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Facile Synthesis of Halogen Decorated *para*-/*meta*-Hydroxybenzoates by Iridium-Catalyzed Borylation and Oxidation

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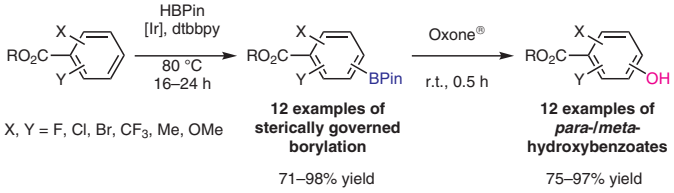

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Abstract Hydroxybenzoates are an important class of phenols that are widely used as preservatives and antiseptics in the food and pharmaceutical industries. In this report, a facile preparation of 2,6- and 2,3-disubstituted 4/5-hydroxybenzoates by iridium-catalyzed borylation of respective disubstituted benzoate esters followed by oxidation is described. This synthetic route allows for the incorporation of halogens in the final hydroxybenzoates with substitution patterns not readily accessible by the traditional routes of aromatic functionalization.

Key words iridium-catalyzed C–H borylation, oxidation, Oxone®, hydroxybenzoates, parabens, preservatives, halogen, trifluoromethyl

Hydroxybenzoates are important synthetic precursors to many drugs, polymers, herbicides, and antioxidants.[1–4] 4-Hydroxybenzoates, also known as parabens, are widely used as antimicrobial preservatives in food, pharmaceuticals, and cosmetics.[5–7] Approximately 8000 tons of parabens are consumed annually around the globe.[8] This scaffold is also found in many natural products and molecules of biological relevance (Figure 1). Recently, 3,5-dihalogen-substituted 4-hydroxybenzoates have been reported to possess enhanced antimicrobial properties along with reduced risk of breast cancer as compared to the parent paraben.[9] 3-Hydroxybenzoates have shown excellent antifungal properties[10] and 2-hydroxybenzoates such as methyl salicylate are active ingredient of many analgesics.

Classical approaches to access hydroxybenzoates include esterification of hydroxybenzoic acids using sulfuric acid, *p*-toluenesulfonic acid, or cation-exchange resins as catalyst.[11] The starting hydroxybenzoic acids used for esterification are in turn synthesized either using Kolbe–Schmitt process by heating potassium phenoxide in a stream of carbon dioxide, or by heating *p*-cresol with various metallic oxides.[12] The harsh reaction conditions used in these traditional approaches result in limited functional group tolerance. These classical routes also rely on early incorporation of the hydroxyl functional group, which limits the subsequent derivatizations *ortho* to the hydroxyl group.

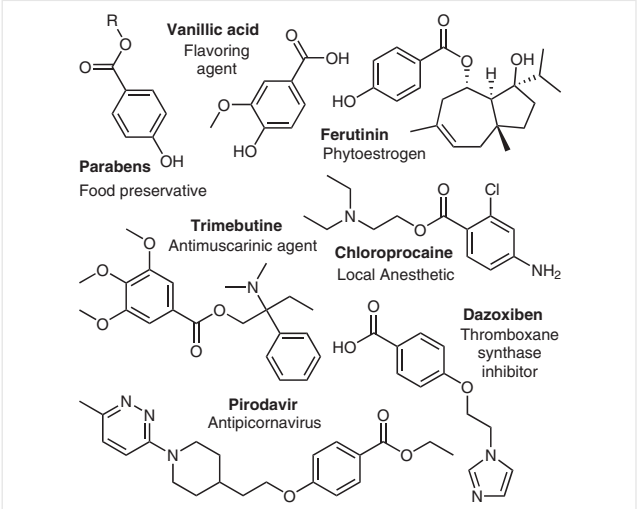


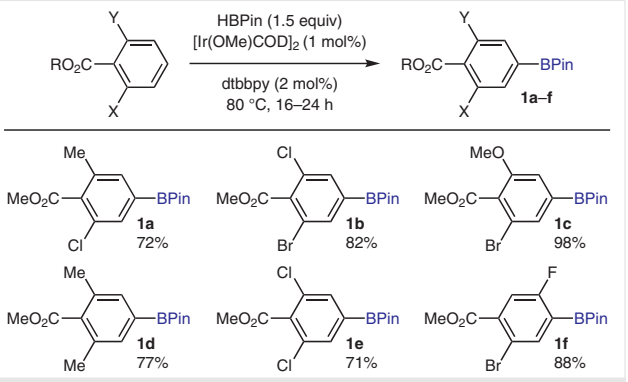
Figure 1 Hydroxybenzoic acid derivatives of commercial significance

Keeping in view of their immense utility in pharmaceutical, cosmetic, and food industries, there is need to develop new green synthetic methodologies to access novel hydroxybenzoates with additional useful functional groups to find next generation compounds with better activities and reduced side effects.[9,13–16] In this direction, development of methodologies that allow introduction of a hydroxyl group later in the synthetic route is an ideal approach for obtaining new and unique substitution patterns not accessible through the traditional routes.

During the last two decades, several new methodologies have been developed to synthesize substituted phenols under mild reaction conditions and with improved functional group compatibilities. Among these, the most convenient route is through the oxidation of arylboronic acids and esters.[17] Various oxidizing agents utilized for this purpose include Oxone®,[18] hydrogen peroxide,[19] hydrazine derivatives,[20–22] sodium ascorbate,[23] photocatalysts,[24,25] and electrocatalysts,[26] etc. In addition, alternative synthetic routes recently reported for the preparation of phenols include nucleophilic aromatic substitutions,[27,28] transition-metal-catalyzed hydroxylation of aryl halides,[29,30] and hydroxylation of arylsilanes.[31–33] However, all these methods need pre-functionalization of the aromatic ring in the form of halogen or nitro groups, which are ultimately converted to the hydroxyl group. Since incorporation of halogens often results in improved bioactivities,[9] it is desirable to develop methods for the preparation of halogenated hydroxybenzoates with new substitution patterns not readily accessible through the traditional aromatic functionalization routes.

