%)[a] |
|---|---|---|---|---|---|
| **4a** | H | H | H | H | 78 |
| **4b** | H | H | F | H | 69 |
| **4c** | H | Me | H | Me | 75 |
| **4d** | OMe | H | OMe | H | 74 |
| **4e** | OMe | H | H | H | 67 |
| **4f** | H | H | OMe | H | 54 |
| **4g** | OEt | H | H | H | 76 |
| **4h** | H | Me | Me | H | 58 |
| **4i** | H | H | Et | H | 78 |

[a] Yields of isolated products.

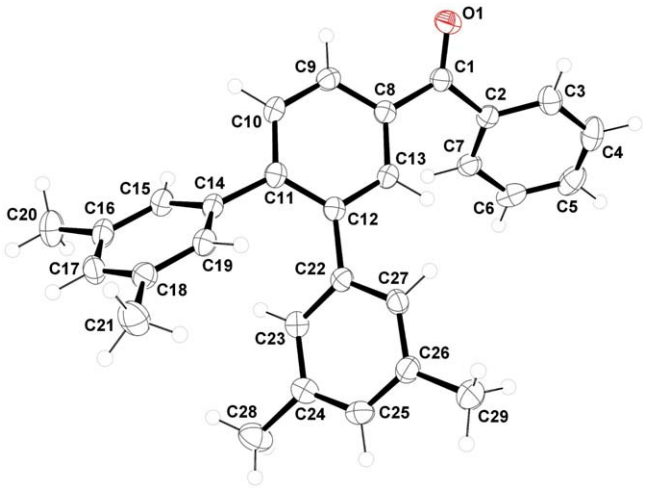
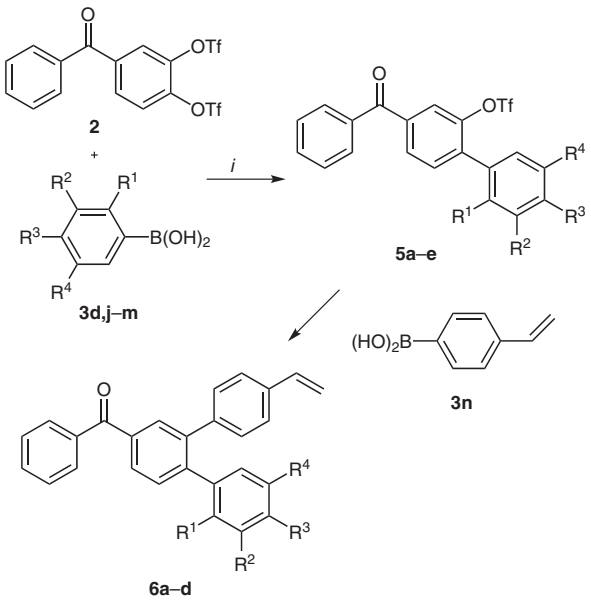



**Figure 1** ORTEP plot of **4c**

of **5a–e** with (4-vinylphenyl)boronic acid (**3n**, 1.3 equiv) gave 2,4-diarylbenzoates **6a–d** containing two different aryl groups. The structures of the products were proved by 2D NMR experiments (NOESY, HMBC).

The oxidative addition of palladium usually occurs first at the most electron-deficient carbon atom.[10] The site-selective formation of **5a–e** can be explained by the fact that carbon atom C-4 (located *para* to the keto group) is more electron deficient than C-3 (located *meta* to the keto group). Steric parameters have presumably no effect, due to the similar steric environment of carbon atoms C-4 and C-3 (Figure 2).

In conclusion, we have reported the synthesis of 3,4-diarylbenzophenones based on what are, to the best of our knowledge, the first palladium(0)-catalyzed cross-coupling reactions of bis(triflates) of 3,4-dihydroxybenzophenone. The reactions proceed with very good site selectivity.




**Scheme 3** Synthesis of **5a–e** and **6a–d**. *Reagents and conditions*: *i*, **2** (1.0 equiv), **3d**,**j–m** (1.3 equiv), $K_3PO_4$ (1.5 equiv), $Pd(PPh_3)_4$ (3 mol%), 1,4-dioxane, 110 °C, 4 h; *ii*, **5a**,**c–e** (1.0 equiv), **3n** (1.3 equiv), $K_3PO_4$ (1.5 equiv), $Pd(PPh_3)_4$ (3 mol%), 1,4-dioxane, 110 °C, 4 h.

