One-Pot Synthesis of Difluorinated *ortho*-Terphenyls by Site-Selective Suzuki–Miyaura Reactions of 1,2-Dibromo-3,5-difluorobenzene

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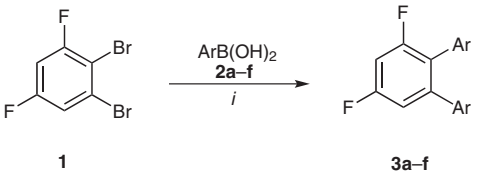
Abstract: The Suzuki–Miyaura reaction of 1,2-dibromo-3,5-difluorobenzene with two equivalents of arylboronic acids gave difluorinated *ortho*-terphenyls. The reaction with one equivalent of arylboronic acid resulted in site-selective formation of 2-bromo-3,5-difluoro-biphenyls. The one-pot reaction of 1,2-dibromo-3,5-difluorobenzene with two different arylboronic acids afforded difluorinated *ortho*-terphenyls containing two different terminal aryl groups.

Key words: catalysis, palladium, Suzuki–Miyaura reaction, site selectivity, organofluorine compounds

Fluorinated arenes have found widespread applications in medicinal chemistry and crop protection.[1] While no fluorine containing drug had been developed until 1957, more than 150 fluorinated drugs have come to market since then and now constitute approx. 20% of all pharmaceuticals,[2] with even higher figures for agrochemicals (up to 30%).[3] The strategic use of fluorine substitution in drug design has culminated with the production of some of the key drugs available on the market.[4] The fluorine atom combines a high electronegativity with a small size which often results in an improvement of drug–receptor interactions. Aryl fluorides are more stable towards undesired metabolic transformations than the corresponding unsubstituted arenes, due to the high biological stability of the carbon–fluorine bond. In addition, the transport of the drug 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.[5] Last but not the least, organofluorine compounds are used as ligands[6] in catalytic reactions and as organocatalysts.[7]

In recent years, a number of site-selective palladium(0)-catalyzed cross-coupling reactions of polyhalogenated heterocycles have been developed. The site selectivity of these reactions is generally influenced by electronic and steric parameters.[8] We have reported site-selective Suzuki–Miyaura (S–M) reactions of tetrabrominated thiophene, *N*-methylpyrrole, selenophene, and of other polyhalogenated heterocycles.[9] Site-selective S–M reactions of the bis(triflate) of methyl 2,5-dihydroxybenzoate have also been studied.[10] Site-selective palladium(0)-catalyzed cross-coupling reactions of dibromides, diiodides, or bis(triflates) of fluorinated arenes have, to the best of our knowledge, not been reported to date. Herein, we report first results of our study related to S–M reactions of 1,2-dibromo-3,5-difluorobenzene. The products, difluorinated *ortho*-terphenyls, are not readily available by other methods.

The S–M reaction of commercially available 1,2-dibromo-3,5-difluorobenzene (**1**) with two equivalents of arylboronic acids **2a–f** afforded the difluorinated *ortho*-terphenyls **3a–f** in moderate to good yields (Scheme 1, Table 1). The best yields were obtained using 2.2 equivalents of the arylboronic acid, $Pd(PPh_3)_4$ (0.03 equiv) as the catalyst, and Cs_2CO_3 (2.2 equiv) as the base (1,4-dioxane, 90 °C, 8 h).[11,12]



1 3a–f

Scheme 1 Synthesis of **3a–f**. *Reagents and conditions*: *i*, **1** (1.0 equiv), **2a–f** (2.2 equiv), Cs_2CO_3 (2.2 equiv), $Pd(PPh_3)_4$ (3 mol%), 1,4-dioxane, 90 °C, 8 h.

Table 1 Synthesis of **3a–f**

2, **3**	Ar	Yield of **3** (%)[a]
a	4-$MeOC_6H_4$	70
b	4-$EtOC_6H_4$	68
c	4-MeC_6H_4	45
d	2,4-$(MeO)_2C_6H_3$	58
e	2,6-$(MeO)_2C_6H_3$	65
f	2-$MeOC_6H_4$	60

[a] Yields of isolated products.

The S–M reaction of **1** with arylboronic acids **2a–g** (1.0 equiv) afforded the 2-bromo-3,5-difluoro-biphenyls **4a–g** in good yields and with very good site selectivity (Scheme 2, Table 2).[11,13] The formation of the opposite regioisomers was not observed.

