Site-Selective Suzuki–Miyaura Reactions of the Bis(triflate) of 5,10-dihydroxy-11*H*-benzo[*b*]fluoren-11-one

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Abstract: 5,10-Diaryl-11*H*-benzo[*b*]fluoren-11-ones were prepared by Suzuki–Miyaura reactions of the bis(triflate) of 5,10-dihydroxy-11*H*-benzo[*b*]fluoren-11-one. The reactions proceed with excellent site-selectivity. The first attack occurs at position 10, due to electronic reasons.

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

Natural and synthetic fluorenones exhibit a broad spectrum of biological activities and also occur in many natural products. This includes, for example, dengibsin, dengibsinin, or dendroflorin isolated from the orchidee *Dendrobium gibsonii Lindl.*[1] Fluorenones are of great pharmacological importance.[2] They have been used as probes for the redox activity of DNA.[3] Amidofluorenone derivatives have been shown to act as telomerase inhibitors.[4] Kinamycin derivatives of the family of kinamycin natural products have been reported to display antitumor and antimicrobial activity against Gram-positive bacteria.[5] In recent years, new kinamycin analogues, containing a 6,6,5,6-ring system, have also been isolated. For example, kinafluorenone (**A**; Figure 1) was found to be a major metabolite of a mutant strain of *Streptomyces murayamaensis*. The fluorenone alkaloid cauliphine (**B**; Figure 1), which possesses antimyocardial ischemia activity, has also been isolated from *Caulophyllum robustum*.[6] Arylated fluorenones, fluorenes and benzofluorenones along with their oligomers and polymers have been studied extensively for the development of organic light-emitting devices (OLEDs).[7] Fluorenones are also important compounds in photochemistry.[8]

Fluorenones have been prepared by intramolecular Friedel–Crafts acylations of biaryls,[9] by [4+2]-cycloadditions of conjugated enynes,[10] by oxidation of fluorenes,[11] based on remote aromatic metalations,[12] by reaction of malonic acid dinitrile with aromatic aldehydes and methylketones,[13] by Suzuki reaction of boronic acids of benzoic acid amides with aryl triflates and subsequent cyclization,[14] by acid-mediated intramolecular Friedel–Crafts cyclization of 2-methoxycarbonylbiaryls, and by Suzuki reactions of salicylate-derived enol triflates.[15] We have recently reported a synthetic approach to functionalized fluorenones based on formal [3+3]-cyclizations of 1,3-bis(silyloxy)-1,3-butadienes.[16] Due to the importance of fluorenones and benzofluorenones, the development of efficient and regioselective methods for the synthesis of aryl-substituted derivatives is of considerable current importance. Herein, we report a convenient approach to 5,10-diaryl-11*H*-benzo[*b*]fluoren-11-ones by site-selective[17] Suzuki–Miyaura reactions of the bis(triflate)[18] of 5,10-dihydroxy-11*H*-benzo[*b*]fluoren-11-one. These reactions provide a convenient access to products which are difficult to prepare by other methods.

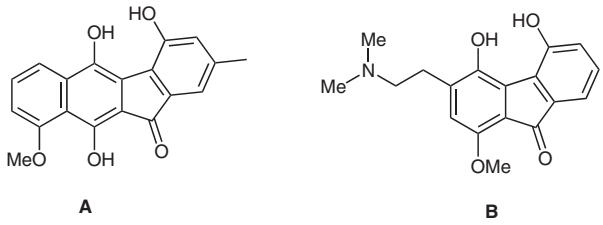
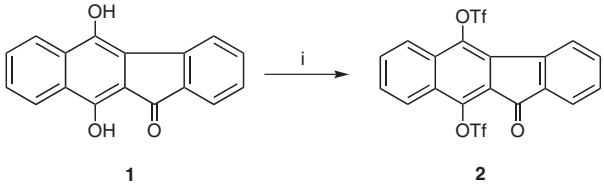


Figure 1 Fluorenone natural products: **A**: a major metabolite isolated from mutant strain of *Streptomyces murayamaensis*; **B**: cauliphine, a fluorenone alkaloid with antimyocardial ischemia activity

The reaction of 5,10-dihydroxy-11*H*-benzo[*b*]fluoren-11-one (**1**) with triflic anhydride (2.4 equiv) afforded the bis(triflate) **2** (Scheme 1).[19]



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 → 20 °C, 14 h.

