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Site-selective Suzuki cross-coupling reactions of 2,3-dibromobenzofuran

Nguyen Thai Hung [a], Munawar Hussain [a], Imran Malik [a], 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 e. V. an der Universität Rostock, Albert-Einstein-Str. 29a, 18059 Rostock, Germany

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ABSTRACT

The Suzuki–Miyaura reaction of 2,3-dibromobenzofuran with two equivalents of boronic acids gave 2,3-diarylbenzofurans. The reaction with one equivalent of arylboronic acids resulted in site-selective formation of 2-aryl-3-bromobenzofurans. 2,3-Diarylbenzofurans containing two different aryl groups were prepared from 2,3-dibromobenzofuran in a one-pot protocol by sequential addition of two different boronic acids.

Benzofurans are pharmacologically important heterocycles.[1] For example, synthetic amiodarone represents a potent antiarrythmic and antianginal drug.[2] 7-Alkanoylbenzofurans and 7-alkanoyl-2,3-dihydrobenzofurans occur in various natural products, such as longicaudatin,[3] flemistrictin E, tovophenone C, vismiaguianone C, piperaduncin B and sessiliflorols A and B.[4]

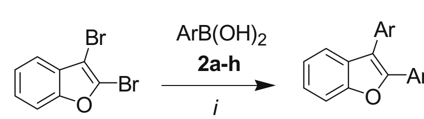
In recent years, it has been shown that polyhalogenated heterocycles can be site-selectively functionalized in palladium(0)-catalyzed cross-coupling reactions by selective activation of a single halogen atom. The site-selectivity is controlled by electronic and steric parameters.[5] Recently, we have reported the synthesis of aryl-substituted thiophenes,[6] pyrroles[7] and selenophenes[8] based on site-selective Suzuki reactions of tetrabrominated thiophene, *N*-methylpyrrole and selenophene, respectively. 2,3-Dibromobenzofuran and 2,6-dibromobenzofuran represent interesting starting materials which have been used in site-selective Sonogashira,[9] Negishi[9] and Stille[10] coupling reactions. Site-selective Negishi and Kumada cross-coupling reactions of 2,3,5-tribromobenzofuran have also been reported.[11] Recently, we have reported Heck reactions of 2,3-dibromobenzofuran.[12] Herein, we report what are, to the best of our knowledge, the first Suzuki–Miyaura reactions of 2,3-dibromobenzofuran. These reactions proceed with excellent site-selectivity. We also have developed a one-pot protocol for the synthesis of unsymmetrical 2,3-diarylbenzofurans in one step.

The Suzuki–Miyaura reaction of 2,3-dibromobenzofuran (**1**) with various arylboronic acids (2.0 equiv) afforded the 2,3-diarylbenzofurans **3a**–**h** (Scheme 1, Table 1).[13] High yields were obtained for products derived from both electron-rich and electron-poor boronic acids.

The Suzuki–Miyaura reaction of **1** with 1.0 equiv of arylboronic acids **2c**,**e**,**g**–**i** afforded the 2-aryl-3-bromobenzofurans **4a**–**e** in very good yields (Scheme 2, Table 2).[13,14] The reactions proceeded with very good site-selectivity.

In all the reactions, the best yields were obtained when $Pd(PPh_3)_4$ (5 mol %) was used as the catalyst. The use of $Pd(OAc)_2$ in the presence of XPhos[15] or SPhos[15] proved to be less successful in terms of yield. All the reactions were carried out at 70–80 °C. For the mono-coupling it proved to be important to carry out the reaction at 70 °C. An aqueous solution of K_2CO_3 (2 M) was used as the base. The employment of K_3PO_4 gave equally good results. 1,4-Dioxane was used throughout as the organic solvent.

The sequential addition of two different arylboronic acids allowed the direct synthesis of 2,3-diarylbenzofurans **5a**,**b** containing two different aryl groups (Scheme 3, Table 3).[16,17] The yields of the products were significantly higher when the reactions were carried out in a one-pot procedure without isolation of the mono-coupling product.



Scheme 1. Synthesis of **3a**–**h**. Conditions: (i) **2a**–**h** (2.0 equiv), $Pd(PPh_3)_4$ (5 mol %), aq K_2CO_3 (2 M), dioxane, 80 °C, 8 h.

* Corresponding author. Tel.: +49 381 4986410; fax: +49 381 4986412.
E-mail address: peter.langer@uni-rostock.de (P. Langer).

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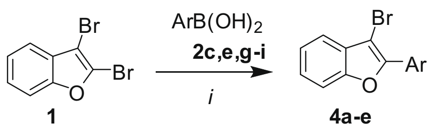
Table 1
Synthesis of 2,3-diarylbenzofurans **3a–h**

2,3	Ar	% (3)[a]
a	4-MeC_6H_4	92
b	2-MeC_6H_4	81
c	4-EtC_6H_4	86
d	4-$tBuC_6H_4$	88
e	4-ClC_6H_4	83
f	4-FC_6H_4	81
g	2-$(MeO)C_6H_4$	82
h	3,5-$Me_2C_6H_3$	79

[a] Yields of isolated products.

