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

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ABSTRACT

The palladium(0)-catalyzed Suzuki cross-coupling reaction of the bis(triflate) of 1,3-dihydroxythioxanthone afforded various aryl-substituted thioxanthones. The reactions proceeded with very good site-selectivity in favour of position 3, due to steric reasons.

Thioxanthones are of considerable pharmacological relevance and occur in various natural products.[1] Thioxanthone derivatives have been studied extensively owing to their medicinal properties such as antihistaminic, antiparasitic, neuroleptic, and antitumor activities.[1–9] Lucanthone and hycanthone, a metabolite, represent bioactive natural products with thioxanthone core structure.[10] A series of hycanthone derivatives have been recently reported to display high levels of in vivo activity against murine pancreatic adenocarcinoma.[11–13] Thioxanthone-dioxides are also known to exhibit significant pharmacological activities, including antitumor, cytotoxic and monoamine oxidase (MAO) inhibitory activity.[14] A number of plants, such as *Cartoxylum cochinchinense* (Lour.), contain thioxanthone derived natural products and have been used as traditional medicines to treat fever, coughing, diarrhoea, itching, ulcers, and abdominal complaints.[15] Thioxanthones are also important in the field of material sciences. Various derivatives of thioxanthones are used as activators in the photopolymerization of ethylene-derived unsaturated monomers (particularly acrylate derivatives).[5,16] Moreover, alkyl-, alkoxy- and hydroxy-substituted thioxanthones are particularly useful as heat and ultraviolet stabilizers of polyolefins.[5]

Several methods have been used to synthesize thioxanthones.[2–8,15,17] A rather general procedure is based on the condensation of substituted potassium 2-chlorobenzoates with thiophenols or on the condensation of substituted thiosalicylic acids with benzene derivatives to give 2-phenylmercaptobenzoic acids which are subsequently cyclized by reaction with sulfuric acid,[13,18,19] $AlCl_3$,[3,6] or polyphosphoric acid (PPA).[5] However, these classical methods have some disadvantages, such as low yields, long reaction times, use of large amounts of concentrated sulfuric acid, and lack of regiochemical control in the ring closure step. Moreover, some of these methods require several synthetic steps, because the starting materials are not readily available, and are limited to activated benzoic acids and benzene derivatives containing electron-withdrawing groups.

We have envisaged an alternative approach to substituted thioxanthones based on the functionalization of readily available hydroxylated thioxanthones by site-selective palladium catalyzed cross-coupling reactions. In recent years, site-selective palladium(0) catalyzed reactions of polyhalogenated substrates have gained increasing importance.[20] In this context, Suzuki–Miyaura reactions of bis(triflates) have also been developed.[21] Recently, we have reported site-selective Suzuki–Miyaura reactions of the bis(triflate) of 1,2- and 1,3-dihydroxyanthraquinone.[21g] The first attack occurred at the sterically more hindered position 1 next to the carbonyl group. This result was explained by the fact that position 1 is more electron deficient than positions 2 and 3. In addition, a catalyst-directive effect of the carbonyl group (by chelation) can account for the selectivity observed. Because of the pharmacological and technical importance of thioxanthones, we were interested in the question whether site-selective Suzuki–Miyaura (S–M) reactions of the bis(triflate) of 1,3-dihydroxythioxanthone are possible and by which parameters the selectivity is controlled.

1,3-Dihydroxythioxanthone (**1**) was prepared, following a known procedure,[22] by $AlCl_3$ mediated reaction of thiosalicylic acid

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with 1,3,5-trihydroxybenzene. The bis(triflate) **2** was prepared by reaction of **1** with triflic anhydride (Scheme 1).[23]

The Suzuki–Miyaura reaction of **2** with arylboronic acids **3a–f** (2.4 equiv) afforded the 1,3-diarylthioxanthones **4a–f** (Scheme 2, Table 1). Good yields were obtained both for reactions of electron rich and poor arylboronic acids. The best yields were obtained when the reactions were carried out using $Pd(PPh_3)_4$ as the catalyst and K_3PO_4 as the base (dioxane, 90 °C, 8 h).[24,25]

