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Regioselective Suzuki–Miyaura Reactions of the Bis(triflate) of 6,7-Dihydroxy-2,2-dimethylchroman-4-one

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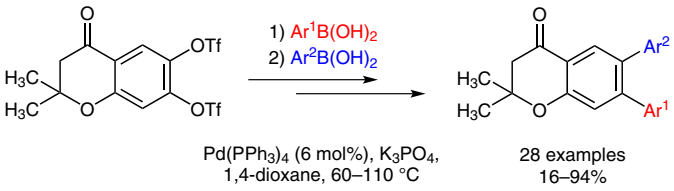

Dedicated in memory to our dear colleague and friend Professor Tamás Patonay, PhD, DSc

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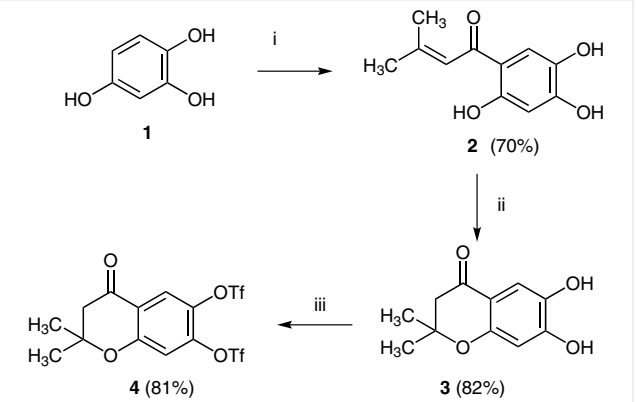
Abstract 6,7-Diarylchromanone derivatives were prepared by Suzuki–Miyaura reactions of the bis(triflate) of 6,7-dihydroxy-2,2-dimethylchroman-4-one. Due to electronic factors the first attack proceeded with very good site selectivity at position 7.

Key words Suzuki–Miyaura reaction, regioselectivity, palladium, catalysis, heterocycles

Chromanones (2*H*-benzopyran-4-ones) are widespread in nature, for example, as plants metabolites.[1–4] They show versatile biological activities, including antibacterial,[5–7] HIV inhibitor,[8] enzyme modulator,[9] and insecticidal[10] properties. Besides their pharmacological activity, chromanone derivatives are valuable precursors of molecules with benzopyrane substructure. The 2,2-dimethyl-2*H*-1-benzopyran moiety is represented in many natural products formed by the polyketide biosynthesis pathway.[11] Likewise, related molecules, such as coumarins, chromenes, chromene glycosides, and flavanoids, occur as natural products or are present in biologically relevant synthetic molecules.[12] Many studies and investigations on the syntheses and chemical transformations of 2,2-dimethyl-2*H*-benzopyrans have been performed in the past decades. In fact, the synthesis of 2,2-dimethyl-2*H*-benzopyran-4-ones[13] and 2,2-dimethyl-2*H*-benzopyrans[14] play a central role in drug discovery.

Although the synthesis of 2,2-dimethylchromanone[15–18] is well-known, derivatives containing aryl groups located at the benzene moiety have, to the best of our knowledge, only scarcely been reported to date. This prompted us to develop a new synthesis of mono- and diarylated 2,2-dimethylchromanones by regioselective Suzuki–Miyaura reactions[19,20] starting with the corresponding triflate derivative. As compared to other palladium-catalyzed reactions, the Suzuki coupling has the advantage of mild reaction conditions, easy availability of arylboronic acids, and high functional-group tolerance.[21–35] Several catalysts and ligands have been used in this coupling reaction.[36–39] The chemoselectivity depends on the type of the leaving groups, the reactivity follows the next sequence: ArI > ArBr > ArOTf > ArCl > ArOTs.[40–45] In the case of identical leaving groups, the regioselectivity is controlled by steric and electronic factors.[46–49] In the last few years, regioselective Suzuki coupling reactions became a useful approach for synthesizing new differently substituted benzopyrane derivatives.[49–51]