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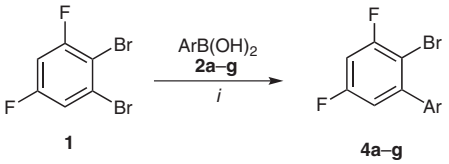


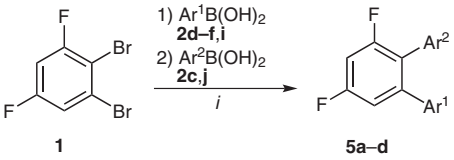
Scheme 2 Synthesis of **4a–g**. *Reagents and conditions*: *i*, **1** (1.0 equiv), **4a–g** (1.0 equiv), Cs_2CO_3 (1.5 equiv), $Pd(PPh_3)_4$ (3 mol%), 1,4-dioxane, 90 °C, 9 h.

Table 2 Synthesis of **4a–g**

2, 4	Ar	Yield of **4** (%)[a]
a	4-$MeOC_6H_4$	60
b	4-$EtOC_6H_4$	65
c	4-MeC_6H_4	45
d	2,4-$(MeO)_2C_6H_3$	67
e	2,6-$(MeO)_2C_6H_3$	68
f	2-$MeOC_6H_4$	60
g	3,4-$(MeO)_2C_6H_3$	60

[a] Yields of isolated products.

The one-pot reaction of 1,2-dibromo-3,5-difluorobenzene with two different arylboronic acids afforded the unsymmetrical difluorinated *ortho*-terphenyls **5a–d** containing two different terminal aryl groups (Scheme 3, Table 3).[14,15]



Scheme 3 One-pot synthesis of **5a–d**. *Reagents and conditions:* 1) **1** (1.0 equiv), **2d–f,i** (1.0 equiv), Cs_2CO_3 (1.5 equiv), $Pd(PPh_3)_4$ (3 mol%), 1,4-dioxane, 90 °C, 8 h; 2) **2c,j** (1.2 equiv), Cs_2CO_3 (1.5 equiv), 90 °C, 8 h.

Table 3 Synthesis of **5a–d**

2	5	Ar^1	Ar^2	Yield of **5** (%)[a]
d,**c**	**a**	2,4-$(MeO)_2C_6H_3$	4-MeC_6H_4	48
e,**c**	**b**	2,6-$(MeO)_2C_6H_3$	4-MeC_6H_4	60
f,**c**	**c**	2-$MeOC_6H_4$	4-MeC_6H_4	62
i,**j**	**d**	4-FC_6H_4	4-ClC_6H_4	45

[a] Yields of isolated products.

The structures of all products were established by 2D NMR experiments (NOESY, HMBC). The structures of **4e** and **3c** were independently confirmed by X-ray crystal-structure analyses (Figure 1 and Figure 2).[16]

