Synthesis of 3,5-Diaryl-4-fluorophthalates by [4+2]-Cycloaddition and Subsequent Site-Selective Suzuki–Miyaura Reactions

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Abstract: The [4+2] cycloaddition of 1-ethoxy-2-fluoro-1,3-bis(trimethylsilyloxy)-1,3-diene with dimethyl acetylenedicarboxylate (DMAD) afforded dimethyl 4-fluoro-3,5-dihydroxyphthalate. Site-selective Suzuki–Miyaura reactions of its bis(triflate) provide a convenient approach to 3,5-diaryl-4-fluorophthalates.

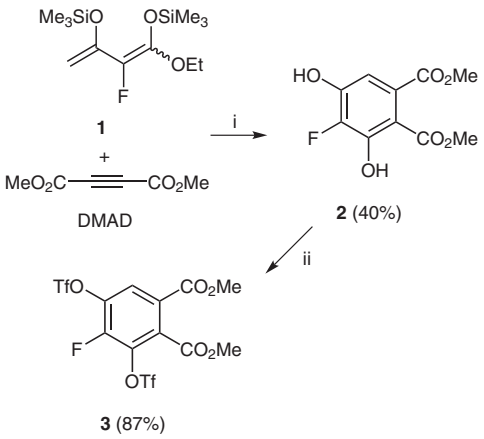
Key words: arenes, cyclizations, organofluorine compounds, site-selectivity, Suzuki–Miyaura reaction

In the last decade, we have witnessed a dramatic increase of the interest in organofluorine compounds because of their great pharmacological relevance.[1] While the size of the fluorine atom is relatively small, its high electronegativity often results in an improvement of drug-receptor interactions. Due to the chemical and biological stability of the carbon–fluorine bond, undesired metabolic transformations are rather rare and the transport of the drug in vivo is facilitated by the high lipophilicity of organofluorine compounds. Fluorinated arenes and heteroarenes are also versatile building blocks in transition-metal-catalyzed cross-coupling reactions.[2] In addition, organofluorine compounds, such as fluorinated thioureas, are used as organocatalysts[3] and ligands.[4]

Direct fluorination reactions of arenes often suffer from their low chemo- and regioselectivity. Multiple fluorination represents an additional drawback. Cyclization reactions of fluorinated building blocks provide a powerful alternative for the synthesis of fluorinated arenes and hetarenes. Schlosser et al. reported the synthesis of fluorinated arenes by Diels–Alder reactions of alkenes or alkynes with fluorinated 1,3-butadienes.[5] Portella et al. developed a versatile approach to fluorinated phenols from 2,2-difluoro-1,5-diketones.[6]

Recently, we studied the synthesis of fluorinated arenes and hetarenes based on formal [3+3] and [3+2] cyclizations of 1,3-bis(silyloxy)-1,3-butadienes.[7–9] Herein, we report, for the first time, the synthesis of dimethyl 4-fluoro-3,5-dihydroxyphthalate by [4+2] cycloaddition of 1-ethoxy-2-fluoro-1,3-bis(trimethylsilyloxy)-1,3-diene with dimethyl acetylenedicarboxylate (DMAD). Suzuki–Miyaura reactions of the bis(triflate) of this product proceeded with very good site-selectivity[10] and provided a convenient approach to novel 3,5-diaryl-4-fluorophthalates which are not readily available by other methods.

The [4+2] cycloaddition of 1-ethoxy-2-fluoro-1,3-bis(trimethylsilyloxy)-1,3-diene (**1**) with DMAD afforded dimethyl 4-fluoro-3,5-dihydroxyphthalate (**2**) in 40% yield (Scheme 1).[11] The latter was transformed into bis(triflate) **3** in high yield.[12] The structure of **2** was independently confirmed by X-ray crystal structure analysis (Figure 1).[13]



Scheme 1 Synthesis of **2** and **3**. *Reagents and conditions*: (i) (1) **1** (1.0 equiv), DMAD (1.5 equiv), –78 °C → 20 °C, 20 h; (2) HCl (10%); (ii) (1) **2** (1.0 equiv), pyridine (4.0 equiv), CH_2Cl_2, –78 °C, 10 min; (2) Tf_2O (2.4 equiv), –78 °C → 0 °C, 4 h.

