Regioselective C–C Bond Formation Reactions on 2,3-Dibromo- and 2,3,5-
Tribromobenzofuran as an Access to Multiply Substituted Benzofurans.
Total Syntheses of Eupomatenoids 3, 4, 5, 6, and 15

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Dedicated to Professor Gernot Boche on the occasion of his 65th birthday.

Abstract: Regioselective C–C-bond formation reactions at 2,3-di-
brombobenzofuran (1) and 2,3,5-tribromobenzofuran (6) were studied. Pd-catalyzed Sonogashira and Negishi cross-coupling occurred with perfect regioselectivity at carbon atom C-2 to provide 2-substi-
tuted 3-bromobenzofurans (12, 14) and 3,5-dibromobenzofurans (17, 18) in 50–91% yield. A regioselective displacement of the bro-
mine substituents in 3,5-dibromobenzofurans 18 was achieved by a halogen-metal exchange reaction at carbon atom C-3 and by a Ni-
catalyzed Kumada cross-coupling at C-5. The methodology was ap-
plied to the synthesis of eupomatenoids 3, 4, 5, 6, and 15 (5). The synthesis of these compounds was achieved in overall yields of up to 60%.

Key words: benzofurans, cross coupling, natural products, oxygen
heterocycles, regioselectivity

Conventional strategies for the synthesis of multiply sub-
stituted benzofurans center either on the formation of the heterocyclic framework after introduction of the appropri-
ate substitution pattern or on the introduction of the sub-
stituents to the pre-formed heterocycle.1 For the latter purpose transition-metal catalyzed cross-coupling reac-
tions have been frequently employed to replace a halogen
atom by a carbon substituent.2 Pd(0)-catalysis has been
applied in many instances and there is precedence for
cross-coupling reactions to occur at almost all relevant
carbon atoms of the benzofuran skeleton, i.e. at atoms C-2,3 C-3,3a,4 C-5,4b,5 C-6,5d and C-7,4b,5d,6 Cu-mediated
C–C-bond forming reactions have also been observed and
examples include the nucleophilic displacement of halog-
en atoms at positions C-2,7 C-3,8 C-5,9 C-6,8c,f and C-7,10
Along the same lines, Heck reactions have been conduct-
et at atoms C-3,11 C-5,12 and C-7,13 In all these cases, po-
sition- or regioselectivity problems were not addressed as
the substitution position was unambiguously determined by
the location of the halogen atom. Reactions of multiply
halogen-substituted benzofurans in which a halogen atom
is selectively replaced are limited. The selective bromine-
lithium exchange at the 2-position of 2,3-dibromobenzo-
fururan (1) was reported by Cugnon de Sevricrot and Robb14
and has been first observed by Wittig15 (Scheme 1). The crystal structure of 3-bromo-2-lithiobi-

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ence of a base (e.g. KOAc). Typically, mixtures of 2,3-dibromobenzofuran (1) and the corresponding 2,3-dibromo-2,3-dihydrobenzofuran (7) were obtained which could not be separated (Figure 1). To circumvent this problem, the reaction was conducted in a step-by-step fashion. A quantitative bromine addition was achieved in 89% yield under controlled conditions (see Experimental Section). The addition product 7 was converted to 3-bromobenzofuran 9 by treatment with ethanolic KOH (84%). The final bromination to the desired product 1 occurred quantitatively.

Starting from 5-bromobenzofuran the same sequence was not as straightforward. Upon treatment with bromine, addition product 8 and substitution product 6 were obtained in varying amounts depending on the amount of bromine used. For best results, it was ideal to employ two equivalents of bromine and to separate the products subsequently (41% 8, 23% 6). In analogy to the conversion 7→1, the addition product 8 was treated with KOH in EtOH to yield a mixture of the dibromobenzofurans 10 and 11 (86%) which were brominated subsequently (95%). Overall, 2,3-dibromobenzofuran (1) could be obtained in a total yield of 75% from benzoferan and 2,3,5-tribromobenzofuran (6) from 5-bromobenzofuran in 52%.

The first set of cross-coupling reactions was conducted with dibromobenzofuran 1 and acetylenes (Sonogashira cross-coupling) under varying conditions. Based on previous experience, PdCl₂(PPh₃)₂ and CuI were used as the catalysts. Best results were obtained using the Krause modification of the Sonogashira cross-coupling, i.e. the stoichiometric use of the amine base in THF as the solvent (Figure 2, Table 1). Contrary to our preliminary observations we found that triethylamine was suitable in several reactions (entry 2, 5, 7). As the reactions were performed on small scale the use of 10 mol% Pd-catalyst was chosen for convenience. On larger scale, 5 mol% catalyst was equally sufficient.

In further experiments with compound 1, a Negishi cross-coupling was attempted. The Grignard reagent obtained from aryl bromide (Mg, THF) was transmetalated to zinc by treatment with a solution of anhydrous zinc chloride in THF. The subsequent reaction with 2,3-dibromobenzofuran (1) was not successful, however. A more reactive arylzinc compound was generated by bromine-lithium exchange with t-butylthiium and transmetalation. This reagent underwent a clean regioselective cross-coupling and afforded the 3-bromobenzofuran (Scheme 3).

The synthetic strategy for the construction of multiply substituted heterocycles by cross-coupling reactions requires not only an initial regioselective reaction but also subsequent reactions to occur at the less reactive position. In the furan series we found the introduction of a methyl group in the 3-position of 2-alkynyl substituted 3-bromo-
Furans was possible with MeZnCl/PdCl2(PPh3)2 in THF under reflux.17 The same reaction failed for 2-allyl- and 2-aryl-3-bromofurans. As an alternative, we described the Stille reaction with SnMe4 and PdCl2(Po-Tol3)2 in N,N-dimethylacetamide (DMA) at elevated temperature. It was consequently a pleasant surprise that the installation of a methyl group in 3-bromobenzofurans, such as 12a and 14, could be achieved under mild conditions with a less toxic reagent. The reaction proceeded with MeZnCl/PdCl2(PPh3)2 in THF at room temperature and yielded the 2,3-dibromofurans 15 and 16.21a

By analogy with the cross-coupling reactions at the 2-position of 2,3-dibromobenzofuran (1), similar reactions with 2,3,5-tribromobenzofuran (6) were conducted. The reactions proceeded uneventfully. Again, no regiosomer could be detected. The Sonogashira cross-coupling [alkyne, PdCl2(PPh3)2, CuI, Et2NH in THF] gave access to the 3,5-dibromofurans 17 (Figure 3). As previously observed, the reaction with propargyl methyl ether was sluggish and the yield of product 17d was only moderate. All other reactions proceeded nicely in high yields. The arylzinc reagents, which had to be coupled with benzo furan 6, were selected based on the occurrence of the 2-aryl substituents in eupomatenoids. The organometallic reagents were prepared from the corresponding bromoarenes by bromine-lithium exchange and transmetalation. The cross-coupling yields improved slightly upon lowering the amount of catalyst from 10 mol% to 5 mol%. The yields given in Figure 3 refer to the use of 5 mol% of PdCl2(PPh3)2 and 1.5 equivalents of ArZnCl relative to substrate 6. The latter was employed as the limiting reagent (THF, r.t.). The position at which the coupling occurred was easily detected by the 13C NMR high-field shift of the relevant carbon atom. This phenomenon has been extensively observed in previous reactions.17,18,21