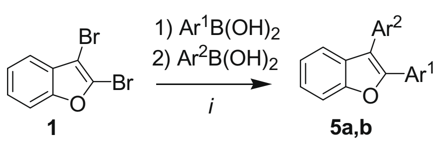


Scheme 2. Synthesis of **4a–e**. Conditions: (i) **2c**,**e**,**g–i** (1.0 equiv), $Pd(PPh_3)_4$ (5 mol %), aq K_2CO_3 (2 M), dioxane, 70 °C, 6 h.

Table 2
Synthesis of 2-aryl-3-bromobenzofuran **4a–e**

2	4	Ar	% (4)[a]
c	a	4-EtC_6H_4	86
e	b	4-ClC_6H_4	90
g	c	2-$(MeO)C_6H_4$	87
h	d	3,5-$Me_2C_6H_3$	79
i	e	2,3-$(MeO)_2C_6H_3$	82

[a] Yields of isolated products.



Scheme 3. Synthesis of **5a**,**b**. Conditions: (i) (1) **2a** (1.0 equiv), $Pd(PPh_3)_4$ (5 mol %), aq K_2CO_3 (2 M), dioxane, 70 °C, 6 h; (2) **2f**,**j** (1.0 equiv), 80 °C, 6 h.

Table 3
Synthesis of unsymmetrical 2,3-diarybenzofuran **5a**,**b**

5	Ar^1	Ar^2	% (5)[a]
a	4-MeC_6H_4	3-$(MeO)C_6H_4$	76
b	4-MeC_6H_4	4-FC_6H_4	79

[a] Yields of isolated products.

The structures of all the products **3**, **4** and **5** were established by spectroscopic methods. The structure of **5b** was independently confirmed by X-ray crystal structure analysis (Fig. 1).[18]

The first attack of palladium(0)-catalyzed cross-coupling reactions generally occurs at the less electron-rich position.[5] A simple guide for the prediction of the site-selectivity of palladium(0)-catalyzed cross-coupling reactions of polyhalogenated molecules is based on the ^{1}H NMR chemical shift values of those analogues in which the halide atom is replaced by a hydrogen atom.[19] In fact, the ^{1}H NMR signal of proton 2-H of benzofuran (7.52 ppm) appears at much lower field than the signal of proton 3-H (6.66 ppm). Position 2 of dibromobenzofuran is much less electron-rich than position 3 (Fig. 2). This is further supported by preliminary semi-empirical calculations and HMO calculations.[20]

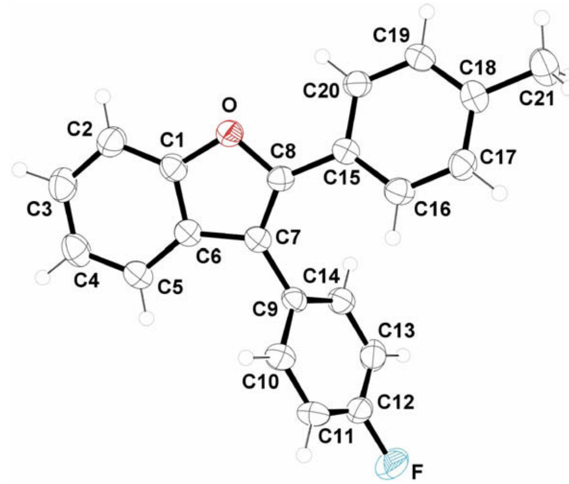


Figure 1. Crystal structure of **5b**.

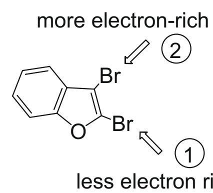


Figure 2. Possible explanation for the site-selectivity of the Suzuki–Miyaura reactions of **1**.

In conclusion, 2,3-diarylbenzofurans were prepared by Suzuki–Miyaura reactions of 2,3-dibromobenzofuran with two equivalents of boronic acids. The reaction with one equivalent of arylboronic acids resulted in site-selective formation of 2-aryl-3-bromobenzofurans. 2,3-Diarylbenzofurans containing two different aryl groups were prepared from 2,3-dibromobenzofuran in a one-pot protocol by sequential addition of two different boronic acids.