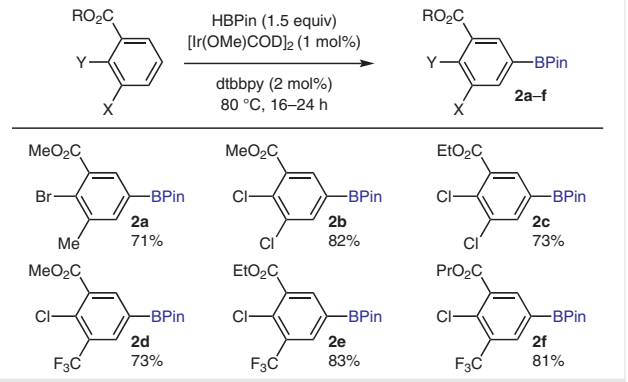
The group of Smith and Maleczka has reported iridium-catalyzed aromatic C–H borylation/oxidation route for the synthesis of *meta*-substituted phenols directly from the hydrocarbon feedstock.[34–37] This transition-metal-catalyzed reaction is highly selective for aromatic C–H activation in the presence of other functional groups and thus allows for the incorporation of various substituents including halogens into the final phenol products. Moreover, sterically governed regioselectivity observed in this C–H functionalization reaction is complementary to that obtained through the traditional electrophilic aromatic substitution and directed *ortho*-metalation approaches. Building on the foundations of Smith and Maleczka methodology for the preparation of halogenated phenols, we explored the application of this route to the borylation/oxidation of 2,6- and 2,3-substituted benzoic esters to prepare the corresponding 4- and 5-hydroxybenzoate esters.

We started with the iridium-catalyzed borylation of 2,6-disubstituted benzoate esters. Using the standard borylation protocol, precatalyst $[Ir(OMe)(COD)]_2$ and dtbbpy ligand were weighed in air and transferred to a Schlenk flask under nitrogen atmosphere. Pinacolborane (HBpin) and benzoate ester substrate were subsequently added to the flask and the mixture was heated at 80 °C using an oil bath. The progress of reaction was monitored by GC-MS. Since regioselectivity in iridium-catalyzed C–H borylation is governed by sterics, catalytic borylation selectively took place at the least hindered site, that is, the 4-position (Scheme 1, entries **1a–e**). In the case of 2-bromo-5-fluoro-substituted benzoate ester, the small size of fluorine allowed borylation *ortho* to itself (Scheme 1, entry **1f**).[38] The resulting arylboronate esters were isolated in good to excellent yields.



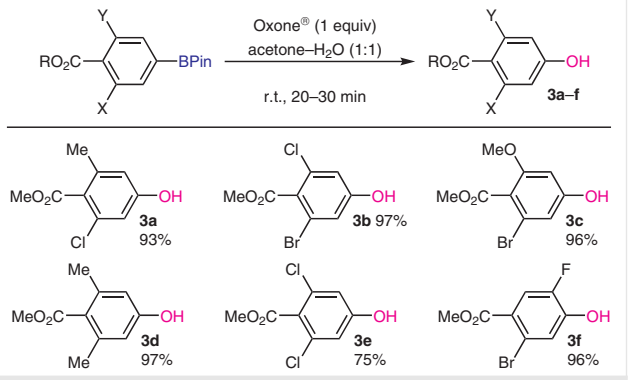
Scheme 1 Iridium-catalyzed C–H borylation of 2,6- and 2,5-disubstituted benzoates

Catalytic borylation of 2,3-disubstituted benzoate esters also took place on the least sterically hindered 5-position (Scheme 2). Halogenated and trifluoromethyl-substituted benzoic esters were examined. Since it has been known that the antimicrobial activity of the parabens increases with increasing the alkyl chain length of benzoic ester, the ethyl and *n*-propyl esters were also included in this study (Scheme 2, entries **2c**, **2e**, and **2f**).



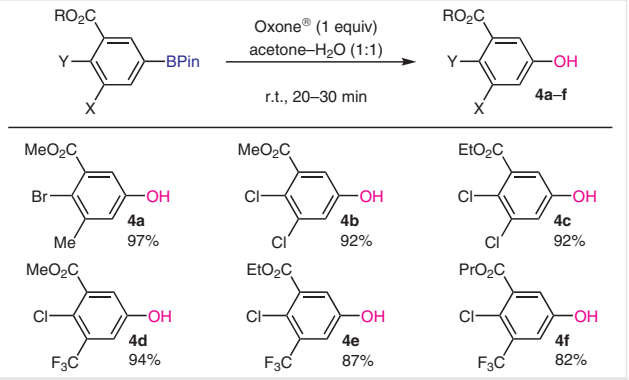
Scheme 2 Iridium-catalyzed C–H borylation of 2,3-disubstituted benzoates

The synthesized boronic esters were then subjected to oxidation using Oxone® (Scheme 3).[34] The desired hydroxyl benzoates were isolated in good to excellent yields. In the case of **3b** and **3f**, small amounts (<1%) of protodeborylation was detected by GC-MS. This synthetic route allowed the ready preparation of 2,6- and 2,5-halo-substituted 4-hydroxybenzoates. It is interesting to note that the closely related isomeric 3,5-disubstituted 4-hydroxylbenzoate esters have recently been reported to exhibit improved antimicrobial activities together with diminished side effects commonly associated with unsubstituted parabens.[9]



Scheme 3 Synthesis of 2,6- and 2,5-disubstituted 4-hydroxybenzoates

Similarly, 2,3-disubstituted 5-borylated benzoate esters were oxidized to the corresponding 5-hydroxy benzoates (Scheme 4). Although *ortho*-substituted phenols are readily available by traditional electrophilic aromatic substitution, however, access to *meta*-substituted phenols is more challenging and requires long synthetic routes.[39] The current synthetic route provides ready access to these difficult to prepare *meta*-halogenated phenols.