Whereas the cross-coupling reactions at C-2 proceeded equally well for both the dibromobenzofuran 1 and the tribromobenzofuran 6 significant differences in reactivity became apparent comparing the bromobenzofurans 12a and 14 and the dibromobenzofurans 17a and 18a. The reaction conditions, which had facilitated a clean cross-coupling at the carbon atom C-3 of substrate 14 (Scheme 3) failed completely with dibromobenzofuran 18a. After some experimentation we found that PdCl2(dppf) [dppf = bis(diphenylphosphino)ferrocene] is a catalyst suitable to promote the desired bromine displacement but the regioselectivity was unsatisfactory. With 3 equivalents of MeZnCl as the reagent in THF at reflux a statistical mixture of four compounds was observed, i.e. the starting material 18a, a 3-methyl-5-bromobenzofuran, the isomeric 5-methyl-3-bromobenzofuran and the trisubstituted 3,5-dimethylbenzofuran 19. A complete conversion to the latter product was achieved upon treating substrate 18a with an excess (6 equiv) of the reagent (Equation 1) and heating the mixture for 18 hours in refluxing THF. Microwave irradiation can replace the thermal heating. The same reaction was conducted in a microwave oven (CEM Mars X, P = 150 W, T = 50 °C, t = 1 h) in 64% yield.

Equation 1 Unselective Negishi cross-coupling reaction of MeZnCl and 3,5-dibromobenzofuran 18a

As an alternative nucleophile 1-prop-1-enyl zinc chloride was tested in cross-coupling reactions with substrate 18a. The reagent was prepared by transmetalation from commercially available Grignard reagent or from the lithium reagent, which in turn was prepared by reductive metalation of 1-bromo-1-propene. The choice of the nucleophile was due to the presence of a prop-1-enyl group in the...

Figure 3 Products 17 and 18 of the regioselective cross coupling reactions conducted with 2,3,5-tribromobenzofuran (6) and yields under optimized conditions
eupomatenoids (cf. Scheme 2). No cross-coupling reactions were observed irrespective of the Pd catalyst chosen. Parallel to the cross-coupling studies we started to look at other methods for the differentiation between carbon atom C-3 and C-5. Preliminary experiments were conducted by treatment of 3,5-dibromobenzofuran 17a with t-butyl-lithium (2.1 equiv) at −78 °C and subsequent quenching with water. A selective bromine–lithium exchange at carbon atom C-3 was indicated by the selective formation of a 5-bromobenzofuran relative to its 3-bromoisomer (11:1). Given the high preference for one isomer, the analogous reactions conducted with substrate 18a were disappointing at first. A bromine–lithium exchange at −78 °C and a subsequent methylation at 0 °C yielded a 1:1 mixture of regioisomers. The selectivity could, however, be improved to a ratio of 3:1 in favor of product 21a (Scheme 4) by the addition of methyl iodide at −78 °C. Although the substitution did not occur to a significant extent at this temperature it apparently set in upon slowly warming the reaction mixture to room temperature. Quenching the same reaction mixture at −78 °C with water delivered a 4:1 ratio of the corresponding bromobenzofurans. The selectivity for the bromine displacement achieved with the dibromobenzofurans 18b and 18c was even higher. The 5-bromobenzofuran 21b was the exclusive product formed in the reaction of 18b. The regioselectivity in favor of product 21c was 10:1 and it was isolated as a single isomer in 75% yield. Quenching experiments with water at −78 °C yielded similar results concerning the regioselectivity.

Scheme 4 Selective bromine–lithium exchange/methylation for the synthesis of the 2,3-disubstituted 5-bromobenzofurans 21

While searching for possible methods for the further transformation of compounds 21 to the corresponding eupomatenoids we again faced the problem of introducing a prop-1-enyl group at carbon atom C-5. It required some experimentation to find out that the Kumada cross-coupling of the Grignard reagent is an excellent solution to this problem (Equation 2). NiCl₂(dppe) was the catalyst of choice [dppe = bis(diphenylphosphino)ethane]. The reaction yielded directly eupomatenoids 5a and 5b as a mixture of (E)/(Z)-isomers. The TBDMs-protected eupomatenoid-6 (5c) was also obtained. It should be mentioned that Engler et al. have described the transformation of iodides related to 21 to the corresponding propenyl substitution products by the use of 1-prop-1-enyltributyltin.²³

Equation 2 Kumada cross-coupling of 5-bromofurans 21 to the 3-prop-1-enyl-substituted products 5

Although the isomerization of the diastereoisomeric product mixtures (E)/(Z)-5 to the naturally occurring (E)-isomers is facile³⁴,²⁵ and the deprotection of compound 5c is straightforward, these reactions were not conducted at this stage. Instead, we tested the Kumada cross-coupling for its regioselectivity in the conversion of compounds 18. Gratifyingly, a complete regioselectivity in favor of the desired cross-coupling products 22 was observed (Scheme 5)! The reaction was generally applicable and yielded the desired products in high yields (Table 2). In a subsequent reaction step the methyl-de-bromination was achieved at position C-3. MeZnCl was used as the reagent of choice for the latter transformation under conditions previously established for the cross-coupling at positions C-3 and C-5 (cf. Equation 1). The required amount of MeZnCl was slightly lower than the amount used for the double substitution. In general, 3.5–4 equivalents of the zinc compound were used to achieve a complete conversion.

Scheme 5 Kumada cross-coupling at the C-5 position of benzofurans 18 and sequential Negishi cross-coupling at the C-3 position of benzofurans 22
The syntheses of eupomatenoids was completed by equilibrating the mixture of (E)/(Z)-5 to the thermodynamically more stable, naturally occurring (E)-isomers. To this end, the mixture was treated with catalytic amounts of iodine and irradiated with visible light.\textsuperscript{20d,25} The reaction proceeded quantitatively in all cases and gave access to the eupomatenoids depicted in Scheme 6. The removal of the silyl protective groups was conducted with tetrabutylammonium fluoride (TBAF) in THF.

Further functional group transformations are conceivable which allow for the synthesis of oxygenated eupomatenoids. For example, eupomatenoid-9 can be prepared from O-acetylepomatenoid-5\textsuperscript{19b} or from intermediate 5e\textsuperscript{21b} by a dihydroxylation sequence.

In summary, we have demonstrated that the introduction of up to three different substituents into the benzofuran nucleus is possible by sequential organometallic reactions. The most straightforward entry is based on three consecutive cross-coupling reactions, which enable the substitution of three bromine atoms in 2,3,5-tribromobenzofuran (6) in the order C-2 (Sonogashira or Negishi cross-coupling), C-5 (Kumada cross-coupling) and C-3 (Negishi cross-coupling). Based on previous experience\textsuperscript{17,18} a broad range of other reagents is expected to follow the same reactivity pattern. The introduction of alkyl groups at C-2 by a Negishi cross-coupling should be feasible or it should be possible to install other substituents than methyl at C-3 using Stille and Suzuki type cross-coupling reactions. In this respect, our method appears to offer a versatile and flexible route to 2,3-disubstituted and 2,3,5-trisubstituted benzofurans.