The Suzuki reaction of **3** with boronic acids **4a–f** (2.3 equiv) afforded the novel 3,5-diaryl-4-fluorophthalates **5a–f** in good yields (Scheme 2, Table 1). The best yields were obtained when $Pd(PPh_3)_4$ (3 mol%) was used as the catalyst, when 2.3 equivalents of the boronic acid was employed, and when the reaction was carried out in 1,4-dioxane (110 °C, 8 h) using K_3PO_4 as the base.[14,15]

The Suzuki–Miyaura reaction of **3** with arylboronic acids **4a**,**g–l** (1.1 equiv) afforded the 5-aryl-4-fluorophthalates **6a–g** in good yields and with very good site-selectivity (Scheme 3, Table 2).[16] The formation of the opposite regioisomers was not observed.

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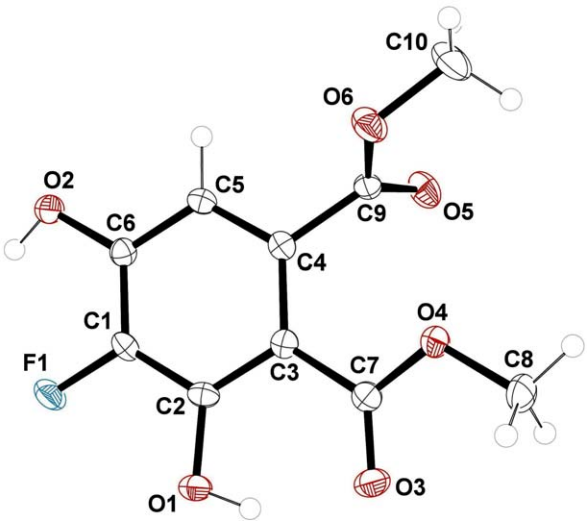
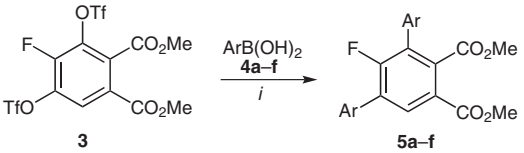


Figure 1 Crystal structure of **2**

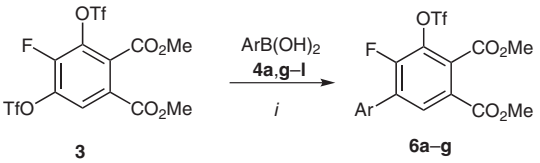


Scheme 2 Synthesis of **5a–f**. *Reagents and conditions*: (i) **3** (1.0 equiv), **4a–f** (2.3 equiv), K_3PO_4 (3.0 equiv), $Pd(PPh_3)_4$ (3 mol%), 1,4-dioxane, 110 °C, 8 h.

Table 1 Synthesis of **5a–f**

4,**5**	Ar	**5** (%)[a]
a	4-$(CF_3)C_6H_4$	67
b	Ph	83
c	4-ClC_6H_4	75
d	3-ClC_6H_4	63
e	4-EtC_6H_4	72
f	3,5-$Me_2C_6H_3$	77

[a] Yields of isolated products.



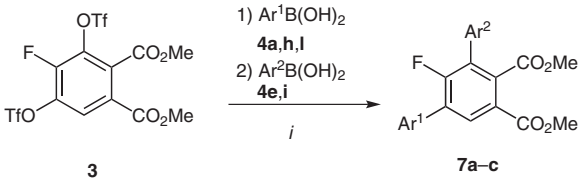
Scheme 3 Synthesis of **6a–g**. *Reagents and conditions*: (i) **3** (1.0 equiv), **4a**,**g–l** (1.1 equiv), K_3PO_4 (1.5 equiv), $Pd(PPh_3)_4$ (3 mol%), 1,4-dioxane, 90 °C, 9 h.

3,5-Diaryl-4-fluorophthalates **7a–c**, containing two different aryl groups, were prepared directly from bis(triflate) **3** by application of a one-pot procedure (Scheme 4, Table 3). The Suzuki reaction of **3** with arylboronic acids

Table 2 Synthesis of **6a–g**

4	**6**	Ar	**6** (%)[a]
g	**a**	2-$(CF_3)C_6H_4$	59
h	**b**	3-FC_6H_4	71
i	**c**	3,4-$(MeO)_2C_6H_3$	56
a	**d**	4-$(CF_3)C_6H_4$	68
j	**e**	3,5-$Me_2C_6H_3$	75
k	**f**	3-$(CF_3)C_6H_4$	57
l	**g**	2-$(EtO)C_6H_4$	60

[a] Yields of isolated products.



