Tetrahedron Letters 50 (2009) 3929–3932

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Efficient synthesis of functionalized dibenzofurans by domino 'twofold Heck/6π-electrocyclization' reactions of 2,3-di- and 2,3,5-tribromobenzofuran

Munawar Hussain [a], Nguyen Thai Hung [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

ARTICLE INFO

Article history:
Received 16 March 2009
Revised 15 April 2009
Accepted 17 April 2009
Available online 23 April 2009

Keywords:
Benzofurans
Catalysis
Domino reactions
Oxygen heterocycles
Palladium

ABSTRACT

Functionalized dibenzofurans were prepared based on domino 'twofold Heck/6π-electrocyclization' reactions of 2,3-di- and 2,3,5-tribromobenzofuran.

Natural and non-natural benzofurans are of considerable pharmacological relevance and occur in many natural products.[1] For example, synthetic amiodarone represents a potent antiarrythmic and antianginal drug.[2] 7-Alkanoylbenzofurans and 7-alkanoyl-2,3-dihydrobenzofurans occur in a number of natural products, such as longicaudatin,[3] the sessiliflorols A and B, flemistrictin E, tovophenone C, vismiaguianone C or piperaduncin B.[4] Dibenzofurans are also present in a variety of pharmacologically active natural products. Examples include simple hydroxylated derivatives (such as α- and γ-cotonefuran, norascomatic acid and γ-pyrufuran) (Chart 1),[5] aryl-substituted hydroxylated derivatives (e.g., candidusin A and vialinin B),[6] brominated derivatives (e.g., corallinafuran),[7] polycyclic derivatives (such as phlorofucofuroeckol A or mallotusinin)[8] and complex glycosylated derivatives (e.g., fulicineroside).[9] A number of synthetic approaches to dibenzofurans have been reported.[10]

In recent years, it has been shown that polyhalogenated heterocycles can be regioselectively functionalized in palladium(0)-catalyzed cross-coupling reactions by selective activation of a single halogen atom. The regioselectivity is controlled by electronic and steric parameters.[11] Recently, we have reported the synthesis of aryl-substituted thiophenes,[12] pyrroles[13] and selenophenes[14] based on regioselective Suzuki reactions of tetrabromothiophene, tetrabromo-*N*-methylpyrrole and tetrabromoselenophene, respectively. Sonogashira,[15] Negishi[15] and Stille[16] coupling reactions of 2,3- and 2,6-dibromobenzofuran have been reported to regioselectively occur at position C-2. Bach and Bartels reported regioselective Negishi and Kumada cross-coupling reactions of 2,3,5-tribromobenzofuran.[17] Herein, we report what are, to the best of our knowledge, the first Heck reactions of 2,3-dibromo- and 2,3,5-tribromobenzofuran. In this context, functionalized dibenzofurans were efficiently prepared based on domino 'twofold Heck/6π-electrocyclization' reactions.[18,19]

Bach and Bartels reported that the direct bromination of benzofuran (**1**), following the conditions reported by Antognazza and co-workers ,[20] resulted in the formation of a mixture of di- and tribrominated products. Therefore, a useful and reliable stepwise protocol was developed for the synthesis of 2,3-dibromobenzofuran (**2a**).[15b] In our hands, the direct reaction of **1** with bromine (2.0 equiv) and KOAc (2.0 equiv) in CH_2Cl_2 (reflux, 4 h) afforded 2,3-dibromobenzofuran (**2a**) in 84% yield (Scheme 1). However, the reaction tends to be unreliable and depends on the scale of the reaction and on minor changes of the conditions. Bach and Bartels also reported a reliable stepwise synthesis of

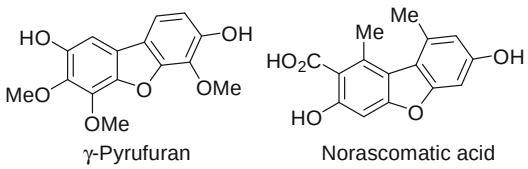
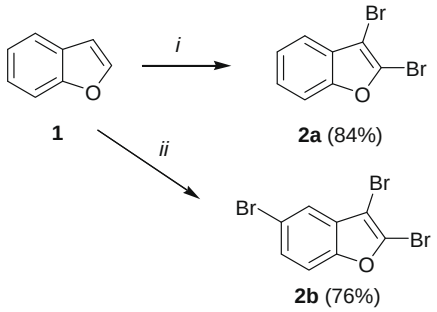


Chart 1. Structures of some naturally occurring dibenzofurans.