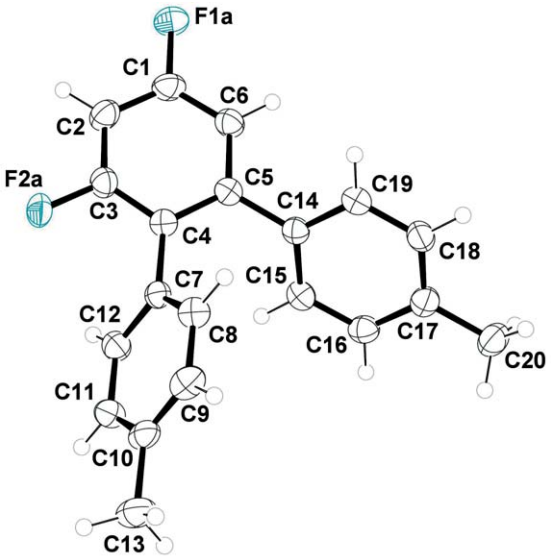


Figure 1 Crystal structure of **3c**

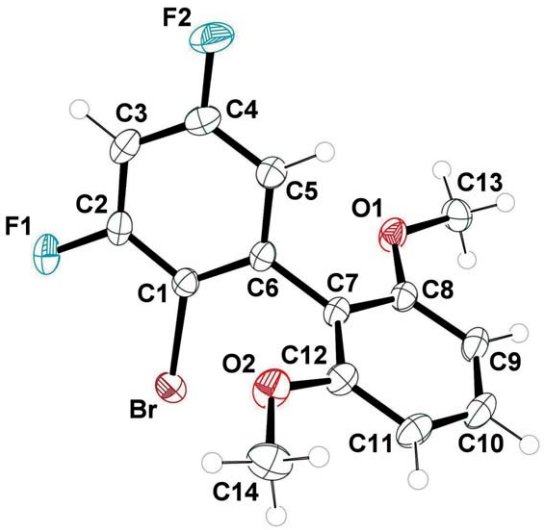


Figure 2 Crystal structure of **4e**

The site-selective formation of **4a–g** and **5a–d** can be explained by steric and by electronic reasons. The first attack of palladium(0)-catalyzed cross-coupling reactions generally occurs at the more electron-deficient and sterically less hindered position.[8,17] Position 1 of 1,2-dibromo-3,5-difluorobenzene (**1**) is sterically less hindered because it is located next to a bromine and to a hydrogen atom while position 2 is located next to a bromine and to a fluorine atom (Figure 3). In addition, position 1 (located *meta* to the fluorine atoms) is considerably more electron-deficient than position 2 (located *ortho* and *para* to the fluorine atoms), due to the π-donating effect of the fluorine atom. In fact, the ^1H NMR signals of aromatic protons located *ortho* or *para* to a fluorine atom are generally shifted to higher field compared to the proton located in *meta* position.[17]

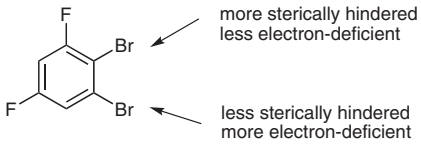


Figure 3 Possible explanation for the site selectivity of cross-coupling reactions of **1**

In conclusion, we have reported site-selective Suzuki–Miyaura reactions of 1,2-dibromo-3,5-difluorobenzene which provide a convenient approach to difluorinated *ortho*-terphenyls and 2-bromo-3,5-difluoro-biphenyls. The application of the concept outlined herein to other fluorinated arenes is currently studied in our laboratories.

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References and Notes

(1) (a) *Fluorine in Bioorganic Chemistry*; Filler, R.; Kobayasi, Y.; Yagupolskii, L. M., Eds.; Elsevier: Amsterdam, **1993**. (b) Filler, R. *Fluorine Containing Drugs in Organofluorine Chemicals and their Industrial Application*; Pergamon: New York, **1979**, Chap. 6. (c) Hudlicky, M. *Chemistry of Organic Compounds*; Ellis Horwood: Chichester, **1992**. (d) Kirsch, P. *Modern Fluoroorganic Chemistry*; VCH: Weinheim, **2004**. (e) Chambers, R. D. *Fluorine in Organic Chemistry*; Blackwell Publishing CRC Press: Boca Raton, **2004**. See also: (f) Ryckmanns, T.; Balancon, L.; Berton, O.; Genicot, C.; Lamberty, Y.; Lallemand, B.; Passau, P.; Pirlot, N.; Quéré, L.; Talaga, P. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 261. (g) Malamas, M. S.; Sredy, J.; Moxham, C.; Katz, A.; Xu, W.; McDevitt, R.; Adebayo, F. O.; Sawicki, D. R.; Seestaller, L.; Sullivan, D.; Taylor, J. R. *J. Med. Chem.* **2000**, *43*, 1293. (h) Ciha, A. J.; Ruminski, P. G. *J. Agric. Food Chem.* **1991**, *39*, 2072. (i) Albrecht, H. A.; Beskid, G.; Georgopapadakou, N. H.; Keith, D. D.; Konzelmann, F. M.; Pruess, D. L.; Rossman, P. L.; Wei, C. C.; Christenson, J. G. *J. Med. Chem.* **1991**, *34*, 2857. (j) Albrecht, H. A.; Beskid, G.; Christenson, J. G.; Deitcher, K. H.; Georgopapadakou, N. H.; Keith, D. D.; Konzelmann, F. M.; Pruess, D. L.; Wie, C. C. *J. Med. Chem.* **1994**, *37*, 400. (k) Song, C. W.; Lee, K. Y.; Kim, C. D.; Chang, T.-M.; Chey, W. Y. *J. Pharmacol. Exp. Ther.* **1997**, *281*, 1312. (l) De Voss, J. J.; Sui, Z.; DeCamp, D. L.; Salto, R.; Babe, L. M.; Craik, C. S.; Ortiz de Montellano, P. R. *J. Med. Chem.* **1994**, *37*, 665. (m) Anjaiah, S.; Chandrasekhar, S.; Gree, R. *Adv. Synth. Catal.* **2004**, *346*, 1329. (n) Iorio, M. A.; Paszkowska, R. T.; Frigeni, V. *J. Med. Chem.* **1987**, *30*, 1906. (o) Popp, J. L.; Musza, L. L.; Barrow, C. J.; Rudewicz, P. J.; Houck, D. R. *J. Antibiot.* **1994**, *47*, 411. (p) Chen, T. S.; Petuch, B.; MacConnell, J.; White, R.; Dezeny, G. *J. Antibiot.* **1994**, *47*, 1290. (q) Lam, K. S.; Schroeder, D. R.; Veitch, J. M. J. M.; Colson, K. L.; Matson, J. A.; Rose, W. C.; Doyle, T. W.; Forenza, S. *J. Antibiot.* **2001**, *54*, 1. (r) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.