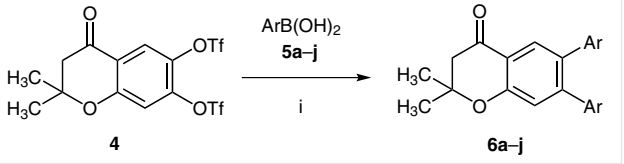
2,2-Dimethyl-6,7-dihydroxychroman-4-one (**3**) was synthesized by the method of Tímár and Jászberényi.[52] Commercially available hydroxyquinol (**1**) was transformed into α,β-unsaturated ketone **2** which was transformed, upon addition of potassium hydroxide, to **3**. The reaction of



Scheme 1 Synthesis of **4**. *Reagents and conditions*: (i) **1** (1.0 equiv), 3-methylbut-2-enoic acid (1.0 equiv), $ZnCl_2$ (1.5 equiv), $POCl_3$ (8.8 equiv), r.t., 2 h; (ii) 5% NaOH solution, r.t., 1 h, then pH = 1 with concd HCl solution; (iii) Tf_2O (2.4 equiv), pyridine (4.0 equiv), dry CH_2Cl_2, –78 °C to r.t., 2 h.

3 with trifluoromethanesulfonic anhydride in dry dichloromethane in the presence of pyridine provided bis(triflate) **4** (Scheme 1).

The Suzuki–Miyaura reaction of **4** with arylboronic acids **5a–j** (2.2 equiv) afforded 6,7-diaryl-2,2-dimethylchromanones **6a–j** in good yields (Scheme 2,Table 1).[53] Both electron-poor and electron-rich arylboronic acids were successfully employed. The reactions were carried out in dry 1,4-dioxane at 90–100 °C using $Pd(PPh_3)_4$ (6 mol%) as catalyst and K_3PO_4 (3.0 equiv) as base. However, the first coupling occurred quickly at position 7, the second one went slower, due to the lower reactivity of position 6 and the steric hindrance caused by the aryl group introduced in the first coupling step. In one case (**6i**) the use of a larger amount of boronic acid provided a higher yield.



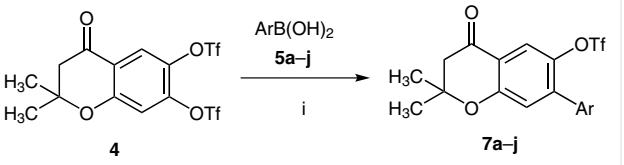
Scheme 2 Synthesis of **6a–j**. *Reagents and conditions*: (i) **4** (1.0 equiv), **5a–j** (2.2 equiv), $Pd(PPh_3)_4$ (6 mol%), K_3PO_4 (3.0 equiv), dry 1,4-dioxane.

Table 1 Synthesis of **6a–j**

5	6	Ar	T (°C)	t (h)	Yield of **6** (%)[a]
a	**a**	4-$F_3CC_6H_4$	90	1,5	83
b	**b**	4-$MeOC_6H_4$	90	2,5	68
c	**c**	4-MeC_6H_4	90	2,5	71
d	**d**	Ph	90	6	57
e	**e**	4-HOC_6H_4	90	6	49
f	**f**	4-ClC_6H_4	90	10	56
g	**g**	4-FC_6H_4	90	24	78
h	**h**	3-vinylC_6H_4	90	24	16
i	**i**	3,4-$(MeO)_2C_6H_3$	90	24	75[b]
j	**j**	5-F-2-$MeOC_6H_3$	100	24	61

[a] Isolated yields.
[b] Conditions: 4.4 equiv boronic acid.

The Suzuki–Miyaura reaction of **4** with arylboronic acids **5a–j** (1.1 equiv) afforded the 7-aryl-2,2-dimethyl-6-triflyloxychromanones **7a–j** in moderate to good yields (Scheme 3,Table 2).[54] The reactions proceeded with very good site selectivity. The first coupling occurred at position 7. Isomeric byproducts were not formed. Both electron-poor and electron-rich arylboronic acids were successfully used. During the optimization, the best yields were obtained using 1.1 equivalents of boronic acid with $Pd(PPh_3)_4$ (3 mol%) in dry 1,4-dioxane at a temperature of 60 °C or, in some cases, at 110 °C.