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

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.04.069



Scheme 1. Bromination of benzofuran (**1**). Reagents and conditions: (i) Br_2 (2.0 equiv), KOAc (2.0 equiv) CH_2Cl_2, reflux, 4 h; (ii) Br_2 (4.5 equiv), KOAc (4.5 equiv), CH_2Cl_2, reflux, 18 h.

2,3,5-tribromobenzofuran (**2b**) which was prepared from 5-bromobenzofuran in 52% yield.[15b] We have found that **2b** is available in 76% yield by reaction of **1** with bromine (4.5 equiv) and KOAc (4.5 equiv) in CH_2Cl_2 (reflux, 18 h).[21]

The Heck reaction of **2a** with acrylates **3a,d,e** (2.5 equiv) afforded the 2,3-di(alkenyl)benzofurans **4a,d,e** in good yields (Scheme 2, Table 1). The best yields were obtained when the reactions were carried out using $Pd(OAc)_2$ (5 mol %) and the biaryl monophosphine ligand SPhos (10 mol %) which was recently developed by Buchwald and coworkers.[22] The reactions were carried out in DMF at 70 °C for 12 h.[23] The employment of $Pd(PPh_3)_4$ was less successful in terms of yield. The $Pd(OAc)_2$/SPhos-catalyzed reaction of **2a** with acrylates **3a–c,e**, carried out at 100 °C rather than at 70 °C, afforded the 1,2-dihydrodibenzofurans **5a–c,e** as unseparable mixtures of isomers **B** and **C**. The formation of **5a–c,e** can be explained by a domino 'twofold Heck/thermal 6π-electrocyclization' reaction to give intermediate **A** which subsequently underwent a double bond migration. The formation of an isomeric mixture suggests that the double bond migration may proceed by a pericyclic mechanism (1,5-hydrogen shift), since an ionic mechanism (induced by protonation of the enol ether moiety of **A**) should have resulted in the exclusive formation of **B**. Heating of a xylene solution of crude **5a–c,e** in the presence of Pd/C afforded dibenzofurans **6a–c,e** in 73–84% overall yields (based on **2a**).

Table 1
Synthesis of **4a**,**d**,**e** and **6a–c**,**e**

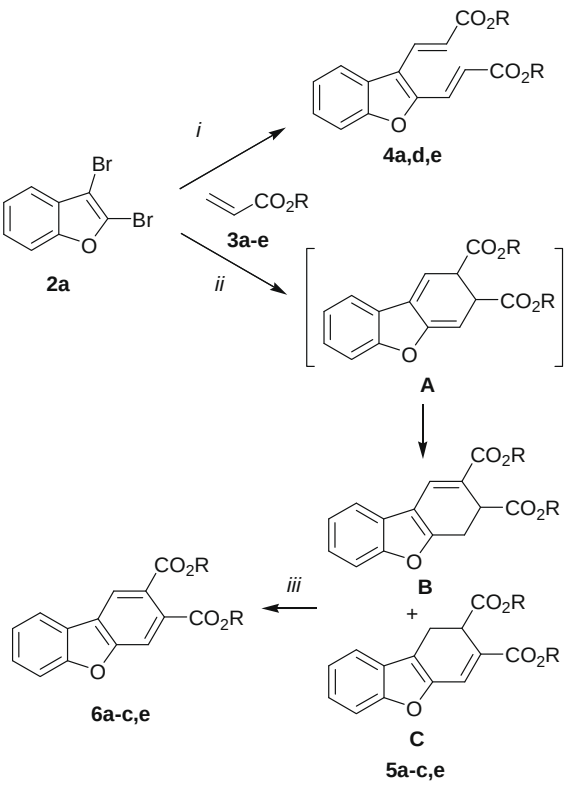
4,**6**	R	(**4**) (%)[a]	(**6**)[b] (5)
a	Et	93	73
b	*n*Bu	—[c]	76
c	*i*Bu	—[c]	84
d	*n*Hex	79	—[c]
e	*t*Bu	72	75

[a] Yields of isolated products (based on **2a**, T = 70 °C).
[b] Yields of isolated products over two steps (based on **2a**, T = 100 °C for the first step).
[c] Experiment was not carried out.