**Table 2** Synthesis of **5a–e** and **6a–d**

| 5 | 6 | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Yield of **5** (%)[a] | Yield of **6** (%)[a] |
|---|---|---|---|---|---|---|---|
| **5a** | **6a** | H | OMe | H | H | 68 | 68 |
| **5b** | | OMe | H | H | OMe | 72 | –[b] |
| **5c** | **6b** | H | H | Me | H | 64 | 78 |
| **5d** | **6c** | H | OMe | OMe | OMe | 76 | 64 |
| **5e** | **6d** | H | H | *t*-Bu | H | 70 | 62 |

[a] Yields of isolated products.
[b] Experiment was not carried out.

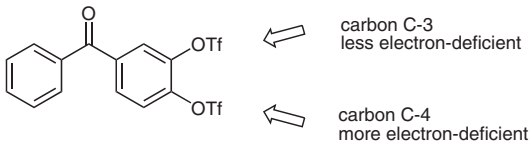



**Figure 2** Possible explanation for the site-selective formation of products **5a–e**

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(12) **3,4-Bis(trifluoromethylsulfonyloxy)benzophenone (2)**
To a $CH_2Cl_2$ solution (10 mL/mmol) of **1** (1.0 equiv) was added pyridine (4.0 equiv) at –78 °C under argon atmosphere. After 10 min, $Tf_2O$ (2.4 equiv) was added at –78 °C. The mixture was allowed to warm to 0 °C during 4 h with stirring. The reaction mixture was filtered, and the filtrate was concentrated in vacuo. The product was isolated by rapid column chromatography (flash silica gel, heptanes–EtOAc). Starting with **1** (214 mg, 1.0 mmol), pyridine (0.32 mL, 4.0 mmol), and $Tf_2O$ (0.38 mL, 2.4 mmol), **2** was isolated as a highly viscous oil (401 mg, 84%). $^1$H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.60 (m, 5 H, ArH), 7.68–7.74 (m, 2 H, ArH), 7.86 (s, 1 H, ArH). $^{13}$C NMR (62.89 MHz, $CDCl_3$): δ = 115.9 (q, $J_{F,C}$ = 320.0 Hz, $CF_3$), 121.1 (q, $J_{F,C}$ = 321.3 Hz, $CF_3$), 123.6, 125.2, 128.7, 129.9, 130.9, 133.6 (CH), 135.7, 138.7, 140.2, 142.9 (C), 192.6 (C=O). $^{19}$F NMR (282 MHz, $CDCl_3$): δ = –73.3, 72.0 (2 CF). IR (KBr): ν = 3061, (w), 1598, 1589, 1580 (m), 1496, 1431, 1414, 1319, 1291 (m), 1265 (s), 1165, 1077, 1028, 989, 976, 932 (m), 887, 787, 757 (s), 680, 595, 572 (m) cm$^{-1}$. GC-MS (EI, 70 eV): *m/z* (%) = 478 (74) [M$^+$], 401 (5), 345 (08), 253 (26), 225 (32), 204 (04), 167 (22), 156 (06), 128 (27), 105 (100), 77 (43), 69 (30), 51 (14). HRMS (EI, 70 eV): *m/z* calcd for $C_{15}H_8F_6O_7S_2$ [M$^+$]: 477.96101; found: 477.960958.

(13) **General Procedure for the Synthesis of 4a–i, 5a–e, and 6a–d**
The reaction was carried out in a pressure tube. To a dioxane suspension (5 mL) of **2** or **5**, $Pd(PPh_3)_4$, arylboronic acid, and $K_3PO_4$ were added. The mixture was stirred at 110 °C under argon atmosphere for the indicated period of time (6–8 h). The reaction mixture was diluted with $H_2O$ and extracted with $CH_2Cl_2$ (3 × 25 mL). The combined organic layers were dried ($Na_2SO_4$), filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (silica gel, EtOAc–heptanes).