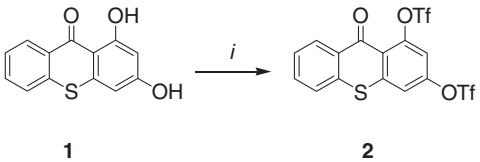
The S–M reaction of **2** with arylboronic acids **3b, c, e, g–i** (1.1 equiv) afforded the 3-aryl-1-(trifluorosulfonyloxy)-thioxanthones **5a–f** in good yields (Scheme 3, Table 2).[24,26] Good yields were again obtained both for reactions of electron rich and poor arylboronic acids. It proved to be important to carry out the reaction at 60 instead of 90 °C in order to induce a good site-selectivity and to avoid double attack. The structure of **5b** was independently confirmed by X-ray crystal structure analysis (Fig. 1).[27] The thioxanthone moiety is slightly twisted out of plane.

The reaction of **5a, c, e** with arylboronic acids **3c, g, j** (1.1 equiv) gave the 1,3-diarylthioxanthones **6a–c**, containing two different aryl groups, in good yields (Table 2).[24,28] The structure of **6b** was independently confirmed by X-ray crystal structure analysis (Fig. 2).[27]

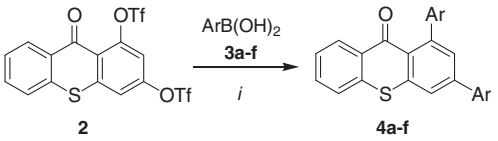
Products **5a** and **e** were selected for optimization studies (Table 3). Thioxanthone **5a** is derived from an electron rich arylboronic acid, while **5e** is derived from an electron poor arylboronic acid. During the optimization we have found that the best yields were obtained when the reactions were carried out at 60 °C. Higher temperatures led to the formation of significant amounts of bis-arylated products. In addition, it proved to be important to use exactly 1.1 equiv of the arylboronic acids. While the use of 1,4-dioxane as the solvent gave the best results in the case of the synthesis of 1,3-diarylthioxanthones **4**, it was observed that employment of THF was advantageous in the case of monoarylated products **5**. The employment of potassium phosphate gave better yields than the use of an aqueous solution of potassium carbonate. The use of $Pd(PPh_3)_4$ gave higher yields than the use of $[Pd(PPh_3)_2Cl_2]$.

The one-pot reaction of **2** with two different arylboronic acids, which were added in a sequential manner, allowed to prepare 1,3-diarylthioxanthone **6d** in 75% yield (Scheme 4, Table 4). 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. The reaction was carried out by adding one portion of the catalyst (5 mol %) at the start of the reaction.

In general, the site-selectivity of palladium catalyzed reactions of poly-halides or -triflates is controlled by steric and electronic parameters. The first attack usually occurs at the sterically less hindered or electronically more deficient position.[29] The S–M reactions of the bis(triflates) of 1,2- and 1,3-dihydroxyanthraquinone proceed by initial attack at position 1 (next to the carbonyl group) which can be explained by the fact that position 1 is more electronically deficient than positions 2 and 3. In addition, a chelation of the catalyst by the carbonyl group might play a role. In contrast, the S–M reactions of **2** proceed by initial attack at position 3. The different site-selectivity is surprising. Obviously, the regiodirecting effect of the carbonyl group of **2** seems to be less pronounced than



Scheme 1. Synthesis of **2**. Reagents and conditions: (i) CH_2Cl_2, 1 (1.0 equiv), Et_3N (4.0 equiv), Tf_2O (2.4 equiv), −78 °C → 20 °C, 8 h.

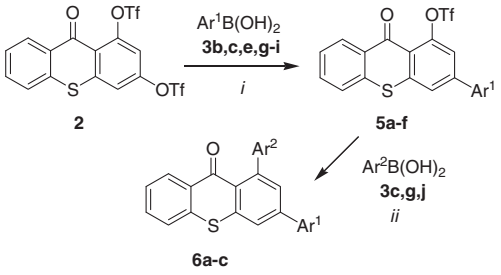


Scheme 2. Synthesis of **4a–f**. Reagents and conditions: (i) **2** (1.0 equiv), **3a–f** (2.4 equiv), $Pd(PPh_3)_4$ (10 mol %), K_3PO_4 (3.0 equiv), 1,4-dioxane, 90 °C, 8 h.