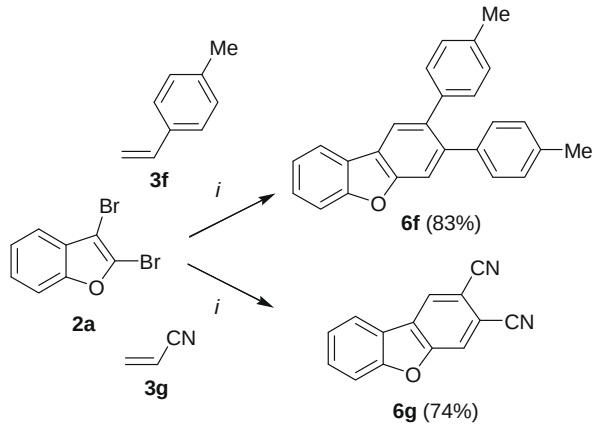
It is worth noting that, in contrast to Sonogashira and Stille reactions, the Heck reaction proved to be not regioselective. The reaction of **2a** with only 1 equiv of acrylate **3e** mainly resulted in the formation of **4e** and of starting material. This might be explained as follows. As other Pd(0)-catalyzed cross-coupling reactions of **2a** are known to regioselectively occur at position C-2,[15,16] it is expected (albeit not experimentally proven) that the Heck reaction of **2a** also first occurs at C-2. Due to the electron-withdrawing character of the (*tert*-butoxycarbonyl)alkenyl group, which is introduced at carbon C-2 in the first step, carbon C-3 becomes more electron deficient and, thus, more reactive with respect to carbon C-3 of **2a**. Alternatively, a neighbourhood effect (chelation of the Pd(0) species by the alkenyl substituent located at C-2) can be discussed.

The Heck reaction of **2a** with styrene **3f** directly afforded the dibenzofuran **6f** in 83% yield (Scheme 3). The dehydrogenation spontaneously occurred under the reaction conditions and did not require the use of Pd/C. Likewise, the Heck reaction of **2a** with acryl nitrile (**3g**) directly afforded 2,3-dicyanodibenzofuran (**6g**) in 74% yield.

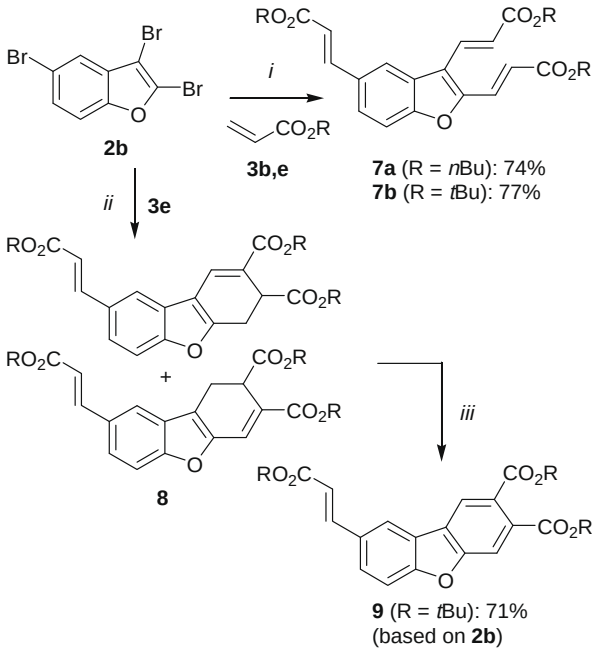
The Heck reaction of 2,3,5-tribromobenzofuran (**2b**) with acrylates **3b,e** afforded the 2,3,5-tri(alkenyl)benzofurans **7a,b** in good yields (Scheme 4). The reactions were carried out in DMF at 70 °C for 12 h. The $Pd(OAc)_2$/SPhos-catalyzed reaction of **2b** with



Scheme 2. Synthesis of **4a,d,e** and **6a–c,e**. Reagents and conditions: (i) $Pd(OAc)_2$ (5 mol %), SPhos (10 mol %), NEt_3 (8.0 equiv), DMF, 70 °C, 12 h; (ii) $Pd(OAc)_2$ (5 mol %), SPhos (structure see below, 10 mol %), NEt_3, DMF, 100 °C, 48 h; isomeric ratio **B**/**C** (assignment arbitrary): **5a** (2:1.1), **5c** (2:1), **5e** (2:0.9); (iii) Pd/C (10 mol %), xylene, reflux, 48 h.