Scheme 4 Synthesis of **7a–c**. *Reagents and conditions*: (1) **3** (1.0 equiv), **4a**,**h**,**l** (1.1 equiv), K_3PO_4 (1.5 equiv), $Pd(PPh_3)_4$ (3 mol%), 1,4-dioxane, 90 °C, 9 h; (2) **4e**,**i** (1.3 equiv), K_3PO_4 (1.5 equiv), 110 °C, 6 h.

Table 3 Synthesis of **7a–c**

4	**7**	Ar^1	Ar^2	**7** (%)[a]
a,**i**	**a**	4-$(CF_3)C_6H_6$	3,4-$(MeO)_2C_6H_3$	51
h,**i**	**b**	3-FC_6H_6	3,4-$(MeO)_2C_6H_3$	49
l,**e**	**c**	2-$(EtO)C_6H_4$	4-EtC_6H_4	58

[a] Yields of isolated products.

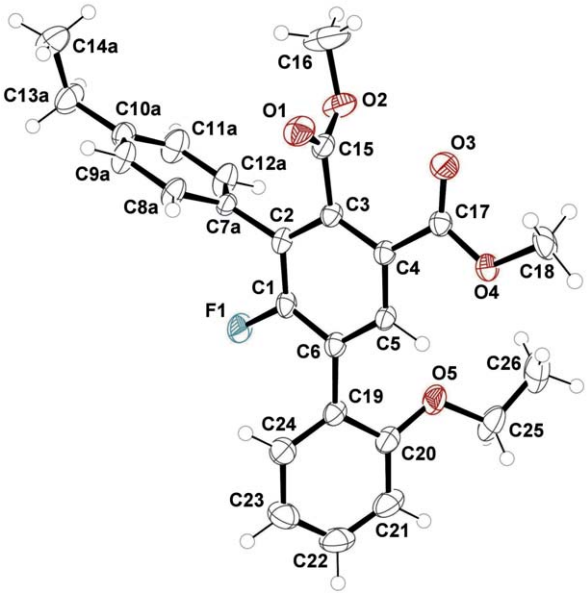


Figure 2 Crystal structure of **7c**

4a,**h**,**l** (1.1 equiv, 90 °C) and subsequent addition of arylboronic acids **4e**,**i** (1.3 equiv, 110 °C) to the in situ formed monocoupling product afforded products **7a–c** in acceptable yields.[17,18]

The structure of products **6** and **7** were established by 2D NMR experiments (NOESY, HMBC). The structure of **7c** was independently confirmed by X-ray crystal structure analysis (Figure 2).[13]

In conclusion, we have reported the synthesis of dimethyl 4-fluoro-3,5-dihydroxyphthalate by [4+2] cycloaddition of 1-ethoxy-2-fluoro-1,3-bis(trimethylsilyloxy)-1,3-diene with dimethyl acetylenedicarboxylate (DMAD). Site-selective Suzuki–Miyaura reactions of the bis(triflate) of dimethyl 4-fluoro-3,5-dihydroxyphthalate provide a convenient approach to 3,5-diaryl-4-fluorophthalates.

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(11) **Synthesis of Dimethyl 4-Fluoro-3,5-dihydroxyphthalate (2)**: Diene **1** (9.0 g, 30.8 mmol) was added to DMAD (6.5 g, 5.5 mL, 46.2 mmol) at –78 °C. The mixture(neat) was allowed to warm to 20 °C during 20 h with stirring. To the mixture were added hydrochloric acid (10%) and dichloromethane (50 mL each). The organic and the aqueous layer 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 to give **2** as a crystalline colorless solid (3.0 g, 40%); mp 140–142 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.87 (s, 3 H, OMe), 3.90 (s, 3 H, OMe), 6.15 (s, 1 H, OH), 6.60 (d, 1 H, J_{FH} = 7.5 Hz, ArH), 10.96 (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.8 (OMe), 53.0 (OMe), 104.6 (C), 108.4 (CH), 131.6 (d, J_{FC} = 4.5 Hz, C), 140.5 (d, J_{FC} = 239 Hz, CF), 148.3 (d, J_{FC} = 11.7 Hz, COH), 151.1 (d, J_{FC} = 11.0 Hz, COH), 168.6 (C=O), 168.8 (d, J_{FC} = 3.0 Hz, C=O). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –160.80 (F). IR (ATR): 3292 (m), 2962 (w), 2859 (w), 1716 (s), 1682 (s), 1621 (s), 1599 (s), 1515 (w), 1434 (s), 1325 (s), 1236 (s), 1093 (s), 933 (w) cm^{-1}. GC–MS (EI, 70 eV): *m/z* (%) = 244 (24) [M$^+$], 212 (53), 181 (11), 154 (100), 137 (4), 126 (12), 97 (9). HRMS (EI): *m/z* [M$^+$] calcd for $C_{10}H_9O_6F$: 244.03777; found: 244.037617.