Table 1
Synthesis of **4a–f**

3,4	Ar	4[a] (%)
a	2-(MeO)C_6H_4	90
b	4-EtC_6H_4	81
c	4-*t*BuC_6H_4	86
d	3,5-$Me_2C_6H_3$	77
e	4-ClC_6H_4	70
f	3-(CF_3)C_6H_4	75

[a] Yields of isolated products.



Scheme 3. Synthesis of **5a–f** and of **6a–c**. Reagents and conditions: (i) **2** (1.0 equiv), **3b**, **c**, **e**, **g–i** (1.1 equiv), $Pd(PPh_3)_4$ (5 mol %), K_3PO_4 (1.5 equiv), THF, 60 °C, 8 h; (ii) **5a**, **c**, **e** (1.0 equiv), **3c**, **g**, **j** (1.1 equiv), $Pd(PPh_3)_4$ (5 mol %), K_3PO_4 (1.5 equiv), 1,4-dioxane, 90 °C, 6 h.

Table 2
Synthesis of **5a–f** and of **6a–c**

5	6	Ar^1	% (**5**)[a]	Ar^2	% (**6**)[a]
a	**a**	4-(MeO)C_6H_4	88	4-*t*BuC_6H_4	80
b		4-EtC_6H_4	84		
c	**b**	4-*t*BuC_6H_4	75	4-(MeO)C_6H_4	79
d		C_6H_5	71		
e	**c**	4-ClC_6H_4	78	3,4-$(MeO)_2C_6H_3$	71
f		4-FC_6H_4	80		

[a] Yields of isolated products.

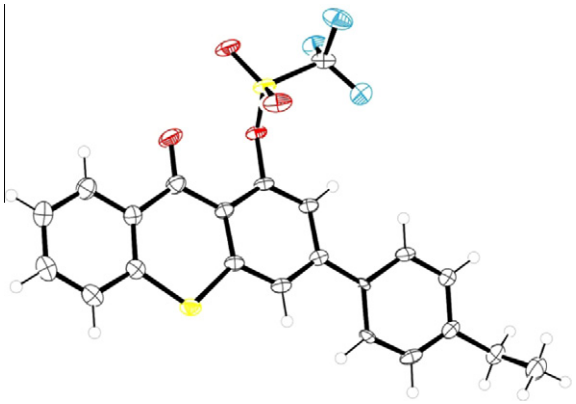


Figure 1. Crystal structure of **5b**.

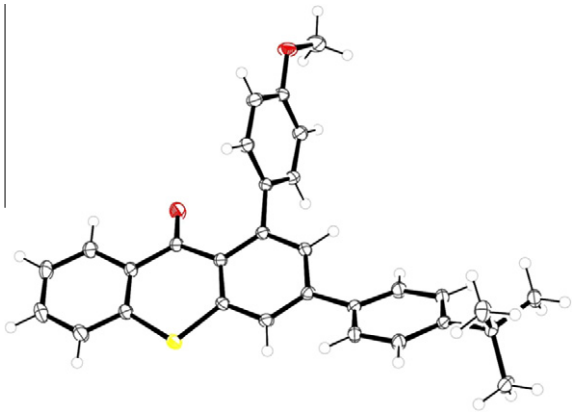
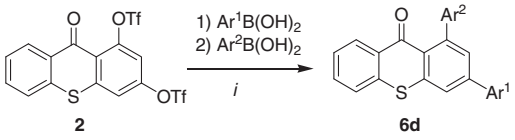


Figure 2. Crystal structure of **6b**.