Scheme 4 Synthesis of 2,3-disubstituted 5-hydroxybenzoates

In summary, iridium-catalyzed borylation and subsequent oxidation of benzoates esters is an efficient protocol for synthesis of various substituted hydroxybenzoates. This method is particularly attractive for the preparation of halogenated hydroxybenzoates where the halogen substituent is present *meta* to the *ortho*/*para* directing hydroxyl group.

All reactions were carried out under N_2 atmosphere. All commercially available chemicals and reagents were used without further purification unless otherwise noted. EtOAc, hexanes, and CH_2Cl_2 were distilled before use. Carboxylate esters, if not readily commercially available, were prepared by acid-catalyzed esterification of the corresponding carboxylic acid. Iridium-catalyzed borylation reactions were carried out in air-free 25 mL Schlenk flask (0–4 mm valve, 175 mm OAH). Analytical TLC was carried out using 250 µm thick SiliaPlate™ TLC Plates. Visualization was achieved under a UV lamp (254 nm and 365 nm). Column chromatography was carried out using SiliaFlash® (particle size: 40–63 µm, 230–400 mesh). All reported yields are for isolated materials. Reaction times and yields are not optimized. HBPin: pinacolborane; dtbbpy: 4,4′-di-*tert*-butyl-2,2′-bipyridyl.

IR spectra were recorded as neat using a Bruker Alpha-P IR instrument in the ATR geometry with a diamond ATR unit. Melting points were taken on Electrothermal IA9100 melting point apparatus. Reactions were monitored by a GC-MS operating in EI mode. ^{1}H NMR spectra were recorded at 500 MHz, and ^{13}C NMR spectra were recorded at 125 MHz at ambient temperature. The chemical shifts in ^{1}H NMR spectra are reported using TMS as internal standard and were referenced with the residual proton resonances of the corresponding deuterated solvent (DMSO-d_6: δ = 2.50). The chemical shifts in the ^{13}C NMR spectra are reported relative to TMS (δ = 0) or the central peak of DMSO-d_6 (δ = 39.5) for calibration.

Standard abbreviations were used for denoting the multiplicities. All coupling constants are apparent *J* values measured at the indicated field strengths. In ^{13}C NMR spectra of arylboronic esters, the carbon atom attached to the boron atom of BPin group is typically not observed due to broadening from and coupling with boron. Regiochemistry of the borylated products was assigned by NMR spectroscopy (^{1}H and ^{13}C NMR).

Borylation of Arenes; General Procedure

In a fume hood, an oven dried Schlenk flask equipped with a magnetic stirring bar was filled with N_2 and evacuated (three cycles). Under N_2 atmosphere [Ir(OMe)(COD)]$_2$ (13.3 mg, 0.01 mmol, 1 mol%), 4,4-di-*tert*-butyl-2,2′-bipyridyl (10.7 mg, 0.02 mmol, 2 mol%), and pinacolborane (HBPin) (436 µL, 384 mg, 3 mmol, 1.5 equiv) were added. The appropriate arene substrate (2 mmol, 1 equiv) was added via micropipette under N_2 atmosphere. The Schlenk flask was closed and the reaction mixture was heated at 80 °C in an oil bath. The progress of reaction was monitored by GC-MS and TLC. Upon completion of reaction, Schlenk flask was cooled to r.t. and exposed to air. The contents of the flask were dissolved in CH_2Cl_2 (3–5 mL) and taken out in a round-bottomed flask. The volatile organics were removed under reduced pressure using a rotary evaporator. The crude product was purified by column chromatography (silica gel, hexanes–CH_2Cl_2 1:1).

Methyl 2-Chloro-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (1a)

General borylation procedure was applied to methyl 2-methyl-6-chlorobenzoate (368 mg, 2 mmol, 1 equiv) for 24 h; colorless solid; yield: 447 mg (72%); mp 73–74 °C; R_f = 0.3 (hexanes–CH_2Cl_2 1:1).

FT-IR (ATR): 2977, 1732, 1550, 1442, 1354, 1269, 1124, 1080, 958, 886, 848, 860, 813, 686 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.54 (s, 1 H), 7.51 (s, 1 H), 3.89 (s, 3 H, CH_3), 2.27 (s, 3 H, CH_3), 1.30 (s, 12 H, 4 × CH_3 of BPin).

^{13}C NMR {^{1}H} (125 MHz, DMSO-d_6): δ = 166.8 (C=O), 136.3 (C), 135.7 (C), 134.5 (CH), 131.7 (CH), 129.0 (C), 84.3 (2 C), 52.7 (CH_3), 24.6 (4 × CH_3 of BPin), 18.7 (CH_3).

GC-MS (EI): *m*/*z* (%) = 310 [20, (M)$^+$], 295 (16), 279 (26), 275 (17), 243 (100), 233 (89), 211 (54), 201 (26), 179 (21), 175 (18).

Methyl 2-Bromo-6-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (1b)

General borylation procedure was applied to 2-bromo-6-chlorobenzoate (500 mg, 2 mmol, 1 equiv) for 18 h; colorless solid; yield: 614 mg (82%); mp 83–84 °C; R_f = 0.3 (hexanes–CH_2Cl_2 1:1).

FT-IR (ATR): 2975, 1736, 1531, 1469, 1370, 1349, 1331, 1278, 1193, 1138, 1116, 1056 956, 880, 847, 815, 783, 756, 705 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 7.80 (d, J = 1.0 Hz, 1 H), 7.70 (d, J = 0.5 Hz, 1 H), 3.92 (s, 3 H, CH_3), 1.30 (s, 12 H, 4 × CH_3 of BPin).

^{13}C NMR {^1H} (125 MHz, DMSO-d_6): δ = 165.1 (C=O), 137.1 (C), 136.2 (CH), 133.5 (CH), 130.3 (C), 119.10 (C), 84.8 (2 C), 53.3 (CH_3), 24.6 (4 × CH_3 of BPin).

