Synthesis of 7,8-Diarylflavones by Site-Selective Suzuki–Miyaura Reactions

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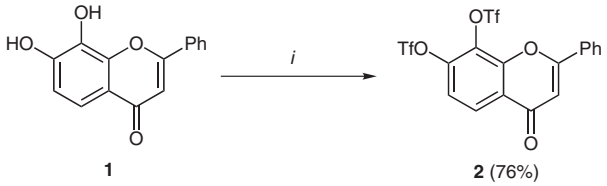
Abstract: 7,8-Diarylflavones were prepared by Suzuki–Miyaura reactions of the bis(triflate) of 7,8-dihydroxyflavone. The first attack proceeded with very good site selectivity at position 7, due to steric and electronic reasons.

Key words: catalysis, palladium, Suzuki–Miyaura reaction, flavones, regioselectivity

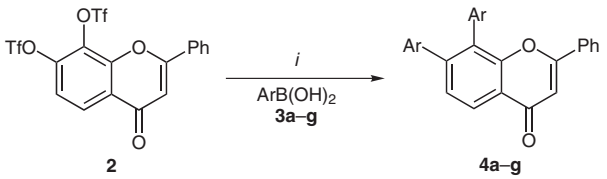
Flavones (2-arylchromones, 2-aryl-4*H*-1-benzopyran-4-ones) are of considerable pharmacological relevance and are widespread in nature as plant metabolites.[1] Pharmacological activities include antioxidant, antimicrobial, anti-inflammatory, antiproliferative, and vasculo-protective activity.[1–3] Most syntheses of flavones rely on the assembly of the chromone core structure by conventional methods.[2,3] The selective modification of naturally occurring flavones is mainly limited to date to the O-alkylation and acylation of hydroxy groups.[2]

Polyhalogenated molecules represent interesting substrates in palladium(0)-catalyzed cross-coupling reactions.[4] Recently, we have reported Suzuki–Miyaura and Heck reactions of tetrabromothiophene, tetrabromo-*N*-methylpyrrole, tetrabromoselenophene, and other polyhalogenated heterocycles.[5] We have also reported site-selective Suzuki–Miyaura reactions[6] of the bis(triflate) of methyl 2,5-dihydroxybenzoate and related substrates.[7] Despite the great pharmacological importance of flavones, only a few applications of palladium-catalyzed cross-coupling reactions to flavone-derived halides or triflates have been reported to date.[8] Regioselective palladium-catalyzed transformations of flavone-derived bis(halides) or bis(triflates) have, to the best of our knowledge, not yet been reported. Herein, we report the synthesis of 7,8-diaryl-flavones by site-selective Suzuki–Miyaura reactions of the bis(triflate) of 7,8-dihydroxyflavone.

Commercially available 7,8-dihydroxyflavone (**1**) was transformed to its bis(triflate) **2** in good yield (Scheme 1).[9] The Suzuki–Miyaura reaction of **2** with arylboronic acids **3a–g** (2.6 equiv) afforded the 7,8-diarylflavones **4a–g** in 59–74% yield (Scheme 2, Table 1).[10,11] Both electron-poor and electron-rich arylboronic acids could be successfully employed. The best yields were obtained using $Pd(PPh_3)_4$ (5 mol%) as the catalyst and K_3PO_4 (1.5 equiv) as the base. The reactions were carried out in 1,4-dioxane at 100 °C. GC-MS analysis of crude product mixtures showed that less than 10% of monoadduct was present when the reactions were carried out under the optimized conditions.



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



Scheme 2 Synthesis of **4a–g**. *Reagents and conditions*: (*i*), **2** (1.0 equiv), **3a–g** (2.6 equiv), $Pd(PPh_3)_4$ (5 mol%), K_3PO_4 (4.0 equiv), 1,4-dioxane, 100 °C, 4 h.

Table 1 Synthesis of **4a–g**

3	4	R	Yield of **4** (%)[a]
3a	**4a**	4-EtC_6H_4	70
3b	**4b**	4-*t*-BuC_6H_4	59
3c	**4c**	4-ClC_6H_4	72
3d	**4d**	4-FC_6H_4	62
3e	**4e**	4-$MeOC_6H_4$	68
3f	**4f**	4-MeC_6H_4	74
3g	**4g**	3,5-$Me_2C_6H_3$	71

[a] Yields of isolated products.