All reactions involving water-sensitive chemicals were carried out in flame-dried glassware with magnetic stirring under Ar. All experiments were performed in Fluka p.a. solvents. Common solvents for chromatography (Et\textsubscript{2}O, pentane, EtOAc) were distilled prior to use. TLC was performed on aluminum sheets (0.2 mm silica gel 60 F\textsubscript{254}) with detection by UV (254 nm) or by coloration with ceric ammonium molybdate (CAM). Flash chromatography was performed on silica gel 60 (Merck, 230–400 mesh) (ca. 50 g for 1 g of material

Table 2 Yields Achieved in the Cross-Coupling Reactions at the C-5 Position of Benzofurans 18 and at the C-3 Position of Benzofurans 22

<table>
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<th>Yield (%)\textsuperscript{a}</th>
<th>Product</th>
<th>Yield (%)\textsuperscript{a}</th>
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<td>64</td>
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<tr>
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<tr>
<td>18e X = OMe; Y = OTBDMS</td>
<td>22e</td>
<td>89</td>
<td>5e</td>
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</table>

\textsuperscript{a}Yield of isolated product.

Scheme 6 Overview of the eupomatenoids obtained by regioselective cross-coupling reactions starting from 2,3,5-tribromobenzofuran (6)

Table 3 \textsuperscript{13}C NMR Data for the 2-Alkynylbenzofurans 12, 15, and 17

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to be separated) with the indicated eluent. Melting points (uncorrected) were recorded on a Reichert hot bench. IR were obtained on a Bruker IFS-200 FT-IR, Perkin Elmer PE 241. MS were recorded on a Varian CH7 (EI). HRMS were obtained using a Finnigan MAT 95S or MAT 8200. GC-MS were carried out on a Agilent 6890 (GC system), Agilent N7873 (Mass selective detector). 1H- and 13C NMR spectra were conducted on a Bruker ARX-200, Bruker AMX-250 and AV-360. 1H- and 13C NMR spectra were recorded at 303 K. Chemical shifts are reported relative to tetramethylsilane as an internal reference. The multiplicities of the 13C NMR signal were determined by DEPT experiments.

### 2,3,5-Tribromo-2,3-dihydrobenzofuran (8)

A solution of Br$_2$ (1.92 mL, 6.00 g, 30.5 mmol) in CH$_2$Cl$_2$ (5 mL) was slowly added to a solution of 5-bromobenzofuran (2.00 g, 10.1 mmol) in CH$_2$Cl$_2$ (5 mL). The reaction mixture was heated to reflux for 5 h and after cooling to r.t., the reaction was quenched with a sat. solution of NaHSO$_3$ (15 mL). The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na$_2$SO$_4$. Filtration, evaporation of the solvent, and further purification by flash chromatography on silica gel (pentane) gave 1.48 g (4.14 mmol, 41%) of 2,3,5-tribromo-2,3-dihydrobenzofuran (8) and 0.83 g (2.34 mmol, 23%) of 2,3,5-tribromobenzofuran (6).

### 3,5-Dibromobenzofuran (10)

A solution of Br$_2$ (0.51 mL, 10.0 mmol, 1.60 g) in CH$_2$Cl$_2$ (5 mL) was slowly added to a solution of 3,5-dibromobenzofuran (10) (2.35 g, 8.50 mmol) in CH$_2$Cl$_2$ (20 mL). The solution was heated to reflux for 16 h. After cooling to r.t. a solution of sat. NaHSO$_3$ (15 mL) was added. The aqueous layer was extracted with CH$_2$Cl$_2$ (15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na$_2$SO$_4$. Filtration, evaporation of the solvent, and further purification by flash chromatography on silica gel (pentane) gave 2.84 g (7.41 mmol, 95%) of 2,3,5-dibromobenzofuran (6).

### Benzo furan 1

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<td>128.0</td>
<td>112.7</td>
<td>151.9</td>
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<td>122.4</td>
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<td>56.0, 56.1; 109.9; 111.2; 120.3; 121.8; 149.0; 150.3</td>
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<td>91.2</td>
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<td>128.0</td>
<td>112.6</td>
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<td>109.2</td>
<td>133.4</td>
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<td>126.6</td>
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<td>152.4</td>
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<tr>
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<td>-4.4, 9.3, 18.2, 25.7, 120.4, 124.1, 128.2, 156.0</td>
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### 1H NMR (200 MHz, CDCl$_3$): δ = 7.28 (dd, 1 H), 7.18 (dd, 1 H), 7.09 (dd, 1 H), 6.83 (dd, 1 H), 5.90 (dd, 1 H), 5.80 (dd, 1 H), 5.69 (s, 1 H), 5.59 (s, 1 H), 3.06 (s, 2 H), 2.79 (s, 2 H), 2.73 (s, 2 H), 2.58 (s, 2 H), 2.50 (s, 2 H), 2.23 (s, 2 H), 2.15 (s, 2 H), 2.07 (s, 2 H), 1.99 (s, 2 H), 1.92 (s, 2 H), 1.84 (s, 2 H), 1.77 (s, 2 H), 1.70 (s, 2 H), 1.59 (s, 2 H), 1.52 (s, 2 H), 1.44 (s, 2 H), 1.36 (s, 2 H), 1.28 (s, 2 H), 1.20 (s, 2 H), 1.12 (s, 2 H), 1.04 (s, 2 H), 0.96 (s, 2 H), 0.88 (s, 2 H), 0.80 (s, 2 H), 0.72 (s, 2 H), 0.64 (s, 2 H), 0.56 (s, 2 H), 0.48 (s, 2 H), 0.40 (s, 2 H), 0.32 (s, 2 H), 0.24 (s, 2 H), 0.16 (s, 2 H), 0.08 (s, 2 H), 0.00 (s, 2 H).

#### Synthesis 2003, No. 6, 925–939 ISSN 0039-7881 © Thieme Stuttgart · New York
aqueous layer was extracted with Et₂O (2 × 5 mL/mmol). The combined organic layers were washed with brine (5 mL/mmol) and dried over Na₂SO₄. The mixture was filtered, the solvent evaporated and the crude product purified by flash chromatography.

3-Bromo-2-(3,3-dimethyl-but-1-ynyl)-benzofuran (12a)
Prepared according to general procedure A. Benzofuran (552 mg, 2.0 mmol), CuI (38.0 mg, 0.2 mmol), PdCl₂(PPh₃)₂ (70.2 mg, 0.1 mmol) and Et₂NH (0.16 mL, 1.5 mmol) were used. Purification by flash chromatography on neutral aluminum oxide (pentane) gave 432 mg (1.56 mmol, 78%) of 3-bromo-2-(3,3-dimethyl-but-1-ynyl)-benzofuran (12a).

R₁: 0.56 (pentane).

IR (film): 2971 (s, C=O), 2930 (s, C alkyl H), 2219 (m, C=O), 1732 (w, C=O), 1568 (m, C=C), 1446 (s, C=C), 1353 (m), 1259 (m), 1213 (s), 1025 (s), 750 cm⁻¹ (s, C aryl H).