GC-MS (EI): m/z (%) = 376 [19, (M + 2)$^+$], 374 [15, (M)$^+$], 359 (22), 343 (10), 290 (100), 275 (19), 257 (13), 244 (11), 217 (10).

Methyl 2-Bromo-6-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (1c)

General borylation procedure was applied to methyl 2-bromo-6-methoxybenzoate (488 mg, 2 mmol, 1 equiv) for 40 h; colorless solid; yield: 730 mg (98%); mp 116–118 °C; R_f = 0.5 (hexanes–CH_2Cl_2 1:1).

FT-IR (ATR): 2979, 1739, 1387, 1350, 1264, 1249, 1122, 1078, 1036, 964, 909, 851 767, 712 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 7.42 (s, 1 H), 7.25 (s, 1 H), 3.84 (s, 6 H, 2 × CH_3), 1.31 (s, 12 H, 4 × CH_3 of BPin).

^{13}C NMR {^1H} (125 MHz, DMSO-d_6): δ = 165.7 (C=O), 156.3 (C), 129.4 (CH), 127.8 (C), 118.5 (C), 115.3 (CH), 84.5 (2 C), 56.3 (CH_3), 52.7 (CH_3), 24.6 (4 × CH_3 of BPin).

GC-MS (EI): m/z (%) = 372 [58, (M + 2)$^+$], 370 [62, (M)$^+$], 339 (68), 284 (42), 270 (34), 253 (59), 239 (100), 196 (23).

Methyl 2,6-Dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (1d)

General borylation procedure was applied to methyl 2,6-dimethylbenzoate (164 mg, 1 mmol, 1 equiv) for 36 h; colorless solid; yield: 223 mg (77%); mp 77–78 °C; R_f = 0.5 (hexanes–CH_2Cl_2 1:1).

FT-IR (ATR): 2980, 1732, 1610, 1365, 1321, 1260, 1126, 1077, 965, 909, 887, 850, 810, 739, 686 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 7.39 (s, 2 H), 3.85 (s, CH_3), 2.22 (s, 6 H, 2 × CH_3), 1.29 (s, 12 H, 4 × CH_3 of BPin).

^{13}C NMR {^1H} (125 MHz, DMSO-d_6): δ = 169.4 (C=O), 136.4 (C), 133.5 (2 C), 133.4 (2 × CH), 83.8 (2 C), 52.0 (CH_3), 24.6 (4 × CH_3 of BPin), 18.9 (2 CH_3).

GC-MS (EI): m/z (%) = 290 [52, (M)$^+$], 275 (42), 258 (46), 204 (100), 191 (90), 172 (26), 158 (72), 131 (32), 105 (23).

Methyl 2,6-Dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (1e)

General borylation procedure was applied to methyl 2,6-dichlorobenzoate (412 mg, 2 mmol, 1 equiv) for 20 h; colorless solid; yield: 472 mg (71%); mp 75–76 °C; R_f = 0.5 (hexanes–CH_2Cl_2 1:1).

FT-IR (ATR): 2983, 2951, 1745, 1609, 1359, 1341, 1271, 1160, 1100, 797 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 7.67 (s, 2 H), 3.93 (s, 3 H, CH_3), 1.31 (s, 12 H, 4 × CH_3 of BPin).

^{13}C NMR {^1H} (125 MHz, DMSO-d_6): δ = 164.3 (C=O), 135.0 (C), 133.1 (2 × CH), 130.5 (2 C), 84.8 (2 C), 53.3 (CH_3), 24.6 (4 × CH_3 of BPin).

GC-MS (EI): m/z (%) = 332 [10, (M + 2)$^+$], 330 [17, (M)$^+$], 315 (28), 299 (21), 244 (100), 231 (25), 213 (17), 199 (24).

Methyl 2-Bromo-5-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (1f)

General borylation procedure was applied to methyl 2-bromo-5-fluorobenzoate (464 mg, 2 mmol, 1 equiv) for 24 h; colorless solid; yield: 634 mg (88%); mp 95 °C; R_f = 0.3 (hexanes–CH_2Cl_2 1:1).

FT-IR (ATR): 2978, 2930, 1724, 1593, 1482, 1447, 1371, 1253, 1195, 1127, 1025, 965, 849, 777, 712, 670 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 7.84 (d, $^4J_{H,F}$ = 5.0 Hz, 1 H), 7.60 (d, $^3J_{H,F}$ = 9.0 Hz, 1 H), 3.87 (s, 3 H, CH_3), 1.31 (s, 12 H, 4 × CH_3 of BPin).

^{13}C NMR {^1H} (125 MHz, DMSO-d_6): δ = 165.3 (d, $^4J_{C,F}$ = 1.6 Hz, C=O), 164.3 (d, $^1J_{C,F}$ = 250.5 Hz, C=O), 140.9 (d, $^3J_{C,F}$ = 8.2 Hz, CH), 136.7 (d, $^3J_{C,F}$ = 8.1 Hz, C), 117.9 (d, $^2J_{C,F}$ = 27.5 Hz, CH), 114.3 (d, $^4J_{C,F}$ = 3.5 Hz, C), 84.5 (2 C), 52.9 (CH_3), 24.5 (4 × CH_3 of BPin).

GC-MS (EI): m/z (%) = 358 [40, (M)$^+$], 343 (36), 316 (80), 300 (27), 298 (95), 259 (58), 254 (100), 227 (85).

Methyl 2-Bromo-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (2a)

General borylation procedure was applied to methyl 2-bromo-3-methylbenzoate (456 mg, 2 mmol, 1 equiv) for 24 h; colorless solid; yield: 502 mg (71%); mp 75–76 °C; R_f = 0.4 (hexanes–CH_2Cl_2 1:1).

FT-IR (ATR): 2978, 2965, 1724, 1593, 1275, 1252, 1194, 1128, 1025, 965, 849, 777, 712, 670 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 7.75–7.74 (m, 1 H), 7.71–7.70 (m, 1 H), 3.85 (s, 3 H, CH_3), 2.42 (s, 3 H, CH_3), 1.30 (s, 12 H, 4 × CH_3 of BPin).