The Suzuki–Miyaura reaction of **2** with arylboronic acids **3a**,**c**,**f**,**h**,**i** (1.0 equiv) afforded the 7-aryl-8-trifluorosulfonyloxy-flavones **5a–e** in 66–76% yield with very good site selectivity (Scheme 3, Table 2).[10,12] During the optimization, it proved to be important to use exactly 1.0 equivalent of the arylboronic acid and to carry out the reaction at 70 °C instead of 100 °C. Both electron-poor

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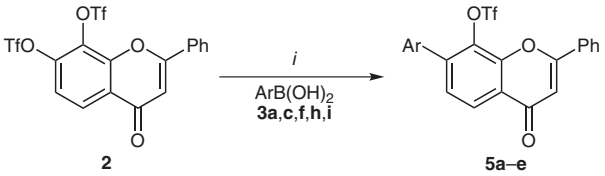
and electron-rich arylboronic acids were successfully used. Some crude reaction mixtures were analyzed by GC-MS. Besides the desired products **5**, a small amount of the corresponding bisadducts **4** were also present. When the reaction was carried out at 100 °C, the amount of bis-adduct was considerably higher compared to the situation when the reaction was carried out at 70 °C (<10%).



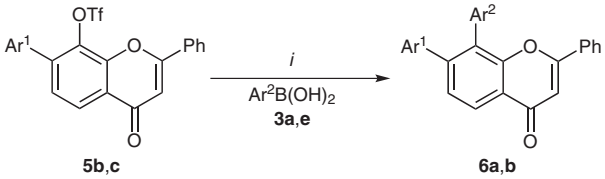
Scheme 3 Synthesis of **5a–e**. *Reagents and conditions*: (*i*) **2** (1.0 equiv), **3a**,**c**,**f**,**h**,**i** (1.0 equiv), K_3PO_4 (1.5 equiv), $Pd(PPh_3)_4$ (5 mol%), 1,4-dioxane, 70 °C, 4 h.

Table 2 Synthesis of **5a–e**

3	5	R	Yield of **5** (%)[a]
3a	**5a**	4-EtC_6H_4	72
3c	**5b**	4-ClC_6H_4	66
3f	**5c**	4-MeC_6H_4	76
3h	**5d**	4-F_3C-C_6H_4	69
3i	**5e**	4-HC=$CH_2C_6H_4$	74

[a] Yields of isolated products.

The Suzuki–Miyaura reaction of **5c** and **5b** with arylboronic acids **3a** and **3e** (1.3 equiv) afforded the 7,8-diarylflavones **6a** and **6b**, respectively (Scheme 4, Table 3).[10,13] The reactions were carried out at 100 °C.



Scheme 4 Synthesis of **6a**,**b**. *Reagents and conditions*: (*i*) **5b**,**c** (1.0 equiv), **3a**,**e** (1.3 equiv), K_3PO_4 (1.5 equiv), $Pd(PPh_3)_4$ (5 mol%), 1,4-dioxane, 100 °C, 4 h.

Table 3 Synthesis of 7,8-Diarylflavones **6a**,**b**

3	5	6	Ar^1	Ar^2	Yield of **6** (%)[a]
3a	**5c**	**6a**	4-MeC_6H_4	4-EtC_6H_4	66
3e	**5b**	**6b**	4-ClC_6H_4	4-MeOC_6H_4	73

[a] Yields of isolated products.

All products were characterized by spectroscopic methods. The constitution of products **5a–e** and **6a**,**b** were proved by 2D NMR experiments (HMBC, NOESY). The structure of **4f** was independently confirmed by X-ray crystal structure analysis (Figure 1).[14]

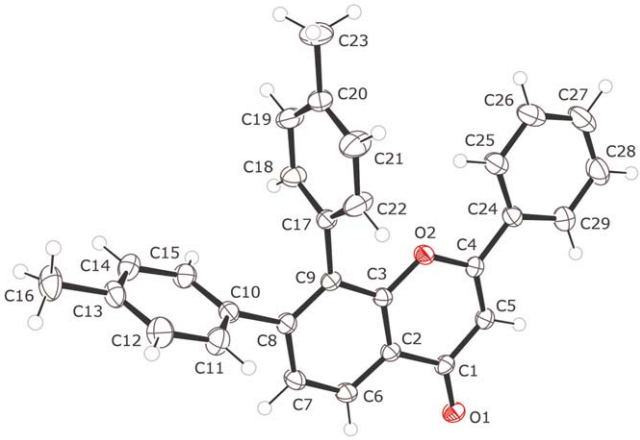


Figure 1 Crystal structure of **4f**

The site-selective formation of **5a–e** can be explained with steric and electronic arguments. The first attack of palladium(0)-catalyzed cross-coupling reactions generally occurs at the more electronical deficient and sterically less hindered position.[4,15] Position 7 of **2** is sterically less hindered than position 8. In addition, position 7 (located *meta* to the ether oxygen atom and *para* to the carbonyl group) is considerably more electron-deficient than position 1 (located *ortho* to the ether oxygen atom and *meta* to the carbonyl group).