(12) **Dimethyl 4-Fluoro-3,5-bis(trifluoromethylsulfonyloxy)-phthalate (3)**: To a solution of **2** (1.0 equiv) in CH_2Cl_2 (10 mL/mmol) was added pyridine (4.0 equiv) at – 78 °C under an argon atmosphere. After 10 min, Tf_2O (2.4 equiv) was added at –78 °C. The mixture was allowed to warm up to 0 °C and stirred for 4 h. The reaction mixture was filtered and

the filtrate was concentrated in vacuo. The products of the reaction mixture were isolated by rapid column chromatography (flash silica gel, heptanes–EtOAc). Starting with **2** (2.00 g, 8.0 mmol), pyridine (2.6 mL, 32.0 mmol), CH_2Cl_2 (80 mL), Tf_2O (3.2 mL, 19.2 mmol), **3** was isolated as a viscous colorless liquid (3.54 g, 87%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.87 (s, 3 H, OMe), 3.90 (s, 3 H, OMe), 7.96 (d, $^4J_{FH}$ = 6.4 Hz, 1 H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.6 (OMe), 52.7 (OMe), 117.5 (q, $^1J_{CF}$ = 321 Hz, CF_3), 117.6 (q, $^1J_{CF}$ = 321 Hz, CF_3), 124.3 (br s, CH), 124.9 (d, $^3J_{FC}$ = 5.0 Hz, C), 130.9 (C), 133.8 (d, $^2J_{FC}$ = 13.2 Hz, C), 136.7 (d, ^2J = 12.2 Hz, C), 148.0 (d, ^1J = 268 Hz, CF), 161 (CO), 161.4 (d, $^4J_{FC}$ = 1.6 Hz, CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = 129.34, –72.81 (d, $^5J_{FCF3}$ = 5.1 Hz, CF_3), –72.51 (d, $^5J_{FCF3}$ = 14.31 Hz, CF_3). IR (ATR): 2960 (w), 2922 (w), 1739 (s), 1616 (w), 1595 (w), 1502 (w), 1426 (s), 1326 (m), 1209 (s), 1128 (m), 1045 (m), 1011 (s), 971 (s), 887 (m), 821 (m), 787 (s), 750 (m), 736 (m), 650 (w), 601 (s) cm^{-1}. GC–MS (70 eV): *m/z* (%) = 510 (1) [M$^+$ + 2], 509 (2) [M$^+$ + 1], 508 (12) [M$^+$], 477 (100), 439 (5), 413 (44), 349 (52), 283 (33), 253 (6), 222 (19), 183 (16), 155 (14), 127 (4), 81 (8), 69 (63), 59 (15), 45 (4). HRMS (EI): *m/z* [M$^+$] calcd for $C_{12}H_7O_{10}F_7S_2$: 507.93634; found: 507.936470.

(13) CCDC 753087 and CCDC 753088 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(14) **General Procedure for Suzuki–Miyaura Reactions**: A 1,4-dioxane solution (4 mL per 3 mmol of **3**) of **3**, K_3PO_4, $Pd(PPh_3)_4$ and arylboronic acid **4** was stirred at 110 °C or 90 °C for 8 h. After cooling to 20 °C, a saturated aqueous solution of NH_4Cl 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.