MS (EI, 70 eV):
- m/z (%) = 266/264 (31/49) [M⁺], 235/233 (40/38) [M⁺ – Me], 183 (18), 139 (10), 85 (6).
- m/z (%) = 298/296 (19/20) [M⁺], 229/227 (29/31), 171 (100), 155 (27), 143 (22), 127 (24), 115 (42), 98 (20), 86 (24), 62 (18).


3-Bromo-2-phenylethenyl-benzofuran (12b)
Prepared according to general procedure A. Benzofuran (552 mg, 2.0 mmol), CuI (38.0 mg, 0.2 mmol), PdCl₂(PPh₃)₂ (70.2 mg, 0.1 mmol) and Et₂NH (0.32 mL, 3.0 mmol) in THF (10 mL) were used. Purification by flash chromatography on silica gel (pentane–EtOAc, 99:1) yielded 200 mg (0.68 mmol, 68%) of (3-bromobenzofuran-2-yl)-ethynyl-trimethyl-silane (12b).

R₁: 0.46 (pentane).

IR (film): 2960 (m, C=O), 2907 (w, C alkyl H), 2215 (w, C=O), 1732 (m, C=O), 1568 (w, C=C), 1446 (s, C=C), 1353 (m), 1259 (m), 1213 (s), 1025 (s), 750 cm⁻¹ (s, C aryl H).

HR-MS: m/z calcd for C₁₃H₁₃BrOSi (293.2): C, 53.25; H, 4.47. Found: C, 53.39; H, 4.53.

4-(3-Bromobenzofuran-2-yl)-but-3-yn-1-ol (12c)
Prepared according to general procedure A. Benzofuran (552 mg, 2.0 mmol), CuI (38.0 mg, 0.2 mmol), PdCl₂(PPh₃)₂ (70.2 mg, 0.1 mmol) and Et₂NH (0.32 mL, 3.0 mmol) in THF (10 mL) were used. Purification by flash chromatography on silica gel (pentane–EtOAc, 99:1) gave 424 mg (1.60 mmol, 80%) of 4-(3-bromobenzofuran-2-yl)-but-3-yn-1-ol (12c).

Mp 96 °C; R₁: 0.52 (pentane–EtOAc).

IR (KBr): 3250 (m, OH), 2925 (w, C=O), 2208 (w, C=O), 1737 (m, C=O), 1568 (m, C=C), 1446 (s, C=C), 1345 (m), 1259 (m), 1187 (m), 1066 (s), 746 cm⁻¹ (s, C=C=O).


3-Bromo-2-(3-methoxy-prop-1-ynyl)-benzofuran (12d)
Prepared according to general procedure A. Benzofuran (552 mg, 2.0 mmol), CuI (38.0 mg, 0.2 mmol), PdCl₂(PPh₃)₂ (140.4 mg, 0.2 mmol) and Et₂NH (0.32 mL, 3.0 mmol) in THF (10 mL) were used. Purification by flash chromatography on silica gel (pentane–EtOAc, 99:1) gave 267 mg (1.00 mmol, 50%) of 3-bromo-2-(3-methoxy-prop-1-ynyl)-benzofuran (12d).

R₁: 0.51 (pentane).

IR (film): 2930 (m, C=O), 2907 (w, C alkyl H), 2215 (w, C=O), 1732 (m, C=O), 1568 (w, C=C), 1446 (s, C=C), 1353 (m), 1259 (m), 1213 (s), 1025 (s), 750 cm⁻¹ (s, C aryl H).

HR-MS: m/z calcd for C₁₆H₁₉BrO (295.9): C, 54.37; H, 4.53. Found: C, 54.38; H, 4.53.
EtOAc, 99:1) gave 133 mg (0.50 mmol, 50%) of 4-(3-bromobenzofuran-2-yl)-3-yn-2-ol (12g).

Mp 90 °C; Rf 0.31 (pentane–EtOAc, 99:1).

IR (KBr): 3298 (s, OH), 2986 (w, C=H), 2363 (w, C=C), 1656 (w, C=C), 1445 (s, C=C), 1321 (s), 1113 (s), 1071 (s), 1047 (s), 1018 (s, CBr), 899 (m), 862 (m), 741 cm–1 (s, C=C).

1H NMR (200 MHz, CDCl3): δ = 1.61 (d, J = 6.5 Hz, 3 H), 2.41 (s, 1 H), 4.85 (q, J = 6.5 Hz, 2 H), 7.25–7.39 (m, 4 H).

MS (EI, 70 eV): m/z (%) = 266/264 (41/40) [M+], 251/249 (28/34) [M–Me], 185 (100) [M–Br], 170 (18), 142 (46), 128 (14), 113 (12).


Negishi Cross-Coupling: General Procedure B

The aryl bromide (1.5 equiv) was dissolved in THF and cooled to –78 °C and t-BuLi (1.5 M solution in pentane; 3 equiv) was slowly added. After stirring for 30 min at –78 °C ZnCl2 (0.5 or 1.0 mol solution in THF, 1.7–2.0 equiv) was added and after an additional 10 min at –78 °C the solution was warmed to r.t. This solution was then added to a mixture of the benzofuran derivative [2,3-dibromobenzofuran (1) or 2,3,5-tribromobenzofuran (6), 1 equiv] and...
PdCl₂(PPh₃)₂ (5 or 10 mol%) in THF. The reaction mixture was stirred for 2–18 h at r.t. Subsequently, Et₂O (10 mL/mmol benzofuran) was added and the mixture was washed with 2 N HCl (10 mL/mmol) and H₂O (10 mL/mmol). The aqueous layers were extracted with Et₂O (10 mL/mmol), the combined organic layers were washed with brine (10 mL/mmol) and dried over Na₂SO₄. After filtration and evaporation of the solvent the crude product was purified by flash chromatography.

3-Bromo-2-(4-methoxy-phenyl)-benzofuran (14)
Prepared according to general procedure B. 1-Bromo-4-methoxy-benzene (0.56 mL, 4.5 mg, 4.5 mmol), t-BuLi (1.5 M solution in pentane; 6.30 mL, 9.5 mmol), ZnCl₂ (1 M solution in THF; 5.80 mL, 5.80 mmol), benzofuran (890 mg, 4.10 mmol), and PdCl₂(PPh₃)₂ (105 mg, 0.15 mmol) were used. The reaction mixture was stirred at r.t. for 18 h. Purification by flash chromatography on silica gel (pentane:EtOAc, 98:2) gave 382 mg (0.97 mmol, 67%) of 3-bromo-2-(4-methoxy-phenyl)-benzofuran (14).

IR (KBr): 2988 (w, C alkyl H), 1606 (m, C=C), 1537 (s, C=C), 1440 (m, C=C), 1417 (m), 1385 (m), 1320 (s), 1175 (m), 1132 (m), 1081 (m), 1031 (s), 970 cm⁻¹ (m, C aryl H).