In conclusion, we have reported an efficient synthesis of 7,8-diarylflavones were prepared by Suzuki–Miyaura reactions of the bis(triflate) of 7,8-dihydroxyflavone. The first attack proceeded with very good site selectivity at position 7.

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(9) **Synthesis of 4-Oxo-2-phenyl-4*H*-chromene-7,8-diyl-bis(trifluoromethanesulfonate (2)**
To a CH_2Cl_2 solution (10 mL) of **1** (254 mg, 1.0 mmol) was added pyridine (0.32 mL, 4.0 mmol) at –78 °C under argon atmosphere. After stirring for 10 min, Tf_2O (0.40 mL, 2.4 mmol) 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. Product **2** was isolated by rapid column chromatography (flash silica gel, heptanes–EtOAc) as a white solid (393 mg, 76%), mp 142–143 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.82 (s, 1 H), 7.43–7.52 (m, 4 H, ArH), 7.88–7.91 (m, 2 H, ArH), 8.25 (d, *J* = 9.4 Hz, 1 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 108.3 (CH), 118.6 (q, $J_{F,C}$ = 321.6 Hz, CF_3), 118.7 (q, $J_{F,C}$ = 320.4 Hz, CF_3), 118.9 (CH), 124.7 (C), 126.6, 126.7, 129.3 (CH), 129.9, 130.2 (C), 132.6 (CH), 143.9, 149.5, 164.5, 175.3 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –72.66, –72.85. IR (KBr): ν = 3080 (w), 1660 (s), 1613 (m), 1427 (s), 1359 (m), 1210, 1126 (s), 1053, 996, 955, 836, 794, 756 (m), 733 (w), 684 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 518 (95) [M$^+$], 385 (7), 357 (15), 321 (29), 293 (100), 219 (66), 191 (79). HRMS (EI, 70 eV): *m/z* calcd for $C_{17}H_8F_6O_8S_2$ [M$^+$]: 517.95700; found: 517.95651.

(10) **General Procedure for Suzuki–Miyaura Cross-Coupling Reactions**
A 1,4-dioxane solution (3–4 mL) of **2** (1.0 equiv), arylboronic acid **3** (1.0–1.3 equiv per desired cross-coupling reaction), K_3PO_4 (1.5–2.0 equiv per desired cross-coupling reaction), and $Pd(PPh_3)_4$ (5 mol%) was heated at 70–100 °C for 4 h. After cooling to 20 °C, a sat. aq solution of NH_4Cl was added, the organic and aqueous layers 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.

(11) **2-Phenyl-7,8-di(*p*-tolyl)-4*H*-chromen-4-one (4f)**
Starting with **2** (259 mg, 0.5 mmol), K_3PO_4 (424 mg, 2.0 mmol), $Pd(PPh_3)_4$ (5 mol%), 4-methylphenylboronic acid (**3f**, 177 mg, 1.3 mmol), and 1,4-dioxane (5 mL), **4f** was isolated as a crystalline light yellow solid (148 mg, 74%), mp 248–249 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.19 (s, 3 H, CH_3), 2.29 (s, 3 H, CH_3), 6.75 (s, 1 H), 6.90–7.04 (m, 8 H, ArH), 7.24–7.33 (m, 3 H, ArH), 7.39 (d, 1 H, *J* = 8.2 Hz, ArH), 7.48–7.51 (m, 2 H, ArH), 8.16 (d, 1 H, *J* = 8.2 Hz, ArH). ^{13}C NMR (75MHz, $CDCl_3$): δ = 21.2, 21.4 (CH_3), 106.7 (CH), 122.8 (C), 124.4, 126.2, 127.4, 128.6, 128.7, 128.9, 129.7 (CH), 130.2 (C), 131.0, 131.4 (CH), 131.6, 131.7, 137.0, 137.1, 146.7, 153.9, 163.2, 178.6 (C). IR (KBr): ν = 2917 (w), 1631 (m), 1592 (w), 1446, 1371 (m), 1238 (w), 1145, 1016 (m), 917 (w), 816, 773, 690 (s), 665 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 402 (100) [M$^+$], 387 (34), 359 (3), 331 (4), 299 (4), 285 (7), 243 (9), 229 (12). HRMS (EI): *m/z* calcd for $C_{29}H_{22}O_2$ [M$^+$]: 402.16143; found: 402.161442.

