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Site-selective Suzuki-Miyaura reactions of the bis(triflate) of 1,3-dihydroxyanthraquinone

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ABSTRACT

Various aryl-substituted anthraquinones were prepared by palladium(0)-catalyzed Suzuki-Miyaura cross-coupling reactions of the bis(triflate) of 1,3-dihydroxyanthraquinone. A very good site-selectivity in favor of position 1 was observed which can be explained by the electronic influence of the neighboring carbonyl group.

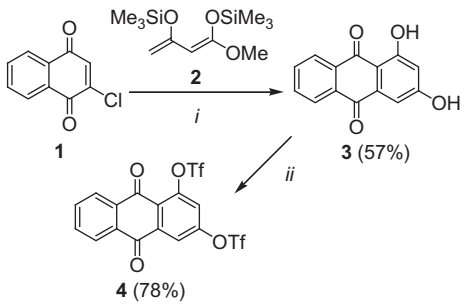
Anthraquinones are of considerable pharmacological relevance and occur in various natural products.[1] Anthracyclines are polycyclic hydroxylated anthraquinones, which represent important antitumor agents and antibiotics.[2] More simple hydroxylated anthraquinones include, for example, chrysophanic acid, vismiaquinone, anthragallol, or mumbaistatin.[3] Aryl-substituted anthraquinones possess many applications because of their redox, UV, and fluorescence properties.[4]

Because of the multifold applications of anthraquinones in medicinal or materials chemistry, the development of synthetic methods for their synthesis is of considerable current interest. In recent years, site-selective palladium(0) catalyzed reactions of polyhalogenated substrates have gained increasing importance.[5] In this context, Suzuki-Miyaura reactions of bis(triflates) have also been developed.[6] Recently, we have reported site-selective Suzuki-Miyaura reactions of the bis(triflate) of alizarin.[7] Interestingly, the selectivity is controlled by electronic parameters and the first attack occurred at the sterically more hindered position next to the carbonyl group. Because of the pharmacological importance of anthraquinones, we were interested in the question of whether this selectivity is general and thus started a program to study Suzuki-Miyaura reactions of the bis(triflate) of 1,3-dihydroxyanthraquinone and related derivatives.

1,3-Dihydroxyanthraquinone (**3**) was prepared in 57% yield by [4+2] cycloaddition of 1,3-bis(silyloxy)-1,3-butadiene **2** with **1** (Scheme 1).[8] The product was transformed into its bis(triflate) **4** in good yield.[9]

The Suzuki-Miyaura reaction of **4** with arylboronic acids **5a–h** (2.2 equiv) afforded the 1,3-diaryl-anthraquinones **6a–h** (Scheme 2 and Table 1). The employment of $Pd(PPh_3)_4$ as the catalyst and K_3PO_4 as the base gave the best yields.[10,11] Equally good yields were obtained for the reactions of arylboronic acids containing electron donating or electron withdrawing substituents.

The Suzuki-Miyaura reaction of **4** with arylboronic acids **5a** and **5f–j** (1.0 equiv) afforded the 1-aryl-3-trifluorosulfonyloxy-anthraquinones **7a–f** in good yields (Scheme 3 and Table 2).[12,13] The best yields were obtained when the reaction was carried out at 60 in-



Scheme 1. Synthesis of **3** and **4**. Reagents and conditions: (i) (1) **1** (1.5 equiv), **2** (1.0 equiv), neat, 20 °C, 12 h; (2) H_2O; (ii) **3** (1.0 equiv), Tf_2O (2.4 equiv), pyridine (4.0 equiv), CH_2Cl_2, 20 °C, 8 h.

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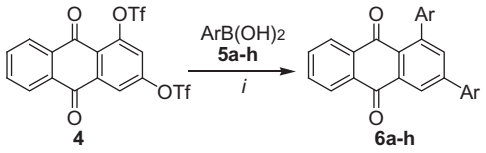
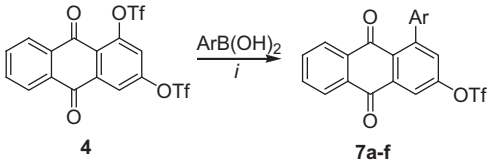


Scheme 2. Synthesis of **6a–h**. Reagents and conditions: (i) **4** (1.0 equiv), $ArB(OH)_2$ (2.2 equiv), $Pd(PPh_3)_4$ (5 mol %), K_3PO_4 (3.0 equiv), dioxane, 100 °C, 7 h.