Table 3
Optimization of the synthesis of **5a** and **5e** (all reactions were carried out at 60 °C for 8 h)

Entry	Base[a]	Solvent[b]	Catalyst[c]	% (**5a**)[d]	% (**5e**)[d]
1	K_2CO_3	Dioxane	$[Pd(PPh_3)_2Cl_2]$	35	24
2	K_2CO_3	THF	$[Pd(PPh_3)_2Cl_2]$	41	32
3	K_2CO_3	Dioxane	$[Pd(PPh_3)_4]$	46	37
4	K_2CO_3	THF	$[Pd(PPh_3)_4]$	41	33
5	K_3PO_4	Dioxane	$[Pd(PPh_3)_2Cl_2]$	55	47
6	K_3PO_4	THF	$[Pd(PPh_3)_2Cl_2]$	66	50
7	K_3PO_4	Dioxane	$[Pd(PPh_3)_4]$	63	57
8	**K_3PO_4**	**THF**	**$[Pd(PPh_3)_4]$**	**88**	**78**

[a] 1.5 equiv per 0.2 mmol of **2**.
[b] 5 mL per 0.2 mmol of **2**.
[c] 5 mol % per 0.2 mmol of **2**.
[d] Yields of isolated products.



2 6d

Scheme 4. Synthesis of **6d**. Reagents and conditions: (i) (1) **2** (1.0 equiv), **3k** (1.1 equiv), $Pd(PPh_3)_4$ (5 mol %), K_3PO_4 (1.5 equiv), 1,4-dioxane, 60 °C, 6 h; (2) **6g** (1.1 equiv), 90 °C, 6 h.

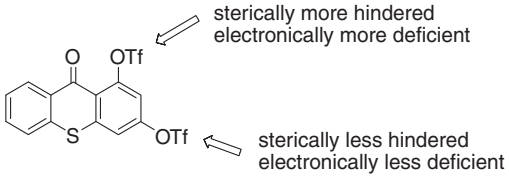
Table 4
Synthesis of **6a-d**

3	**6**	Ar^1	Ar^2	% (**6**)[a]
k, g	**d**	2-MeC_6H_4	4-(MeO)C_6H_4	75

[a] Yields of isolated products.

in the case of the bis(triflates) of 1,2- and 1,3-dihydroxyanthraquinone. Therefore, the sterically less hindered position 3 is attacked first (Scheme 5).

In conclusion, we have reported an efficient synthesis of arylated thioxanthones by Suzuki–Miyaura reactions of the bis(triflate) of 1,3-dihydroxythioxanthone. The reactions proceed with excellent site-selectivity and follow a different pattern than the reactions of the bis(triflates) of 1,2- and 1,3-dihydroxyanthraquinone. Future studies are directed towards extending the scope of the methodology (use of nitro-substituted arylboronic acids and heterocyclic boronic acids).



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

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23. *Synthesis of 9-oxo-9H-thioxanthene-1,3-diyl bis(trifluoro-methanesulfonate)* (**2**): To a solution of **1** (0.34 g, 1.39 mmol) in CH_2Cl_2 (20 mL) was added Et_3N (0.77 mL, 5.56 mmol), at 20 °C under an argon atmosphere. After stirring for 10 min at −78 °C, Tf_2O (0.56 mL, 3.34 mmol) was added. The mixture was allowed to warm to 20 °C and stirred for further 8 h. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was chromatographed without work up (flash silica gel, heptanes–EtOAc) and **2** was isolated as a yellow solid (0.57 g, 80%), mp = 149–150 °C (CH_2Cl_2/EtOH = 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.11 (d, 1H, J = 2.3 Hz, ArH), 7.45–7.51 (m, 3H, ArH), 7.58–7.65 (m, 1H, ArH), 8.49–8.52 (m, 1H, ArH). ^{19}F NMR

(282.4 MHz, $CDCl_3$): δ = −72.26, −73.19. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 114.7 (CH), 118.6 (q, $J_{F,C}$ = 321.3 Hz, CF_3), 118.7 (q, $J_{F,C}$ = 320.9 Hz, CF_3), 118.9, 125.4, 127.7 (CH), 129.9 (C), 130.3, 133.3 (CH), 134.3, 142.7, 149.9, 150.8 (C), 177.8 (CO). IR (KBr): ν = 3081, 3030, 2958, 2923, 2851, 1728 (w), 1602, 1599, 1590 (m), 1554, 1465 (w), 1426 (s), 1399 (m), 1317, 1295 (w), 1246 (m), 1198 (s), 1150 (m), 1133, 1099 (s), 1080 (m), 1033 (w), 989, 929, 904, 884, 819, 807, 798 (m), 768 (w), 751, 714 (m), 684, 666, 655, 635 (w), 590, 569, 542, 530 (m) cm^{-1}. GC–MS (EI, 70 eV): m/z (%) = 508 (M^+, 100), 347 (28), 283 (62), 255 (19). HR-MS (EI, 70 eV): calcd for $C_{15}H_6O_7S_3F_6$ (M^+): 507.91744; found: 507.916890.