(15) **Dimethyl 4-Fluoro-3,5-di(4-ethylphenyl)phthalate (5e)**: Starting with **3** (152 mg, 0.3 mmol), K_3PO_4 (191 mg, 0.9 mmol), $Pd(PPh_3)_4$ (3 mol%), 4-ethylphenylboronic acid (105 mg, 0.7 mmol) and 1,4-dioxane (4 mL), **5e** was isolated as a colorless solid (91 mg, 72%); mp 151–153 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (t, *J* = 7.5 Hz, 3 H, Me), 1.20 (t, *J* = 7.5 Hz, 3 H, Me), 2.62 (q, *J* = 7.6 Hz, 2 H, CH_2), 2.63 (q, *J* = 7.6 Hz, 2 H, CH_2), 3.56 (s, 3 H, OMe), 3.83 (s, 3 H, OMe), 7.16–7.23 (m, 9 H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.3, 15.5 (2 × Me), 28.6 (2 × CH_2), 52.4 (OMe), 52.6 (OMe), 123.6 (d, $^3J_{CF}$ = 4.4 Hz, C), 127.7 (2 × CH), 128.2 (2 × CH), 129.0 (d, $^4J_{CF}$ = 2.8 Hz, 2 × CH), 129.3 (C), 129.6 (d, $^4J_{FC}$ = 1.2 Hz, 2 × CH), 130.2 (d, $^2J_{FC}$ = 15.9 Hz, C), 131.5 (C), 131.9 (d, $^3J_{FC}$ = 5.5 Hz, CH), 136.6 (d, $^4J_{FC}$ = 3.8 Hz, C), 144.7 (d, $^2J_{FC}$ = 23.7 Hz, C), 159.1 (d, $^1J_{FC}$ = 256 Hz, CF), 165.4 (CO), 167.9 (d, $^4J_{FC}$ = 2.7 Hz, CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –111.4. IR (ATR): 3037 (w), 3002 (w), 2961 (m), 2947 (m), 2931 (m), 2671 (w), 1739 (m), 1717 (s), 1613 (w), 1514 (m), 1429 (m), 1396 (m), 1345 (m), 1274 (m), 1247 (m), 1219 (s), 1146 (m), 1118 (m), 1069 (m), 1020 (m), 1003 (m), 968 (m), 848 (m), 835 (m), 794 (m), 683 (m), 575 (m), 531 (m) cm^{-1}. GC–MS (70 eV): *m/z* (%) = 421 (28) [M$^+$ + 1], 420 (100) [M$^+$], 405 (20), 389 (52), 373 (3), 357 (18), 329 (7), 315 (2), 301 (4), 287 (5), 273 (6), 272 (5), 259 (4), 257 (6), 252 (2), 244 (3), 195 (7), 170 (2), 143 (3), 135 (3), 129 (2), 77 (1), 59 (1), 29 (2). HRMS (EI): *m/z* [M$^+$] calcd for $C_{26}H_{25}O_4F$: 420.17314: found: 420.173423.

(16) **Dimethyl 4-Fluoro-5-(3,5-dimethylphenyl)-3-(trifluoromethylsulfonyloxy)phthalate (6e)**: Starting with **3** (152 mg, 0.3 mmol), K_3PO_4 (95 mg, 0.45 mmol), $Pd(PPh_3)_4$ (3 mol%), 3,5-dimethylphenylboronic acid (50 mg, 0.33 mmol) and 1,4-dioxane (4 mL), **6e** was isolated as a colorless solid (104 mg, 75%); mp 79–80 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.31 (br s, 6 H, 2 × Me), 3.85 (s, 3 H, OMe), 3.92 (s, 3 H, OMe), 7.02 (s, 1 H, ArH), 7.06 (s, 2 H, ArH), 8.01 (d, $^4J_{FH}$ = 6.6 Hz, 1 H, ArH). ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 20.3 (2 × Me), 52.1 (OMe), 52.3 (OMe), 117.5 (q, $^1J_{CF}$ = 321 Hz, CF_3), 124.4 (d, $^3J_{FC}$ = 4.4 Hz, C), 125.6 (d, $^4J_{FC}$ = 2.75, 2 × CH), 128.8 (C), 130.1 (CH), 130.9 (d, $^3J_{FC}$ = 4.6 Hz, CH), 131.1 (d, ^4J = 1.8 Hz, C), 131.9 (d, ^2J = 13.0 Hz, C), 133.3 (d, $^2J_{F,C}$ = 17.0 Hz, C), 137.6 (s, 2 × C), 152.3 (d, $^1J_{FC}$ = 261 Hz, C), 162.7 (d, $^4J_{FC}$ = 2.7 Hz, CO). 163.1 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –72.58 (d, *J* = 13.4 Hz, CF_3), –122.34 (q, *J* = 13.4 Hz, ArF). IR (ATR): 2959 (w), 2921 (w), 1737 (s), 1729 (s), 1620 (w), 1602 (w), 1495 (w), 1428 (s), 1408 (m), 1343 (m), 1275 (s), 1205 (s), 1133 (m), 1006 (m), 945 (m), 854 (m), 813 (s), 757 (m), 731 (m), 598 (s), 532 (s) cm^{-1}. GC–MS (70 eV): *m/z* (%) = 466 (8) [M$^+$ + 2], 465 (21) [M$^+$ + 1], 464 (100) [M$^+$], 433 (35), 395 (2), 369 (16), 331 (6), 303 (10), 272 (9), 242 (15), 214 (10), 185 (6), 160 (7), 99 (1), 69 (5), 59 (2). HRMS (ESI, +ve): *m/z* [M + H]$^+$ calcd for $C_{19}H_{17}F_4O_7S$: 465.06256; found: 465.06268.

