Synthesis of Trifluoromethyl-Substituted Di- and Terphenyls by Site-Selective Suzuki–Miyaura Reactions of 1,4-Dibromo-2-trifluoromethyl-benzene

Ihsan Ullah,[a] Muhammad Nawaz, Alexander Villinger,[a] Peter Langer*[a,b]

[a] Institut für Chemie, Universität Rostock, Albert Einstein Str. 3a, 18059 Rostock, Germany

[b] Leibniz-Institut für Katalyse an der Universität Rostock e.V., Albert Einstein Str. 29a, 18059 Rostock, Germany
Fax +49(381)4986412; E-mail: peter.langer@uni-rostock.de

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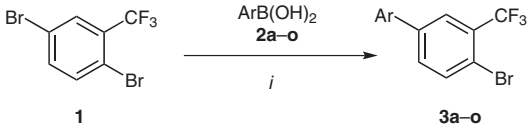
Abstract: The Suzuki–Miyaura reaction of 1,4-dibromo-2-(trifluoromethyl)benzene provides a convenient route for the synthesis of various trifluoromethylated di- and terphenyls. The reactions proceed with excellent site selectivity in favor of the 4-position due to steric and electronic reasons.

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

Trifluoromethyl-substituted arenes and heterocycles are of considerable importance in agricultural and medicinal chemistry.[1] On the one hand, the CF_3 group has a strong electron-withdrawing effect; whilst on the other hand, it has a similar size to a CH_3 group. Trifluoromethyl-substituted molecules show a high lipophilicity and, thus, excellent bioavailability. In addition, the CF_3 group is chemically and biologically stable which is an important feature to avoid undesired metabolic transformations. The CF_3 group also plays an important role in the field of catalysis. This includes new substrates, fluorous reaction media, fluorinated ligands,[2,3] and fluorinated organocatalysts.[4] Trifluoromethyl-substituted arenes and heteroarenes have been prepared by reaction of aryl halides with trifluoromethylcopper.[5] This strategy is limited by the unstable nature of the reagents and its failure for problematic substrates. Trifluoromethyl-substituted arenes have also been prepared by using CF_3-containing building blocks in cyclization reactions. Examples include cyclocondensations of enamines, Diels–Alder reactions, and formal [3+3] cyclizations.[6]

An alternative strategy relies on transition-metal cross-coupling reactions of trifluoromethyl-substituted substrates. In recent years, site-selective palladium(0)-catalyzed cross-coupling reactions of polyhalogenated arenes and heteroarenes have been studied. It has been shown for various nonfluorinated substrates that such reactions provide a valuable tool for the rapid assembly of highly substituted arenes and heteroarenes.[7,8] Recently, we have reported the first examples of site-selective cross-coupling reactions of fluorinated substrates, such as 1,2-dibromo-3,5-difluorobenzene.[9] Site-selective reactions of CF_3-substituted substrates have, to the best of our knowledge, not been reported to date. Herein, we report our first results in this field: the Suzuki–Miyaura reaction of 1,4-dibromo-2-(trifluoromethyl)benzene with various arylboronic acids allowing for a convenient synthesis of various CF_3-substituted di- and terphenyls which are not readily available by other methods.



1 3a–o

Scheme 1 Synthesis of **3a–o**. *Reagents and conditions*: *i*, **2a–o** (1.0 equiv), $Pd(PPh_3)_4$ (5 mol%), K_2CO_3 (H_2O, 2 M), dioxane, 70 °C, 8 h.