Scheme 3 Synthesis of **7a–j**. *Reagents and conditions*: (i) **4** (1.0 equiv), **5a–j** (1.1 equiv), $Pd(PPh_3)_4$ (3 mol%), K_3PO_4 (2.0 equiv), dry 1,4-dioxane, 60–110 °C, 5–18 h.

Table 2 Synthesis of **7a–j**

5	7	Ar	T (°C)	t (h)	Yield of **7** (%)[a]
a	**a**	4-$F_3CC_6H_4$	60	6.5	34
b	**b**	4-O MeC_6H_4	60	8	68
c	**c**	4-MeC_6H_4	60	9	70
d	**d**	Ph	60	10	77
e	**e**	4-HOC_6H_4	110	18	65
f	**f**	4-ClC_6H_4	60	6.5	38
g	**g**	4-FC_6H_4	60	6.5	76
h	**h**	3-vinylC_6H_4	60	5	80
i	**i**	3,4-$(MeO)_2C_6H_3$	110	18	73
j	**j**	5-F-2-$MeOC_6H_3$	60	6.5	59

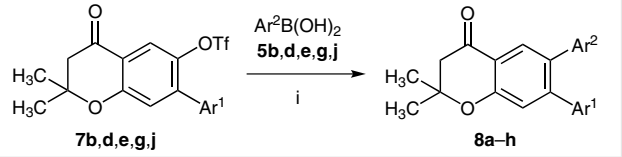
[a] Isolated yields.

The Suzuki–Miyaura reaction of monoarylated products **7b,d,e,g,j** with arylboronic acids **5b,d,e,g,j** (2.2 equiv) afforded 2,2-dimethyl-6,7-diarylchromanones **8a–h** (Scheme 4, Table 3).[55] The reactions were carried out at 90 °C in 1,4-dioxane and resulted in high yields.

Table 3 Synthesis of **8a–h**

5	7	8	Ar^1	Ar^2	Yield of **8** (%)[a]
d	**e**	**a**	4-HOC_6H_4	Ph	94
e	**d**	**b**	Ph	4-HOC_6H_4	82
j	**e**	**c**	4-HOC_6H_4	5-F-2-$MeOC_6H_3$	89
e	**j**	**d**	5-F-2-$MeOC_6H_3$	4-HOC_6H_4	71
g	**e**	**e**	4-HOC_6H_4	4-FC_6H_4	91
e	**g**	**f**	4-FC_6H_4	4-HOC_6H_4	82
e	**b**	**g**	4-$MeOC_6H_4$	4-HOC_6H_4	83
b	**e**	**h**	4-HOC_6H_4	4-$MeOC_6H_4$	72

[a] Isolated yields.



Scheme 4 Synthesis of **8a–h**. *Reagents and conditions*: (i) **7b,d,e,g,j** (1.0 equiv), **5b,d,e,g,j** (2.2 equiv), $Pd(PPh_3)_4$ (6 mol%), K_3PO_4 (3.0 equiv), dry 1,4-dioxane, 90 °C, 2–4 h.

All products were fully characterized by various spectroscopic methods. The structure of products **7a–j** was proved by 2D NMR experiments (HMBC, NOESY). Figure 1 shows the example of **7e**. All structures were also confirmed by GC–MS, HRMS, and IR analysis.

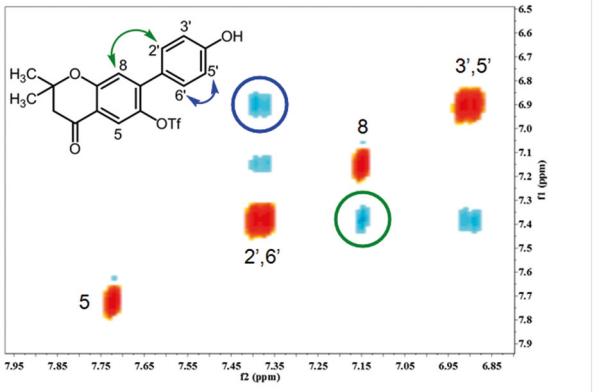


Figure 1 NOESY measurement of **7e**

In conclusion, we have reported the synthesis of a variety of arylated chromanones by site-selective Suzuki–Miyaura reactions of 6,7-ditriflyloxy-2,2-dimethylchroman-4-one. The first attack occurred at the position 7. The site selectivity can be explained by electronic effects.