^{13}C NMR {^1H} (125 MHz, DMSO-d_6): δ = 166.7 (C=O), 138.9 (C), 138.7 (CH), 133.7 (C), 133.1 (CH), 125.5 (C), 84.2 (2 C), 52.6 (CH_3), 24.6 (4 × CH_3 of BPin), 22.9 (CH_3)

GC-MS (EI): m/z (%) = 354 [38, (M)$^+$], 339 (18), 311 (100), 279 (19), 255 (29), 223 (30), 143 (41).

Methyl 2,3-Dichloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (2b)

General borylation procedure was applied to methyl 2,3-dichlorobenzoate (408 mg, 2 mmol, 1 equiv) for 24 h; colorless solid; yield: 541 mg (82%); mp 89–91 °C; R_f = 0.4 (hexanes–CH_2Cl_2 1:1).

FT-IR (ATR): 2977, 1727, 1592, 1439, 1351, 1268, 1242, 1205, 1129, 1047, 984, 963, 904, 851 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 7.94 (d, J = 1.5 Hz, 1 H), 7.92 (d, J = 1.5 Hz, 1 H), 3.88 (s, 3 H, CH_3), 1.31 (s, 12 H, 4 × CH_3 of BPin).

^{13}C NMR {^1H} (125 MHz, DMSO-d_6): δ = 164.7 (C=O), 138.1 (CH), 134.5 (CH), 133.2 (C), 132.8 (C), 132.4 (C), 84.7 (2 C), 52.9 (CH_3), 24.6 (4 × CH_3 of BPin).

GC-MS (EI): m/z (%) = 332 [12, (M + 2)$^+$], 330 [17, (M$^+$)], 315 (17), 299 (23), 287 100), 255 (38), 231 (52), 199 (43).

Ethyl 2,3-Dichloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (2c)

General borylation procedure was applied to ethyl 2,3-dichlorobenzoate (436 mg, 2 mmol, 1 equiv) for 18 h,; colorless solid; yield: 502 mg (73%); mp 66–67 °C; R_f = 0.4 (hexanes–CH_2Cl_2 1:1).

FT-IR (ATR): 2979, 1730, 1590, 1470, 1353, 1239, 1127, 1030, 968, 904, 847, 777, 748, 704 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.91 (d, J = 1.5 Hz, 1 H), 7.89 (d, J = 1.5 Hz, 1 H), 4.35 (q, J = 7.0 Hz, 2 H, CH_2), 1.34 (s, 12 H, 4 × CH_3 of BPin), 1.32 (t, J = 7.0 Hz, 3 H, CH_3).

^{13}C NMR {^{1}H} (125 MHz, DMSO-d_6): δ = 164.4 (C=O), 137.9 (CH), 134.1 (CH), 133.1 (C), 132.9 (C), 132.6 (C), 84.7 (2 C), 61.9 (CH_2), 24.9 (4 × CH_3 of BPin), 13.9 (CH_3).

GC-MS (EI): m/z (%) = 346 [11, (M + 2)$^+$], 344 [17, (M)$^+$], 301 (95), 273 (100), 255 (36), 245 (31), 217 (40), 199 (47).

Methyl 2-Chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)benzoate (2d)

General borylation procedure was applied to methyl 2-chloro-3-(trifluoromethyl)benzoate (476 mg, 2 mmol, 1 equiv) for 24 h; colorless solid; yield: 531 mg (73%); mp 125–126 °C; R_f = 0.4 (hexanes–CH_2Cl_2 1:1).

FT-IR (ATR): 2980, 1723, 1601, 1299, 1271, 1138, 980, 847, 685 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.22 (d, J = 1.5 Hz, 1 H), 8.08 (d, J = 1.5 Hz, 1 H), 3.90 (s, 3 H, CH_3), 1.32 (s, 12 H, 4 × CH_3 of BPin).

^{13}C NMR {^{1}H} (125 MHz, DMSO-d_6): δ = 164.7 (C=O), 139.6 (CH), 134.8 (q, $^3J_{C,F}$ = 4.8 Hz, CH), 133.3 (C), 132.4 (C), 127.8 (q, $^2J_{C,F}$ = 30.5 Hz, C), 122.5 (q, $^1J_{C,F}$ = 271.7 Hz, CF_3), 84.8 (2 C), 53.1 (CH_3), 24.6 (4 × CH_3 of BPin).

GC-MS (EI): m/z (%) = 364 [6, (M)$^+$], 349 (21), 333 (19), 321 (100), 303 (7), 289 (36), 265 (36), 233 (49), 205 (37).

Ethyl 2-Chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)benzoate (2e)

General borylation procedure was applied to ethyl 2-chloro-3-(trifluoromethyl)benzoate (504 mg, 2 mmol, 1 equiv) for 24 h; colorless solid; yield: 629 mg (83%); mp 65–68 °C; R_f = 0.4 (hexanes–CH_2Cl_2 1:1).

FT-IR (ATR): 2981, 2934, 1735, 1601, 1297, 1135, 1016, 964, 917 848 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.17 (d, J = 1.5 Hz, 1 H), 8.07 (d, J = 1.5 Hz, 1 H), 4.37 (q, J = 7.0 Hz, 2 H, CH_2), 1.33 (s, 12 H, 4 × CH_3 of BPin), 1.31 (t, J = 7.0 Hz, 3 H, CH_3).

^{13}C NMR {^{1}H} (125 MHz, DMSO-d_6): δ = 164.4 (C=O), 139.2 (CH), 134.7 (q, $^3J_{C,F}$ = 5.1 Hz, CH), 133.8 (C), 132.2 (C), 127.7 (q, $^2J_{C,F}$ = 30.3 Hz, C), 122.5 (q, $^1J_{C,F}$ = 271.6 Hz, C), 84.8 (C), 62.1 (CH_2), 24.6 (4 × CH_3 of BPin), 13.9 (CH_3).