The Suzuki–Miyaura reaction of **2** with arylboronic acids **3a–f** (2.4 equiv) afforded the 5,10-diaryl-11*H*-benzo[*b*]fluoren-11-ones **4a–f** in 70–85% yield (Scheme 2, Table 1). The yield of product **4c**, derived from the (less reactive) electron-poor arylboronic acid **3c**, was lower than the yields of the other products. The best yields were obtained when the reactions were carried out using

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2 4a–f

Scheme 2 Synthesis of **4a–f**. *Reagents and conditions*: (i) **2** (1.0 equiv), **3a–f** (2.2 equiv), $Pd(PPh_3)_4$ (6 mol%), K_3PO_4 (3.0 equiv), 1,4-dioxane, 90 °C, 10 h.

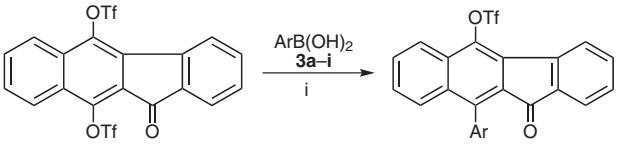
Table 1 Synthesis of **4a–f**

3,4	Ar	Yield of **4** (%)[a]
a	4-$MeOC_6H_4$	80
b	4-*t*-BuC_6H_4	75
c	4-ClC_6H_4	70
d	3,5-$Me_2C_6H_3$	85
e	3-MeC_6H_4	78
f	4-EtC_6H_4	75

[a] Yields of isolated products.

$Pd(PPh_3)_4$ as the catalyst and K_3PO_4 as the base and when 1,4-dioxane was used as the solvent.[20,21]

The Suzuki–Miyaura reaction of **2** with arylboronic acids **3a–i** (1.0 equiv) afforded the 10-aryl-5-trifluoromethylsulfonyloxy-11*H*-benzo[*b*]fluoren-11-ones **5a–i** in good yields (Scheme 3, Table 2).[20,22] The yields of reactions of electron-rich arylboronic acids were higher than those of electron-poor arylboronic acids. During the optimization, it proved to be important to carry out the reaction at 60 °C instead of 90 °C.



2 5a–i

Scheme 3 Synthesis of **5a–i**. *Reagents and conditions*: (i) **2** (1.0 equiv), **3a–i** (1.1 equiv), $Pd(PPh_3)_4$ (3 mol%), K_3PO_4 (2 equiv), 1,4-dioxane, 60 °C, 10 h.

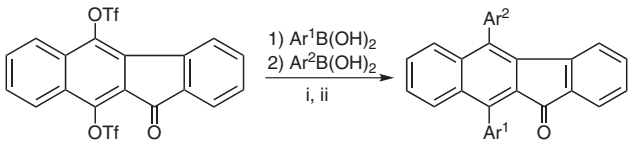
The one-pot reaction of **2** with two different arylboronic acids (sequential addition) afforded the 5,10-diaryl-11*H*-benzo[*b*]fluoren-11-ones **6a–e** containing two different aryl groups (Scheme 4, Table 3).[20,23] During the optimization, it proved to be important to carry out the first step of the one-pot reaction at 60 °C and the second step at 90 °C.

All products were characterized by spectroscopic methods. The constitution was established by 2D NMR experiments (HMBC, NOESY). The structure of **5a** was independently confirmed by X-ray crystal structure analysis (Figure 2).[24]

Table 2 Synthesis of **5a–i**

3	5	Ar	Yield of **5** (%)[a]
a	**a**	4-$MeOC_6H_4$	90
b	**b**	4-*t*-BuC_6H_4	76
c	**c**	4-ClC_6H_4	78
d	**d**	3,5-$Me_2C_6H_3$	87
e	**e**	3-MeC_6H_4	80
f	**f**	4-EtC_6H_4	85
g	**g**	3,5-$(MeO)_2C_6H_3$	88
h	**h**	4-FC_6H_4	75
i	**i**	4-$CF_3C_6H_4$	70

[a] Yields of isolated products.



2 6a–e

Scheme 4 Synthesis of **6a–e**. *Reagents and conditions*: (i) **2** (1.0 equiv), **3a**,**b**,**g** (1.0 equiv), $Pd(PPh_3)_4$ (3 mol%), K_3PO_4 (3 equiv), 1,4-dioxane, 60 °C, 10 h; (ii) **3b**,**d**,**e**,**f** (1.1 equiv), $Pd(PPh_3)_4$ (3 mol%), 90 °C, 10 h.