(2) Bégué, J. P.; Bonnet-Delpon, D. *J. Fluorine Chem.* **2006**, *127*, 992.

(3) Isanbor, C.; O'Hagan, D. *J. Fluorine Chem.* **2006**, *127*, 303.

(4) Beller, M.; Neumann, H.; Anbarasan, P. *Angew. Chem. Int. Ed.* **2009**, *48*, 1.

(5) *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A.; Diederich, F., Eds.; Wiley-VCH: Weinheim, **2004**.

(6) (a) Schmidbaur, H.; Kumberger, O. *Chem. Ber.* **1993**, *126*, 3. (b) Dinger, M. B.; Henderson, W. *J. Organomet. Chem.* **1998**, *560*, 233. (c) Liedtke, J.; Loss, S.; Widauer, C.; Grützmacher, H. *Tetrahedron* **2000**, *56*, 143. (d) Schneider, S.; Tzschucke, C. C.; Bannwarth, W. *Multiphase Homogeneous Catalysis*; Cornils, B.; Herrmann, W. A.; Horvath, I. T.; Leitner, W.; Mecking, S.; Olivier-Booubigou, H.; Vogt, D., Eds.; Wiley-VCH: Weinheim, **2005**, Chap. 4, 346. (e) Clarke, D.; Ali, M. A.; Clifford, A. A.; Parratt, A.; Rose, P.; Schwinn, D.; Bannwarth, W.; Rayner, C. M. *Curr. Top. Med. Chem.* **2004**, *7*, 729.

(7) Reviews: (a) Wittkopp, A.; Schreiner, P. R. *The Chemistry of Dienes and Polyenes*, Vol. 2; John Wiley and Sons: Chichester, **2000**. (b) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289. See also: (c) Wittkopp, A.; Schreiner, P. R. *Chem. Eur. J.* **2003**, *9*, 407. (d) Kleiner, C. M.; Schreiner, P. R. *Chem. Commun.* **2006**, 4315. (e) Kotke, M.; Schreiner, P. R. *Synthesis* **2007**, 779. Review: (f) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701.

(8) For reviews of cross-coupling reactions of polyhalogenated heterocycles, see: (a) Schröter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, *61*, 2245. (b) Schnürch, M.; Flasik, R.; Khan, A. F.; Spina, M.; Mihovilovic, M. D.; Stanetty, P. *Eur. J. Org. Chem.* **2006**, 3283.

(9) (a) Dang, T. T.; Dang, T. T.; Rasool, N.; Villinger, A.; Langer, P. *Adv. Synth. Catal.* **2009**, *351*, 1595. (b) Dang, T. T.; Dang, T. T.; Ahmad, R.; Reinke, H.; Langer, P. *Tetrahedron Lett.* **2008**, *49*, 1698. (c) Dang, T. T.; Villinger, A.; Langer, P. *Adv. Synth. Catal.* **2008**, *350*, 2109. (d) Hussain, M.; Dang, T. T.; Langer, P. *Synlett* **2009**, 1822.

(10) Nawaz, M.; Farooq, M. I.; Obaid-Ur-Rahman, A.; Khera, R. A.; Villinger, A.; Langer, P. *Synlett* **2010**, 150.