(14) **3,4-Bis(3,5-dimethylphenyl)benzophenone (4c)**
Starting with **2** (220 mg, 0.46 mmol), $K_3PO_4$ (292 mg, 1.38 mmol), $Pd(PPh_3)_4$ (6 mol%), 3,5-dimethylphenylboronic acid (180 mg, 1.2 mmol), and 1,4-dioxane (5 mL per mmol of **2**), **4c** was isolated as a crystalline solid (134 mg, 75%); mp 140–142 °C. $^1$H NMR (250 MHz, $CDCl_3$): δ = 2.09 (s, 6 H, 2 $CH_3$), 2.11 (s, 6 H, 2 $CH_3$), 6.67–6.77 (m, 5 H, ArH), 7.38–7.48 (m, 5 H, ArH), 7.68–7.78 (m, 4 H, ArH). $^{13}$C NMR (75.46 MHz, $CDCl_3$): δ = 21.2 (2 $CH_3$), 21.3 (2 $CH_3$), 125.1, 127.5, 127.7, 128.3, 128.6, 128.8, 130.0, 130.4, 132.1, 132.3 (CH), 136.3, 137.1, 137.2, 137.8, 140.4, 140.5, 140.9, 144.9 (C), 196.4 (C=O). IR (KBr): ν = 3289, 3013, 2916, 2857, 2732 (w), 1732, (s), 1574 1505 (m), 1495, 1455, 1436, 1386, 1328, 1296 (m), 1250 (s), 1199, 1118, 1067, 1036, 959, 902 (m), 882, 842, 793, 738 (s), 695, 648, 596, 567 (m) cm$^{-1}$. GC-MS (EI, 70 eV): *m/z* (%) = 390 (100) [M$^+$], 313 (29), 270 (13), 239 (7), 148 (4), 105 (22), 77 (11). HRMS (EI): *m/z* calcd for $C_{29}H_{26}O$ [M$^+$]: 390.19782; found: 390.197629.

(15) CCDC-759141 contains all crystallographic details of this publication and is available free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: +44 (1223)336033; or deposit@ccdc.cam.ac.uk.

(16) **4-(3,4,5-Trimethoxyphenyl)-3-(trifluorosulfonyloxy)-benzophenone (5d)**
Starting with **2** (220 mg, 0.46 mmol), $K_3PO_4$ (146 mg, 0.69 mmol), $Pd(PPh_3)_4$ (3 mol%), 3,4,5-trimethoxyphenylboronic acid (125 mg, 0.59 mmol), and 1,4-dioxane (5mL per mmol of triflate), **5d** was isolated as a viscous oil (173 mg, 76%); mp 139–140 °C. $^1$H NMR (300 MHz, $CDCl_3$): δ = 3.82 (s, 6 H, 2 $OCH_3$), 3.83 (s, 3 H, $OCH_3$), 6.62 (s, 2 H, ArH), 7.39–7.47 (m, 3 H, ArH), 7.56 (s, 1 H, ArH), 7.68–7.78 (m, 3 H, ArH), 7.88 (d, 1 H, *J* = 6.4 Hz, ArH). $^{13}$C NMR (75.47 MHz, $CDCl_3$): δ = 56.2 (2 $OCH_3$), 61.0 ($OCH_3$), 106.8 (CH), 120 (q, $J_{F,C}$ = 320 Hz, $CF_3$), 122.0, 128.5, 130.0, 130.4, 133.1, 133.3 (CH), 135.8, 136.7, 137.7, 138.6, 149.0, 153.3 (C), 194.8 (C=O). $^{19}$F NMR (282 MHz, $CDCl_3$): δ = –73.8 ($CF_3$). IR (KBr): ν = 3065, 2999, 2936 (w), 1660, 1609 (s),1584, 1514, 1488 (m), 1463, 1418, 1393, 1317, 1291, 1278 (m), 1241 (s), 1170, 1104, 1063, 1001, 978 (m), 889, 831, 790, 745 (s), 675, 630, 598, 569 (m) cm$^{-1}$. GC-MS (EI, 70 eV): *m/z* (%) = 496 (92) [M$^+$], 363 (26), 332 (100), 317 (17), 255 (12), 227 (07), 185 (05), 105 (57), 77 (19). HRMS (EI): *m/z* calcd for $C_{23}H_{19}F_3O_7S$ [M$^+$]: 496.07981; found: 496.079887.