Table 3 Synthesis of **6a–e**

3	6	Ar^1	Ar^2	Yield of **6** (%)[a]
a,**d**	**a**	4-$MeOC_6H_4$	3,5-$Me_2C_6H_3$	72
g,**b**	**b**	3,4-$(MeO)_2C_6H_3$	4-*t*-BuC_6H_4	75
g,**e**	**c**	3,4-$(MeO)_2C_6H_3$	3-MeC_6H_4	77
b,**d**	**d**	4-*t*-BuC_6H_4	3,5-$Me_2C_6H_3$	80
g,**f**	**e**	3,4-$(MeO)_2C_6H_3$	4-EtC_6H_4	65

[a] Yields of isolated products.

The first attack of palladium(0)-catalyzed cross-coupling reactions generally occurs at the electronically more deficient and sterically less hindered position.[25] Position 10 of bis(triflate) **2** is sterically more hindered than position 5 because of the neighborhood of the carbonyl group (Scheme 5). Therefore, the site-selective formation of **5a–i** and **6a–e** can be explained by electronic reasons. In addition, chelation of the catalyst by the carbonyl group might play a role. A related site-selectivity has been previously observed for the bis(triflates) of alizarin and phenyl 1,4-dihydroxynaphthoate.[18b,d]

In conclusion, we have reported an efficient synthesis of 5,10-diaryl-11*H*-benzo[*b*]fluoren-11-ones by Suzuki–Miyaura reactions of the bis(triflate) of 5,10-dihydroxy-

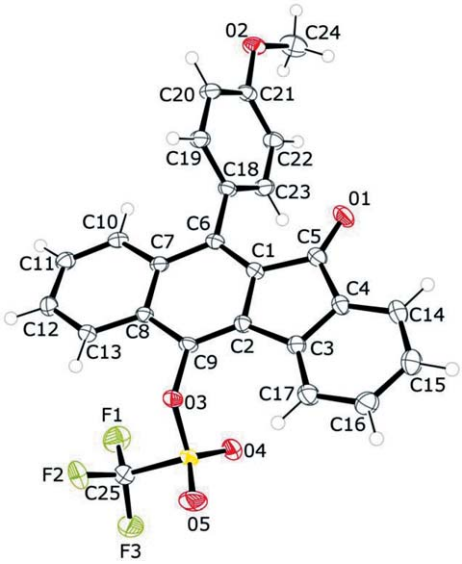
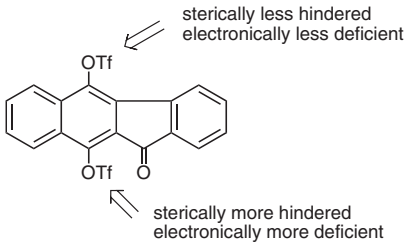


Figure 2 Crystal structure of **5a**



Scheme 5 Possible explanation for the site-selectivity of the reactions of bis(triflate) **2**

11*H*-benzo[*b*]fluoren-11-one. The site-selectivity in favor of position 10 can be explained by electronic reasons.

Acknowledgment

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(18) For Suzuki–Miyaura reactions of bis(triflates) from our laboratory, see, for example: (a) Methyl 2,5-dihydroxybenzoate: Nawaz, M.; Ibad, M. F.; Abid, O.-U.-R.; Khera, R. A.; Villinger, A.; Langer, P. *Synlett* **2010**, 150. (b) Alizarin: Mahal, A.; Villinger, A.; Langer, P. *Synlett* **2010**, 1085. (c) 3,4-Dihydroxybenzophenone: Nawaz, M.; Khera, R. A.; Malik, I.; Ibad, M. F.; Abid, O.-U. R.; Villinger, A.; Langer, P. *Synlett* **2010**, 979. (d) Phenyl 1,4-dihydroxynaphthoate: Abid, O.-U.-R.; Ibad, M. F.; Nawaz, M.; Ali, A.; Sher, M.; Rama, N. H.; Villinger, A.; Langer, P. *Tetrahedron Lett.* **2010**, *51*, 1541.

(19) **Synthesis of 11-Oxo-11*H*-benzo[*b*]fluorene-5,10-diyl Bis(trifluoromethanesulfonate) (2)**: To a solution of **1** (2.0 g, 7.6 mmol) in CH_2Cl_2 (80 mL) was added pyridine (2.5 mL, 30.5 mmol), at 20 °C under an argon atmosphere. After stirring for 10 min, Tf_2O (3.0 mL, 18 mmol) was added at –78 °C. The mixture was allowed to warm to 20 °C and stirred overnight. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (flash silica gel, heptanes–EtOAc) without aqueous work up to give **2** as a yellow solid (3.5 g, 88%); mp 186–188 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43 (t, 1 H, *J* = 7.7 Hz, ArH), 7.59–7.79 (m, 4 H, ArH), 8.01 (t, 2 H, *J* = 8.0 Hz, ArH), 8.10 (d, 1 H, *J* = 8.3 Hz, ArH). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –72.29, –72.3. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 118.6 (q, $J_{F,C}$ = 320.5 Hz, CF_3), 118.7 (q, $J_{F,C}$ = 321.4 Hz, CF_3), 122.8, 124.0, 125.36 (CH), 128.2 (C), 129.4, 131.2, 131.3 (CH), 132.0, 135.7 (C), 135.9 (CH), 136.8, 140.2, 141.2 (C), 187.2 (CO). IR (KBr): 3085,