The Suzuki–Miyaura reaction of commercially available 1,4-dibromo-2-trifluoromethylbenzene (**1**) with arylboronic acids **2a–o** (1.0 equiv) afforded the 4-aryl-1-bromo-2-trifluoromethylbenzenes **3a–o** in 79–94% yields (Scheme 1, Table 1). All reactions proceeded with very good site selectivity in favor of position 4. Very good

Table 1 Synthesis of **3a–o**

2,3	Ar	Yield of **3** (%)[a]
a	Ph	82
b	2-MeC_6H_4	87
c	2-ClC_6H_4	84
d	3-ClC_6H_4	86
e	3-vinylC_6H_4	84
f	4-EtC_6H_4	87
g	4-*t*-BuC_6H_4	88
h	4-ClC_6H_4	83
i	4-FC_6H_4	80
j	2-naphthyl	79
k	2,5-$(MeO)_2C_6H_3$	92
l	2,6-$(MeO)_2C_6H_3$	87
m	3,4-$(MeO)_2C_6H_3$	94
n	3,5-$Me_2C_6H_3$	83
o	2,3,4-$(MeO)_3C_6H_2$	82

[a] Yields of isolated products.

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Table 2 Optimization of the Synthesis of **3g** and **3m**[a]

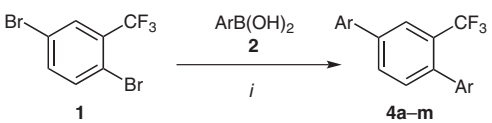
Entry	solvent	base	Temp (°C)	Time (h)	Yield of **3m** (%)	Yield of **3g** (%)
1	dioxane	K_2CO_3 (2 M)	60	8	–[b]	–[b]
2	THF	K_2CO_3 (2 M)	60	8	–[b]	–[b]
3	DME	K_2CO_3 (2 M)	70	8	–[b]	–[b]
4	dioxane	Cs_2CO_3 (3 equiv)	70	8	traces	traces
5	dioxane	K_3PO_4 (3 equiv)	70	8	traces	traces
6	toluene	K_3PO_4 (3 equiv)	70	8	traces	traces
7	toluene	K_2CO_3 (2 M)	70	8	traces	traces
8	toluene	K_2CO_3 (2 M)	90	8	traces	traces
9	dioxane	K_2CO_3 (2 M)	90	6	–[c]	–[c]
10	dioxane	K_2CO_3 (2 M)	80	6	–[c]	–[c]
11	THF	K_2CO_3 (2 M)	75	6	–[d]	–[d]
12	dioxane	K_2CO_3 (2 M)	70	3	87	82
13	dioxane	K_2CO_3 (2 M)	70	8	94	88

[a] $Pd(PPh_3)_4$ was used as the catalyst in all reactions.
[b] No conversion.
[c] Inseparable mixture of mono- and diarylated products.
[d] Inseparable mixture, mainly diarylated product.

yields were obtained for products derived from both electron-rich and electron-poor arylboronic acids.

The best yields were obtained using exactly 1.0 equivalent of the arylboronic acid, $Pd(PPh_3)_4$ (5 mol%) as the catalyst, and K_2CO_3 (2 M aq solution) as the base (1,4-dioxane, 70 °C, 8 h; Table 2).[10,11] The employment of other solvents or bases resulted in the formation of only trace amounts of product or no conversion at all. Increase in reaction temperature resulted in the formation of mixtures due to the formation of significant amounts of terphenyls. The length of reaction time had only a small effect on the yields.

The Suzuki–Miyaura reaction of **1** with 2.5 equivalents of various arylboronic acids **2** afforded the 2,5-diaryl-1-trifluoromethylbenzene derivatives **4a–m** in good yields (Scheme 2, Table 3).[10,12] The reactions had to be carried out at 90 °C instead of 70 °C to ensure a complete conversion. Very good yields were again obtained for products derived from both electron-rich and electron-poor arylboronic acids.



Scheme 2 Synthesis of 1,4-diarylbenzenes **4a–m**. *Reagents and conditions*: *i*, **2** (2.5 equiv), $Pd(PPh_3)_4$ (5 mol%), K_2CO_3 (H_2O, 2 M), dioxane, 90 °C, 8 h.