(11) **General Procedure for Suzuki Reactions**
A 1,4-dioxane solution (4 mL per 0.3 mmol of **1**) of **1**, Cs_2CO_3, $Pd(PPh_3)_4$, and arylboronic acid **2** was stirred at 90 °C for 6 or 8 h. After cooling to r.t. 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.

(12) **1,2-Di(2-Methoxyphenyl)-3,5-difluorobenzene (3f)**
Starting with **1** (100 mg, 0.37 mmol), Cs_2CO_3 (263 mg, 0.81 mmol), $Pd(PPh_3)_4$ (3 mol%), 2-methoxyphenylboronic acid (123 mg, 0.81 mmol), and 1,4-dioxane (4 mL), **3f** was isolated as a colorless solid (72 mg, 60%), mp 111–113 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.42 (s, 3 H, OCH_3), 3.55 (s, 3 H, OCH_3), 6.60 (dd, *J* = 8.3, 0.7 Hz, 1 H, ArH), 6.67–6.88 (m, 6 H, ArH), 6.94 (dd, *J* = 7.5, 1.7 Hz, 1 H, ArH), 7.05–7.12 (m, 2 H, ArH). ^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 54.9 (OCH_3), 55.2 (OCH_3), 102.6 (t, $^2J_{CF}$ = 26.5 Hz, CH), 110.2 (CH), 110.3 (CH), 113.2 (dd, J_{CF} = 21.2, 3.5 Hz, CH), 119.7 (CH), 119.9 (CH), 122.1 (dd, *J* = 17.1, 3.8 Hz, C), 123.1 (C), 128.6 (t, *J* = 2.1 Hz, C), 128.90 (CH), 128.92 (CH), 131.0 (CH), 131.7 (CH), 141.9 (t, *J* = 4.9 Hz, C), 156.0 (C), 157.0 (C), 160.1 (dd, J_{CF} = 247.2, 12.8 Hz, CF), 161.6 (dd, J_{CF} = 247.2, 13.3 Hz, CF). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –112.82 (CF), –118.20 (CF). IR (ATR): ν = 3067 (w), 2956 (w), 2926 (w), 2835 (w), 1616 (w), 1596 (w), 1503 (w), 1494 (w), 1455 (w), 1421 (w), 1338 (w), 1287 (w), 1247 (m), 1201 (w), 1180 (w), 1120 (w), 1089 (w), 1024 (m), 928 (w), 877 (w), 865 (w), 800 (w), 755 (w), 744 (m), 701 (w), 635 (w), 586 (m), 537 (w) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 326 (100) [M]$^+$, 295 (12), 251 (21), 238 (10).

HRMS (EI): *m/z* calcd for $C_{20}H_{16}O_2F_2$ [M^+]: 326.11129; found: 326.11090.

(13) **2-Bromo-3,5-difluoro-2′,4′-dimethoxybiphenyl (4d)**
Starting with **1** (100 mg, 0.37 mmol), Cs_2CO_3 (119 mg, 0.37 mmol), $Pd(PPh_3)_4$ (3 mol%), 2,4-dimethoxyphenylboronic acid (67 mg, 0.37 mmol), and 1,4-dioxane (4 mL), **4d** was isolated as a colorless solid (81 mg, 67%), mp 64–66 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.75 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 6.53–6.57 (m, 2 H, Ar), 6.82–6.88 (m, 2 H, Ar), 7.04 (d, *J* = 8.9 Hz, 1 H, Ar). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 55.4 (OCH_3), 55.6 (OCH_3), 98.7 (CH), 103.4 (t, $^2J_{CF}$ = 26.6 Hz, CH), 104 (CH), 106.9 (dd, *J* = 20.4, 4.0 Hz, C), 114.5 (dd, *J* = 22.3, 3.3 Hz, CH), 121.0 (t, *J* = 2.2, C), 131.1 (CH), 142.9 (d, *J* = 9.8 Hz, C), 157.4 (C), 159.22 (dd, *J* = 248.0, 13.7 Hz, CF), 161.3 (dd, *J* = 248.6, 13.2 Hz, CF) 161.4 (C). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –100.5 (CF), –112.4 (CF). IR (ATR): ν = 3079 (w), 3002 (w), 2958 (w), 2937 (w), 2836 (w), 1692 (s), 1785 (s), 1509 (s), 1463 (m), 1447 (m), 1468 (w), 1435 (s), 1345 (w), 1304 (s), 1281 (m), 1256 (m), 1206 (s), 1146 (m), 1127 (s), 1101 (s), 1031 (s), 997 (s), 924 (m), 833 (s), 796 (m), 716 (w), 637 (w), 599 (s), 587 (m) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 328 (95) [M^+], 330 (93), 329 (15), 331 (14), 235 (15), 234 (100), 219 (35), 204 (12), 191 (20), 175 (26), 163 (13). ESI-HRMS: *m/z* calcd for $C_{14}H_{12}BrF_2O_2$ [M + H]$^+$: 328.9983; found: 328.9979.