(17) **General Procedure for the Synthesis of 7a–c**: The reaction was carried out in a pressure tube. To a dioxane suspension (4 mL) of **3** (228 mg, 0.45 mmol), $Pd(PPh_3)_4$ (3 mol%) and $Ar^1B(OH)_2$ (0.5 mmol) was added K_3PO_4 (143 mg, 0.67 mmol), and the resultant solution was degassed by bubbling argon through the solution for 10 min. The mixture was heated at 90 °C under an argon atmosphere for 9 h. The mixture was cooled to 20 °C. $Ar^2B(OH)_2$ (0.6 mmol) and K_3PO_4 (143 mg, 0.67 mmol) were added. The reaction mixtures were heated under an argon atmosphere for 6 h at 110 °C. They were diluted with H_2O and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (silica gel, EtOAc–heptanes).

(18) **Dimethyl 4-Fluoro-5-(2-ethoxyphenyl)-3-(4-ethylphenyl)-phthalate (7c)**: Starting with **3** (228 mg, 0.45 mmol), K_3PO_4 (286 mg, 1.34 mmol), $Pd(PPh_3)_4$ (3 mol%), 2-ethoxyphenylboronic acid (82 mg, 0.5 mmol), 1,4-dioxane (4 mL), and 4-ethylphenylboronic acid (85 mg, 0.6 mmol), **7c** was isolated as transparent crystals (114 mg, 58%); mp 104–106 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15–1.25 (m, 6 H, 2 × Me), 2.61 (q, *J* = 7.5 Hz, 2 H, CH_2), 3.57 (s, 3 H, OMe), 3.78 (s, 3 H, OMe), 3.95 (q, ^3J = 7.0 Hz, 2 H, OCH_2), 6.87 (d, *J* = 8.4 Hz, 1 H, ArH), 6.93 (dt, *J* = 7.5 Hz, 1 H, ArH), 7.14–7.30 (m, 6 H, ArH), 7.98 (d, $^4J_{FH}$ = 6.7 Hz, 1 H, ArH). ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 14.7 (Me), 15.2 (Me), 28.6 (CH_2), 52.3 (OMe), 52.5 (OMe), 64.0 (OCH_2), 112.1, 120.5 (2 × CH), 123.7 (C), 127.6 (2 × CH), 127.8 (d, $^2J_{FC}$ = 19.0 Hz, C), 128.5 (d, ^2J = 20.7 Hz, C), 129.4, 129.5, 130.1 (3 × CH), 131.0 (d, ^4J = 1.4 Hz, CH), 133.3 (d, $^3J_{F,C}$ = 5.6 Hz, CH), 136.8 (d, $^3J_{F,C}$ = 4.1 Hz, C), 144.3, 156.3 (2 × C), 159.6 (d, $^1J_{FC}$ = 256 Hz, CF), 165.5 (C=O), 168.1 (d, ^4J = 2.7 Hz, C=O). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –106.42 (CF). IR (ATR): 2973 (w), 2944 (w), 2929 (w), 2881 (w), 1724 (br s), 1609 (w), 1580 (w), 1563 (w), 1516 (w), 1497 (m), 1451 (m), 1428 (m), 1390 (m), 1341 (m), 1273 (s), 1249 (s), 1215 (s), 1149 (s), 1123 (m), 1067 (m), 1041 (s), 969 (m), 919 (m), 858 (w), 839 (w), 793 (m), 754 (s), 689 (m), 611 (m), 537 (w) cm^{-1}. GC–MS (70 eV): *m/z* (%) = 438 (5) [M$^+$ + 2], 437 (30) [M$^+$ +1], 436 (100) [M$^+$], 405 (19), 376 (30), 361 (16), 348 (20), 317 (20), 289 (9), 271 (9), 244 (5), 171 (3), 151 (2), 128 (2), 59 (2), 29 (4). HRMS (EI): *m/z* [M$^+$] calcd for $C_{26}H_{25}FO_5$: 436.16805; found: 436.168135.