Table 1
Synthesis of 1,3-diaryanthraquinones **6a–h**

5,6	Ar	% (**6**)[a]
a	4-(MeO)C_6H_4	76
b	4-EtC_6H_4	88
c	4-MeC_6H_4	70
d	4-*t*BuC_6H_4	75
e	3-MeC_6H_4	71
f	3,5-$Me_2C_6H_3$	82
g	4-ClC_6H_4	84
h	4-FC_6H_4	78

[a] Yields of isolated compounds.

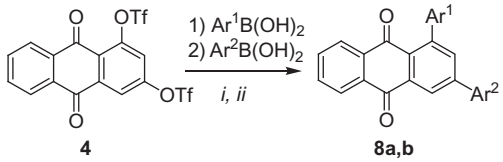


Scheme 3. Synthesis of **7**. Reagents and conditions: (i) **4** (1.0 equiv), $ArB(OH)_2$ (1.0 equiv), $Pd(PPh_3)_4$ (3 mol %), K_3PO_4 (1.5 equiv), dioxane, 60 °C, 30 h.

Table 2
Synthesis of **7a–f**

5	7	Ar	% (**7**)[a]
a	**a**	4-(MeO)C_6H_4	70
f	**b**	3,5-$Me_2C_6H_3$	77
g	**c**	4-ClC_6H_4	74
h	**d**	4-FC_6H_4	73
i	**e**	3,4-$(MeO)_2C_6H_3$	81
j	**f**	3-ClC_6H_4	68

[a] Yields of isolated compounds.



Scheme 4. Synthesis of **8a,b**. Reagents and conditions: (i) **4** (1.0 equiv), $Ar^1B(OH)_2$ (1.0 equiv), $Pd(PPh_3)_4$ (3 mol %), K_3PO_4 (3.0 equiv), dioxane, 60 °C, 30 h; (ii) $Ar^2B(OH)_2$ (1.2 equiv), $Pd(PPh_3)_4$ (3 mol %), 100 °C, 5 h.

stead of 100 °C. Good yields were obtained for the reactions of both electron rich and poor arylboronic acids. The regioselectivity was established by 2D NMR experiments (HMBC, NOESY).

The one-pot reaction of **4** with two different arylboronic acids (sequential addition) afforded the 1,2-diaryl-anthraquinones **8a,b** that contain two different aryl groups (Scheme 4 and Table 3).[14,15] Following the conditions developed for the synthesis of **7a–f**, the first step of the one-pot reaction had to be carried out at 60 °C and the second step at 100 °C.

Table 3
Synthesis of **8a,b**

5	8	Ar^1	Ar^2	% (**8**)[a]
a,d	**a**	4-(MeO)C_6H_4	4-*t*BuC_6H_4	65
j,c	**b**	3-ClC_6H_4	4-MeC_6H_4	74

[a] Yields of isolated compounds.

The oxidative addition of the palladium(0) catalyst generally occurs first at the electronically more deficient and sterically less hindered position.[5,16] On the one hand, position 1 of bis(triflate) **4** is sterically more hindered than position 3. On the other hand, position 1 (located in β-position to the carbonyl group) is more electron-deficient than position 3. Besides, the regioselectivity might be explained by chelation of the approaching palladium catalyst by the carbonyl group (neighboring effect).

In conclusion, we have reported an efficient synthesis of arylated anthraquinones by site-selective Suzuki-Miyaura reactions of the bis(triflate) of 1,3-dihydroxy-anthraquinone.

