Regioselective Suzuki-Miyaura Cross-Coupling Reactions of the Bis(triflate) of 1,4-dihydroxy-9H-fluoren-9-one

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Regioselective Suzuki-Miyaura Cross-Coupling Reactions of the Bis(triflate) of 1,4-dihydroxy-9H-fluoren-9-one

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Dedicated to Professor Steven V. Ley on the occasion of his 70th birthday

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Abstract: 1,4-Diaryl-9H-fluoren-9-ones were prepared by regioselective Suzuki-Miyaura cross-coupling reaction of the bis(triflate) of 1,4-dihydroxy-9H-fluoren-9-one. The reactions proceeded with excellent site-selectivity. The first attack occurs at postion 1, due to electronic reasons.

Key Words: catalysis; Suzuki-Miyaura reaction; regioselectivity; palladium; heterocycles

Fluorenones from natural and synthetic sources show a wide spectrum of biological properties.[1] Amidofluorenones[2] are inhibitors of telomerase enzyme, kinamycin derivatives show antitumor and antimicrobial activity against Gram-positive bacteria.[3] Other fluorenone derivatives also exhibit pharmaceutical properties and are important components of many naturals products.[4-7] Dendroflorin (**A**, Figure 1), Denchrysan A (**B**, Figure 1) and 1,4,5-trihydroxy-7-methoxyfluoren-9-on (**C**, Figure 1) are natural products which can be isolated from the orchid *Dendrobium chrysotoxum* and show a wide range of biological activities.[6]

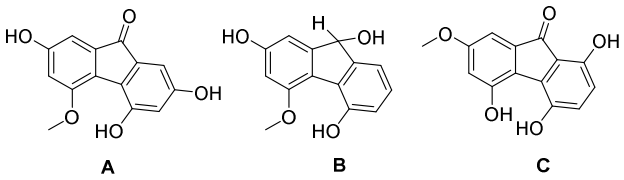
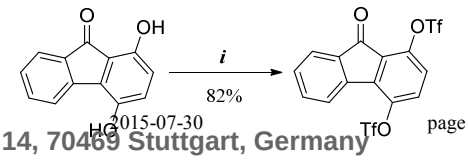


Figure 1. Structure of biologically active Dendroflorin (**A**), Denchrysan A (**B**) and 1,4,5-trihydroxy-7-methoxyfluoren-9-one (**C**)

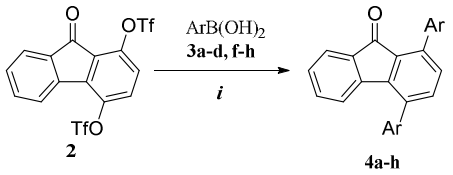
These natural products were examined for their inhibitory activity against the growth of human lung adenocarcinoma, and the human stomach cancer. Furthermore, they are used as drugs for the treatment of viral diseases, such as diarrhea, herpes, and hepatitis.[8,9] Fluorenes, arylated fluorenones and benzofluorenones have been incorporated in oligomers and polymers which have been examined widely for potential applications as organic light-emitting devices (OLEDs).[10]

We have reported a synthetic approach to functionalized fluorenones based on formal [3+3]-cyclizations of 1,3-bis(silyloxy)-1,3-butadienes.[11] Since the importance of fluorenones and benzofluorenones are obvious, the development of efficient and regioselective methods for the synthesis of aryl-substituted derivatives is of actual importance. Herein, we show a convenient pathway to 1,4-diaryl-9H-fluoren-9-one by site-selective[12] Suzuki–Miyaura reactions of the bis(triflate)[13] of 1,4-dihydroxy-9H-fluoren-9-one (**1**). The preparation of these products is difficult by other methods.