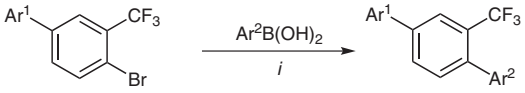
Table 3 Synthesis of 1,4-Diarylbenzenes **4a–m**

2	**4**	Ar	Yield of **4** (%)[a]
a	**a**	Ph	84
b	**b**	2-MeC_6H_4	85
p	**c**	3-MeC_6H_4	86
q	**d**	3-$F_3CC_6H_4$	82
r	**e**	3-$MeOC_6H_4$	89
s	**f**	4-MeC_6H_4	85
f	**g**	4-EtC_6H_4	87
t	**h**	4-$MeOC_6H_4$	93
u	**i**	2,3-$(MeO)_2C_6H_3$	87
k	**j**	2,5-$(MeO)_2C_6H_3$	79
m	**k**	3,4-$(MeO)_2C_6H_3$	95
n	**i**	3,5-$Me_2C_6H_3$	87
o	**m**	2,3,4-$(MeO)_3C_6H_2$	91

[a] Yields of isolated products

Bromobiaryls **3** also easily undergo Suzuki–Miyaura reactions. The reaction of **3f**,**j**,**m** with arylboronic acids afforded terphenyls **5a–d** in high yields (Scheme 3, Table 4).[10,13] A one-pot synthesis of **5a–d** starting with **1** also proved to be possible (sequential addition of the two

different boronic acids). However, the yields proved to be lower compared to the stepwise procedure. Therefore, this strategy was not further studied.



3f,j,m 5a–d

Scheme 3 Synthesis of **5a–d**. *Reagents and conditions*: *i*, **2i**,**m**,**n** (1.0 equiv), $Pd(PPh_3)_4$ (5 mol%), K_2CO_3 (H_2O, 2 M), dioxane, 80 °C, 8 h.

Table 4 Synthesis of **5a–d**

5	3	2	Ar^1	Ar^2	Yield of **5** (%)[a]
a	**f**	**m**	4-EtC_6H_4	3,4-$(MeO)_2C_6H_3$	88
b	**j**	**m**	2-Naph	3,4-$(MeO)_2C_6H_3$	85
c	**m**	**i**	3,4-$(MeO)_2C_6H_3$	4-FC_6H_4	80
d	**m**	**n**	3,4-$(MeO)_2C_6H_3$	3,5-$Me_2C_6H_3$	86

[a] Yields of isolated products.

The structures of **3j** and **4i** were independently confirmed by X-ray crystal-structure analyses (Figure 1 and Figure 2).[14]

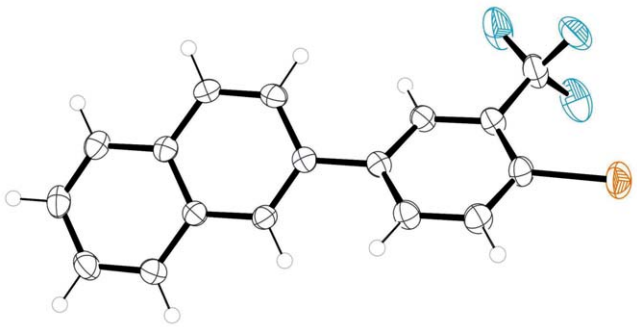


Figure 1 ORTEP plot of **3j**

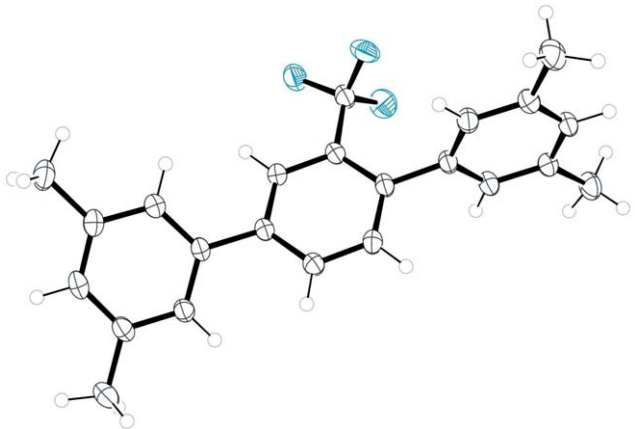


Figure 2 Crystal structure of **4i**

The first attack of palladium(0)-catalyzed cross-coupling reactions generally occurs at the more electron-deficient and sterically less hindered position.[7,15] From the electronic viewpoint, position C-1 is expected to be slightly more electron deficient than C-4. On the other hand, carbon atom C-4 is sterically less hindered than carbon C-1, due to its location *meta* to the CF_3 group (Figure 3). Therefore, initial attack C-4 can be explained by steric effects.

