Tetrahedron Letters 51 (2010) 2810–2812

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

One-pot synthesis of fluorinated terphenyls by site-selective Suzuki–Miyaura reactions of 1,4-dibromo-2-fluorobenzene

Muhammad Sharif [a,b], Muhammad Zeeshan [a], Sebastian Reimann [a,b], 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

ARTICLE INFO

Article history:
Received 2 February 2010
Revised 15 March 2010
Accepted 16 March 2010
Available online 20 March 2010

Keywords:
Catalysis
Suzuki–Miyaura reaction
Site-selectivity
Palladium
Organofluorine compounds

ABSTRACT

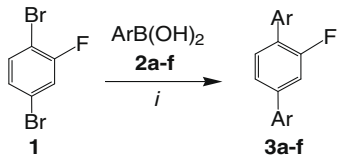
The Suzuki–Miyaura reaction of 1,4-dibromo-2-fluorobenzene with two equivalents of arylboronic acids gave fluorinated *para*-terphenyls. The reaction with 1 equiv of arylboronic acid resulted in site-selective formation of biphenyls. The one-pot reaction of 1,4-dibromo-2-fluorobenzene with two different arylboronic acids afforded fluorinated *para*-terphenyls containing two different terminal aryl groups.

Fluorinated arenes and hetarenes have a remarkable record in medicinal and agricultural chemistry and play an important role as lead compounds.[1] The solubility, bioavailability and metabolic stability of fluorinated compounds is often enhanced compared to those of non-fluorinated analogues.[2–4] Fluorinated arenes and heteroarenes are useful substrates in transition metal-catalyzed cross-coupling reactions.[5] Aryl fluorides 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] For example, we have reported site-selective Suzuki–Miyaura (S–M) reactions of tetrabrominated *N*-methylpyrrole, thiophene, selenophene and of several other polyhalogenated arenes and hetarenes such as 2,3,5-tribromothiophene and 2,3-dibromoindole.[9] We have also developed site-selective S–M reactions of the bis(triflate) of methyl 2,5-dihydroxybenzoate and of related substrates.[10] Herein, we report the first results of our study related to S–M reactions of 1,4-dibromo-2-fluorobenzene.

The S–M reaction of commercially available 1,4-dibromo-2-fluorobenzene (**1**) with 2 equiv of arylboronic acids **2a–f** afforded the fluorinated *para*-terphenyls **3a–f** in moderate to good yields (Scheme 1, Table 1). The best yields were obtained using 2.2 equiv 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]

The S–M reaction of **1** with arylboronic acids **2a–g** (1.0 equiv) afforded the biaryls **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.



Scheme 1. Synthesis of **3a–f**. 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, 6–8 h.

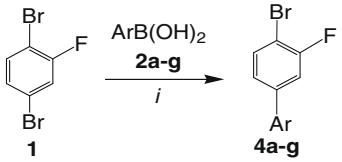
Table 1
Synthesis of **3a–f**

2,3	Ar	3[a] (%)
a	4-(MeO)C_6H_4	52
b	4-*t*BuC_6H_4	63
c	4-(Vinyl)C_6H_4	45
d	3,4-$(MeO)_2C_6H_3$	58
e	4-(EtO)C_6H_4	65
f	4-MeC_6H_4	60

[a] Yields of isolated products.

* Corresponding author.
E-mail address: peter.langer@uni-rostock.de (P. Langer).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.03.067

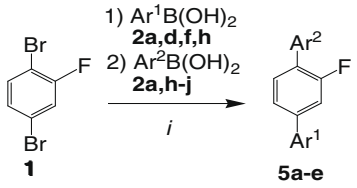


Scheme 2. Synthesis of **4a–g**. Conditions: (i) **1** (1.0 equiv), **2a–g** (1.0 equiv), Cs_2CO_3 (1.5 equiv), $Pd(PPh_3)_4$ (3 mol %), 1,4-dioxane, 90 °C, 6–8 h.

Table 2
Synthesis of **4a–g**

2,4	Ar	4[a] (%)
a	4-(MeO)C_6H_4	60
b	4-(*t*Bu)C_6H_4	58
c	4-(Vinyl)C_6H_4	45
d	3,4-$(MeO)_2C_6H_3$	67
e	4-(EtO)C_6H_4	68
f	4-MeC_6H_4	60
g	4-ClC_6H_4	60

[a] Yields of isolated products.



Scheme 3. One-pot synthesis of **5a–e**. Conditions:(1) **1** (1.0 equiv), **2a,d,f,h** (1.0 equiv), Cs_2CO_3 (1.5 equiv), $Pd(PPh_3)_4$ (3 mol %), 1,4-dioxane, 90 °C, 8 h, 2) **2a,h–j** (1.2 equiv), Cs_2CO_3 (1.5 equiv), 100 °C, 6 h.