GC-MS (EI): m/z (%) = 378 [7, (M)$^+$], 335 (92), 307 (100), 289 (36), 251 (42), 233 (44), 205 (27).

Propyl 2-Chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)benzoate (2f)

General borylation procedure was applied to propyl 2-chloro-3-(trifluoromethyl)benzoate (532 mg, 2 mmol, 1 equiv) for 24 h; colorless oil; yield: 635 mg (81%); R_f = 0.4 (hexanes–CH_2Cl_2 1:1).

FT-IR (ATR): 2978, 1736, 1601, 1374, 1297, 1279, 1193, 1136, 1050, 965, 848, 689 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.16 (d, J = 1.5 Hz, 1 H), 8.07 (d, J = 1.5 Hz, 1 H), 4.29 (t, J = 6.5 Hz, 2 H, CH_2), 1.73 (m, 2 H, CH_2), 1.31 (s, 12 H, 4 × CH_3 of BPin), 0.95 (t, J = 7.0 Hz, 3 H, CH_3).

^{13}C NMR {^{1}H} (125 MHz, DMSO-d_6): δ = 164.5 (C=O), 139. 2 (CH), 134.7 (q, $^3J_{C,F}$ = 4.9 Hz, C), 133.8 (CH), 132.1 (C), 127.7 (q, $^2J_{C,F}$ = 30.1 Hz, C), 122.5 (q, $^1J_{C,F}$ = 272.1 Hz, CF_3), 84.8 (2 C), 67.5 (CH_2), 24.6 (4 × CH_3 of BPin), 21.4 (CH_2), 10.3 (CH_3).

GC-MS (EI): m/z (%) = 392 [5, (M$^+$)], 377 (20), 333 (23), 307 (100), 289 (21), 251 (36), 233 (43), 205 (37).

Oxidation Boronic Estes 1 and 2; General Procedure

An oven-dried round-bottomed flask equipped with a magnetic stirring bar was charged with the respective boronic ester substrate **1** or **2** (1 mmol, 1 equiv) and acetone (3 mL). The mixture was stirred to generate a homogeneous solution. An aqueous solution of Oxone® (1 equiv in 3 mL/mmol H_2O) was added dropwise over 2–4 min. The reaction mixture was vigorously stirred for 20–30 min. After the completion of reaction, an aq solution of $NaHSO_3$ (1 mL) was added to quench the reaction. The mixture was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organics were washed with brine. The organic layer was separated, dried (anhyd Na_2SO_4, 2 g), and filtered. Volatile organics were removed using rotary evaporator. The crude product was purified by column chromatography (silica gel, hexanes–EtOAc 1:1).

Methyl 2-Chloro-4-hydroxy-6-methylbenzoate (3a)

General oxidation procedure was applied to methyl 2-chloro-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (**1a**; 310 mg, 1 mmol, 1 equiv) for 0.5 h; pale yellow solid; yield: 186 mg (93%); mp 88–89 °C; R_f = 0.7 (hexanes–EtOAc 1:1).

FT-IR (ATR): 3409, 2979, 1712, 1604, 1450, 1270, 1138, 950, 851 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.23 (br s, 1 H, OH), 6.70 (dd, J = 2.0, 0.5 Hz, 1 H), 6.64 (dd, J = 2.5, 1.0 Hz, 1 H), 3.81 (s, 3 H, CH_3), 2.18 (s, 3 H, CH_3).

^{13}C NMR {^{1}H} (125 MHz, DMSO-d_6): δ = 167.2 (C=O), 158.7 (C), 138.3 (C), 130.4 (C), 124.1 (C), 115.8 (CH), 113.4 (CH), 52.2 (CH_3), 19.4 (CH_3).

GC-MS (EI): m/z (%) = 200 [52, (M)$^+$], 169 (100), 141 (24), 77 (36).

Methyl 2-Bromo-6-chloro-4-hydroxybenzoate (3b)

General oxidation procedure was applied to methyl 2-chloro-6-bromo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (**1b**; 188 mg, 0.5 mmol, 1 equiv) for 0.5 h; colorless solid; yield: 129 mg (97%); mp 115–118 °C; R_f = 0.3 (CH_2Cl_2).

FT-IR (ATR): 3202, 2953, 1686, 1599, 1562, 1424, 1275, 1241, 1134, 933, 848, 770 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.81 (br s, 1 H, OH), 7.05 (d, J = 2.2 Hz, 1 H), 6.94 (d, J = 2.5 Hz, 1 H), 3.85 (s, 3 H, CH_3).

^{13}C NMR {^{1}H} (125 MHz, DMSO-d_6): δ = 165.6 (C=O), 159.5 (C), 131.1 (C), 125.7 (C), 119.6 (C), 118.2 (CH), 115.5 (CH), 52.9 (CH_3).

GC-MS (EI): m/z (%) = 266 [22, (M + 2)$^+$], 264 [18, (M)$^+$], 235 (100), 233 (79), 177 (8).

Methyl 2-Bromo-6-methoxy-4-hydroxybenzoate (3c)

General oxidation procedure was applied to methyl 2-bromo-6-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) (**1c**; 370 mg, 1 mmol, 1 equiv) for 20 min; colorless solid; yield: 251 mg (96%); mp 107–109 °C; R_f = 0.3 (CH_2Cl_2).

FT-IR (ATR): 3235, 2980, 1692, 1598, 1452, 1426, 1293, 1236, 1155, 1106, 1035, 946, 820 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.32 (br s, 1 H, OH), 6.60 (d, J = 2.0 Hz, 1 H), 6.48 (d, J = 2.0 Hz, 1 H), 3.76 (s, 3 H, CH_3), 3.73 (s, 3 H, CH_3).

^{13}C NMR {^{1}H} (125 MHz, DMSO-d_6): δ = 166.2 (C=O), 160.1 (C), 158.1 (C), 119.1 (C), 116.5 (C), 110.6 (CH), 98.7 (CH), 55.9 (CH_3), 52.3 (CH_3).