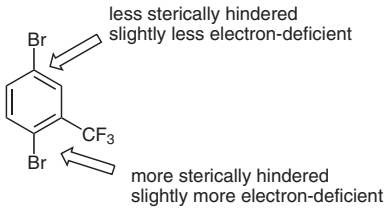


Figure 3 Possible explanation for the site selectivity of cross-coupling reactions of **1**

In conclusion, we have reported site-selective Suzuki–Miyaura reactions of 1,4-dibromo-2-trifluoromethyl-benzene. These reactions provide a convenient and site-selective approach to trifluoromethyl-substituted di- and terphenyls which are not readily available by other methods.

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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*; Wiley-VCH: Weinheim, **2004**. (e) Chambers, R. D. *Fluorine in Organic Chemistry*; Blackwell Publishing CRC Press: Boca Raton, **2004**. (f) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.

(2) (a) 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. (b) 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. (c) Ciha, A. J.; Ruminski, P. G. *J. Agric. Food Chem.* **1991**, *39*, 2072. (d) 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. (e) 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. (f) Song, C. W.; Lee, K. Y.; Kim, C. D.; Chang, T.-M.; Chey, W. Y. *J. Pharmacol. Exp. Ther.* **1997**, *281*, 1312. (g) 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. (h) Anjaiah, S.; Chandrasekhar, S.; Gree, R. *Adv. Synth. Catal.* **2004**, *346*, 1329. (i) Iorio, M. A.; Paszkowska, R. T.; Frigeni, V. *J. Med. Chem.* **1987**, *30*, 1906. (j) Popp, J. L.; Musza, L. L.; Barrow, C. J.; Rudewicz, P. J.; Houck, D. R. *J. Antibiot.* **1994**, *47*, 411. (k) Chen, T. S.; Petuch, B.; MacConnell, J.; White, R.; Dezeny, G. *J. Antibiot.* **1994**, *47*, 1290. (l) 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. (m) Bégué, J. P.; Bonnet-Delpon, D. *J. Fluorine Chem.* **2006**, *127*, 992. (n) Isanbor, C.; O'Hagan, D. *J. Fluorine Chem.* **2006**, *127*, 303.

(3) (a) *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A.; Diederich, F., Eds.; Wiley-VCH: Weinheim, **2004**. (b) Beller, M.; Neumann, H.; Anbarasan, P. *Angew. Chem. Int. Ed.* **2009**, *48*, 1. (c) Schmidbaur, H.; Kumberger, O. *Chem. Ber.* **1993**, *126*, 3. (d) Dinger, M. B.; Henderson, W. *J. Organomet. Chem.* **1998**, *560*, 233. (e) Liedtke, J.; Loss, S.; Widauer, C.; Grützmacher, H. *Tetrahedron* **2000**, *56*, 143. (f) 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. (g) 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.

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

(5) Review: McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555.