The one-pot reaction of 1,4-dibromo-2-fluorobenzene with two different arylboronic acids afforded the unsymmetrical fluorinated *para*-terphenyls **5a–e** containing two different terminal aryl groups (Scheme 3, Table 3).[14,15]

Interestingly, the yields of products **5a–e** are in the same range as the yields of **4a–g**. This might be explained by the assumption that the selectivity and the yield are mainly determined by the first attack of the boronic acid to **1**. The second attack during the synthesis of **5a–e** only has a small influence on the yield because no problem of site-selectivity exists. On the other hand, the yield of products **3a–f** (where no problem of site-selectivity exists) is in a similar range. Therefore, we believe that the chromatographic purification also has a great influence on the yield, due to some loss

Table 3
Synthesis of **5a–e**

2	5	Ar^1	Ar^2	5[a] (%)
h,a	**a**	4-(Acetyl)C_6H_5	4-(MeO)C_6H_4	60
a,i	**b**	4-(MeO)C_6H_4	2-(MeO)C_6H_4	67
f,a	**c**	4-MeC_6H_4	4-(MeO)C_6H_4	48
f,h	**d**	4-MeC_6H_4	4-(Acetyl)C_6H_5	42
d,j	**e**	3,4-$(MeO)_2C_6H_3$	2-Thienyl	53

[a] Yields of isolated products.

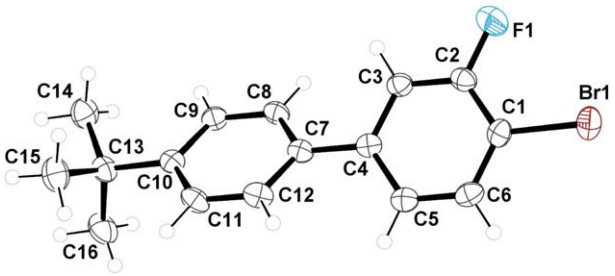
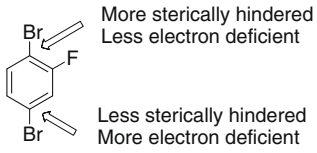


Figure 1. Crystal structure of **4b**.



Scheme 4. Possible explanation for the site-selectivity of cross-coupling reactions of **1**.

of material. For all reactions, only one chromatographic purification has to be carried out. Inspection of the NMR of the crude products **5a–e** (before purification) shows that a small amount of mono-coupling and double-coupling product (containing two Ar^1 groups) is present in most cases. In case of the synthesis of **4a–g**, a small amount of double-coupling product is present in the crude product mixture.

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

The site-selective formation of **4a–g** and **5a–e** can be explained by steric and electronic reasons. The first attack of palladium(0)-catalyzed cross-coupling reactions generally occurs at the more

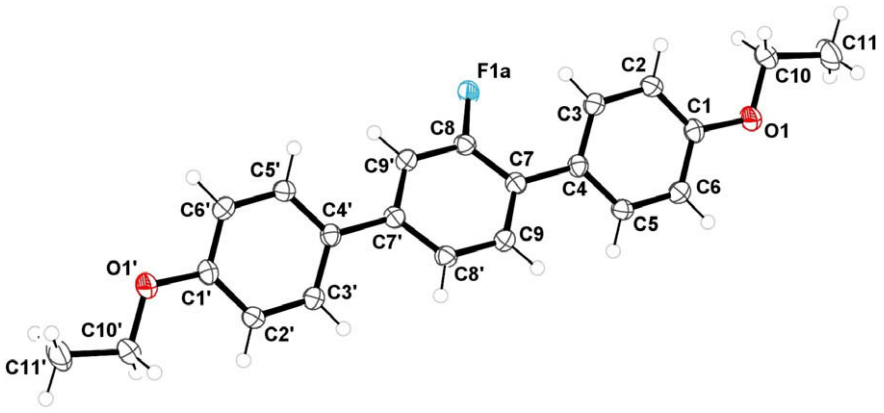


Figure 2. Crystal structure of **3e**.

electronic deficient and sterically less hindered position.[8,17] Position 4 of 1,4-dibromo-2-fluorobenzene (**1**) is sterically less hindered because it is located next to two hydrogen atoms while position 1 is located next to a fluorine atom (Scheme 4). In addition, position 4 (located *meta* to the fluorine atom) is more electron deficient than position 1 (located *ortho* to the fluorine atoms), due to the π-donating effect of the fluorine atom. In fact, the ^{1}H NMR signals of aromatic protons located *ortho* to a fluorine atom are generally shifted to higher field compared to the proton located in *meta* position.

In conclusion, we have reported site-selective Suzuki–Miyaura reactions of 1,4-dibromo-2-fluorobenzene which provide a convenient approach to fluorinated terphenyls and biaryls.

