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Regioselective Suzuki–Miyaura reactions of the bis(triflate) of 1,2,3,4-tetrahydro-9,10-dihydroxyanthracen-1-one

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ABSTRACT

The palladium(0)-catalyzed Suzuki cross-coupling reaction of the bis(triflate) of 1,2,3,4-tetrahydro-9,10-dihydroxyanthracen-1-one afforded various aryl-substituted 1,2,3,4-tetrahydroanthracen-1-ones. The reactions proceeded with very good site-selectivity in favour of position 10, due to electronic reasons.

Functionalized 1,2,3,4-tetrahydroanthracen-1-ones are of considerable pharmacological relevance and occur in various natural products.[1] Examples include the pigments atrochrysone and torosachrysone, isolated from fungi as well as higher plants, which represent key intermediates of the biosynthesis of polyketide-derived pigments (Fig. 1).[2] In fungi (genus *Cortinarius*), they serve as biosynthetic precursors of a large number of anthraquinone pigments.[3] A variety of anthracenones have also been reported to possess potent cytotoxic and anticancer activities.[4–7] For example, olivomycin A is a famous anthracenone and a member of the aureolic acid family of antitumor antibiotics. 4-Hydroxy-α-tetralones act as inhibitors of PTP1B and are considered potential drugs against obesity and type-2 diabetes. In addition, anthracenones are potentially interesting because of their photochemical, photonic, and electronic properties.

Because of potential applications in medicinal or materials chemistry, the development of synthetic approaches to new anthracenone derivatives is of current interest. In recent years, site-selective palladium(0) catalyzed reactions of polyhalogenated substrates have gained increasing importance.[8] In this context, Suzuki–Miyaura reactions of bis(triflates) have also been developed.[9] Herein, we report a new and convenient approach to aryl-substituted 1,2,3,4-tetrahydroanthracen-1-ones by Suzuki–Miyaura reactions of the bis(triflate) of 1,2,3,4-tetrahydro-9,10-dihydroxyanthracen-1-one. The reactions proceed with very good site-selectivity which is controlled by electronic parameters. The synthesis of the products reported herein has, to the best of our knowledge, not been previously described. It can be anticipated that they are not readily available by other methods.

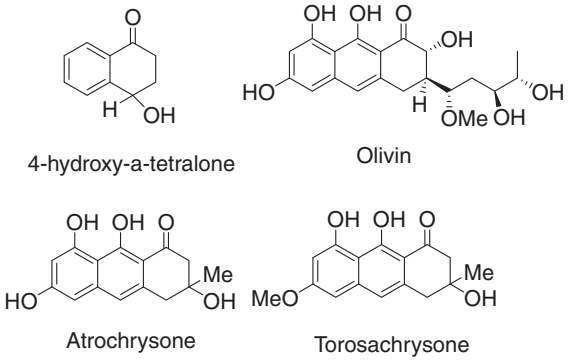

Figure 1. Tetralone and anthracenone natural products.

1,2,3,4-Tetrahydro-9,10-dihydroxyanthracen-1-one (**1**) was transformed into bis(triflate) **2** in 85% yield (Scheme 1).[10]

The Suzuki–Miyaura reaction of **2** with boronic acids **3a–f** (2.4 equiv) afforded the novel 1,2,3,4-tetrahydro-9,10-diarylanthracen-1-ones **4a–f** in 70–90% yields (Scheme 2, Table 1). The best yields were obtained when $Pd(PPh_3)_4$ (6 mol %) was used as the

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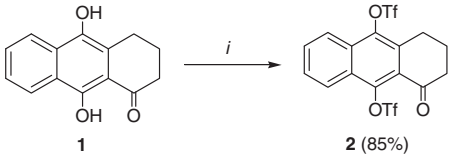
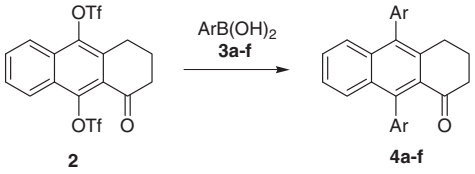


Scheme 1. Synthesis of **2**. Reagents and conditions: (i) CH_2Cl_2, **1** (1.0 equiv), −78 °C, pyridine (4.0 equiv), Tf_2O (2.4 equiv), −78 °C → 20 °C, 14 h.