(6) (a) Ding, W.; Pu, J.; Zhang, C. *Synthesis* **1992**, 635. (b) Guan, H.-P.; Hu, C.-M. *Synthesis* **1996**, 1363. (c) Guan, H.-P.; Hu, C.-M. *J. Fluorine Chem.* **1996**, *78*, 101. (d) Hojo, M.; Masuda, R.; Kokuryo, Y.; Shioda, H.; Matsuo, S. *Chem. Lett.* **1976**, 499. (e) Hojo, M.; Masuda, R.; Sakaguchi, S.; Takagawa, M. *Synthesis* **1986**, 1016. (f) Colla, A.; Martins, M. A. P.; Clar, G.; Krimmer, S.; Fischer, P. *Synthesis* **1991**, 483. (g) Hojo, M.; Masuda, R.; Okada, E. *Synthesis* **1989**, 215. (h) Reviews: Zanatta, N.; Barichello, R.; Bonacorso, H. G.; Martins, M. A. P. *Synthesis* **1999**, 765. (i) Nenaidenko, V. G.; Sanin, A. V.; Balenkova, E. S. *Russ. Chem. Rev.* **1999**, *68*, 437. (j) Billard, T. *Chem. Eur. J.* **2006**, *12*, 974. (k) Druzhinin, S. V.; Balenkova, E. S.; Nenajdenko, V. G. *Tetrahedron* **2007**, *63*, 7753. (l) Marzi, E.; Mongin, F.; Spitaleri, A.; Schlosser, M. *Eur. J. Org. Chem.* **2001**, 2911. (m) Dmowski, W.; Piasecka-Maciejewska, K. *J. Fluorine Chem.* **1996**, *78*, 59. (n) Abubakar, A. B.; Booth, B. L.; Suliman, N. N. E.; Tipping, A. E. *J. Fluorine Chem.* **1992**, *56*, 359. (o) Barlow, M. G.; Suliman, N. N. E.; Tipping, A. E. *J. Fluorine Chem.* **1995**, *70*, 59. (p) Volochnyuk, D. M.; Kostyuk, A. N.; Sibgatulin, D. A.; Chernega, A. N.; Pinchuk, A. M.; Tolmachev, A. A. *Tetrahedron* **2004**, *60*, 2361. (q) Volochnyuk, D. M.; Kostyuk, A. N.; Sibgatulin, D. A.; Chernega, A. N. *Tetrahedron* **2005**, *61*, 2839. (r) Mamat, C.; Pundt, T.; Schmidt, A.; Langer, P. *Tetrahedron Lett.* **2006**, *47*, 2183. (s) Mamat, C.; Pundt, T.; Dang, T. H. T.; Klassen, R.; Reinke, H.; Köckerling, M.; Langer, P. *Eur. J. Org. Chem.* **2008**, 492. (t) For a review, see: Bunescu, A.; Reimann, S.; Lubbe, M.; Spannenberg, A.; Langer, P. *J. Org. Chem.* **2009**, *74*, 5002. (u) Langer, P. *Synlett* **2009**, 2205.

(7) 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.

(8) (a) Dang, T. T.; Dang, T. T.; Ahmad, R.; Reinke, H.; Langer, P. *Tetrahedron Lett.* **2008**, *49*, 1698. (b) Dang, T. T.; Villinger, A.; Langer, P. *Adv. Synth. Catal.* **2008**, *350*, 2109. (c) Hussain, M.; Nguyen, T. H.; Langer, P. *Tetrahedron Lett.* **2009**, *50*, 3929. (d) Tengho Toguem, S.-M.; Hussain, M.; Malik, I.; Villinger, A.; Langer, P. *Tetrahedron Lett.* **2009**, *50*, 4962. (e) Hussain, M.; Malik, I.; Langer, P. *Synlett* **2009**, 2691. (f) Dang, T. T.; Dang, T. T.; Rasool, N.; Villinger, A.; Langer, P. *Adv. Synth. Catal.* **2009**, *351*, 1595. (g) Ullah, I.; Khera, R. A.; Hussain, M.; Langer, P. *Tetrahedron Lett.* **2009**, *50*, 4651. (h) Nawaz, M.; Farooq, M. I.; Obaid-Ur-Rahman, A.; Khera, R. A.; Villinger, A.; Langer, P. *Synlett* **2010**, 150. (i) Nawaz, M.; Farooq, M. I.; Obaid-Ur-Rahman, A.; Khera, R. A.; Villinger, A.; Langer, P. *Synlett* **2010**, 150. (j) Hussain, M.; Nguyen, T. H.; Khera, R. A.; Villinger, A.; Langer, P. *Tetrahedron Lett.* **2011**, *52*, 184.