The reaction of 1,4-dihydroxy-9H-fluoren-9-one (**1**) with triflic anhydride provided bis(triflate) **2** (Scheme 1).[14] The Suzuki–Miyaura reaction of **2** with arylboronic acids **3a-h** (2.4 equiv) gave 1,4-diaryl-9H-fluoren-9-one **4a-h** in 86-98% yield (Scheme 2, Table 1).[15,16] In addition, the application of DMF (instead of dioxane) was important in case of **4g** due to the low solubility of the starting material. Both electron rich and poor arylboronic acids were successfully employed in these transformations.



Scheme1. Synthesis of **2**, Conditions; i, 1 (1.0 equiv.), abs. pyridine, CH_2Cl_2, Tf_2O (2.4 equiv.), 20 °C, 20 h.



Scheme 2. . Synthesis of **4a-h**, Conditions: i, **2** (1.0 equiv.), **3a-d, f-h** (2.4 equiv.), $Pd(PPh_3)_4$ (6 mol %), K_3PO_4 (3.0 equiv.), 1,4-dioxane, 100 °C, 8 h

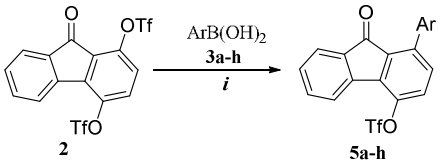
Table 1. Synthesis of compounds **4a-h**

3	Ar	% (4)[a]	4
a	3,4-$(MeO)_2C_6H_3$	97	**a**
b	4-$MeOC_6H_4$	98	**b**
c	4-MeC_6H_4	97	**c**
d	C_6H_5	98	**d**
f	4-OHC_6H_4	98	**f**
g	5-F-2-$MeOC_6H_3$	86[b]	**g**
h	4-$(CF_3)C_6H_4$	87	**h**

[a] Yield of isolated products

[b] DMF was used as solvent.

The Suzuki–Miyaura reaction of **2** with one equivalent of arylboronic acids gave 1-aryl-4-(trifluormethane-sulfonyloxy)-9H-fluoren-9-ones **5a-h** in 66-92% yield (Scheme 3, Table 2).[17,18] The reactions proceeded by regioselective attack onto the 1-position. During the optimization, it proved to be important to perform the reaction at lower temperature (60 °C) with lower catalyst amount as compared to the synthesis of 1,4-diarylated-9H-fluoren-9-ones. Repeatedly, both electron rich and poor arylboronic acids afforded the corresponding compounds in good yields. The structure of **5b** was independently confirmed by X-ray crystal structure analyses[19] (Figure 2) and by 2D NMR measurements.



Scheme 3. Synthesis of **5a-h**, Conditions: i, **2** (1.0 equiv.), **3a-h** (1.2 equiv.), $Pd(PPh_3)_4$ (3 mol %), K_3PO_4 (2.0 equiv.), 1,4-dioxane, 60 °C, 12 h

Table 2. Synthesis of compounds **5a-h**

3	Ar	% (5)[a]	5
a	3,4-$(MeO)_2C_6H_3$	66	**a**
b	4-$MeOC_6H_4$	84	**b**
c	4-MeC_6H_4	85	**c**
d	C_6H_5	92	**d**
e	3-$(CH_2{=}CH)C_6H_4$	85	**e**
f	4-OHC_6H_4	86	**f**
g	5-F-2-$MeOC_6H_3$	83	**g**
h	4-$(CF_3)C_6H_4$	73	**h**

[a] Yield of isolated products

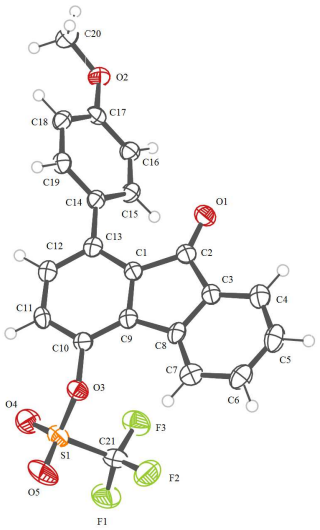
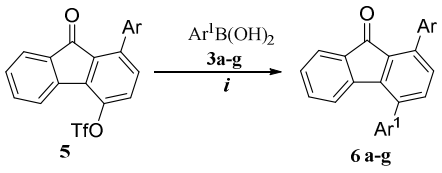


Figure 2. Ortep plot for compound **5b**[19]

The reaction of **5** with different arylboronic acids provided 1,4-diarylated-9H-fluoren-9-ones **6a-g** in high yields (Scheme 4, Table 3).[20,21] These transformations were successful even at lower temperature and with shorter reaction time.