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, 120 °C, 10 h.

Table 1
Synthesis of **4a–f**

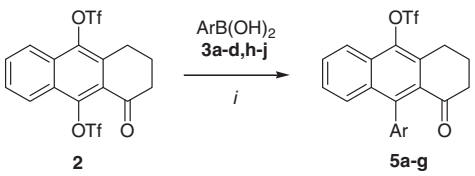
3,4	Ar	% (**4**)[a]
a	4-(MeO)C_6H_4	75
b	4-EtC_6H_4	80
c	4-ClC_6H_4	72
d	4-MeC_6H_4	85
e	4-FC_6H_4	70
f	3-ClC_6H_4	74
g	3,5-$Me_2C_6H_3$	90

[a] Yields of isolated products.

catalyst, when 2.4 equiv of the boronic acid was employed, and when the reaction was carried out in 1,4-dioxane (120 °C, 10 h) using K_3PO_4 as the base.[11,12] No systematic trend was observed for the relationship of yields and arylboronic acids employed.

The Suzuki reaction of **2** with arylboronic acids **3a–d,h–j** (1.0 equiv), in the presence of $Pd(PPh_3)_4$ (3 mol %), proceeded with very good site-selectivity at position 10 and afforded the 10-aryl-1,2,3,4-tetrahydro-9-trifluoromethyl-sulfonyloxy-anthracen-1-ones 5a–**g** in 70–88% yield (Scheme 3, Table 2).[11,13] The products were isolated in pure form after chromatography which was necessary to remove a small amount of bis-coupled product detected in the crude product mixture. During the optimization it proved to be important to employ exactly 1.0 equiv of the arylboronic acid and to carry out the reaction at 100 °C instead of 120 °C to avoid double coupling.

The one-pot reaction of **2** with two different arylboronic acids, which were sequentially added, afforded the 1,2,3,4-tetrahydro-9,10-diarylanthracen-1-ones **6a–f**, containing two different aryl groups, in 70–80% yields (Scheme 4, Table 3).[11,14] Following the observations made during the optimization of the synthesis of **5a–g**, the first step of the one-pot protocol was carried out at 100 °C and using exactly 1.0 equiv of the arylboronic acid.

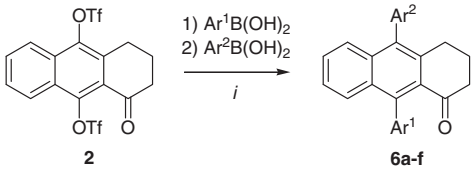


Scheme 3. Synthesis of **5a–g**. Reagents and conditions: (i) **2** (1.0 equiv), **3a–d,h–j** (1.0 equiv), $Pd(PPh_3)_4$ (3 mol %), K_3PO_4 (2 equiv), 1,4-dioxane, 100 °C, 10 h.

Table 2
Synthesis of **5a–g**

3	5	Ar	% (**5**)[a]
a	**a**	4-(MeO)C_6H_4	75
b	**b**	4-EtC_6H_4	74
c	**c**	4-ClC_6H_4	70
d	**d**	4-MeC_6H_4	87
h	**e**	4-*t*BuC_6H_4	75
i	**f**	3-$CF_3C_6H_4$	73
j	**g**	2,6-$Me_2C_6H_3$	88

[a] Yields of isolated products.



Scheme 4. Synthesis of **6a–f**. Reagents and conditions: (i) **2** (1.0 equiv), **3a,c,d,h,i** (1.0 equiv), $Pd(PPh_3)_4$ (3 mol %), K_3PO_4 (3 equiv), 1,4-dioxane, 100 °C, 10 h; (ii) **3a,d,f,h** (1.1 equiv), $Pd(PPh_3)_4$ (3 mol %), 120 °C, 10 h.

Table 3
Synthesis of **6a–f**

3	6	Ar^1	Ar^2	% (**6**)[a]
a,h	**a**	4-(MeO)C_6H_4	4-*t*BuC_6H_4	77
c,h	**b**	4-ClC_6H_4	4-*t*BuC_6H_4	75
c,a	**c**	4-ClC_6H_4	4-(MeO)C_6H_4	70
h,d	**d**	4-*t*BuC_6H_4	4-MeC_6H_4	80
i,d	**e**	3-$CF_3C_6H_4$	4-MeC_6H_4	68
d,f	**f**	4-MeC_6H_4	3-ClC_6H_4	70

[a] Yields of isolated products.