(9) (a) Sharif, M.; Zeeshan, M.; Reimann, S.; Villinger, A.; Langer, P. *Tetrahedron Lett.* **2010**, *51*, 2810. (b) Sharif, M.; Reimann, S.; Villinger, A.; Langer, P. *Synlett* **2010**, 913.

(10) **Typical Procedure for Suzuki–Miyaura Reactions**

The reaction was carried out in a pressure tube. To a dioxane suspension (5 mL) of **1**, $Pd(PPh_3)_4$ (3–5 mol%), and of the arylboronic acid **2a**–**o** was added an aq solution of K_2CO_3 (2 M, 1–2 mL). The mixture was heated at 70 °C (**3a**–**o**) or 90 °C (**4a**–**o**) under argon for 8 h. The solution was cooled to 20 °C, poured into H_2O and CH_2Cl_2 (5 mL each), and the organic and the aqueous layers were separated. The latter was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with H_2O (3 × 10 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by chromatography (flash silica gel, heptanes–EtOAc).

(11) **4-Bromo-4′-*tert*-butyl-3-(trifluoromethyl)biphenyl (3g)**

Starting with **1** (150 mg, 0.5 mmol) and **2g** (90 mg, 0.5 mmol), **3g** was isolated as a colorless viscous oil (158 mg, 88%). ^{1}H NMR (300 MHz, 298 K, $CDCl_3$): δ = 1.28 [s, 9 H, $(CH_3)_3$], 7.42 (s, 4 H, H_{Ar}), 7.50 (dd, *J* = 2.1, 8.3 Hz, 1 H, H_{Ar}), 7.67 (d, *J* = 8.2 Hz, 1 H, H_{Ar}), 7.80 (d, *J* = 2.1 Hz, 1 H, H_{Ar}). ^{19}F NMR (282 MHz, 298 K, $CDCl_3$): δ = –62.61. ^{13}C NMR (75 MHz, 298 K, $CDCl_3$): δ = 31.2 [$(CH_3)_3$], 34.6 [$C(CH_3)_3$], 118.3 (J_{C-F} = 1.9 Hz, C_{Ar}), 123.0 (J_{C-F} = 272 Hz, CF_3), 126.1, 126.3 (J_{C-F} = 5.4 Hz), 126.6 (CH_{Ar}), 130.4 (J_{C-F} = 31.7 Hz, C_{Ar}), 131.1, 135.2 (CH_{Ar}), 135.7, 140.6, 151.6 (C_{Ar}). IR (neat): 3034, 2961, 2868, 1601 (w), 1473, 1418 (m), 1325 (s), 1251, 1172 (m), 1129, 1100 (s), 1021 (m), 962 (w), 902 (m), 818 (s), 743, 697, 659 (m), 603 (w), 566 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 358 (28) [M^+, ^{81}Br], 344 (18), 343 (98), 342 (19), 341 (100), 315 (20), 313 (20), 262 (10), 233 (7), 222 (8), 165 (7), 157 (8), 156 (9). HRMS (EI): *m/z* calcd for $C_{17}H_{16}{}^{81}BrF_3$ $[M]^+$: 358.036150; found: 358.036852.

(12) **2-Trifluoromethyl-1,4-bis(4-methoxyphenyl)benzene (4h)**

Starting with **1** (150 mg, 0.5 mmol) and **2t** (190 mg, 1.25 mmol), **4h** was isolated as a viscous oil (167 mg, 93%). ^{1}H NMR (300 MHz, 298 K, $CDCl_3$): δ = 3.77, 3.78 (s, 6 H, 2 OCH_3), 6.86 (d, *J* = 8.7 Hz, 2 H, H_{Ar}), 6.93 (d, *J* = 8.7 Hz, 2 H, H_{Ar}), 7.18–7.27 (m, 3 H, H_{Ar}), 7.48 (d, *J* = 8.8 Hz, 2 H, H_{Ar}), 7.62 (dd, *J* = 8.8, 1.6 Hz, 1 H, H_{Ar}), 7.82 (d, *J* = 1.6 Hz, 1 H, H_{Ar}). ^{19}F NMR (282 MHz, 298 K, $CDCl_3$): δ = –56.83.