Acknowledgements

We are grateful to Mr. Obaid-ur-Rahman Abid and to Mr. Rasheed Ahmad Khera for their help. Financial support by the DAAD (scholarships for M.S. and M.Z.) and by the University of Rostock (scholarship of the interdisciplinary faculty of the University of Rostock for S.R.) is gratefully acknowledged.

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. Chapter 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, 2004; (f) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.
2. Heidelberger, C.; Chaudhuri, K. N.; Danneberg, P.; Mooren, D.; Griesbach, L.; Duschinsky, R.; Schnitzer, J. R. *Nature* **1957**, *179*, 663.
3. Wong, T. D.; Bymaster, P. F.; Engleman, A. E. *Life Sci.* **1995**, *57*, 411.
4. Roman, L. D.; Walline, C. C.; Rodriguez, J. G.; Barker, L. E. *Eur. J. Pharmacol.* **2003**, *479*, 53.
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. In *Multiphase Homogeneous Catalysis*; Cornils, B., Herrmann, W. A., Horvath, I. T., Leitner, W., Mecking, S., Olivier-Booubigou, H., Vogt, D., Eds.; Wiley-VCH, 2005; p 346. Chapter 4; (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. (a) Wittkopp, A.; Schreiner, P. R.. In *The Chemistry of Diens and Polyenes*; John Wiley & Sons Ltd, 2000; Vol. 2; (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**, *5*, 779; Reviews: (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) Tengho Toguem, S.-M.; Villinger, A.; Langer, P. *Synlett* **2009**, 3311; (e) Farooq, M. I.; Hussain, M.; Obaid-Ur-Rahma, A.; Ali, A.; Ullah, I.; Zinad, D. S.; Langer, P. *Synlett* **2010**, 411.
10. (a) Nawaz, M.; Farooq, M. I.; Obaid-Ur-Rahman, A.; Khera, R. A.; Villinger, A.; Langer, P. *Synlett* **2010**, 150; (b) Farooq, M. I.; Obaid-Ur-Rahma, A.; Adeel, M.; Nawaz, M.; Villinger, A.; Langer, P. *Synlett* **2010**, 195.
11. *General procedure for Suzuki–Miyaura 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** were stirred at 90 °C for 6 or 8 h. After cooling to room temperature, 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.
12. *1,4-Di(4-tert-butylphenyl)-2-fluorobenzene* (**3b**): Starting with **1** (100 mg, 0.39 mmol), Cs_2CO_3 (263 mg, 0.81 mmol), $Pd(PPh_3)_4$ (3 mol %), 4-*tert*-butylphenylboronic acid (138 mg, 0.78 mmol) and 1,4-dioxane (4 mL), **3b** was isolated as a colourless solid (89 mg, 63%), mp 184–186 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (s, 18H, CH_3), 7.30 (dd, *J* = 12.1, 1.6 Hz, 1H, ArH), 7.36–7.42 (m, 6H, ArH), 7.45–7.50 (m, 4H, ArH). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 31.3 (CH_3), 34.6 (C), 111.3 (CH), 114.3 (d, *J* = 23.9 Hz, CH), 122.7 (d, J_{CF} = 3.2 Hz, CH), 125.4 (2CH), 125.9 (2CH), 126.6 (2CH), 127.3 (d, J_{CF} = 13.6 Hz, C), 128.6 (d, J_{CF} = 3.2 Hz, CH), 130.8 (d, J_{CF} = 4.3 Hz, C), 132.6 (d, J_{CF} = 1.4 Hz, CH), 136.7 (d, J_{CF} = 1.9 Hz, C), 141.8 (C), 141.9 (C), 150.8 (d, J_{CF} = 19.3 Hz, C), 160.1 (d, J_{CF} = 247 Hz, C). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ −117.97 (CF). IR (ATR, cm^{-1}): *ν* 3033 (w), 2950 (m), 2860 (w), 2705 (w), 2163 (w), 1977 (w), 1910 (w), 1741 (w), 1616 (w), 1543 (w), 1486 (m), 1428 (w), 1394 (m), 1305 (w), 1261 (m), 1200 (w), 1187 (m), 1122 (w), 1045 (w), 1004 (w), 948 (w), 894 (m), 816 (s), 829 (w), 750 (w), 675 (w), 586 (m), 548 (m). MS (EI, 70 eV): *m*/*z* (%) 360 (54) [M^+], 346 (26), 345 (100), 137 (12). HRMS (EI) calcd for $C_{26}H_{29}F$ [M^+]: 360.22478, found 360.224193.