The structures of all products were proved by 2D NMR experiments (NOESY, HMBC). The structure of **5a** was independently confirmed by X-ray crystal structure analysis (Fig. 2).[15]

Steric and electronic parameters can control the site-selectivity of palladium(0) catalyzed cross-coupling reactions.[16] The regiose-

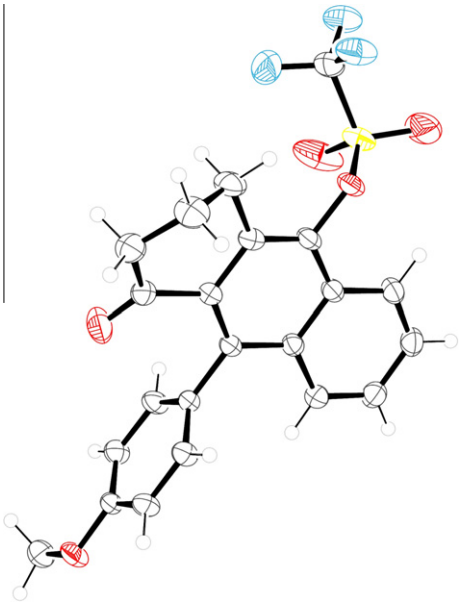
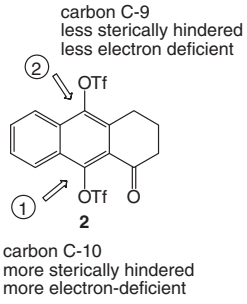


Figure 2. Crystal structure of **5a**.



Scheme 5. Possible explanation for the site-selective reactions of **2**.

lective formation of products **5a–g** and **6a–f** can be explained by the fact that position 10 is electronically more deficient than position 9 (Scheme 5). In addition, chelation of the catalyst to the carbonyl group might play a role.

In conclusion, the site-selectivity of Suzuki–Miyaura reactions of the bis(triflate) of 1,2,3,4-tetrahydro-9,10-dihydroxyanthracen-1-one is controlled by electronic parameters. The first attack occurs at the electronically more deficient position 10.