Scheme 4. Synthesis of **6a-g**, Conditions: i, **5** (1.0 equiv.), **3a-g** (1.2 equiv.), $Pd(PPh_3)_4$ (5 mol %), K_3PO_4 (2.0 equiv.), 1,4-dioxane, 90 °C, 10h

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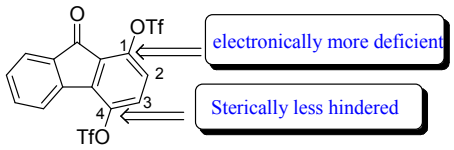
Table 3. Synthesis of compounds **6a-g**

5	3	Ar	Ar[1]	% [6][a]	6
g	**b**	5-F-2-(MeO)C_6H_3	4-(MeO)C_6H_4	99	**a**
g	**c**	5-F-2-(MeO)C_6H_3	4-MeC_6H_4	99	**b**
b	**a**	4-(MeO)C_6H_4	3,4-$(MeO)_2C_6H_3$	97	**c**
e	**b**	3-(CH_2=CH)C_6H_4	4-(MeO)C_6H_4	42	**d**
a	**f**	3,4-$(MeO)_2C_6H_3$	4-(HO)C_6H_4	94	**e**
d	**a**	C_6H_5	3,4-$(MeO)_2C_6H_3$	99	**f**
c	**g**	4-MeC_6H_4	5-F-2-(MeO)C_6H_3	96[b]	**g**

[a] Yield of isolated products

[b] DMF was used as solvent.



2

Scheme 5. Possible explanation for the regioselectivity of the reactions of bis(triflate) **2**

In conclusion, we have report the first Suzuki–Miyaura reactions of 1,4-bis(trifluoromethylsulfonyl-oxy)-9H-fluoren-9-one. These reactions provide a convenient access to a variety of 1,4-diarylated 9H-fluoren-9-ones. The reactions showed a very good regioselectivity in favour of the 1-position. Palladium catalyzed cross-coupling reactions of polyhalogenated substrates and of bis(triflates) usually proceed in favour of the sterically less hindered and electronically more deficient position. The first attack of palladium(0)-catalyzed cross-coupling reactions generally occurs at the electronically more deficient and sterically less hindered position.[22] Position 1 of bis(triflate) **2** is sterically more hindered compared to position 4, because of the neighbourhood of the carbonyl group (Scheme 5). Therefore, the site-selective formation of **5a–h** and **6a–g** can be interpreted by electronic reasons. In addition, chelation of the palladium catalyst by the carbonyl group might play a role. The selectivity can be explained by the highly electron deficient nature of the 1-position of the 9H-fluoren-9-one moiety (due to electron-withdrawing effect of the carbonyl group).