(12) **7-(4-Ethylphenyl)-4-oxo-2-phenyl-4*H*-chromen-8-yl Trifluoromethanesulfonate (5a)**
Starting with **2** (156 mg, 0.30 mmol), K_3PO_4 (96 mg, 0.45 mmol), $Pd(PPh_3)_4$ (5 mol%), (4-ethylphenyl)boronic acid (**3a**, 45 mg, 0.30 mmol), and 1,4-dioxane (3mL), **5a** was isolated as a white solid (102 mg, 72%), mp 167–168 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.22 (t, 3 H, *J* = 7.7 Hz, CH_3), 2.66 (q, 2 H, *J* = 7.5 Hz, CH_2), 6.83 (s, 1 H), 7.27 (d, 2 H, *J* = 8.0 Hz, ArH), 7.38 (d, 2 H, *J* = 8.3 Hz, ArH), 7.44 (d, 1 H, *J* = 8.3 Hz, ArH), 7.46–7.50 (m, 3 H, ArH), 7.95–7.97 (m, 2 H, ArH), 8.18 (d, 1 H, *J* = 8.3 Hz, ArH). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 15.5 (CH_3), 28.7 (CH_2), 108.2 (CH), 118.0 (q, $J_{F,C}$ = 320 Hz, CF_3), 124.2 (C), 125.1, 126.7, 127.4, 128.3, 129.1, 129.2 (CH), 130.8, 131.6 (C), 132.1 (CH), 135.1, 140.7, 145.9, 149.0, 163.8, 176.7 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –74.3. IR (KBr): ν = 2916, 2850 (w), 1622, 1568, 1447 (m), 1386 (s), 1271 (m), 1164 (s), 1041 (m), 906 (w), 811, 767, 681 (s), 634 (w) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 474 (40) [M$^+$], 410 (28), 395 (18), 366 (3), 341 (100), 326 (8), 313 (20), 281 (4). HRMS (EI): *m/z* calcd for $C_{24}H_{17}F_3O_5S$ [M$^+$]: 474.07471; found: 474.07492.

(13) **8-(4-Ethylphenyl)-2-phenyl-7-(*p*-tolyl)-4*H*-chromen-4-one (6a)**
Following the general procedure starting with **5c** (101 mg, 0.22 mmol), K_3PO_4 (93 mg, 0.44 mmol), $Pd(PPh_3)_4$ (5 mol%), 4-(ethylphenyl)boronic acid (**3a**, 44 mg, 0.29 mmol), and 1,4-dioxane (3 mL), **6a** was isolated as a yellow solid (60 mg, 66%), mp 198–199 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.20 (t, 3 H, *J* = 7.9 Hz, CH_3), 2.23 (s, 3 H, CH_3), 2.62 (q, 2 H, *J* = 7.5 Hz), 6.79 (s, 1 H), 6.95–7.01 (m, 4 H, ArH), 7.07–7.12 (m, 4 H, ArH), 7.26–7.38 (m, 3 H, ArH), 7.43 (dd, 1 H, *J* = 3.4, 8.3 Hz, ArH), 7.50–7.54 (m, 2 H, ArH), 8.18 (d, 1 H, *J* = 8.3 Hz, ArH). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ = 15.8, 21.1 (CH_3), 28.7 (CH_2), 122.8 (C), 124.3, 126.2, 127.4, 128.6, 128.7, 128.8, 128.9, 129.6, 131.0, 131.3 (CH), 131.6, 131.7, 132.0, 137.0, 143.5, 146.5, 146.7, 153.9, 136.1, 178.7 (C). IR (KBr): ν = 2962, 2923, 1644 (s), 1597 (w), 1371 (m), 1202, 1096, 1016 (w), 815, 771 (m), 688 (w) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 416 (100) [M$^+$], 402 (16), 387 (49), 313 (6), 285 (14), 271 (5), 253 (6), 239 (9). HRMS (EI): *m/z* calcd for $C_{30}H_{24}O_2$ [M$^+$]: 416.17783; found: 416.17762.

(14) CCDC-781627 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, GB-Cambridge CB21EZ; fax: +44 (1223)336033; or deposit@ccdc.cam.ac.uk.

(15) For a simple guide for the prediction of the site-selectivity of palladium(0)-catalyzed cross-coupling reactions based on the ^{1}H NMR chemical shift values, see: Handy, S. T.; Zhang, Y. *Chem. Commun.* **2006**, 299.