Acknowledgement

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References and Notes

(1) Lemos, L. M. S.; Martins, T. B.; Tanajura, G. H.; Gazoni, V. F.; Bonaldo, J.; Strada, C. L.; Silva, M. G.; Dall'Oglio, E. L.; Sousa, J. P. T.; Martins, D. T. O. *J. Ethnopharmacol.* **2012**, *141*, 432.
(2) Nascimento, A. M.; Oliveira, D. C. R. *Helv. Chim. Acta* **2014**, *97*, 146.
(3) Wanga, H.; Sun, Q.-Y.; Yang, F.-M.; Long, C.-L.; Wang, Y.-H.; Tang, G.-H.; Zhao, F.-W.; Niua, H.-M.; Huang, Q.-Q.; Xu, J.-J.; Wataya, Y.; Ma, L.-J. *Helv. Chim. Acta* **2010**, *93*, 2183.
(4) Tanaka, Y.; Honma, D.; Tamura, M.; Yanagida, A.; Zhao, P.; Shoji, T.; Tagashira, M.; Shibusawa, Y.; Kanda, T. *Phytochem. Lett.* **2012**, *5*, 514.
(5) Albrecht, U.; Lalk, M.; Langer, P. *Bioorg. Med. Chem.* **2005**, *13*, 1531.
(6) Cottiglia, F.; Dhanapal, B.; Sticher, O.; Heilmann, J. *J. Nat. Prod.* **2004**, *67*, 537.
(7) Hoettecke, N.; Rotzoll, S.; Albrecht, U.; Lalk, M.; Fischer, C.; Langer, P. *Bioorg. Med. Chem.* **2008**, *16*, 10319.
(8) Park, J. H.; Lee, S. U.; Kim, S. H.; Shin, S. Y.; Lee, J. Y.; Shin, C.-G.; Yoo, K. H.; Lee, Y. S. *Arch. Pharm. Res.* **2008**, *31*, 1.
(9) Gamal-Eldeena, A. M.; Abdel-Lateff, A.; Okinoc, T. *Environ. Toxicol. Pharmacol.* **2009**, *28*, 317.
(10) Zhao, P.-L.; Li, J.; Yang, G.-F. *Bioorg. Med. Chem.* **2007**, *15*, 1888.
(11) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-G.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939.
(12) Nicolaou, K. C.; Pfefferkorn, J. A.; Cao, G.-G. *Angew. Chem. Int. Ed.* **2000**, *39*, 739.
(13) Tímár, T.; Lévai, A.; Eszenyi, T.; Sebők, P. *J. Heterocycl. Chem.* **2000**, *37*, 1389.
(14) Lévai, A.; Tímár, T.; Sebők, P.; Eszenyi, T. *Heterocycles* **2000**, *53*, 1193.
(15) Dubrovskiy, A. V.; Larock, R. C. *Tetrahedron* **2013**, *69*, 2789.
(16) López, C. S.; Erra-Balsells, R.; Bonesi, S. M. *Tetrahedron Lett.* **2010**, *51*, 4387.
(17) Iguchi, D.; Erra-Balsells, R.; Bonesi, S. M. *Tetrahedron Lett.* **2014**, *55*, 4653.
(18) Dubrovskiy, A. V.; Larock, R. C. *Org. Lett.* **2010**, *12*, 3117.
(19) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *36*, 3437.
(20) Miyaura, N.; Suzuki, A. *Chem. Commun.* **1979**, 866.
(21) Suzuki, A. *Pure Appl. Chem.* **1985**, *57*, 1749.
(22) Negishi, E.-i. *Handbook of Organopalladium for Organic Synthesis*; Vol. 1 and 2; Wiley-Interscience: New York, **2002**.
(23) Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals*; Wiley-VCH: Weinheim, **2004**, 2nd ed., Vol. 1 and 2.
(24) de Meijere, A.; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, **2004**, 2nd ed., Vol. 1 and 2.
(25) King, A. O.; Yasuda, N. *Organometallics in Process Chemistry*; Larsen, R. D., Ed.; Springer: Berlin, **2004**.
(26) Ackermann, L. *Modern Arylation Methods*; Wiley-VCH: Weinheim, **2009**.
(27) Tsuji, J. *Palladium Reagents and Catalysts*, 2nd ed.; Wiley: Chichester, **2004**.
(28) Suzuki, A. *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, **2002**.
(29) Suzuki, A. *J. Organomet. Chem.* **2002**, *653*, 54.
(30) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.
(31) Wu, X. F.; Anberasan, P.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 9047.
(32) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651.
(33) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11.
(34) Roglans, A.; Pla-Quintana, A.; Moreno-Mañas, M. *Chem. Rev.* **2006**, *106*, 4622.
(35) Yin, L.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133.
(36) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.
(37) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617.
(38) Zapf, A.; Jackstell, R.; Rataboul, F.; Riermeier, T.; Monsees, A.; Fuhrmann, C.; Shaikh, N.; Dingerdissen, U.; Beller, M. *Chem. Commun.* **2004**, 38.