GC-MS (EI): *m*/*z* (%) = 262 [18, $(M + 2)^+$], 260 [22, $(M)^+$], 231 (95), 229 (100), 214 (6), 186 (11), 158 (4), 150 (5).

Methyl 2,6-Dimethyl-4-hydroxybenzoate (3d)

General oxidation procedure was applied to methyl 2,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (**1d**; 145 mg, 0.5 mmol, 1 equiv) for 0.5 h; colorless solid; yield: 87 mg (97%); mp 111–113 °C; R_f = 0.5 (hexanes–EtOAc 1:1).

FT-IR (ATR): 3188, 2965, 1689, 1605, 1299, 1125, 930, 692 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 9.64 (br s, 1 H, OH), 6.46 (s, 2 H, 2 × CH), 3.77 (s, 3 H, CH_3), 2.16 (s, 6 H, 2 × CH_3).

^{13}C NMR {^1H} (125 MHz, DMSO-d_6): δ = 169.5 (C=O), 158.0 (C), 136.9 (2 C), 124.3 (C), 114.4 (2 CH), 51.5 (CH_3), 19.8 (2 × CH_3).

GC-MS (EI): *m*/*z* (%) = 180 [54, $(M)^+$], 149 (100), 121 (25), 103 (3), 91 (16).

Methyl 2,6-Dichloro-4-hydroxybenzoate (3e)

General oxidation procedure was applied to methyl 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (**1e**; 161 mg, 0.5 mmol, 1 equiv) for 0.5 h; colorless solid; yield: 166 mg (75%); mp 106–107 °C; R_f = 0.5 (hexanes–EtOAc 1:1).

FT-IR (ATR): 3385, 2980, 1696, 1434, 1352, 1136 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 10.85 (br s, 1 H, OH), 6.91 (s, 2 H, 2 × CH), 3.85 (s, 3 H, CH_3).

^{13}C NMR {^1H} (125 MHz, DMSO-d_6): δ = 164.9 (C=O), 159.5 (C), 131.3 (2 C), 123.6 (C), 115.2 (2 CH), 52.9 (CH_3).

GC-MS (EI): *m*/*z* (%) = 222 [22, $(M + 2)^+$], 220 [37, $(M)^+$], 189 (100), 161 (5), 133 (17), 97 (3).

Methyl 2-Bromo-5-fluoro-4-hydroxybenzoate (3f)

General oxidation procedure was applied to methyl 2-bromo-5-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (**1f**; 358 mg, 1 mmol, 1 equiv) for 0.5 h; colorless solid; yield: 238 mg (96%); mp 148–151 °C; R_f = 0.6 (hexanes–EtOAc 1:1).

FT-IR (ATR): 3360, 3086, 2979, 1747, 1704, 1445, 1261, 1159, 892 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 11.25 (br s, 1 H, OH), 7.68 (d, *J* = 11.5 Hz, 1 H), 7.26 (s, *J* = 8.0 Hz, 1 H), 3.80 (s, 1 H, CH_3).

^{13}C NMR {^1H} (125 MHz, DMSO-d_6): δ = 164.3 (d, $^4J_{C,F}$ = 1.5 Hz, C), 149.5 (d, $^1J_{C,F}$ = 242.2 Hz, C), 149.2 (d, $^2J_{C,F}$ = 12.7 Hz, C), 122.7 (d, $^3J_{C,F}$ = 3.1 Hz, CH), 121.3 (d, $^3J_{C,F}$ = 5.7 Hz, C), 119.2 (d, $^2J_{C,F}$ = 21.1 Hz, CH), 116.3 (d, $^4J_{C,F}$ = 3.1 Hz, C), 52.3 (s, CH_3).

GC-MS (EI): *m*/*z* (%) = 250 [25, $(M + 2)^+$], 248 [26, $(M)^+$], 219 (100), 217 (95), 189 (11), 161 (6).

Methyl 2-Bromo-5-hydroxy-3-methylbenzoate (4a)

General oxidation procedure was applied to methyl 2-bromo-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (**2a**; 177 mg, 0.5 mmol, 1 equiv) for 0.5 h; colorless semi-solid; yield: 118 mg (97%); R_f = 0.7 (hexanes–EtOAc 1:1).

FT-IR (ATR): 3359, 2979, 1712, 1587, 1436, 1327, 1141, 980, 850, 672 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 9.97 (br s, 1 H, OH), 6.91 (dd, *J* = 3.0, 0.5 Hz, 1 H), 6.85 (dd, *J* = 2.5, 0.5 Hz, 1 H), 3.82 (s, 3 H, CH_3), 2.31 (s, 3 H, CH_3).

^{13}C NMR {^1H} (125 MHz, DMSO-d_6): δ = 167.1 (C=O), 156.3 (C), 140.0 (C), 134.7 (C), 120.2 (CH), 114.3 (CH), 110.0 (C), 52.5 CH_3), 23.2 (CH_3).

GC-MS (EI): *m*/*z* (%) = 246 [57, $(M + 2)^+$], 244 [60, $(M)^+$], 213 (100), 185 (25), 106 (7).

Methyl 2,3-Dichloro-5-hydroxybenzoate (4b)

General oxidation procedure was applied to methyl 2,3-dichloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (**2b**; 331 mg, 1 mmol, 1 equiv) for 0.5 h; colorless solid; yield: 202 mg (92%); mp 145–147 °C; R_f = 0.7 (hexanes–EtOAc 1:1).

FT-IR (ATR): 3304, 2953, 1704, 1589, 1456, 1413, 1311, 1241, 996, 949, 854, 778, 742, 630 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 10.55 (br s, 1 H, OH), 7.18 (d, *J* = 3.0 Hz, CH), 7.10 (d, *J* = 3.0 Hz, CH), 3.85 (s, 3 H, CH_3).

^{13}C NMR {^1H} (125 MHz, DMSO-d_6): δ = 165.1 (C=O), 156.6 (C), 133.24 (C), 133.17 (C), 119.8 (CH), 118.7 (C), 116.2 (CH), 52.8 (CH_3).