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14. **Synthesis of 9-oxo-9*H*-fluorene-1,4-diaryl-bis(trifluoromethanesulfonate) (2).** To a CH_2Cl_2 solution (150 ml) of **1** (1.8 g, 8.543 mmol) was added dry pyridine (10 ml) and the solution was cooled to -78°C under argon atmosphere. Then Tf_2O (5.785, 20.503 mmol, 2.4 equiv.) was added dropwise to the solution and stir for 20h at room temperature. After removal of the solvent with reduced pressure water (100 ml) was added to the resulting oil and the precipitate was filtered of und recrystallized with hot heptane. After cooling to room temperature the precipitated pure product **2** was filtered and washed with heptane. To obtain the residual product the heptane was concentrated in vacuum and the product **2** was isolated by column chromatography (silica gel heptane/EtOAc 3:1) as a yellow fluffy solid (3.318g, 82%); **Mp:** 131-133°C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.88 (d, ^3J = 7.6 Hz, 1H, ArH), 7.78 (d, ^3J = 7.4 Hz, 1H, ArH), 7.64 (dt, ^3J = 7.6 Hz, ^4J = 1.2 Hz, 1H, ArH), 7.53 (d , ^3J = 9.1Hz, 1H, ArH), 7.48 (dt, ^3J = 7.5 Hz, ^4J = 0.9 Hz, 1H, ArH), 7.21 (d, ^3J = 9.1Hz, 1H, ArH). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 187.40 (CO), 144.29, 143.06, 139.32, 138.13 (C), 136.09 (CH), 133.49 (C), 131.48 (CH), 129.39 (C), 127.62 (CH), 125.70, 124.5, 124.38 (C), 118.85 (q, $J_{F,C}$ = 321.00 Hz, CF_3), 118.66 (q, $J_{F,C}$ = 321.00 Hz, CF_3). **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -73.02, -73.17 (2* CF_3). **IR** (ATR, cm^{-1}): ν = 3104.6 (w), 3089 (w), 2921 (w), 2849 (w), 1726 (s), 1427 (s), 1224 (s), 1207 (s), 1166 (m), 1134 (s), 1104 (m), 905 (s), 886 (s), 845 (s), 812 (m), 803 (s), 762 (m), 754 (s), 598 (s). **MS** (EI, 70eV): *m/z* = 476 (M^+, 52); 343 (13), 279 (100), 251 (49), 223 (35), 185 (14), 154 (16), 128 (33), 100 (12), 69 (43). **HRMS** (EI): calculated for $C_{15}H_6F_6O_7S_2$ (M^+) 475.94536, found 475.94491.**CH-Analysis:** calculated for $C_{15}H_6F_6O_7S_2$ (476.32): C, 37.82; H, 1.27. Found: C, 37.92; H, 1.08.
15. **General Procedure for the synthesis of 4a-h.** In a pressure tube **2** (0,315 mmol), K_3PO_4 (3.0 equiv.), $Pd(PPh_3)_4$ (6.0 mol %) and arylboronic acid (2.4 equiv.) were mixed with dry 1,4-Dioxan , degassed with Argon und stirred for 12h at 100°C. After cooling to room temperature the solution was filtered through cellite, washed with CH_2Cl_2 and the filtrate was concentrated by reduced pressure. The residue was purified by column chromatography to receive the bis-substituted fluorenone **4a-h** in good yields**.**
16. **1,4-Bis-(3,4-dimethoxyphenyl)-9*H*-fluoren-9-one (4a).