(39) Rataboul, F.; Zapf, A.; Jackstell, R.; Harkal, S.; Riermeier, T.; Monsees, A.; Dingerdissen, U.; Beller, M. *Chem. Eur. J.* **2004**, *10*, 2983.
(40) Littke, A. F.; Dai, C. Y.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.
(41) Hassan, Z.; Hussain, M.; Villinger, A.; Langer, P. *Tetrahedron* **2012**, *68*, 6305.
(42) Espino, G.; Kurbangalieva, A.; Brown, J. M. *Chem. Commun.* **2007**, 1742.
(43) Kamikawa, T.; Hayashi, T. *Tetrahedron Lett.* **1997**, *38*, 7087.
(44) Roy, A. H.; Hartwig, J. F. *Organometallics* **2004**, *23*, 194.
(45) Hassan, Z.; Hussain, M.; Langer, P. *Synlett* **2011**, 1827.
(46) Schnürch, M.; Flasik, R.; Khan, A. F.; Spina, M.; Mihovilovic, M. D.; Stanetty, P. *Eur. J. Org. Chem.* **2006**, 3283.
(47) Wang, R.; Manabe, K. *Synthesis* **2009**, 1405.
(48) Handy, S. T.; Zhang, Y. *Chem. Commun.* **2006**, 299.
(49) Zahid, H.; Patonay, T.; Langer, P. *Synlett* **2013**, *24*, 412.
(50) Malik, I.; Hussain, M.; Hung, N. T.; Villinger, A.; Langer, P. *Synlett* **2010**, 2244.
(51) Eleya, N.; Malik, I.; Reimann, S.; Wittler, K.; Hein, M.; Patonay, T.; Villinger, A.; Ludwig, R.; Langer, P. *Eur. J. Org. Chem.* **2012**, 1639.
(52) Tímár, T.; Jászberényi, J. C. *J. Heterocycl. Chem.* **1988**, *25*, 871.
(53) **Procedure for Synthesizing 6,7-Diaryl-2,2-dimethylchroman-4-one Derivatives**

To a mixture of 2,2-dimethyl-6,7-ditriflyloxychroman-4-one (150 mg, 0.318 mmol), K_3PO_4 (202 mg, 0,95 mmol), and boronic acid (0.70 mmol) in dry 1,4-dioxane (4 mL) was added $Pd(PPh_3)_4$ (22 mg, 0.019 mmol) in a dried pressure tube under argon. The reaction mixture was stirred and heated in an aluminium heating block. The solvent was evaporated in vacuum, and the solid mixture was submitted to adsorptive filtration on silica gel using acetone as eluent removing the inorganic compounds. Silica was added to the solution, the acetone was evaporated, and the mixture was purified by column chromatography (eluent: heptane–EtOAc, the ratio is given below) giving the diarylated product.