Scheme 3. Synthesis of **6f**, **g**. Reagents and conditions: (i) $Pd(OAc)_2$ (5 mol %), SPhos (10 mol %), NEt_3, DMF, 100 °C, 48 h.



Scheme 4. Synthesis of **7a**, **b** and **9**. Reagents and conditions: (i) $Pd(OAc)_2$ (5 mol %), SPhos (10 mol %), NEt_3 (8.0 equiv), DMF, 70 °C, 12 h; (ii) $Pd(OAc)_2$ (5 mol %), SPhos (10 mol %), NEt_3, DMF, 100 °C, 48 h (isomeric ratio: 2:1, assignment arbitrary); (iii) Pd/C (10 mol %), xylene, reflux, 48 h.

acrylate **3e**, carried out at 100 °C, afforded **8** as a mixture of two isomers. Heating of a xylene solution of crude **8** in the presence of Pd/C afforded the 5-alkenyldibenzofuran **9** in 71% yield. The Heck reaction of **2b** with acrylates **3b, e**, carried out at >120 °C, mainly resulted in the formation of the hydrogenated products **10a** and **10b** which were isolated as single isomers (Chart 2). However, the exact structure (isomer **D** or **E**) could not be unambiguously assigned.

Bach and Bartels reported that the Kumada coupling of 2-aryl-3,5-dibromobenzofuran **11**, derived from **2b**, occurs at carbon atom C-5 (Chart 3).[17] We have found that the Heck reaction of **2b** with 2 equiv of acrylate **3e** resulted in functionalization of carbon atoms C-2 and C-3 and in reduction of C-5 to give **4e**. This result can be explained by the following assumption which has not yet been experimentally proven: the first reaction of **3e** with **2b** occurs at position C-2 to give intermediate **F** (Chart 3). The reactivity of carbon C-3 is increased by the neighbourhood effect of the (*tert*-butoxycarbonyl)alkenyl substituent located at carbon C-2 (vide supra). Therefore, the second attack occurs at carbon C-3 rather than at C-5.

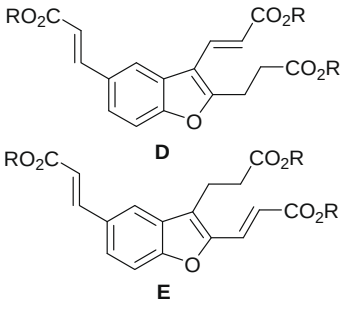


Chart 2. Products formed at temperatures higher than 120 °C.

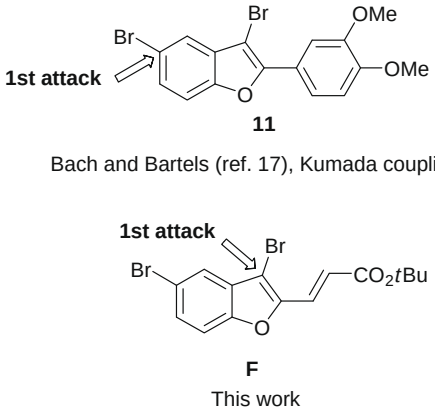


Chart 3. Regioselective reactions of **2b**.

In conclusion, 2,3-dialkenylbenzofurans and functionalized dibenzofurans were prepared based on domino 'twofold Heck/6π-electrocyclization' reactions of 2,3-di- and 2,3,5-tribromobenzofuran. The first attack of Pd(0) occurs at carbon C-2 which results in a dramatic increase of the reactivity of C-3. Therefore, the Heck reaction of 2,3-dibromobenzofuran proceeds with low regioselectivity.