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10. *Synthesis of 1-oxo-1,2,3,4-tetrahydroanthracene-9,10-diyl-bis(trifluoromethanesulfonate* (**2**). To a solution of **1** (2.0 g, 8.8 mmol) in CH_2Cl_2 (88 mL) was added pyridine (2.8 mL, 35.0 mmol) at 20 °C under an argon atmosphere. After stirring for 10 min, Tf_2O (3.5 mL, 21 mmol) was added at −78 °C. The mixture was allowed to warm to 20 °C and was 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 prior aqueous work up to give **2** as a yellow solid (3.67 g, 85%), mp 162–164. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.10–2.18 (m, 2H, CH_2), 2.76 (t, 2H, J = 6.9 Hz, CH_2), 3.15 (t, 2H, J = 6.4 Hz, CH_2), 7.65–7.79 (m, 2H, ArH), 8.05 (d, 1H, J = 8.5 Hz, ArH), 8.18 (d, 1H, J = 8.5 Hz, ArH). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = −72.56, −72.55. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.6, 25.2, 39.6 (CH_2), 118.5 (q, $J_{F,C}$ = 320.2 Hz, CF_3), 118.6 (q, $J_{F,C}$ = 319.6 Hz, CF_3), 121.5 (CH), 123.2 (q, $J_{F,C}$ = 1.4 Hz, CH), 123.9, 126.4 (C), 128.8 (CH), 129.8 (C), 131.3 (CH). 133.3, 140.4, 143.8 (C), 195.9 (CO). IR (KBr): $\tilde{\nu}$ = 2849, 2880, 2915, 2964 (w), 1697 (m), 1625, 1594, 1564, 1494, 1442 (w), 1422 (s), 1384, 1353, 1326, 1278 (w), 1205, 1185, 1129 (s), 1076, 1027 (m), 962 (s), 909 (m), 862 (s), 823, 809, 785 (w), 771 (m), 749 (s), 709 (m), 670 (s), 654, 644, 631 (w), 595 (s), 564, 532 (w) cm^{-1}. GC/MS (EI, 70 eV): m/z (%) = 492 (M^+, 92), 359 (82), 295 (97), 253 (54). HRMS (EI, 70 eV): calcd for $C_{16}H_{10}O_7S_2F_6$: 491.97666; found: 491.976129.
11. *General procedure for Suzuki–Miyaura reactions*: A 1,4-dioxane solution (4–5 mL per 0.3 mmol of **2**), 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 100–120 °C for 10 h under argon atmosphere. 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.
12. *Synthesis of 9,10-bis(4-methoxyphenyl)-3,4-dihydroanthracen-1(2H)-one* (**4a**): Starting with **2** (150 mg, 0.3 mmol), 4-methoxyphenylboronic acid **3a** (83 mg, 0.66 mmol), $Pd(PPh_3)_4$ (21 mg, 6 mol %), K_3PO_4 (191 mg, 0.9 mmol) and 1,4-dioxane (5 mL), **4a** was isolated as yellow solid (93 mg, 75%); mp 277–278 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.89–1.98 (m, 2H, CH_2), 2.54 (t, 2H, J = 6.7 Hz, CH_2), 2.71 (t, 2H, J = 6.3 Hz, CH_2), 3.82 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 6.95 (d, 2H, J = 8.7 Hz, ArH), 7.00 (d, 2H, J = 8.7 Hz, ArH), 7.08 (d, 2H, J = 8.7 Hz, ArH), 7.15 (d, 2H, J = 8.7 Hz, ArH), 7.20–7.25 (m, 1H, ArH), 7.30 (td, 1H, J = 1.6, 8.5 Hz, ArH), 7.36–7.39 (m, 1H, ArH), 7.49–7.52 (m, 1H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 22.7, 29.4, 40.8 (CH_2), 55.2, 55.3 (OCH_3), 113.5, 114.1, 125.4, 126.3, 127.7, 128.6 (CH), 129.7 (C), 130.3 (CH), 131.1 (C), 131.2 (CH), 132.4, 132.5, 134.7, 137.4, 137.6, 141.6, 158.5, 158.9 (C), 200.2 (CO). IR (KBr): $\tilde{\nu}$ = 3064, 3033, 3001, 2950, 2904, 2833 (w), 1689, 1607 (m), 1573, 1556 (w), 1509 (s), 1494, 1461, 1455, 1440, 1408, 1373, 1349, 1325, 1303 (w), 1283 (m), 1238 (s), 1172, 1154, 1104 (m), 1031 (s), 1004 (m), 959, 939, 927, 901, 865 (w), 834, 795, 767 (m), 728, 681, 648, 637, 623 (w), 589 (m), 542 (s) cm^{-1}. GC/MS (EI, 70 eV): m/z (%) = 408 (M^+, 100), 279 (05), 349 (08), 321 (07). HRMS (EI, 70 eV): calcd for $C_{28}H_{23}O_3$: 407.163709; found: 407.16417.