24. *General procedure for Suzuki–Miyaura reactions*: A 1,4-dioxane or THF solution (4–5 mL), K_3PO_4 (1.5 equiv per cross-coupling), $Pd(PPh_3)_4$ (5 mol % per cross-coupling) and arylboronic acid **3** (1.10–1.25 equiv per cross-coupling) was stirred at 65–90 °C for 8–12 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 (flash silica gel, heptanes–EtOAc).
25. *Synthesis of 1,3-bis(3-(trifluoromethyl)phenyl)-9H-thioxanthen-9-one* (**4f**): Starting with **2** (101 mg, 0.20 mmol), 3-(trifluoromethyl)phenylboronic acid **3f** (86 mg, 0.45 mmol), $Pd(PPh_3)_4$ (23 mg, 10 mol %), K_3PO_4 (127 mg, 0.60 mmol) and 1,4-dioxane (5 mL), **4f** was isolated as **a** light yellow solid (75 mg, 75%); mp = 167–169 °C (CH_2Cl_2/EtOH = 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.38 (m, 2H, ArH), 7.42–7.54 (m, 6H, ArH), 7.56–7.62 (m, 1H, ArH), 7.58–7.59 (m, 1H, ArH), 7.73 (d, 1H, J = 1.9 Hz, ArH), 7.77–7.83 (m, 2H, ArH), 7.73 (dq, 1H, J = 0.5, 8.1 Hz, ArH). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = −62.6, −62.3. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 122.7 (q, $J_{F,C}$ = 3.7 Hz, CH), 122.9 (q, $J_{F,C}$ = 272.5 Hz, CF_3), 123.2 (q, $J_{F,C}$ = 272.5 Hz, CF_3), 123.2 (q, $J_{F,C}$ = 3.9 Hz, CH), 123.3 (CH), 123.6 (q, $J_{F,C}$ = 3.9 Hz, CH), 124.4 (CH), 124.5 (q, $J_{F,C}$ = 3.9 Hz, CH), 125.4 (C), 125.6, 127.2, 128.0, 128.6, 128.7 (CH), 129.5 (q, $J_{F,C}$ = 32.2 Hz, C-CF_3), 129.7 (CH), 130.1 (C), 130.3 (CH), 130.9 (q, $J_{F,C}$ = 32.5 Hz, C-CF_3), 131.2 (CH), 134.7, 138.3, 138.7, 141.2, 142.9, 144.4 (C), 179.3 (CO). IR (KBr): ν = 3270, 3063, 2959, 2852 (w), 1641 (s), 1615 (w), 1588 (s), 1547, 1496, 1486, 1462, 1455 (w), 1435 (m), 1380 (w), 1326, 1304 (s), 1268, 1251, 1226 (m), 1195 (w), 1174 (m), 1154, 1112, 1095, 1069, 1052 (s), 1033, 1000, 961, 928, 897, 887, 871, 859 (m), 797, 755 9 (s), 748 (m), 720, 698 (m), 686, 672, 654 (s), 627, 611, 562, 542 (m) cm^{-1}. MS (EI, 70 eV): m/z (%) = 500 (M^+, 45), 499 ([M-H]$^+$, 100), 356 (19), 277 (07), 240 (08). HR-MS (EI, 70 eV): calcd for $C_{27}H_{13}OSF_6$ [M-H]$^+$: 499.05858; found: 499.058160.
26. *Synthesis of 3-(4-methoxyphenyl)-9-oxo-9H-thioxanthen-1-yl trifluoromethanesulfonate* (**5a**): Starting with **2** (101 mg, 0.20 mmol), 4-methoxyphenylboronic acid **3g** (34 mg, 0.22 mmol), $Pd(PPh_3)_4$ (12 mg, 5 mol %), K_3PO_4 (64 mg, 0.30 mmol) and THF (5 mL), **5a** was isolated as a light yellow solid (82 mg, 88%); mp = 186–188 °C (CH_2Cl_2/EtOH = 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 3.81 (s, 3H, OCH_3), 6.96 (d, 2H, J = 8.8 Hz, ArH), 7.33 (d, 1H, J = 1.1 Hz, ArH), 7.41–7.58 (m, 5H, ArH), 7.64 (d, 1H, J = 1.7 Hz, ArH), 8.53 (dd, 1H, J = 1.1, 8.2 Hz, ArH). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = −73.38. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 55.5 (OCH_3), 114.9 (CH), 118.9 (q, $J_{F,C}$ = 321.3 Hz, CF_3), 119.1 (CH), 120.3 (C), 123.4, 125.4, 126.9, 128.5 (CH), 129.2 (C), 130.1 (CH), 130.2 (C), 132.6 (CH), 135.3, 141.0, 145.4, 150.4, 161.0 (C), 178.5 (CO). IR (KBr): ν = 3082, 3063, 2841, 1651 (w), 1635, 1594 (s), 1558 (w), 1523 (m), 1471, 1460 (w), 1435 (m), 1425 (s), 1404 (w), 1389 (m), 1328, 1317, 1307 (w), 1286, 1256, 1242, 1219 (m), 1191 (s),1135, 1126, 1111(m), 1060 (w), 1030 (m), 1007 (w), 958, 904, 889, 881 (m), 848 (w), 832 (s), 811, 799 (m), 782, 759 (w), 745 (s), 725 (w), 712, 661, 653, 637 (m), 595 (s), 582, 567, 527 (m) cm^{-1}. GC-MS (EI, 70 eV): m/z (%) = 466 (M^+, 100), 334 (13), 305 (44), 262 (17). HRMS (EI, 70 eV): calcd for $C_{23}H_{13}O_5F_3S_2$: 466.01510; found: 466.015129.
27. CCDC-821684 (**5b**) and CCDC-821685 (**6b**) contain all crystallographic details of this publication and are 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.
28. *Synthesis of 3-(4-chlorophenyl)-1-(3,4-dimethoxyphenyl)-9H-thioxanthen-9-one* (**6c**): Starting with **5e** (75 mg, 0.16 mmol), 3,4-dimethoxyphenylboronic acid **3j** (31 mg, 0.18 mmol), $Pd(PPh_3)_4$ (10 mg, 5 mol %), K_3PO_4 (37 mg, 0.18 mmol), and 1,4-dioxane (4 mL), **6c** was isolated as a yellow solid (53 mg, 71%); mp = 168–170 °C (CH_2Cl_2/EtOH = 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 3.79 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.76–6.89 (m, 3H, ArH), 7.32–7.39 (m, 4H, ArH), 7.48–7.55 (m, 4H, ArH), 7.02 (d, 1H, J = 1.9 Hz, ArH), 8.24–8.27 (m, 1H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 54.8, 54.9 (OCH_3), 109.7, 110.7, 119.1, 122.0, 124.3, 125.4, 127.6, 128.1, 128.3, 128.6 (CH), 130.7 (C), 130.9 (CH), 134.0, 134.7, 134.8, 136.1, 138.1, 141.1, 145.5, 147.2, 147.5 (C), 179.8 (CO). IR (KBr): ν = 3052, 2989, 2957, 2925, 2850, 2829, 2247 (w), 1643 (s), 1609 (w), 1589 (m), 1537(w), 1513, 1491, 1469, 1462, 1454, 1434, 1417 (m), 1401, 1372, 1331 (w), 1296 (m), 1281 (w), 1257, 1240, 1216, 1185, 1170, 1153, 1136, 1122, 1102, 1092, 1077, 1056 (m), 1027, 1013 (s), 952, 932 (w), 909, 894, 875, 863 (m), 841 (w), 825 (m), 816 (s), 804, 789, 761 (m), 747, 721 (s), 683, 662, 652, 646, 629, 618, 600, 583, 541 (m) cm^{-1}. GC–MS (EI, 70 eV): m/z (%) = 458 (M^+, 100), 443 (24), 371 (17), 214 (14). HR-MS (ESI$^+$): calcd for $C_{27}H_{19}O_3ClS$: [M]$^+$: 458.07379; found: 458.074006.
29. 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.