¹H NMR (250 MHz, CDCl₃): δ = 3.85 (s, 3 H), 6.99 (d, J = 8.5 Hz, 2 H), 7.30 (d, J = 7.5 Hz, 1 H), 7.38 (dd, J = 7.5 Hz, J = 1.8 Hz, 1 H), 7.62 (d, J = 1.8 Hz, 1 H), 8.06 (dd, J = 8.5 Hz, 2 H).

MS (ES): m/z (%) = 304/302 (99/100) [M⁺], 289/287 (39/38) [M⁺ – Me], 261/259 (21/22) [M⁺ – Br], 195 (23), 180 (15), 152 (44), 126 (14).


Mp 129 °C; Rₜ 0.32 (pentane–EtOAc, 98:2).

IR (KBr): 2988 (w, C=H), 1606 (m, C=C), 1587 (s, C=C), 1440 (m, C=C), 1381 (m), 1256 (s), 1175 (m), 1031 (m), 788 cm⁻¹ (m, C=C), 779 cm⁻¹ (m, C=C), 739 cm⁻¹ (m, C=C).

¹H NMR (250 MHz, CDCl₃): δ = 3.85 (s, 3 H), 6.99 (d, J = 8.5 Hz, 2 H), 7.30 (d, J = 7.5 Hz, 1 H), 7.38 (dd, J = 7.5 Hz, J = 1.8 Hz, 1 H), 7.62 (d, J = 1.8 Hz, 1 H), 8.06 (dd, J = 8.5 Hz, 2 H).

MS (ES): m/z (%) = 304/302 (99/100) [M⁺], 289/287 (39/38) [M⁺ – Me], 261/259 (21/22) [M⁺ – Br], 195 (23), 180 (15), 152 (44), 126 (14).


5-(3,5-Dibromobenzofuran-2-yl)-benzo[1,3]dioxole (18b)
Prepared according to general procedure B. 5-Bromo-benzo[1,3]dioxole (452 mg, 2.20 mmol), t-BuLi (1.5 M solution in pentane, 3.33 mL, 4.70 mmol), ZnCl₂ (0.5 M solution in THF, 4.80 mL, 2.40 mmol), benzofuran (532 mg, 1.5 mmol), and PdCl₂(PPh₃)₂ (50.1 mg, 0.08 mmol) were used. The reaction mixture was stirred at r.t. for 18 h. Purification by flash chromatography on silica gel (pentane–EtOAc, 98:2) gave 382 mg (0.97 mmol, 67%) of 5-(3,5-dibromobenzofuran-2-yl)-benzo[1,3]dioxole (18b).

IR (KBr): 3004 (w, C alkyl H), 2833 (w, C alkyl H), 1606 (m, C=C), 1502 (s, C=C), 1450 (s, C=C), 1258 (s), 1180 (m), 1031 (s), 831 (s), 739 cm⁻¹ (m, C alkyl H).

¹H NMR (250 MHz, CDCl₃): δ = 3.85 (s, 3 H), 6.99 (d, J = 8.5 Hz, 2 H), 7.30 (d, J = 7.5 Hz, 1 H), 7.38 (dd, J = 7.5 Hz, J = 1.8 Hz, 1 H), 7.62 (d, J = 1.8 Hz, 1 H), 8.06 (dd, J = 8.5 Hz, 2 H).

MS (ES): m/z (%) = 414/412/410 (49/100/49) [M⁺], 399/397/395 (72/16/1) [M⁺ – Me], 334/332/329 (67/7/1) [M⁺ – Br], 260 (11), 138 (4).

HRMS: m/z calcd for C₂₃H₁₅BrO₂Si, 409.9153; found, 409.9153.
t-Butyl-[4-(3,5-dibromobenzofuran-2-yl)-2-methoxy-phenylo]-dimethyl-silane (18e)

Prepared according to general procedure B. (4-Bromo-2-methoxy-phenox) t-butyl-dimethyl-silane (1.34 g, 4.20 mmol), t-BuLi (1.5 molar solution in pentane; 5.80 mL, 8.70 mmol), ZnCl₂ (0.5 M solution in THF; 9.50 mL, 4.80 mmol), benzoferan 6 (1.00 g, 2.80 mmol), and (PPh₃)₂PdCl₂ (98.0 mg, 0.14 mmol) were used. The reaction mixture was stirred at r.t. for 6 h. Purification by flash chromatography on silica gel (pentane–EtOAc, 99:1) yielded 1.15 g (2.24 mmol, 80%) of t-butyl-[4-(3,5-dibromobenzofuran-2-yl)-2-methoxy-phenylo]-dimethyl-silane (18e).

Mp 70 °C; Rₜ 0.19 (pentane–EtOAc, 99:1).

IR (KBr): 2960 (m, C=O), 2925 (m, C=H), 2850 (m, C=H), 1608 (w, C=O), 1504 (s, C=O, C=O), 1442 (m, C=O, C=O), 1298 (s), 1253 (s), 1175 (m), 1092 (m), 828 (m), 746 cm⁻¹ (s).

1H NMR (360 MHz, CDCl₃); δ = 8.02 (s, 6 H), 1.02 (s, 9 H), 3.90 (s, 3 H), 6.94 (d, J = 8.8 Hz, 1 H), 7.32 (d, J = 8.7 Hz, 1 H), 7.39 (d, J = 8.7 Hz, 1 H), 7.63 (d, J = 1.9 Hz, 1 H), 7.66 (m, 2 H).

MS (EI, 70 eV): m/z (%) = 514/512/510 (4/6/4) [M⁺], 457/455/453 (28/52/24) [M⁺ – Br], 442/440/438 (53/100/49), 361/359 (109), 333/331 (10/12), 280 (4), 251 (6), 220 (18), 212 (15), 159 (8), 73 (8).

HRMS: m/z calcd for C₈₄H₇₃BrO₅Si, 509.9862; found, 509.9859.

Cross-Coupling with Methyl Zinc Chloride at Elevated Temperature: General Procedure Ca

ZnCl₂ (0.5 or 1.0 M solution in THF; 3.9 equiv) was slowly added to MeLi (1.4 M solution, 3.0 equiv.) in Et₂O at ~78 °C. This solution was added at ambient temperature to a mixture of the benzozofuran derivative 12a or 14 (1 equiv) and bis(triphenylphosphino) palladium(II)-chloride in THF (5 or 10 mol%). The reaction mixture was stirred at r.t. for 18 h. Et₂O (10 mL/mmol benzofuran) was added and the mixture was washed with H₂O (10 mL/mmol). The aqueous layer was extracted with Et₂O (10 mL/mmol), the combined organic layers were washed with brine (10 mL/mmol), and dried over Na₂SO₄. After filtration and evaporation of the solvent the crude product was purified by flash chromatography.

3-Methyl-2-(3,3-dimethyl-but-1-ynyl)-benzofuran (15)

Prepared according to general procedure Ca. MeLi (2.0 M solution, 3.0 mmol) in THF (2.0 mL), ZnCl₂ (0.5 M solution, 7.6 mL, 3.8 mmol), 3,5-dimethyl-benzofuran (47.0 mg, 0.15 mmol), and MeI (0.12 mL, 1.4 M; 1 equiv) in Et₂O (0.075 mL) was added. The reaction mixture was stirred at r.t. for 18 h. Purification by flash chromatography on silica gel (pentane) yielded 28.5 mg (0.12 mmol, 79%) 3-methyl-2-(3,5-dimethyl-phenylo)-benzofuran (16).