13. *1-Bromo-4-methoxyphenyl-2-fluorobenzene* (**4a**): Starting with **1** (100 mg, 0.39 mmol), Cs_2CO_3 (190 mg, 0.50 mmol), $Pd(PPh_3)_4$ (3 mol %), 4-methoxy phenylboronic acid (59.3 mg, 0.39 mmol) and 1,4-dioxane (4 mL), **4a** was isolated as a colourless semi solid (66 mg, 60%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.77 (s, 3H, OCH_3), 6.90 (td, *J* = 8.85, 2.18 Hz, 2H, ArH), 7.20–7.27 (m, 3H, ArH), 7.34–7.39 (m, 2H, ArH). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 55.3 (OCH_3), 114.1 (2CH), 119.6 (d, J_{CF} = 25.9 Hz, H), 120.5 (d, J_{CF} = 9.5 Hz, C), 127.6 (d, J_{CF} = 3.70 Hz, C), 128.5 (d, J_{CF} = 12.4 Hz, CH), 129.9 (d, J_{CF} = 2.8 Hz, CH), 131.4 (d, J_{CF} = 4.07 Hz, CH), 131.9 (d, J_{CF} = 2.77 Hz, C), 132.1 (d, J_{CF} = 9.8 Hz, CH), 159.4 (C), 159.5 (d, J_{CF} = 251 Hz, C). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ −115.31 (CF). IR (ATR, cm^{-1}): *ν* 3067 (w), 2999 (w), 2922 (w), 2835 (w), 2712 (w), 2550 (w), 2158 (w), 2048 (w), 1980 (w), 1891 (w), 1607 (m), 1518 (m), 1477 (s), 1390 (m), 1264 (m), 1247 (s), 1178 (s), 1112 (m), 1037 (m), 963 (w), 869 (s), 807 (s), 719 (m), 636 (w), 570 (m), 539 (s). MS (EI, 70 eV): *m*/*z* (%) 281 (13) [M^+], 280 (100), 267 (30), 265 (31), 239 (29), 158 (15), 157 (35). HRMS (EI) calcd for $C_{13}H_{10}OBrF$ [M^+]: 281.98731 found 281.987694.
14. *General procedure for the synthesis of* **5a**–**e**: The reaction was carried out in a pressure tube. To a dioxane suspension (4 mL) of **1** (200 mg, 0.79 mmol), $Pd(PPh_3)_4$ (3 mol %) and $Ar^1B(OH)_2$ (0.79 mmol) was added Cs_2CO_3 (385 mg, 1.18 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 $Ar^2B(OH)_2$ (0.95 mmol) and Cs_2CO_3 (385 mg, 1.18 mmol) was added. The reaction mixtures were heated under Argon atmosphere for 6 h at 100 °C. They were diluted with water 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. *4-(4-Acetylphenyl)-1-(4-methoxyphenyl)-2-fluorobenzene* (**5a**): Starting with **1** (200 mg, 0.79 mmol), Cs_2CO_3 (385 mg, 1.18 mmol), $Pd(PPh_3)_4$ (3 mol %), 4-acetylphenylboronic acid (129 mg, 0.79 mmol), 1,4-dioxane (4 mL) and 4-methoxylphenylboronic acid (144 mg, 0.95 mmol), **5a** was isolated as a colourless solid (151 mg, 60%). Mp 89–90 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.57 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 7.25 (dd, *J* = 7.6, 1.1 Hz, 1H, ArH), 7.30–7.40 (m, 4H, ArH), 7.64 (td, *J* = 8.53, 2.03 Hz, 2H, ArH), 7.97 (td, *J* = 8.49, 1.9 Hz, 2H, ArH). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 26.6 (CH_3), 55.7 (OCH_3), 111.2 (CH), 114.3 (d, J_{CF} = 23.8 Hz, CH), 120.6 (CH), 122.5 (d, J_{CF} = 3.2 Hz, CH), 124.4 (C), 126.1 (d, J_{CF} = 16.3 Hz, C), 127.1 (2CH), 129.0 (2CH), 129.6 (CH), 131.2 (CH), 132.4 (d, J_{CF} = 4.3 Hz, CH), 136.2 (C), 140.8 (d, *J* = 7.7 Hz, C), 144.3 (C), 156.9 (C), 160.3 (d, J_{CF} = 249 Hz, C), 197.6 (CO). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ −113.40 (CF_3). IR (ATR, cm^{-1}): *ν* 054 (w), 2921 (w), 2851 (w), 2335 (w), 2162 (w), 1980 (w), 1668 (m), 1601 (w), 1539 (w), 1482 (w), 1393 (w), 1301 (w), 1246 (m), 1163 (w), 1078 (w), 1005 (w), 928 (w), 890 (w), 818 (m), 734 (w), 659 (w), 586 (w), 534 (w). MS (EI, 70 eV): *m*/*z* (%) 321 (23) [M^+], 320 (100), 306 (23), 305 (99), 262 (11), 233 (10), 153 (13). HRMS (EI) calcd for $C_{21}H_{17}O_2F$ [M^+]: 320.12071; found 320.120518.
16. CCDC-769080 and 769081 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) 1223-336-033; 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.