** Starting with **2** (150 mg, 0.315 mmol), **3a** (138 mg, 0.756 mmol, 2.4 equiv.), $Pd(PPh_3)_4$ (22 mg, 0.018 mmol, 6 mol %), K_3PO_4 (200 mg, 0.945 mmol, 3.0 equiv.) and 1,4-dioxane (5 ml). After purification by column chromatography (silica gel heptane/EtOAc 1:1) **4a** was isolated as an orange solid (138 mg, 97%); **Mp:** 192-194°C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.62-7.58 (m, 1H, ArH), 7.34 (d, J = 7.9 Hz, 1H, ArH), 7.23 (d, J = 7.9 Hz, 1H, ArH), 7.21-7.17 (m, 2H, ArH), 7.15-7.11 (m, 2H, ArH), 7.02 (s, 2H, ArH), 6.97 (d, J = 9.2 Hz, 2H, ArH), 6.81-6.75 (m, 1H, ArH), 4.00 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 193.09 (CO), 149.35, 149.18, 149.11, 148.43, 143.72, 142.41, 141.17, 136.87 (C), 136.41 (CH), 134.80 (C), 134.20 (CH), 132.29 (C), 131.35 (CH), 130.18 (C), 128.85, 124.03, 123.30, 121.88, 121.20, 113.09, 112.26, 111.57, 110.82 (CH); 56.15, 5615 (OCH_3); 56.06, 56.06 (OCH_3). **IR** (ATR, cm^{-1}): ν = 3008 (w), 2955 (w), 2933 (w), 2905 (w), 2838 (w), 2627 (w), 2577 (w), 1701 (m), 1519 (m), 1441 (s), 1251 (s), 1222 (s), 1146 (s), 1020 (s), 746 (s). **MS** (EI, 70eV): *m/z* = 452 (M^+, 100), 437 (9), 263 (4); 250 (4), 226 (5), 132 (4). **HRMS** (ESI-TOF/MS): calculated for $C_{29}H_{24}O_5$ ($[M+H]^+$) 453.16965, found 453.16995, calculated for $C_{29}H_{24}O_5$ ($[M+Na]^+$) 475.15159, found 475.15191.
17. **General Procedure for the synthesis of 5a-h.** In a pressure tube **2** (0,525 mmol), K_3PO_4 (2.0 equiv.), $Pd(PPh_3)_4$ (3.0 mol %) and arylboronic acid (1.2 equiv.) were mixed with dry 1,4-Dioxane, degassed with Argon und stirred for 12h at 60°C. After cooling to room temperature the solution was filtered through cellite, washed with CH_2Cl_2 and the filtrate was concentrated by reduced pressure. The residue was purified by column chromatography to receive the mono-substituted fluorenone **4a-h** in good yields.
18. **1-(4'-Hydroxyphenyl)-9-oxo-9*H*-fluoren-4-yl-trifluoromethanesulfonate (5f)** Starting with **2** (150 mg, 0.315 mmol), **3f** (53 mg, 0.378 mmol, 1.2 equiv.), $Pd(PPh_3)_4$ (11 mg, 0.009 mmol, 3 mol %), K_3PO_4 (134 mg,0.63 mmol, 2.0 equiv.) and 1,4-dioxane (9 ml). After purification by column chromatography (silica gel heptane/EtOAc 6:1) **5f** was isolated as deep yellow solid (112 mg, 86%); **Mp:** 194-196 °C. **^{1}H NMR** (300 MHz, DMSO): δ = 9.75 (s, 1H, OH), 7.80-7.69 (m, 2H, ArH), 7.64 (t, J = 7.2 Hz, 2H, ArH), 7.51 (t, J = 7.2 Hz, 1H, ArH), 7.40 (m, 3H, ArH), 6.83 (d, J = 8.6 Hz, 2H, ArH). **^{13}C NMR** (63 MHz, $CDCl_3$): δ = 190.03 (CO), 158.21, 142.34, 141.91, 138.63, 135.74 (C), 135.49, 134.00 (CH), 133.54, 133.58 (C), 130.81, 130.81, 130.68, 127.34 (CH), 126.01 (C), 124.47, 123.03 (CH), 118.06 (q, $J_{F,C}$ = 320.70 Hz, CF_3), 114.73, 114.73 (CH). **^{19}F-NMR** (282 MHz, $CDCl_3$): δ = -73.13 (CF_3). **IR** (ATR, cm^{-1}): ν = 3320 (w), 3019 (w), 2920 (w), 2850 (w), 1699 (m), 1422 (s), 1205 (s), 1137 (s), 825 (s), 608 (s), 585 (s), 567 (s), 547 (m), 527 (s). **MS** (EI, 70eV): *m/z* = 420 (M^+, 28), 287 (100), 259 (22), 231 (7), 202 (22); 176 (4); 150 (2); 101 (5); 69 (8). **HRMS** (EI): calculated for $C_{20}H_{11}F_3O_5S_1$ (M^+) 420.02738, found 420.02764. **CH-Analysis:** calculated for $C_{20}H_{11}F_3O_5S$ (420.36): C, 57.15; H, 2.64. Found: C, 57.23; H, 2.52.
19. CCDC-xxx 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)1223-336-033; or deposit@ccdc.cam.ac.uk.
20. **General Procedure for the synthesis of 6a-g.** In a pressure tube **5a-e, 5g** K_3PO_4 (2.0 equiv.), $Pd(PPh_3)_4$