Mp 87 °C; Rₜ 0.14 (pentane).

IR (KBr): 2929 (w, C=O), 2832 (m, C=O), 1609 (w, C=C), 1510 (s, C=C), 1456 (s, C=C), 1298 (m), 1253 (s), 1175 (m), 1092 (m), 828 (m), 746 cm⁻¹ (s).

1H NMR (250 MHz, CDCl₃); δ = 2.43 (s, 3 H), 3.86 (s, 3 H), 7.00 (d, J = 8.9 Hz, 2 H), 7.20–7.28 (m, 2 H), 7.44–7.51 (m, 2 H), 7.73 (d, J = 8.9 Hz, 2 H).

MS (EL, 70 eV): m/z (%) = 238 (100) [M⁺], 223 (70) [M⁺ – Me], 195 (22), 165 (10), 152 (8), 119 (8).

HRMS: m/z calcd for C₈₄H₂₃O₂, 238.0994; found, 238.0993.

Cross-Coupling with Methyl Zinc Chloride at Elevated Temperature: General Procedure Cb

ZnCl₂ (0.5 or 1.0 M solution in THF; 1.3 equiv) was slowly added to MeLi (1.4 M; 1 equiv) in Et₂O at ~78 °C. This solution was added at ambient temperature to a mixture of the benzofuran (0.2–0.5 equiv depending on whether one bromine or two bromine atoms were to be replaced) derivative and PdCl₂(dppf) (10 mol%) in THF. The reaction mixture was heated to reflux for 3–5 h. After cooling to r.t. Et₂O 10 mL were added and the mixture was washed with H₂O (10 mL). The aqueous layer was extracted with Et₂O (10 mL), the combined organic layers were washed with brine (10 mL) and dried over Na₂SO₄. After filtration and evaporation of the solvent the crude product was purified by flash chromatography.

2-(4-Methoxy-phenyl)-3,5-dimethyl-benzofuran (19)

Prepared according to general procedure Cb. MeLi (0.60 mL, 0.76 mmol) in THF (2.0 mL), ZnCl₂ (0.5 M solution, 1.0 mmol), 3,5-dibromo-2-(4-methoxy-phenyl)-benzofuran (50.0 mg, 0.13 mmol), and PdCl₂(dppf) (18.0 mg, 0.02 mmol) were used. The reaction mixture was heated to reflux for 18 h. Purification by flash chromatography on silica gel (pentane) gave 21.0 mg (0.09 mmol, 62%) 2-(4-methoxy-phenyl)-3,5-dimethyl-benzofuran (19).

Mp 83 °C; Rₜ 0.41 (pentane).

IR (KBr): 2915 (m, C=O), 2838 (m, C=O), 1610 (m, C=C), 1504 (s, C=C), 1442 (m, C=C), 1296 (s), 1284 (s), 1180 (m), 1134 (m), 909 (s), 844 (m, C₅H₅), 784 cm⁻¹ (m).

1H NMR (250 MHz, CDCl₃): δ = 7.32 (d, J = 8.7 Hz, 1 H), 7.33 (d, J = 8.7 Hz, 1 H), 7.34 (d, J = 8.9 Hz, 1 H), 7.57 (d, J = 8.7 Hz, 1 H), 7.63 (d, J = 1.9 Hz, 1 H), 7.71 (m, 2 H), 7.72 (m, 2 H), 7.73 (d, J = 8.9 Hz, 2 H), 7.91 (d, J = 7.7 Hz, 1 H), 8.00 (d, J = 8.9 Hz, 2 H).

MS (EL, 70 eV): m/z (%) = 252 (100) [M⁺], 237 (62) [M⁺ – Me], 194 (8), 165 (10), 126 (6).

HRMS: m/z calcd for C₈₄H₂₃O₂, 252.1150; found, 252.1150.

Halogen–Metal Exchange and Methylation: General Procedure D

The 2-arylbenzofuran derivative (1 equiv) was dissolved in THF and cooled to ~78 °C. t-BuLi (solution in pentane; 2.1 equiv) was added slowly and the solution was stirred for 10 min at ~78 °C. After addition of MeLi (5 equiv) the solution was warmed to r.t. and Et₂O (10 mL/mmol benzofuran) was added. The mixture was washed with 2 N HCl (10 mL/mmol) and H₂O (10 mL/mmol). The aqueous layer was extracted with Et₂O (10 mL/mmol), the combined organic layers were washed with brine (10 mL/mmol), dried over Na₂SO₄. After filtration and evaporation of the solvent the crude product was purified by flash chromatography.

5-Bromo-2-(4-methoxy-phenyl)-3-methyl-benzofuran (21a)

Prepared according to general procedure D. 3,5-Dibromo-2-(4-methoxy-phenyl)-benzofuran (18a) (145 mg, 0.38 mmol), t-BuLi (2.0 M solution in pentane; 0.41 mL, 0.83 mmol), and MeI (0.12 mL, 1.4 M; 1 equiv) in Et₂O (0.065 mL) was added. The reaction mixture was stirred at r.t. for 18 h. Purification by flash chromatography.

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ml, 284 mg, 2.00 mmol) were used. Purification by flash chromatography on silica gel (pentane) gave 65.0 mg (0.21 mmol, 75%) of 5-bromo-2-(4-methoxy-phenyl)-3-methyl-benzofuran (21a).

Mp 101 °C; Rf 0.28 (pentane).

IR (KBr): 3025 (w), 2925 (s, C=O), 1606 (w, C=C), 1560 (s, C=O), 1457 (m, C=C), 1281 (s), 1090 (m), 908 (s), 851 (s), 801 cm–1 (s).

δ (400 MHz, CDCl3) = 1.8 (d, J = 6.6 Hz, H), 4.35 (t, J = 6.6 Hz, 2 H), 7.16 (t, J = 6.6 Hz, 1 H), 7.24 (qd, J = 1.8 Hz, 1 H, 7.38 (d, J = 1.8 Hz, 1 H), 7.69 (d, J = 1.8 Hz, 1 H). MS (EI, 70 eV): m/z (%) = 332/330 (96/100) [M+], 318/316 (14/16), [M+–Me], 280 (24), 265 (16), 241 (14), 194 (10), 179 (8), 135 (5)

HRMS: m/z calc for C15H10BrO2 [M+–Me] = 301.0522; found, 301.0521.

3-Bromo-2-(4-methoxy-phenyl)-5-(E/Z)-prop-1-enyl-benzofuran (22a)

Prepared according to general procedure E. 3,5-Dibromo-2-(4-methoxy-phenyl)-benzofuran (18a) (30.0 mg, 0.07 mmol), NiCl2(dppe) (3.7 mg, 0.007 mmol) in THF (2.0 mL), and 1-propenyl magnesium bromide (0.5 M solution; 0.24 mL, 0.12 mmol) were used. The reaction mixture was stirred for 3 h at r.t. Purification by flash chromatography on silica gel (pentane) yielded 18.0 mg (0.05 mmol, 71%) of 3-bromo-2-(4-methoxy-phenyl)-5-(E/Z)-prop-1-enyl-benzofuran (22a).