Acknowledgements

Financial support by State of Pakistan (H.E.C. scholarship for M.H.), by the State of Mecklenburg-Vorpommern (scholarship for M.H.) and by the State of Vietnam (M.O.E.T. scholarship N.T.H.) is gratefully acknowledged.

References and notes

1. (a) Miyata, O.; Takeda, N.; Morikami, Y.; Naito, T. *Org. Biomol. Chem.* **2003**, *1*, 254; (b) Xie, X.; Chen, B.; Lu, J.; Han, J.; She, X.; Pan, X. *Tetrahedron Lett.* **2004**, *45*, 6235; (c) Zhang, H.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 6144; (d) Hagiwara, H.; Sato, K.; Nishino, D.; Hoshi, T.; Suzuki, T.; Ando, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2946; Review: (e) Butin, A. V.; Gutnow, A. V.; Abaev, V. T.; Krapivin, G. D. *Molecules* **1999**, *4*, 52; (f) Fuerst, D. E.; Stoltz, B. M.; Wood, J. L. *Org. Lett.* **2000**, *22*, 3521; (g) Schneider, B. *Phytochemistry* **2003**, *64*, 459; (h) Katritzky, A. R.; Kirichenkok, K.; Ji, Y.; Steel, P. J.; Karelson, M. *ARKIVOC* **2003**, *vi*, 49.
2. (a) Wendt, B.; Ha, H. R.; Hesse, M. *Helv. Chim. Acta* **2002**, *85*, 2990; (b) Carlsson, B.; Singh, B. N.; Temciuc, M.; Nilsson, S.; Li, Y. L.; Mellin, C.; Malm, J. *J. Med. Chem.* **2002**, *45*, 623; and references cited therein (c) Kwiecien, H.; Baumann, E. *J. Heterocycl. Chem.* **1997**, 1587; (d) Larock, R. C.; Harrison, L. W. *J. Am. Chem. Soc.* **1984**, *106*, 4218; (e) Matyus, P.; Varga, I.; Rettegi, T.; Simay, A.; Kallay, N.; Karolyhazy, L.; Kocsis, A.; Varro, A.; Penzes, I.; Papp, J. G. *Curr. Med. Chem.* **2004**, *1*, 61; (f) Wong, H. N. C.; Pei, Yu; Yick, C. Y. *Pure Appl. Chem.* **1999**, *71*, 1041.
3. Longicaudatin: (a) Joshi, A. S.; Li, X.-C.; Nimrod, A. C.; ElSohly, H. N.; Walker, L. A.; Clark, A. M. *Planta Med.* **2001**, *67*, 186; For related natural products, see: (b) Sigstad, E.; Catalan, C. A. N.; Diaz, J. G.; Herz, W. *Phytochemistry* **1993**, *33*, 165; (c) Drewes, S. E.; Hudson, N. A.; Bates, R. B. *J. Chem. Soc., Perkin Trans.1* **1987**, 2809.
4. Sessiliflorol A: (a) Chan, J. A.; Shultis, E. A.; Carr, S. A.; DeBrosse, C. W.; Eggleston, D. S. *J. Org. Chem.* **1989**, *54*, 2098; Sessiliflorol B: (b) Marston, A.; Zagorski, M. G.; Hostettmann, K. *Helv. Chim. Acta* **1988**, *71*, 1210; (c) Drewes, S. E.; Hudson, N. A.; Bates, R. B.; Linz, G. S. *Tetrahedron Lett.* **1984**, *25*, 105; Flemistrictin E: (d) Subrahmanyam, K.; Rao, J. M.; Vemuri, V. S. S.; Babu, S. S.; Roy, C. P.; Rao, K. V. J. *Ind. J. Chem., Sect B* **1982**, *21*, 895; Tovophenone C: (e) Seo, E.-K.; Wall, M. E.; Wani, M. C.; Navarro, H.; Mukherjee, R.; Farnsworth, N. R.; Kinghorn, A. D. *Phytochemistry* **1999**, *52*, 669; Vismiaguianone C: (f) Seo, E.-K.; Wani, M. C.; Wall, M. E.; Navarro, H.; Mukherjee, R.; Farnsworth, N. R.; Kinghorn, A. D. *Phytochemistry* **2000**, *55*, 35; Piperaduncin B: (g) Joshi, A. S.; Li, X.-C.; Nimrod, A. C.; ElSohly, H. N.; Walker, L. A.; Clark, A. M. *Planta Med.* **2001**, *67*, 186; See also: (h) Bohlmann, F.; Zdero, C. *Chem. Ber.* **1976**, *109*, 1436.
5. (a) Kokubun, T.; Harborne, J. B. *Phytochemistry* **1995**, *40*, 1649; (b) Burden, R. S.; Kemp, M. S.; Wiltshire, C. W.; Owen, J. D. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1445.
6. (a) Kobayashi, A.; Takemura, A.; Koshimizu, K.; Nagano, H.; Kawazu, K. *Agric. Biol. Chem.* **1982**, *46*, 585; (b) Ma, B.-J.; Liu, J.-K. *Z. Naturforsch. B* **2005**, *60*, 565; (c) Takahashi, A.; Kudo, R.; Kusano, G.; Nozoe, S. *Chem. Pharm. Bull.* **1992**, *40*, 3194; (d) Xie, C.; Koshino, H.; Esumi, Y.; Onose, J.-i.; Yoshikawa, K.; Abe, N. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5424.