Acknowledgments

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8. *Synthesis of 1,3-dihydroxyanthracene-9,10-dione* (**3**): In an oven dried Schlenck flask **2** (2.37 g, 10 mmol) was placed and, under argon, diene **1** (3.9 g, 15 mmol) was slowly added at 20 °C. This reaction mixture (neat) was stirred for 12 h. Then H_2O and EtOAc (25 mL each) were added. The organic and aqueous layers

were separated and the latter was extracted with EtOAc (2 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptanes) to give **3** as **a** yellow solid (1.37 g, 57%). Mp: 173–175 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.56 (d, 1H, J = 2.4 Hz, ArH), 7.08 (d, 1H, J = 2.4 Hz, ArH), 7.83–7.91 (m, 2H, ArH), 8.08–8.15 (m, 2H, ArH), 11.29 (s, 1H, ArOH), 12.69 (s, 1H, ArOH). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 106.7 (C), 107.6, 108.3, 125.4, 125.8 (CH), 131.9, 132, (C), 133.5, 133.7 (CH), 133.9, 163.8, 164.4 (C), 180.8, 184.9 (CO). IR (KBr): ν = 3368 (m), 3070, 2921, 2854, 1743, 1722, 1711, 1670 (w), 1634, 1587 (m), 1547, 1537, 1512, 1485, 1485 (w), 1452, 1413 (m), 1379 (w), 1336, 1303, 1287, 1258, 1191, 1171, 1155 (m), 1094, 1061, 1029 (w), 1006 (m), 980, 923, 876 (w), 861, 799, 778 (m), 733 (w), 725 (m), 711 (s), 653, 640, 600, 547 (m) cm^{-1}. MS (EI, 70 eV): m/z (%) = 240 ([M]$^+$, 100), 212 (13), 184 (19), 155 (13), 127 (17). HRMS (EI, 70 eV): calcd for $C_{14}H_8O_4$ [M]$^+$: 240.04226; found: 240.042311.

9. *Synthesis of 9,10-dioxo-9,10-dihydroanthracene-1,3-diyl bis(trifluoromethanesulfonate)* (**4**): To a CH_2Cl_2 (50 mL) solution of **3** (1.2 g, 5.0 mmol), pyridine (1.6 mL, 20 mmol) and Tf_2O (2.1 mL, 12 mmol) were added and the reaction mixture was stirred at 20 °C under argon atmosphere for 8 h. To the reaction mixture toluene (5 mL) was added and the solution was concentrated in vacuo. The residue was purified by chromatography (EtOAc/heptanes) without aqueous work up to yield **4** as a light yellow solid (1.97 g, 78%). Mp: 164–166 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46 (d, 1H, J = 2.5 Hz, ArH), 7.77–7.86 (m, 2H, ArH), 8.22–8.33 (m, 3H, ArH). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = −73.1, −72.2. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 118.6 (q, $J_{C,F}$ = 320.8, CF_3), 118.7 (q, $J_{C,F}$ = 320.8, CF_3), 120.7, 122.0 (CH), 125.5 (C), 127.5, 128.1 (CH), 131.2, 133.5 (C), 135.0, 135.5 (CH), 137.5, 148.7, 152.2 (C), 179.6, 179.7 (CO). IR (KBr): ν = 3096, 3067, 2961, 2931, 2861 (w), 1677 (s), 1664, 1601 (w), 1586 (m), 1432 (s), 1331, 1316 (w), 1304, 1286 (m), 1256 (w), 1245 (m), 1203 (s), 1158 (w), 1132 (s), 1104 (m), 1046, 1015 (w), 991 (m), 937, 918 (w), 903, 869, 819, 795, 768, 757, 743, 732, 713 (m), 673, 651, 617 (w), 604, 591, 575 (m), 541 (w) cm^{-1}. GC–MS (EI, 70 eV): m/z (%) = 504 ([M]$^+$, 100), 440 (09), 375 (22), 279 (82), 251 (49). HRMS (EI, 70 eV): calcd. for $C_{16}H_6F_6O_8S_2$ [M]$^+$: 503.94083; found: 503.94066.

10. *General procedure A for the synthesis of* **6a–h**: A 1,4-dioxane solution of 9,10-dioxo-9,10-dihydroanthracene-1,3-diyl bis(trifluoromethanesulfonate) **4** (0.2 mmol), arylboronic acid (2.4 equiv), K_3PO_4 (3.0 equiv) and Pd(PPh_3)$_4$ (6 mol %) was heated at 100 °C for 7 h under argon atmosphere. After cooling to 20 °C, H_2O was added and the reaction mixture was extracted with CH_2Cl_2 (25 × 3 mL). The organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptanes).