Mp 104 °C; Rf 0.20 (pentane).

IR (KBr): 3025 (w), 2925 (s, C=O), 1606 (w, C=C), 1560 (s, C=O), 1457 (m, C=C), 1281 (s), 1090 (m), 908 (s), 851 (s), 801 cm–1 (s).

δ (400 MHz, CDCl3) = 1.8 (d, J = 6.6 Hz, H), 4.35 (t, J = 6.6 Hz, 2 H), 7.16 (t, J = 6.6 Hz, 1 H), 7.24 (qd, J = 1.8 Hz, 1 H, 7.38 (d, J = 1.8 Hz, 1 H), 7.69 (d, J = 1.8 Hz, 1 H). MS (EI, 70 eV): m/z (%) = 332/330 (96/100) [M+], 318/316 (14/16), [M+–Me], 280 (24), 265 (16), 241 (14), 194 (10), 179 (8), 135 (5)

HRMS: m/z calc for C15H10BrO2 [M+–Me] = 301.0522; found, 301.0521.

5-(5-Bromo-3-methyl-benzofuran-2-yl)-benzo[1,3]-dioxole (21b)

Prepared according to general procedure D. 5-(3,5-Dibromo-benzo[1,3]-dioxole (21b)

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Prepared according to general procedure D. 5-(3,5-Dibromo-benzo[1,3]-dioxole (21b)
HRMS: m/z calc for C₉H₂BrO₃, 356.0048; found, 356.0051.

[4-[3-Bromo-5-(E/Z)-prop-1-enyl-benzofuran-2-yl]-phenoxo]-t-butyl-dimethyl-silane (22c)
Prepared according to general procedure E. t-Butyl-[4-(3,5-dibromo-benzofuran-2-yl)-phenoxo]-dimethyl-silane (18c) (195 mg, 0.41 mmol), NiCl₂(dppe) (21.1 mg, 0.04 mmol) in THF (4.0 mL), and 1-propenyl magnesium bromide solution (0.5 M solution; 1.33 mL, 0.60 mmol) were used. The reaction mixture was stirred for 3 h at r.t. Purification by flash chromatography on silica gel (pentane–EtOAc, 99:1) gave 134 mg (0.32 mmol, 80%) of [4-[3-bromo-5-(E/Z)-prop-1-enyl-benzofuran-2-yl]-phenoxo]-t-butyl-dimethyl-silane (22c).

Mp 64 °C; R₆ 0.19 (pentane–EtOAc).

IR (KBr): 2963 (w, C=H), 2925 (w, C=H), 2863 (w, C=H), 1604 (m, C=C), 1469 (m, C=C), 1270 (m), 1171 (m), 900 (s), 838 (s), 781 cm⁻¹ (m, C₅H₃). ¹H NMR (360 MHz, CDCl₃): δ = 0.24 (s, 6 H), 1.00 (s, 9 H), 1.90 [J = 6.6 Hz, Jᵥ = 1.4 Hz, 1.8 H (E)], 1.94 [dd, J = 7.2 Hz, J = 1.6 Hz, 1.2 H (Z)], 5.81 [d, J = 7 Hz, J = 11.5 Hz, 0.4 H (Z)], 6.25 [dq, J = 6.6 Hz, J = 15.4 Hz, 0.6 H (E)], 6.50 [d, J = 15.4 Hz, J = 1.4 Hz, 0.6 H (Z)], 6.93 [d, J = 8.9 Hz, 2 H], 7.29 [dd, J = 8.6 Hz, J = 1.6 Hz, 1 H], 7.36 [d, J = 8.6 Hz, 1 H], 7.42 [d, J = 1.6 Hz, 1 H], 8.03 (d, J = 8.9 Hz, 2 H).

¹³C NMR (90.6 MHz, CDCl₃): δ = −43 (CH₃), 14.6 (CH₃), 18.3 (CH₃), 25.7 (CH₃), 92.3 (2) (C), 110.7 (CH), 111.0 (CH), 116.5 (CH), 119.4 (CH), 120.2 (CH), 122.8 (CH), 123.4 (CH), 125.2 (CH), 126.4 (2) (C), 128.2 (2) (C), 129.7 (2) (C), 130.0 (CH), 130.8 (CH), 133.2 (CH), 133.9 (C), 150.9 (2) (C), 151.8 (C), 152.3 (C), 156.6 (2) (C).

MS (EL 70 eV): m/z (%) = 444/442 (100/98) [M⁺], 404/402 (5/5) [M⁺ − CH₃CH₃], 387/385 (85/78) [M⁺ − t-Bu], 347/345 (7/6). 306 (17), 291 (27), 202 (14), 193 (8), 153 (10), 73 (13).

Anal. Calc. for C₂₀H₂₀BrO₃Si (443.5): C 62.30; H 6.14; Found: C 62.18; H 6.03.

3-Bromo-2-(3,4-dimethoxy-phenyl)-5-(E/Z)-prop-1-enyl-benzofuran (22d)
Prepared according to general procedure B. 3,5-Dibromo-2-(3,4-dimethoxy-phenyl)-benzofuran (18d) (245 mg, 0.60 mmol), NiCl₂(dppe) (31 mg, 0.06 mmol) in THF (3.0 mL), and 1-propenyl magnesium bromide (0.4 M solution; 2.25 mL, 0.90 mmol) were used. The reaction mixture was stirred for 3 h at r.t. Purification by flash chromatography on silica gel (pentane–EtOAc, 98:2) gave 192 mg (0.51 mmol, 86%) of 3-bromo-2-(3,4-dimethoxy-phenyl)-5-(E/Z)-prop-1-enyl-benzofuran (22d).

Mp 113 °C; R₆ 0.34 (pentane–EtOAc).

IR (KBr): 2930 (m, C=H), 1606 (m, C=C), 1508 (s, C=C), 1467 (s, C=C), 1282 (s), 1252 (s), 1228 (s), 1147 (m), 1084 (m), 1028 (m), 956 (s), 808 cm⁻¹ (m, C₅H₃).

¹H NMR (360 MHz, CDCl₃): δ = 1.89 [dd, J = 6.6 Hz, J = 1.3 Hz, 18.8 H (E)], 1.95 [dd, J = 7.2 Hz, J = 1.7 Hz, 1.2 H (Z)], 3.91 (s, 3 H), 3.96 (s, 3 H), 5.81 [d, J = 7.2 Hz, J = 11.7 Hz, 0.4 H (Z)], 6.24 [dq, J = 6.6 Hz, J = 15.6 Hz, 0.6 H (E)], 6.48 [dq, J = 15.6 Hz, J = 1.3 Hz, 0.6 H (E)], 6.53 [d, J = 11.7 Hz, 0.4 Hz (Z)], 6.93 (m, 1 H), 7.23–7.43 (m, 3 H), 7.67–7.69 (m, 1 H), 7.73–7.75 (m, 1 H).