7. Kitamura, M.; Koyama, T.; Nakano, Y.; Uemura, D. *Chem. Lett.* **2005**, *34*, 1272.
8. (a) Jaegers, E.; Hillen-Maske, E.; Steglich, W. *Z. Naturforsch. B* **1987**, *42*, 1349; (b) Anh, M.-J.; Yoon, K.-D.; Min, S.-Y.; Lee, J. S.; Kim, J. H.; Kim, T. G.; Kim, S. H.; Kim, N.-G.; Huh, H.; Kim, J. *Biol. Pharm. Bull.* **2004**, *27*, 544; (c) Liu, K. C. S. C.; Lin, M.-T.; Lee, S.-S.; Chiou, J.-F.; Ren, S.; Lien, E. J. *Planta Med.* **1999**, *65*, 43; (d) Yoshikawa, M.; Xu, F.; Morikawa, T.; Ninomiya, K.; Matsuda, H. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1045.
9. Rezanka, T.; Hanus, L. O.; Kujan, P.; Dembitsky, V. M. *Eur. J. Org. Chem.* **2005**, 2708.
10. See for example: (a) Sanz, R.; Fernández, Y.; Castroviejo, M. P.; Pérez, A.; Fañanás, F. J. *J. Org. Chem.* **2006**, *71*, 6291; (b) Serra, S.; Fuganti, C. *Synlett* **2003**, 2005; (c) Wu, M.-J.; Lee, C.-Y.; Lin, C.-F. *Angew. Chem., Int. Ed.* **2002**, *41*, 4077.
11. Review: Schröter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, *61*, 2245.
12. Dang, T. T.; Rasool, N.; Dang, T. T.; Reinke, H.; Langer, P. *Tetrahedron Lett.* **2007**, *48*, 845.
13. Dang, T. T.; Dang, T. T.; Ahmad, R.; Reinke, H.; Langer, P. *Tetrahedron Lett.* **2008**, *49*, 1698.
14. Dang, T. T.; Villinger, A.; Langer, P. *Adv. Synth. Catal.* **2008**, *350*, 2109.
15. (a) Bach, T.; Bartels, M. *Synlett* **2001**, 1284; (b) Bach, T.; Bartels, M. *Synthesis* **2003**, 925.
16. Lin, S.-Y.; Chen, C.-L.; Lee, Y.-J. *J. Org. Chem.* **2003**, *68*, 2968.
17. Bach, T.; Bartels, M. *Tetrahedron Lett.* **2002**, *43*, 9125.
18. De Meijere and coworkers reported twofold Heck reactions of 1,2-dibromocycloalk-1-enes and related substrates and subsequent 6π-electrocyclization: Voigt, K.; von Zezschwitz, P.; Rosauer, K.; Lansky, A.; Adams, A.; Reiser, O.; de Meijere, A. *Eur. J. Org. Chem.* **1998**, 1521. and references cited therein.
19. For reviews of domino reactions, see: (a) Tietze, L. F.; Beifuss, U. *Angew. Chem.* **1993**, *105*, 137. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131; (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.
20. Benincori, T.; Brenna, E.; Sannicolo, F.; Trimarco, L.; Antognazza, P. *J. Org. Chem.* **1996**, *61*, 6244.
21. *Synthesis of 2,3,5-tribromobenzofuran* (**2b**): To a CH_2Cl_2 solution (100 mL) of benzofuran (**1**) (10 mL, 125 mmol) and KOAc (55.1 g, 562.5 mmol) was added dropwise a CH_2Cl_2 solution (50 mL) of Br_2 (28.9 mL, 562.5 mmol) at 20 °C and the solution was heated under reflux for 18 h. To this solution was added a saturated solution of $Na_2S_2O_3$ and $NaHCO_3$. The organic and the aqueous layers were separated and the latter was extracted with CH_2Cl_2 (3×40 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by column chromatography (flash silica gel, pure heptanes) to yield **2b** as a colourless solid (33.5 g, 76%).
22. Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358. and references cited therein.
23. *General procedure for the synthesis of dibenzofurans* **6a–c**,**e** *and* **9a**: In a pressure tube a DMF suspension (5 mL) of $Pd(OAc)_2$ (12 mg, 0.05 mmol, 2.5 mol % per Br atom of the substrate) and dicyclohexyl (2′,6′-dimethoxybiphenyl-2-yl)phosphine (SPhos) (41 mg, 0.10 mmol) was purged with argon and the mixture was stirred at 20 °C to give a yellowish to brownish clear solution. To the stirred solution were added **2a** or **2b** (1.0 mmol), NEt_3 (1.1 mL, 8.0 mmol) and the acrylate **3** (1.25 equiv per Br atom of the substrate). The reaction mixture was stirred at 100 °C for 48 h. The solution was cooled to 20 °C, poured into H_2O and CH_2Cl_2 (25 mL each), and the organic and the aqueous layers were separated. The latter was extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were washed with H_2O (3×20 mL), dried (Na_2SO_4) and concentrated in vacuo. To the crude material were added xylene (3 mL) and Pd/C (30 mg, 10 mol %). The solution was stirred under reflux for 48 h under argon atmosphere. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (flash silica gel, heptanes/EtOAc) to give **6a–c,e** or **9a**. *Diisobutyl dibenzo[b,d]furan-2,3-dicarboxylate* (**6c**): Starting with **2a** (276 mg, 1.0 mmol), **6c** was prepared as a brownish highly viscous oil (305 mg, 84%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.94 (d, 6H, J = 6.8 Hz, $2CH_3$), 0.95 (d, 6H, J = 6.78 Hz, $2CH_3$), 1.93–2.10 (m, 2H, 2CH), 4.10 (d, 4H, J = 6.8 Hz, $2CH_2O$), 7.30–7.37 (m, 1H, ArH), 7.43–7.56 (m, 2H, ArH), 7.82 (s, 1H, ArH), 7.91–7.95 (m, 1H, ArH), 8.27 (s, 1H, ArH). ^{13}C NMR (62 MHz, $CDCl_3$): δ 19.2 ($4CH_3$), 27.7, 27.8 (CH), 71.9, 72.0, (CH_2O), 112.1, 112.5, 121.4, 122.0 (CH), 123.6 (C), 124.1 (CH), 126.3, 127.3 (C), 128.7 (CH), 131.8, 156.6, 157.5 (C), 167.5, 167.6 (CO). IR (KBr): ν = 3072, 2959, 2873 (m), 1719 (s), 1636, 1602, 1577 (w), 1454, 1393, 1376, 1350, 1306 (m), 1274, 1239, 1219, 1778, 1111, 1100, 1060 (s), 1011, 983 (m), 945, 900, 848, 881, 767 (w), 746 (m), 722, 694, 602, 564 cm^{-1}. MS (EI, 70 eV): m/z (%) = 368 ([M]$^+$, 9), 312 (4), 256 (62), 239 (100), 212 (13), 195 (10). HRMS (EI, 70 eV): calcd for $C_{22}H_{24}NO_5$ [M]$^+$: 368.16183; found: 368.16179.