(14) **General Procedure for the Synthesis of 5a–d**
The reaction was carried out in a pressure tube. To a dioxane suspension (4 mL) of **1** (200 mg, 0.74 mmol), $Pd(PPh_3)_4$ (3 mol%), and $Ar^1B(OH)_2$ (0.74 mmol) was added Cs_2CO_3 (359 mg, 1.11 mmol), and the resultant solution was degassed by bubbling argon through the solution for 10 min. The mixture was heated at 90 °C under Argon atmosphere for 8 h. The mixture was cooled to 20 °C and $Ar^2B(OH)_2$ (0.89 mmol) and Cs_2CO_3 (359 mg, 1.11 mmol) was added. The reaction mixtures were heated under Argon atmosphere for 6 h at 100 °C. They were diluted with H_2O and extracted with CH_2Cl_2 (3 × 50 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–hexane = 1:4).

(15) **1-(2,4-Dimethoxyphenyl)-2-(4-methylphenyl)-3,5-difluorobenzene (5a)**
Starting with **1** (200 mg, 0.74 mmol), Cs_2CO_3 (359 mg, 1.11 mmol), $Pd(PPh_3)_4$ (3 mol%), 2,6-dimethoxyphenylboronic (134 mg, 0.74 mmol), 1,4-dioxane (4 mL), and 4-methylboronic acid (123 mg, 0.89 mmol), **5a** was isolated as a colorless highly viscous oil (120 mg, 48%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.19 (s, 3 H, ArH), 3.32 (s, 3 H, OCH_3), 3.69 (s, 3 H, OCH_3), 6.17 (d, *J* = 2.3 Hz, 1 H, Ar), 6.32 (dd, *J* = 8.3, 2.3 Hz, 1 H, Ar), 6.74–6.83 (m, 2 H, Ar), 6.86–6.91 (m, 5 H, Ar). ^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 21.2 (CH_3), 55.0 (OCH_3), 55.3 (OCH_3), 98.4 (CH), 102.5 (t, $^2J_{CF}$ = 26.3 Hz, CH), 104.1 (CH), 113.6 (dd, J_{CF} = 21.9, 3.6 Hz, CH), 121.5 (t, ^3J = 2.8 Hz, C), 125.7 (dd, *J* = 15.3, 3.6 Hz, C), 128.1 (2 CH), 130.0 (2 CH), 131.1 (C), 131.6 (CH), 136.4 (C), 141.2 (dd, *J* = 9.6, 4.5 Hz, C), 157.0 (C), 159.8 (dd, J_{CF} = 246.8, 13.0 Hz, CF), 160.6 (C), 161.1 (dd, J_{CF} = 247.1, 13.4 Hz, C). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –111.86 (CF), –112.9 (CF). IR (ATR): ν = 3080 (w), 2998 (w), 2956 (w), 2836 (w), 1736 (w), 1609 (s), 1586 (s), 1508 (s), 1454 (s), 1425 (m), 1401 (m), 1372 (w), 1303 (s), 1255 (m), 1184 (w), 1158 (s), 1145 (s), 1092 (s), 1032 (s), 996 (s), 925 (m), 861 (w), 834 (m), 818 (s)796 (m), 736 (w), 718 (w), 663 (w), 607 (w), 587 (m) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 340 (100) [M^+], 294 (11), 265 (13), 238 (12). ESI-HRMS: *m/z* calcd for $C_{21}H_{19}F_2O_2$ [M + H]$^+$: 341.1348; found: 341.1348.

(16) CCDC-762919 and 762920 contain all crystallographic details of this publication and is 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, Cambridge CB21EZ, UK; fax: +44 (1223)336033; or deposit@ccdc.cam.ac.uk.

(17) 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.