2926, 2854 (w), 1721 (m), 1635, 1600, 1591, 1581, 1516, 1466 (w), 1435, 1405 (m), 1391, 1337, 1289, 1274, 1241 (w), 1203 (s), 1173 (m), 1128 (s), 1082 (m), 1043 (w), 1011, 975 (m), 891 (s), 865, 814, 782 (m), 760, 747, 722 (s), 688 (m), 662, 651, 638 (w), 621, 595, 590 (s), 570, 528 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 526 (53) [M^+], 393 (77), 329 (99), 301 (100). HRMS (EI, 70 eV): *m*/*z* calcd for $C_{19}H_8O_7S_2F_6$: 525.96101; found: 525.961568

(20) **General Procedure for Suzuki–Miyaura Reactions**: A 1,4-dioxane solution (4–5 mL/0.3 mmol of **2**) of K_3PO_4 (1.5–2.0 equiv), $Pd(PPh_3)_4$ (3 mol% per cross-coupling) and arylboronic acid **3** (1.0–1.1 equiv per cross-coupling) was stirred at 60–90 °C for 10 h. After cooling to 20 °C, distilled H_2O was added. The organic and the 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.

(21) **Synthesis of 5,10-Bis(4-methoxyphenyl)-11*H*-benzo[*b*]-fluoren-11-one (4a)**: Starting with **2** (150 mg, 0.28 mmol), 4-methoxyphenylboronic acid (**3a**; 96 mg, 0.63 mmol), $Pd(PPh_3)_4$ (19 mg, 6 mol%), K_3PO_4 (178 mg, 0.84 mmol) and 1,4-dioxane (5 mL), **4a** was isolated as a yellow solid (100 mg, 80%); mp 243–245 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.85 (s, 3 H, OMe), 3.90 (s, 3 H, OMe), 6.31–6.36 (m, 1 H, ArH), 7.02 (d, 2 H, *J* = 8.4 Hz, ArH), 7.07–7.12 (m, 4 H, ArH), 7.25–7.31 (m, 5 H, ArH), 7.35 (td, 1 H, *J* = 1.4, 8.1 Hz, ArH), 7.43–7.46 (m, 1 H, ArH), 7.50–7.58 (m, 1 H, ArH), 7.63–7.66 (m, 1 H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 55.3, 55.4 (OMe), 113.6, 114.8, 123.8, 123.9, 126.5, 127.1 (CH), 127.8, 128.4 (C), 128.5, 129.0 (CH), 129.8 (C), 130.9, 131.0 (CH), 133.9, 134.0 (C), 134.3 (CH), 135.8, 136.8, 137.2, 140.5, 144.5, 159.4, 159.6 (C), 192.6 (CO). IR (KBr): 3064, 2997, 2952, 2929, 2849, 2831 (w), 1704 (s), 1606, 1589 (m), 1579 (w), 1510 (s), 1462, 1441, 1410, 1361, 1335, 1311 (w), 1286 (m), 1243 (s), 1215, 1191 (m), 1173 (s), 1107, 1086, 1048 (w), 1034, 1026 (m), 1005 (w), 963 (m), 932, 899 (w), 870, 830, 805, 791 (m), 759, 727 (s), 693, 681, 655, 633 (w), 623, 596 (m), 573 (w), 559, 531 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 442 (100) [M^+], 441 (28), 411 (6), 326 (5). HRMS (EI, 70 eV): *m*/*z* calcd for $C_{31}H_{22}O_3$: 442.15635; found: 442.155487.