(5.0 mol %) and arylboronic acid (1.2 equiv.) were mixed with dry 1,4-Dioxan , degassed with Argon und stirred for 12h at 100°C. After cooling to room temperature the solution was filtered through cellite, washed with CH_2Cl_2 and the filtrate was concentrated by reduced pressure. The residue was purified by column chromatography to receive the cross-substituted fluorenone **6a-g** in good yields**.**

21. **1-(5'-Fluoro-2'-methoxyphenyl)-4-(4''-methoxyphenyl)-9*H*-fluoren-9-one (6a).** Starting with **5g** (75 mg, 0.166 mmol), **3b** (30 mg, 0.199 mmol, 1.2 equiv.), $Pd(PPh_3)_4$ (9 mg, 0.008 mmol, 5 mol %), K_3PO_4 (67 mg, 0.315 mmol, 2.0 equiv.) and 1,4-dioxane (3 ml). After purification by column chromatography (silica gel heptane/EtOAc 4:1) **6a** was isolated as a deep yellow solid (67 mg, 99%); **Mp:** 193-195°C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.58-7.52 (m, 1H, ArH), 7.45-7.39 (m, 2H, ArH), 7.34 (d, *J* = 7.9 Hz, 1H, ArH), 7.20-7.14 (m, 3H, ArH), 7.13-7.03 (m, 3H, ArH), 7.01 (dd, *J* = 8.7 Hz, *J* = 3.1 Hz, 1H, ArH), 6.93 (dd, *J* = 9.0 Hz, *J* = 4.4 Hz, 1H, ArH), 6.84-6.78 (m, 1H, ArH), 3.92 (OCH_3), 3.74 (OCH_3). **^{13}C NMR** (75 MHz, $CDCl_3$): 192.72 (CO), 159.71 (OCH_3), 156.92 (d, $^2J_{F,C}$ = 238.5 Hz, CF), 153.52 (d, ^4J = 2.0 Hz, *C*OCH_3), 144.11, 137.45 (C), 136.57 (CH), 135.42 (d, $^4J_{F,C}$ = 3.1Hz, CH), 134.72 (C), 134.16 (CH), 131.95, 131.61 (C), 131.25, 130.22, 130.22 (CH), 128.68 (d, *J* = 6.6 Hz, CH), 123.94, 123.24 (CH), 117.23 (d, $^2J_{F,C}$ = 23.7 Hz, CH), 115.33 (d, $^2J_{F,C}$ = 22.6 Hz, CH), 114,29 (CH), 111.67 (d, $^3J_{F,C}$ = 8.2 Hz, CH), 56.33 (OCH_3), 55.52 (OCH_3). **^{19}F-NMR** (282 MHz, $CDCl_3$): δ = -124.53 (CF). **IR** (ATR, cm^{-1}): v = 3392 (w), 3068 (w), 3000 (w), 2957 (w), 2945 (w), 2914 (w), 2835 (w), 1704 (s), 1483 (s), 1469 (s), 1175 (s), 1026 (s), 940 (s), 764 (s). **MS** (EI, 70eV): *m/z* = 410 (M^+, 35), 379 (100), 294 (6); 190 (8); 153 (5). **HRMS** (EI): calculated for $C_{27}H_{19}F_1O_3$ (M^+) 410.13127, found 410.13077.

22. Handy, S. T.; Zhang, Y. *Chem. Commun*. **2006**, 299.