6,7-Bis(4-methoxyphenyl)-2,2-dimethylchroman-4-one

Starting with **4** (150 mg, 0.32 mmol), K_3PO_4 (202 mg, 0.95 mmol), $Pd(PPh_3)_4$ (22 mg, 6 mol%), (4-methoxyphenyl)boronic acid (**5b**, 106 mg, 0.70 mmol), and 1,4-dioxane (4 mL), **6b** was isolated as a white solid (84 mg 68%), mp 150–152.5 °C. ^{1}H NMR (300 MHz, 298 K, $CDCl_3$): δ = 7.61 (s, 1 H, 5-H), 7.05 (d, *J*= 10.5 Hz, 2 H, 2′,6″-H) 6.98 (d, *J*= 10.5 Hz, 2 H, 2′,6′-H), 6.93 (s, 1 H, 8-H), 6.81 (m, 4 H, 3′,5′-H, 3″,5″-H), 3.72 (s, 3 H, 4″-OCH_3), 3.71 (s, 3 H, 4′-OCH_3), 2.83 (s, 2 H, 3-H), 1.44 (s, 6 H, 2-CH_3). ^{13}C NMR (75 MHz, 298 K, $CDCl_3$): δ = 191.7.7 (C-4), 158.6 (C-8a), 158.3 (C-4″), 157.9 (C-4′), 147.5 (C-7), 132.5 (C-1″), 132.3 (C-1′), 132.0 (C-6), 130.4 (C-2′,6′, C-2″,6″), 127.4 (C-5), 119.3 (C-8), 118.5 (C-4a), 113.6 (C-3′,5′, C-3″5″), 79.6 (C-2), 55.0 (OCH_3), 48.0 (C-3), 26.2 (CH_3). IR (ATR): υ = 2994, 2954, 2835, 1683, 1606, 1512, 1466, 1430, 1403, 1296, 1243, 1167, 1109, 1025, 951, 831, 655, 564, 549 cm^{-1}. GC–MS (EI, 70 eV): *m*/z = 388 [M$^+$, 100%], 373, 333, 261, 189. HRMS: *m*/*z* calcd for $C_{25}H_{24}O_4$: 388.16691; found: 388.16649.

(54) **Procedure for Synthesizing 7-Aryl-2,2-dimethyl-6-triflyloxychroman-4-one Derivatives**

To a mixture of 2,2-dimethyl-6,7-ditriflyloxychroman-4-one (150 mg, 0.318 mmol), K_3PO_4 (135 mg, 0,64 mmol), and boronic acid (0.349 mmol) in dry 1,4-dioxane (4 mL) was added $Pd(PPh_3)_4$ (11 mg, 0.0095 mmol) in a dried pressure tube under argon. The reaction mixture was stirred and heated in an aluminium heating block. The solvent was evaporated in vacuum, then the solid mixture was submitted to adsorptive filtration on silica gel using acetone as eluent removing the inorganic compounds. Silica was added to the solution, the acetone was evaporated, and the mixture was purified by column chromatography (eluent: heptane–EtOAc mixture, the ratio is given below) giving the monosubsituted product.

7-(4-Methoxyphenyl)-2,2-dimethyl-6-(triflyloxy)chroman-4-one

Starting with **4** (150 mg, 0.32 mmol), K_3PO_4 (135 mg, 0.64 mmol), $Pd(PPh_3)_4$ (11 mg, 3 mol%), (4-methoxyphenyl)boronic acid (**5b**, 53 mg, 0.35 mmol), and 1,4-dioxane (4 mL), **7b** was isolated as a yellow oil (93 mg 68%), eluent: toluene–heptane (6:1). ^{1}H NMR (300 MHz, 298 K, DMSO-d_6): δ = 7.71 (s, 1 H, 5-H), 7.47 (d, 2 H, *J*= 8.7 Hz, 2′,6′-H), 7.06 (d, 2 H, *J*= 8.7 Hz, 3′,5′-H), 3.82 (s, 3 H, OCH_3), 2.92(s, 2 H, 3-H), 1.44 (s, 6 H, CH_3). ^{13}C NMR (75 MHz, 298 K, DMSO-d_6): δ = 190.7 (C-4), 160.0 (C-4′), 158.6 (C-8a), 142.1 (C-6), 140.1 (C-7), 130.5 (C-2′,6′), 126.1 (C-1′), 120.9 (C-5), 118.9 (C-8), 118.8 (C-4a), 114.2 (C-3′,5′), 80.6 (C-2), 55.3 (OCH_3), 47.3 (C-3), 26.0 (CH_3). IR (ATR): υ = 2978, 2839, 1696, 1607, 1518, 1423, 1205, 1136, 1097, 1030, 915, 890, 832, 613, 564, 513 cm^{-1}. GC–MS (EI, 70 eV): *m*/z = 430 [M$^+$], 297, 255, 241 (100%), 215, 185, 157, 83. HRMS: *m*/*z* calcd for $C_{19}H_{17}F_3O_6S$: 430.06979; found: 430.06967.