13. *Synthesis of 10-(4-tert-butylphenyl)-4-oxo-1,2,3,4-(tetrahydroanthracen-9-yl)trifluoromethanesulfonate* (**5e**): Starting with **2** (150 mg, 0.3 mmol), 4-*tert*-butylphenylboronic acid (**3h**, 53 mg, 0.3 mmol), $Pd(PPh_3)_4$ (11 mg, 3 mol %), K_3PO_4 (127 mg, 0.6 mmol) and 1,4-dioxane (5 mL), **5e** was isolated as a yellow solid (104 mg, 75%); mp 137–138 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (s, 9H, $3CH_3$), 2.10–2.14 (m, 2H, CH_2), 2.60 (t, 2H, J = 7.3 Hz, CH_2), 3.17 (t, 2H, J = 6.4 Hz, CH_2), 7.02 (d, 2H, J = 8.2 Hz, ArH), 7.34–7.5 (m, 4H, ArH), 7.59–7.64 (m, 1H, ArH), 8.03 (d, 1H, J = 8.8 Hz, ArH). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = −72.78. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.9, 25.4 (CH_2), 31.5 ($3CH_3$), 34.7 (C), 40.3 (CH_2), 118.7 (q, $J_{F,C}$ = 320.6 Hz, CF_3), 120.7, 125.0, 127.0 (CH), 128.3 (C), 128.4, 129.2 (CH), 129.3 (C), 129.8 (CH), 132.6, 133.7, 135.8, 141.1, 143.8, 150.0 (C), 197.5 (CO). IR (KBr): $\tilde{\nu}$ = 3077, 3047, 3027, 2961, 2903, 2865 (w), 1693 (m), 1617, 1591, 1563, 1515, 1494, 1476, 1462, 1439 (w), 1404 (m), 1361, 1320, 1292 (w), 1202, 1135 (s), 1076, 1051 (w), 1023, 965 (m), 931, 901 (w), 848, 832 (s), 800, 772 (w), 749 (s), 719, 698, 687 (w), 665 (m), 641, 619 (w), 582, 561 (m) cm^{-1}. GC/MS (EI, 70 eV): m/z (%) = 476 (M^+, 4), 343 (14). HRMS (EI, 70 eV): calcd for $C_{25}H_{23}O_4F_3S$: 476.12637; found: 476.124975.
14. *Synthesis of 9-(4-tert-butylphenyl)-10-(4-methoxyphenyl)-3,4-dihydroanthracen-1(2H)-one* (**6a**): The synthesis of **6a** was carried out as a one-pot reaction with sequential addition of two different boronic acids. The first step (addition of **3a**) was carried out at 100 °C (stirring for 10 h). The second step (addition of **3h** and of a fresh amount of catalyst) was carried out at 120 °C (stirring for 10 h). Starting with **2** (150 mg, 0.3 mmol), 4-methoxyphenylboronic acid (**3a**, 46 mg, 0.3 mmol), $Pd(PPh_3)_4$ (2 × 11 mg, 2 × 3 mol %), K_3PO_4 (127 mg, 0.6 mmol), 1,4-dioxane (5 mL), and 4-*tert*-butylphenylboronic acid (**3h**, 58 mg, 0.33 mmol), **6a** was isolated as a yellow solid (102 mg, 77%); mp 272–274 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (s, 9H, $3CH_3$), 1.90–1.98 (m, 2H, CH_2), 2.55 (t, 2H, J = 6.7 Hz, CH_2), 2.71 (t, 2H, J = 6.7 Hz, CH_2), 3.83 (s, 3H, O CH_3), 6.96 (d, 2H, J = 8.8 Hz, ArH), 7.10 (d, 2H, J = 8.9 Hz, ArH), 7.16 (d, 2H, J = 8.9 Hz, ArH), 7.20–7.38 (m, 3H, ArH), 7.45–7.53 (m, 3H, ArH). ^{13}C NMR (75–5 MHz, $CDCl_3$): δ = 22.7, 29.4 (CH_2), 31.5 ($3CH_3$), 34.7 (C), 40.9 (CH_2), 55.3 (OCH_3), 113.5, 125.4, 125.5, 126.4, 127.7, 128.5, 129.8, 130.3 (CH), 132.5, 132.6, 134.6, 136.0, 137.4, 137.8, 141.6, 150.3, 158.5 (C), 200.2 (CO). IR (KBr): $\tilde{\nu}$ = 3064, 3042, 3000, 2956, 2899, 2865, 2833, 2252, 2142 (w), 1689 (m), 1608, 1573, 1553 (w), 1510 (m), 1493, 1459, 1440, 1410, 1395, 1373, 1365, 1349, 1327, 1315, 1304, 1284, 1269 (w), 1239 (s), 1224, 1174 (m), 1158, 1131, 1116, 1108, 1073 (w), 1030 (m), 1006, 971, 938, 926 (w), 912, 837 (m), 817, 803, 796 (w), 765, 726 (s), 692, 676, 646, 638, 619, 586 (w), 561, 543 (m) cm^{-1}. GC/MS (EI, 70 eV): m/z (%) = 434 (M^+, 100), 419 (11), 349 (14). HRMS (ESI$^+$): calcd for $C_{31}H_{31}O_2$: [M+H]$^+$: 435.2319; found: 435.2312.
15. CCDC-800257 contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
16. 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.