^{13}C NMR (75 MHz, 298 K, $CDCl_3$): δ = 55.2, 55.4 (OCH_3), 113.3, 114.5, 124.2 (J_{C-F} = 4.5 Hz) (CH_{Ar}) 124.3 (J_{C-F} = 275 Hz, CF_3), 128.1, 129.2, 130.1 (J_{C-F} = 1.4 Hz, CH_{Ar}), 130.8 (J_{C-F} = 30.9 Hz, C_{Ar}), 132.0 (CH_{Ar}), 132.8, 139.2, 139.3, 139.8 (J_{C-F} = 1.9 Hz), 159.1, 159.7 (C_{Ar}). IR (neat): 3028, 2922 (w), 1605, 1475 (m), 1395 (w), 1321, 1270, 1241, 1165 (m), 1118 (s), 1074, 1050, 1032 (m), 972 (w), 895, 839 (m), 778, 705 (s), 663, 607 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 359 (22) [M + 1], 358 (100) [M^+], 344 (12), 243 (32), 315 (14), 300(14), 271 (17), 251 (41), 207 (15), 202 (22), 179 (49), 157 (28). HRMS (EI): *m/z* calcd for $C_{21}H_{17}O_2F_3$ [$M]^+$: *m/z* = 358.117520; found: 358.116620.

(13) **1-(3′,4′-Dimethoxy)-phenyl-4-naphthyl-2-trifluoromethyl-benzene (5b)**
Starting with **3j** (88 mg, 0.25 mmol) and **2m** (45 mg, 0.25 mmol), **5b** was obtained as a yellowish crystalline solid (87 mg, 85%). ^{1}H NMR (300 MHz, 298 K, $CDCl_3$): δ = 3.81, 3.84 (s, 6 H, 2 OCH_3), 6.82–6.86 (m, 3 H, H_{Ar}), 7.36–7.45 (m, 3 H, H_{Ar}), 7.67 (dd, *J* = 8.5, 1.8 Hz, 1 H, H_{Ar}), 7.77–7.87 (m, 4 H, H_{Ar}), 8.00 (s, 2 H, H_{Ar}). ^{19}F NMR (282 MHz, 298K, $CDCl_3$): δ = –56.72. ^{13}C NMR (75 MHz, 298K, $CDCl_3$): δ = 55.9, 56.0 (OCH_3), 110.4, 112.6, 121.4 (CH_{Ar}), 122.8 (J_{C-F} = 275.2 Hz, CF_3), 125.0, 125.1, 126.0, 126.4, 126.6 (CH_{Ar}), 127.1, 127.3 (C_{Ar}), 127.7, 128.3 (CH_{Ar}), 128.5 (J_{C-F} = 29.7 Hz, C_{Ar}), 128.8, 129.9 (CH_{Ar}), 132.1 (C_{Ar}), 132.9 (CH_{Ar}), 133.6, 136.7, 140.0, 140.2, 148.2, 148.7 (C_{Ar}). IR (neat): 3052, 2954, 2834, 1602 (w), 1495, 1462, 1407 (m), 1369 (w), 1314 (m), 1244, 1217, 1164, 1118 (s), 1071 (m), 1022 (s), 952, 886, 857 (m), 811, 748 (s), 719, 644, 607, 553 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) 409 (27) [M + 1], 408 (100) [M^+], 393 (13), 365 (32), 350 (29), 326 (23), 325 (47), 322 (30), 305 (14), 297 (16), 296 (44), 253 (14), 252 (39), 204 (59), 163 (52), 162 (36). HRMS (EI): *m/z* calcd for $C_{25}H_{19}O_2F_3$ [$M]^+$: 408.133170; found: 408.133547.

(14) CCDC-822983 (**3j**) and CCDC-822984 (**4i**) 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, GB-Cambridge CB21EZ; fax: +44 (1223)336033; or deposit@ccdc.cam.ac.uk.

(15) 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.