¹³C NMR (90.6 MHz, CDCl₃): δ = 14.5 (CH₃), 18.4 (CH₃), 55.8 (CH₃), 55.9 (CH₃), 92.4 (2) (C), 109.7 (2) (C), 110.6 (CH), 110.9 (CH), 111.0 (CH), 111.1 (CH), 116.4 (CH), 119.3 (CH), 119.9 (2) (CH), 122.3 (CH), 122.4 (CH), 125.1 (CH), 126.3 (CH), 126.4 (CH).

129.6 (C), 129.8 (CH), 130.7 (CH), 131.2 (C), 133.8 (C), 148.9 (2) (C), 149.8 (2) (C), 150.6 (C), 151.6 (C), 152.1 (C).

HRMS: m/z calc for C₁₉H₁₇BrO₃, 356.0048; found, 356.0051.

MS (EL 70 eV): m/z (%) = 374/372 (94/100) [M⁺], 359/357 (17/16) [M⁺ − CH₃], 334 (17) [M⁺ − CH₃CH₃], 294 (9) [M⁺ − Br], 250 (28), 187 (9).

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mmol) was added. The reaction mixture was irradiated for 2 h. Purification by flash chromatography on silica gel (pentane–EtOAc, 99:1) yielded 55.5 mg (0.20 mmol, 87%) of 2-(4-methoxy-phenyl)-3-methyl-5-(E)-prop-1-enyl-benzofuran (Eupomatennoid-15) (5a). The analytical data were identical to those previously reported.

5-[3-Methyl-5-(E)-prop-1-enyl-benzofuran-2-yl]-benzo[1,3]dioxole (Eupomatennoid-3) (5b)

Prepared according to general procedure C, MeLi (0.50 mL, 0.70 mmol) in THF (2.0 mL), ZnCl₂ (0.5 M solution; 1.82 mL, 0.91 mmol), [5-[3-bromo-5-(E)-prop-1-enyl-benzofuran-2-yl]-benzo[1,3]dioxole (22b) (50.0 mg, 0.14 mmol), and PdCl₂(dppf) (10.0 mg, 0.014 mmol) in THF (2.0 mL) were used. The reaction mixture was heated to reflux for 5 h. Purification by flash chromatography on silica gel (pentane–EtOAc, 99:1) gave 43.0 mg of a colorless solid.

Prepared according to general procedure F. The above isolated solid (43.0 mg) was dissolved in THF (2.0 mL) and I₂ (3.00 mg, 0.01 mmol) was added. The reaction mixture was irradiated for 2.5 h. Purification by flash chromatography on silica gel (pentane–EtOAc, 99:1) gave 43.0 mg (0.13 mmol, 93%) of 2-(3,4-dimethoxy-phenyl)-3-methyl-5-(E)-prop-1-enyl-benzofuran (Eupomatennoid-4) (5d). The analytical data were identical to those previously reported.

t-Butyl-[2-methoxy-4-[3-methyl-5-(E)-prop-1-enyl-benzofuran-2-yl]-phenoxy]-dimethyl-silane (5e)

Prepared according to general procedure C, MeLi (2.10 mL, 3.30 mmol) in THF (5.0 mL), ZnCl₂ (0.5 M solution; 8.60 mL, 4.30 mmol), [4-[3-bromo-5-(E)-prop-1-enyl-benzofuran-2-yl]-2-methoxy-phenoxy]-t-butyl-dimethyl-silane (22e) (312 mg, 0.66 mmol), and PdCl₂(dppf) (48.1 mg, 0.07 mmol) in THF (5.0 mL) were used. The reaction mixture was heated to reflux for 5 h. Purification by flash chromatography on silica gel (pentane–EtOAc, 99:1) gave 192 mg of a colorless solid.

Prepared according to general procedure F. The above isolated solid (160 mg) was dissolved in THF (5.0 mL) and I₂ (5.00 mg, 0.02 mmol) was added. The reaction mixture was irradiated for 5 h. Purification by flash chromatography on silica gel (pentane) gave 55.5 mg (0.39 mmol, 72%) of t-butyl-[2-methoxy-4-[3-methyl-5-(E)-prop-1-enyl-benzofuran-2-yl]-phenoxy]-dimethyl-silane (5e).

t-Butyl-[4-[3-methyl-5-(E)-prop-1-enyl-benzofuran-2-yl]-phenyoxy]-silane (5c)

Prepared according to general procedure C, MeLi (0.41 mL, 0.60 mmol) solution in THF (2.0 mL), ZnCl₂ (0.5 M solution; 1.56 mL, 0.78 mmol), [4-[3-bromo-5-(E/Z)-prop-1-enyl-benzofuran-2-yl-phenoxy]-t-butyl-dimethyl-silane (22c) (90.0 mg, 0.20 mmol) and PdCl₂(dppf) (14.6 mg, 0.020 mmol) in THF (2.0 mL) were used. The reaction mixture was heated to reflux for 3 h. Purification by flash chromatography on silica gel (pentane–EtOAc, 99:1) gave 26.5 mg of a colorless solid.

Prepared according to general procedure F. The isolated solid above (26.5 mg) was dissolved in THF (2.0 mL) and I₂ (3.00 mg, 0.01 mmol) was added. The reaction mixture was irradiated for 2 h. Purification by flash chromatography on silica gel (pentane–EtOAc, 99:1) yielded 26.1 mg (0.09 mmol, 64%) of 5-[3-methyl-5-(E)-prop-1-enyl-benzofuran-2-yl]-benzo[1,3]dioxole (Eupomatennoid-3) (5b). The analytical data were identical to those previously reported.

t-Butyl-dimethyl-[4-[3-methyl-5-(E)-prop-1-enyl-benzofuran-2-yl]-phenyoxy]-silane (5e)

Prepared according to general procedure C, MeLi (0.50 mL, 0.70 mmol) in THF (5.0 mL), ZnCl₂ (0.5 M solution; 1.82 mL, 0.91 mmol), {4-[3-bromo-5-(E)-prop-1-enyl-benzofuran-2-yl]-benzo[1,3]dioxole (Eupomatennoid-3) (5b). The analytical data were identical to those previously reported.
2-Methoxy-4-(3-methyl-5-(E)-prop-1-enyl-benzofuran-2-yl)phenol (Eupomatienat-5) (5g)

T-Butyl-[2-methoxy-4-(3-methyl-5-(E)-prop-1-enyl-benzofuran-2-yl)-phenoxy]-dimethylsilane (5e) (50.0 mg, 0.12 mmol) was dissolved in THF (2.0 mL) and TBAF (1.0 M solution in THF, 0.13 mL) was slowly added at r.t. The reaction mixture was stirred for 2 h. After addition of Et₂O (10.0 mL) the solution was washed with a sat. solution of NaHCO₃ (5.0 mL). The aqueous layer was extracted with Et₂O (5.0 mL) and the combined organic layers were dried over Na₂SO₄. Filtration, evaporation of the solvent and further purification by flash chromatography on silica gel (pentane–EtOAc, 98:2) yielded 34.0 mg (0.11 mmol, 95%) of 2-methoxy-4-[3-methyl-5-(E)-prop-1-enyl-benzofuran-2-yl]-phenol (Eupomatienat-5) (5g). The analytical data were identical to those previously reported.²⁰,²⁸

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