11. *1,3-Bis(4-ethylphenyl)anthracene-9,10-dione* (**6b**): Starting with **4** (100 mg, 0.2 mmol), arylboronic acid (72 mg, 0.48 mmol), K_3PO_4 (127 mg, 0.6 mmol), and Pd(PPh_3)$_4$ (14 mg, 6 mol %), **6b** was prepared as a yellow solid (73 mg, 88%). Mp: 167–169 °C. Reaction temperature: 100 °C for 7 h. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.17 (t, 3H, J = 7.6 Hz, CH_3), 1.24 (t, 3H, J = 7.6 Hz, CH_3), 2.60 (q, 2H, J = 7.6 Hz, CH_2), 2.67 (q, 2H, J = 7.7 Hz, CH_2), 7.13–7.22 (m, 6H, ArH), 7.56 (d, 2H, J = 8.3 Hz, ArH), 7.60–7.64 (m, 2H, ArH), 7.71 (d, 1H, J = 2.1 Hz, ArH), 8.02–8.06 (m, 1H, ArH), 8.16-8.20 (m, 1H, ArH), 8.50 (d, 1H, J = 2.1 Hz, CH_2). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.3, 14.4 (CH_3), 14.3, 14.4 (CH_3), 27.5, 27.6 (CH_2), 123.9, 125.7, 126.1, 126.3, 126.5, 127.1, 127.6 (CH), 128.2, 131.9 (C), 132.4, 133.1 (CH), 133.7, 134.3 (C), 134.7 (CH), 138.3, 142.1, 144.1 (C), 182.0, 182.4 (CO). IR (KBr): ν = 3054, 3025, 2960, 2929, 2869 (w), 1668, 1588, 1580 (m), 1556, 1513, 1453, 1427, 1410, 1386 (w), 1340, 1307 (m), 1270 (s), 1186, 1165, 1094, 1062, 1050, 1018, 959, 927, 900, 834 (w), 818 (s), 798, 739 (m), 710 (s), 664, 645, 615, 5191, 549 (w) cm^{-1}. GC–MS (EI, 70 eV): m/z (%) = 416 ([M]$^+$, 36), 415 ([M−H]$^+$, 45), 400 (09), 387 (100), 372 (10). HRMS (EI, 70 eV): calcd for $C_{30}H_{23}O_2$ [M−H]$^+$: 415.16926; found: 415.168812.

12. *General procedure B for the synthesis of* **7a–f**: A 1,4-dioxane solution of **4** (0.2 mmol), arylboronic acid (1.0 equiv), K_3PO_4 (1.5 equiv) and Pd(PPh_3)$_4$ (3 mol %) was heated at 60 °C for 30 h under argon atmosphere. After cooling to 20 °C, CH_2Cl_2 (20 mL) was added, the solution was filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptanes).

13. *4-(3-Chlorophenyl)-9,10-dioxo-9,10-dihydroanthracen-2-yl trifluoromethanesulfonate* (**7f**): Starting with **4** (100 mg, 0.2 mmol), **7f** was prepared as a yellow solid (63 mg, 68%). Mp: 134–136 °C. Reaction temperature: 60 °C for 30 h. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.11 (dt, 1H, J = 1.7, 7.1 Hz, ArH), 7.21–7.22 (m, 1H, ArH), 7.31–7.39 (m, 3H, ArH), 7.69–7.77 (m, 2H, ArH), 8.02–8.08 (m, 1H, ArH). 8.19–8.26 (m, 2H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 117.7 (q, $J_{C,F}$ = 320.3, CF_3), 120.0, 126.1, 127.2, 127.7, 127.9, 128.2, 129.6, 129.7 (CH), 130.5, 132.3, 134.1, 134.2 (C), 134.3, 135.0 (CH), 137.4, 141.6, 146.2, 151.6 (C), 181.3, 181.7 (CO). IR (KBr): ν = 3072, 2917, 2849 (w), 1672 (s), 1577, 1567, 1478, 1423, 1320 (m), 1297 (w), 1271, 1244 (m), 1210 (s), 1164 (w), 1134 (s), 1101, 1086, 1078 (m), 1037, 1002, 979 (w), 931 (s), 911, 879, 845, 827, 816, 801, 785 (m), 767, 741 (w), 724, 708, 692, 658, 644, 628 (m), 606, 589 (s), 565 (m) cm^{-1}. GC–MS (EI, 70 eV): m/z (%) = 468 ([M, ^{37}Cl]$^+$, 36), 466 ([M, ^{35}Cl]$^+$, 99), 431 (89), 298 (33), 270 (100), 213 (62). HRMS (EI, 70 eV): calcd. for $C_{21}H_{10}ClO_5F_3S$ [M, ^{35}Cl]$^+$: 465.98841; found: 465.987174.