(22) **Synthesis of 10-(3,4-Dimethoxyphenyl)-11-oxo-11*H*-benzo[*b*]fluoren-5-yl Trifluoromethanesulfonate (5g)**: Starting with **2** (150 mg, 0.28 mmol), 3,4-dimethoxyphenylboronic acid (**3g**; 56 mg, 0.3 mmol), $Pd(PPh_3)_4$ (10 mg, 3 mol%), K_3PO_4 (119 mg, 0.56 mmol) and 1,4-dioxane (5 mL), **5g** was isolated as a yellow solid (129 mg, 88%); mp 221–222 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.79 (s, 3 H, OMe), 3.92 (s, 3 H, OMe), 6.79–6.85 (m, 2 H, ArH), 6.97 (d, 1 H, *J* = 8.2 Hz, ArH), 7.33 (td, 1 H, *J* = 0.8, 7.4 Hz, ArH), 7.39–7.44 (m, 1 H, ArH), 7.53–7.68 (m, 4 H, ArH), 8.02 (d, 2 H, *J* = 7.8 Hz, ArH). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –72.47. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 55.9, 56.0 (OMe), 110.9, 112.9 (CH), 118.7 (q, $J_{F,C}$ = 321.6 Hz, CF_3), 122.1, 124.5, 125.0 (CH), 126.6 (C), 128.0 (CH), 129.4 (C), 129.5, 129.9 (CH), 130.3 (C), 130.4 (CH), 130.9 (C), 135.1 (CH), 135.7, 136.5, 137.7, 140.3, 141.5, 148.8, 149.2 (C), 190.3 (CO). IR (KBr): 3076, 3012, 2966, 2939, 2919, 2838, 2249 (w), 1718 (s), 1623, 1600, 1579 (w), 1517, 1511 (m), 1468, 1448 (w), 1404 (s), 1374, 1345, 1334, 1319, 1297, 1255 (w), 1215 (s), 1172 (m), 1134 (s), 1090, 1054 (w), 1020 (m), 998 (s), 963 (m), 913 (w), 892 (m), 866 (w), 817, 804 (s), 788, 777 (w), 758 (s), 745 (w), 722 (s), 687 (m), 665 (w), 653, 647 (m), 629, 611 (s), 589, 559 (w) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 514 (28) [M^+], 381 (100), 353 (4). HRMS (EI, 70 eV): *m*/*z* calcd for $C_{26}H_{17}O_6F_3S$: 514.06925; found: 514.070130.

(23) **Synthesis of 5-(3,5-Dimethylphenyl)-10-(4-methoxyphenyl)-11*H*-benzo[*b*]fluoren-11-one (6a)**: Starting with **2** (150 mg, 0.28 mmol), 4-methoxyphenylboronic acid (**3a**; 43 mg, 0.28 mmol), $Pd(PPh_3)_4$ (10 mg, 3 mol%), K_3PO_4 (119 mg, 0.56 mmol), 1,4-dioxane (5 mL), and 3,5-dimethylphenylboronic acid (**3d**; 46 mg, 0.31 mmol), **6a** was isolated as a yellow solid (90 mg, 72%); mp 220–222 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.36 (s, 6 H, 2 × Me), 3.85 (s, 3 H, OMe), 6.27–6.33 (m, 1 H, ArH), 6.98 (br s, 2 H, ArH), 7.02 (d, 2 H, *J* = 8.8 Hz, ArH), 7.08–7.14 (m, 3 H, ArH), 7.26 (d, 2 H, *J* = 8.8 Hz, ArH), 7.27–7.30 (m, 1 H, ArH), 7.34 (td, 1 H, *J* = 1.3, 8.2 Hz, ArH), 7.43–7.46 (m, 1 H, ArH), 7.50–7.53 (m, 1 H, ArH), 7.63–7.66 (m, 1 H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.5 (2 × Me), 55.3 (OMe), 113.6, 123.8, 123.9, 126.5, 127.3, 127.4 (CH), 127.8, 128.4 (C), 128.5, 128.9, 129.8, 131.0 (CH), 134.0 (C), 134.4 (CH), 134.5, 135.2, 136.7, 136.8, 137.6, 139.9, 140.4, 144.5, 159.4 (C), 192.6 (CO). IR (KBr): 3068, 3000, 2955, 2923, 2852 (w), 1703, 1695, 1598, 1505 (s), 1466, 1435, 1423, 1363, 1336, 1311, 1302, 1287, 1259 (w), 1244 (s), 1202 (m), 1172 (s), 1130, 1105, 1087, 1049 (w), 1029, 998 (m), 969, 950, 939, 926, 906 (w), 873 (m), 848, 834 (w), 826, 790, 778 (m), 761 (s), 742 (w), 724 (s), 710, 703, 680, 661, 631 (w), 613, 595 (m), 579 (w), 562, 538 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 440 (100) [M^+], 409 (6), 396 (4). HRMS (ESI^+): *m*/z $[M + H]^+$ calcd for $C_{32}H_{24}O_2$: 440.17708; found: 440.176873.

(24) CCDC 799371 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, U.K.; Fax: +44 (1223)336033; or Email: deposit@ccdc.cam.ac.uk.

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