(55) **Procedure for Synthesizing Differently Substituted 6,7-Diaryl-2,2-dimethylchroman-4-one Derivatives**

To a mixture of 7-aryl-2,2-dimethyl-6-triflyloxychroman-4-one (0.120 mmol), K_3PO_4 (76 mg, 0,360 mmol), and boronic acid (0.264 mmol) in dry 1,4-dioxane (4 mL) was added $Pd(PPh_3)_4$ (8.3 mg, 0.0072 mmol) in a dried pressure tube under argon. The reaction mixture was stirred and heated in an aluminium heating block. The solvent was evaporated in vacuum, and then the solid mixture was submitted to adsorptive filtration on silica gel using acetone as eluent removing the inorganic compounds. Silica was added to the solution, the acetone was evaporated, and the mixture was purified by column chromatography (eluent: heptane–EtOAc mixture, the ratio is given below) giving the differently substituted product.

6-(4-Hydroxyphenyl)-7-(4-methoxyphenyl)-2,2-dimethylchroman-4-one

Starting with **7b** (50 mg, 0.12 mmol), K_3PO_4 (76 mg, 0.36 mmol), $Pd(PPh_3)_4$ (8.1 mg, 6 mol%), (4-hydroxyphenyl)boronic acid (**5e**, 35 mg, 0.264 mmol), and 1,4-dioxane (4 mL), **8g** was isolated as a light yellow solid (36 mg 83%), mp 182.5–185°C, eluent: heptane–EtOAc (2:1). ^{1}H NMR(300 MHz, 298 K, $CDCl_3$): δ = 9.37 (s, 1 H, 5-H), 7.59 (s, 1 H, 8-H), 7.06 (d, *J*= 8.7 Hz, 2 H, 2″,6″-H), 6.86 (d, *J*= 8.7 Hz, 2 H, 2′,6′-H), 6.82 (d, *J*= 8.7 Hz, 2 H, 3″,5″-H), 6.62 (d, *J*= 8.7 Hz, 2 H, 3′,5′-H), 6.55 (s, 1 H, OH), 3.73 (s, 3 H, OCH_3), 2.82 (s, 2 H, 3-H), 1.44 (s, 6 H, CH_3). ^{13}C NMR (75 MHz, 298 K, $CDCl_3$): δ = 191.7 (C-4), 158.6 (C-8a), 158.1 (C-4″), 156.1 (C-4′), 147.5 (C-7), 132.9 (C-1″), 132.1 (C-1′), 130.6 (C-6), 130.4 (C-2′,6′, C-2″,6″), 127.2 (C-5), 119.2 (C-8), 118.4 (C-4a), 115.0 (C-3′,5′), 113.5 (C-3″,5″), 79.6 (C-2), 55.0 (OCH_3), 48.0 (C-3), 26.2 (CH_3). IR (ATR): υ = 3299, 2921, 2847, 1737, 1668, 1602, 1512, 1406, 1243, 1163, 1109, 1026, 950, 834, 654, 560 cm^{-1}. GC–MS (EI, 70 eV): *m*/z = 374 [M$^+$, 100%], 359, 319, 290, 247, 219, 202, 179, 152. HRMS: *m*/z calcd for $C_{24}H_{22}O_4$: 374.15126; found: 374.15110.