14. *General procedure C for the synthesis of* **8a,b**: A 1,4-dioxane solution of **4** (0.3 mmol), $Ar^1B(OH)_2$ (1.0 equiv), K_3PO_4, (3.0 equiv) and Pd(PPh_3)$_4$ (3 mol %) was heated at 60 °C for 30 h under argon atmosphere. After cooling to 20 °C, $Ar^2B(OH)_2$ (1.2 equiv), Pd(PPh_3)$_4$ (3 mol %) were added and reaction mixture was heated at 100 °C for a further 5 h. The reaction mixture was cooled again to 20 °C, H_2O was added, and the reaction mixture was extracted with CH_2Cl_2 (25 × 3 mL). The organic layers were dried (Na_2SO_4), filtered, and then concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptanes).

15. *1-(3-Chlorophenyl)-3-(p-tolyl)anthracene-9,10-dione* (**8b**): Starting with **4** (150 mg, 0.3 mmol), 3-chlorophenylboronic acid ($Ar^1B(OH)_2$) (47 mg, 0.30 mmol), K_3PO_4 (191 mg, 0.9 mmol), Pd(PPh_3)$_4$ (21 mg, 6 mol %), and *p*-tolylboronic acid ($Ar^2B(OH)_2$) (49 mg, 0.30 mmol), **8b** was prepared as a yellow solid (91 mg, 74%). Mp: 191–193. Reaction temperature: 60 °C for 30 h, then 100 °C for 5 h. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.33 (s, 3H, CH_3), 7.12–7.33 (m, 6H, ArH), 7.55 (d, 2H, J = 8.1 Hz, ArH), 7.65–7.68 (m, 3H, ArH), 8.03–8.06 (m, 1H, ArH), 8.20–8.23 (m, 1H, ArH), 8.54 (d, 1H, J = 1.9 Hz, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.2 (CH_3), 125.5, 126.4, 126.9, 127.1, 127.2, 127.4, 128.1 (CH), 129.1 (C), 129.3, 129.9 (CH), 132.9 (C), 133.7 (CH), 133.9 (C), 134.3 (CH), 134.5 (C), 135.2 (CH), 135.3, 139.3, 143.5, 143.9, 145.5 (C), 182.8, 183.3 (CO). IR (KBr): ν = 3063, 3034, 2950, 2915, 2852 (w), 1667 (s), 1613 (w), 1587, 1564, 1557 (m), 1537, 1518, 1504, 1476, 1445, 1408, 1386 (w), 1337, 1304, 1294, 1269, 1226, 1194, 1188, 1168 (m), 1153, 1077, 1061, 1034, 1018, 998 (w), 966, 930, 917, 901, 865, 853, 814, 785, 738 (m), 714, 713 (s), 689, 661 (m), 650, 628, 619, 597, 567, 538 (w) cm^{-1}. GC–MS (EI, 70 eV): m/z (%) = 410 ([M, ^{37}Cl]$^+$, 21), 408 ([M, ^{35}Cl]$^+$, 58), 407 ([M−H]$^+$, 100), 373 (27). HRMS (EI, 70 eV): calcd for $C_{27}H_{16}O_2Cl$ [M−H]$^+$: 407.08333; found: 407.082634.

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.