GC-MS (EI): *m*/*z* (%) = 222 [40, $(M + 2)^+$], 220 [64, $(M)^+$], 189 (100), 161 (16), 133 (10).

Ethyl 2,3-Dichloro-5-hydroxybenzoate (4c)

General oxidation procedure was applied to ethyl 2,3-dichloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (**2c**; 345 mg, 1 mmol, 1 equiv) for 20 min; colorless solid; yield: 215 mg (92%); mp 109–111 °C; R_f = 0.7 (hexanes–EtOAc 1:1).

FT-IR (ATR): 3388, 2992, 1702, 1606, 1568, 1434, 1398, 1368, 1284, 1220, 1022, 868, 780, 610 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 10.54 (br s, 1 H, OH), 7.18 (d, *J* = 3.0 Hz, CH), 7.09 (d, *J* = 3.0 Hz, CH), 4.31 (q, *J* = 7.0 Hz, 2 H, CH_2), 1.30 (t, *J* = 70 Hz, 3 H, CH_3).

^{13}C NMR {^1H} (125 MHz, DMSO-d_6): δ = 164.7 (C=O), 156.6 (C), 133.5 (C), 133.2 (C), 119.7 (CH), 118.6 (C), 116.1 (CH), 61.7 (CH_2), 13.1 (CH_3).

GC-MS (EI): *m*/*z* (%) = 236 [34, $(M + 2)^+$], 234 [56, $(M)^+$], 219 (8), 208 (35), 191 (11), 189 (100), 161 (17).

Methyl 2-Chloro-3-(trifluoromethyl)-5-hydroxybenzoate (4d)

General oxidation procedure was applied to methyl 2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)benzoate (**2d**; 365 mg, 1 mmol, 1 equiv) for 20 min; colorless semi-solid; yield: 240 mg (94%); R_f = 0.6 (hexanes–EtOAc 1:1).

FT-IR (ATR): 3385, 2980, 1729, 1434, 1352, 1136 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 10.78 (br s, 1 H, OH), 7.34 (s, 2 H, 2 × CH), 3.87 (s, 3 H, CH_3).

^{13}C NMR {^1H} (125 MHz, DMSO-d_6): δ = 165.0 (C=O), 153.4 (C), 134.8 (CH), 128.8 (q, $^2J_{C,F}$ = 30.5 Hz, C), 122.4 (q, $^1J_{C,F}$ = 271.6 Hz, CF_3), 120.2 (CH), 117.5 (C), 117.1 (q, $^3J_{C,F}$ = 5.4 Hz, C), 52.9 (CH_3).

GC-MS (EI): *m*/*z* (%) = 256 [11, $(M + 2)^+$], 254 (22, $(M)^+$], 225 (32), 223 (100), 195 (35), 132 (13).

Ethyl 2-Chloro-3-(trifluoromethyl)-5-hydroxybenzoate (4e)

General oxidation procedure was applied to ethyl 2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)benzoate (**2e**; 378 mg, 1 mmol, 1 equiv) for 0.5 h; colorless solid; yield: 233 mg (87%); mp 113–115 °C; R_f = 0.6 (hexanes–EtOAc 1:1).

FT-IR (ATR): 3389, 2986, 1700, 1589, 1438, 1376, 1316, 1257, 1136, 1021, 980, 888, 785, 696 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 10.78 (br s, 1 H, OH), 7.34 (d, *J* = 3.0 Hz, CH), 7.33 (d, *J* = 3.0 Hz, CH), 4.34 (q, *J* = 7.5 Hz, CH_2), 1.31 (t, *J* = 7.5 Hz, CH_3).

^{13}C NMR {^{1}H} (151 MHz, $CDCl_3$): δ = 166.1 (C=O), 154.2 (C), 134.6 (C), 130.9 (q, $^{2}J_{C,F}$ = 31.6 Hz, C), 122.2 (q, $^{1}J_{C,F}$ = 274.1 Hz, C), 121.9 (C), 120.3 (CH), 117.8 (q, $^{3}J_{C,F}$ = 5.4 Hz, CH), 62.7 (CH_2), 14.1 (CH_3).

GC-MS (EI): *m*/*z* (%) = 270 [8, $(M + 2)^+$], 268 [24, $(M)^+$], 240 (37), 223 (100), 195 (23).

Propyl 2-Chloro-3-(trifluoromethyl)-5-hydroxybenzoate (4f)

General oxidation procedure was applied to propyl 2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)benzoate (**2f**; 392 mg, 1 mmol, 1 equiv) for 20 min; colorless solid; yield: 231 mg (82%); mp 102–104 °C; R_f = 0.6 (hexanes–EtOAc 1:1).

FT-IR (ATR): 3383, 2979, 1702, 1614, 1590, 1439, 1317, 1258, 1231, 1190, 1144, 996, 956, 886, 783, 696, 671 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.79 (br s, 1 H, OH), 7.339 (s, 1 H, CH), 7.338 (s, 1 H, CH), 4.26 (t, *J* = 6.5 Hz, CH_2), 1.71 (m, CH_2), 0.96 (t, *J* = 7.0 Hz, CH_3).

^{13}C NMR {^{1}H}(151 MHz, $CDCl_3$): δ = 166.0 (C=O), 154.2 (C), 134.7 (C), 130.9 (q, $^{2}J_{C,F}$ = 31.4 Hz, C), 122.2 (q, $^{1}J_{C,F}$ = 273.9 Hz, C), 121.9 (C), 120.3 (CH), 117.8 (q, $^{3}J_{C,F}$ = 5.6 Hz, CH), 68.2 (CH_2), 21.9 (CH_2), 10.5 (CH_3).

GC-MS (EI): *m*/*z* (%) = 282 [18, $(M)^+$], 242 (25), 240 (58), 225 (31), 223 (100), 195 (44), 132 (36).

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Supporting Information

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