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13. *General procedure for the synthesis of* **3a**–**h** *and* **4a**–**e**: The reaction was carried out in a pressure tube. To a dioxane suspension (5 mL) of **1** (274 mg, 1.0 mmol), $Pd(PPh_3)_4$ (58 mg, 5 mol %, 0.05 mmol) and the arylboronic acid (1.0 mmol per coupling) was added an aqueous solution of K_2CO_3 (2 M, 1 mL). The mixture was heated at the indicated temperature (70–80 °C) under an argon atmosphere for the indicated period of time (6–8 h). The reaction mixture was diluted with water 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).
14. *3-Bromo-2-(2-methoxyphenyl)benzofuran* (**4c**). Compound **4c** was prepared from **1** (274 mg, 1.0 mmol) and 2-methoxyphenylboronic acid (152 mg, 1.0 mmol) as a colourless highly viscous oil (262 mg, 87%). Reaction temperature: 70 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.77 (s, 3H, OCH_3), 6.91–7.00 (m, 2H, ArH), 7.19–7.24 (m, 2H, ArH), 7.24–7.28 (m, 2H, ArH), 7.31–7.33 (m, 2H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.7 (OCH_3), 96.7 (C), 111.5, 111.6 (CH), 118.3 (C), 119.8, 120.5, 123.3, 125.2 (CH), 129.0 (C), 131.4, 131.7 (CH), 150.5, 153.9, 157.7 (C). IR (KBr): v = 3062, 3000, 2958, 2933, 2834 (w), 1610, 1586 (m), 1484, 1461, 1446, 1433 (s), 1342, 1313, 1296 (w), 1255, 1243 (s), 1200, 1180, 1162, 1120, 1107, 1073 (m), 1056, 1043, 1023, 984 (s), 932 (w), 737 (s), 667, 636, 588, 577, 534, 541 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 302 ([M]$^+$, 85), 259 (02), 223 (22), 208 (100), 165 (24), 152 (30). HRMS (EI, 70 eV): calcd for $C_{15}H_{11}BrO_2$ [M]$^+$: 301.99369; found: 301.99370.
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16. *Procedure for the synthesis of* **5a**,**b**: The reaction was carried out in a pressure tube. To a dioxane suspension (10 mL) of **1** (348 mg, 2.0 mmol), $Pd(PPh_3)_4$ (116 mg, 5 mol %, 0.10 mmol) and $Ar^1B(OH)_2$ (2.0 mmol) was added an aqueous solution of K_2CO_3 (2 M, 2 mL). The mixture was heated at 70 °C under an argon atmosphere for 6 h. The mixture was cooled to 20 °C, divided into two equal portions and $Ar^2B(OH)_2$ (1.0 mmol) was added to each portion. The reaction mixtures were heated under Argon atmosphere for 6 h at 80 °C. Each reaction mixture was diluted with water 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). Products **5a** (238 mg, 76%) and **5b** (248 mg, 79%) were isolated as colourless oils. *3-(3-Methoxyphenyl)-2-(p-tolyl)benzofuran* (**5a**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.24 (s, 3H, CH_3), 3.69 (s, 3H, OCH_3), 6.82–6.86 (m, 1H, ArH), 6.95–7.12 (m, 4H), ArH), 7.14–7.25 (m, 3H, ArH), 7.39–7.50 (m, 4H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4 (CH_3), 55.3 (OCH_3), 111.1, 113.4, 115.1 (CH), 116.7 (C), 120.0, 122.3, 122.9, 124.5, 127.0 (CH), 127.8 (C), 129.2, 130.0 (CH), 130.3, 134.4, 138.5, 150.9, 153.9, 160.1 (C). IR (KBr): v = 3031, 2997, 2917, 2832 (w), 1606, 1591, 1574, 1511, 1484 (m), 1451 (s), 1426, 1369, 1314, 1282 (m), 1246, 1234 (s), 1205, 1183, 1156, 1065, 1042 (m), 818, 742, 701 (s), 617, 610, 587, 562, 537 (w) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 314 ([M]$^+$, 56), 283 (38), 268 (100), 207 (10), 156 (11), 125 (43). HRMS (EI, 70 eV): calcd for $C_{22}H_{18}O_2$ [M]$^+$: 314.13068; found: 314.13059.
17. *3-(4Fluorophenyl)-2-p-tolylbenzofuran* (**5b**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.41 (s, 3H, CH_3), 7.17–7.31 (m, 5H, ArH), 7.35–7.40 (m, 1H, ArH), 7.50–7.54 (m, 3H, ArH), 7.57–7.61 (m, 3H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.4 (CH_3), 111.1 (CH), 115.8 (C), 116.1 (d, $J_{F,C}$ = 21.0 Hz), 119.6, 123.0, 124.6, 127.0 (CH), 127.7, 128.9 (d, $J_{F,C}$ = 3.3 Hz) (C), 129.2 (CH), 130.2 (C), 131.4 (d, $J_{F,C}$ = 8.1 Hz) (CH), 136.6, 151.1, 153.9, 162.3 (d, $J_{F,C}$ = 246.7 Hz) (C). IR (KBr): v = 3066, 3036 2918, 2853, 2790, 1613, 1601, 1557 (w), 1515, 1495 (m), 1452 (s), 1432, 1371, 1337, 1292 (3), 1254, 1230, 1216, 1205, 1196, 1182, 1156, 1091, 1066 (s), 1037, 1020, 1008, 964, 930, 897 (m), 842, 817, 811, 744 (s), 718, 716, 663, 598, 564 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 302 ([M]$^+$, 16), 283 (42), 261 (100), 188 (07), 200 (20), 148 (33). HRMS (EI, 70 eV): calcd for $C_{21}H_{15}FO$ [M]$^+$: 302.11069; found: 302.11099.
18. CCDC-764171 contains 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.
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