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Efficient synthetic approach to heterocycles possessing the 3,3-disubstituted-2,3-dihydrobenzofuran skeleton via diverse palladium-catalyzed tandem reactions

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Abstract—Various palladium-catalyzed cascade reactions of *O*-alkylated 2-iodophenol were explored in order to synthesize novel dihydrobenzofurans. An efficient tandem cyclization/anion capture reaction was developed to yield 3,3-disubstituted-2,3-dihydrobenzofurans. A small library of these compounds was prepared with a parallel organic synthesizer. A multi-component version of this reaction involving 2-iodophenol, an alkylating agent and a nucleophile, provided the same products. The methoxycarbonyl-substituted heterocyclic ring was hydrolyzed to a free acid, which could be used for further transformations.

1. Introduction

Naturally occurring substituted-2,3-dihydrobenzofurans are an important class of biologically active oxygen-containing heterocycles. Natural products possessing the dihydrobenzofuran skeleton exhibit a wide range of biological activities. For example (Fig. 1), Megapodiol is an anti-leukaemic agent,[1] Conocarpan is an anti-cancer agent,[2] and Furaquinocines are antibiotics.[3] Some other derived compounds present cytotoxic and anti-protozoal activities.[4]

Therefore, organic chemists have made extensive efforts to develop new chemical processes to produce elaborate heterocyclic structures.[5–8] Among the variety of new synthetic approaches, transition metal-catalyzed reactions are part of the most attractive methodologies, since they can directly lead to complicated molecules from readily accessible starting materials under mild conditions.[9] Palladium-catalyzed cascades in particular, provide versatile and efficient methods for the assembly of a wide range of organic compounds via carbon–carbon and carbon–heteroatom bond formation.[10–14] These cascades usually proceed under mild conditions and are tolerant of a wide variety of functional groups. They allow the access to a high degree of molecular complexity in a one-pot protocol, where conventional methodology would require multi-step synthesis.[15] Such reactions minimize reactor time and waste, whilst offering interesting synthetic solutions.

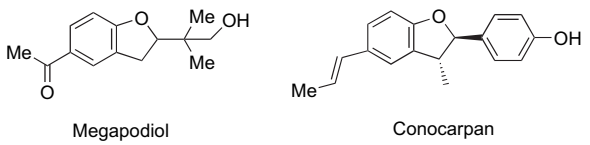

Figure 1. Structures of biologically active dihydrobenzofurans.

To our knowledge, only few Pd-catalyzed cascade reactions have been used to efficiently build 3,3-disubstituted-2,3-dihydrobenzofurans, using very simple starting materials.[16,17] In a preliminary study, we have described the first examples of Pd-catalyzed multi-component reactions involving methyl bromomethylacrylate in an allylation followed by another Pd-catalyzed process (Heck and/or Suzuki reactions).[18,19] We report herein a more extensive study of different Pd-catalyzed cascades starting with a Pd-catalyzed allylic alkylation of 2-iodophenol by methyl bromomethylacrylate, allowing introduction of diversity in a very simple manner (Scheme 1).

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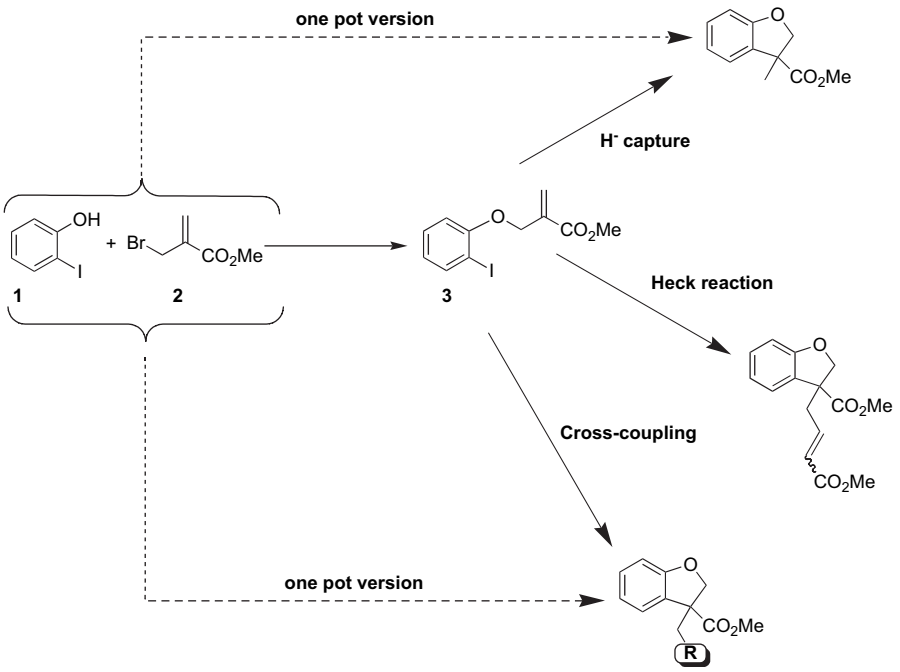


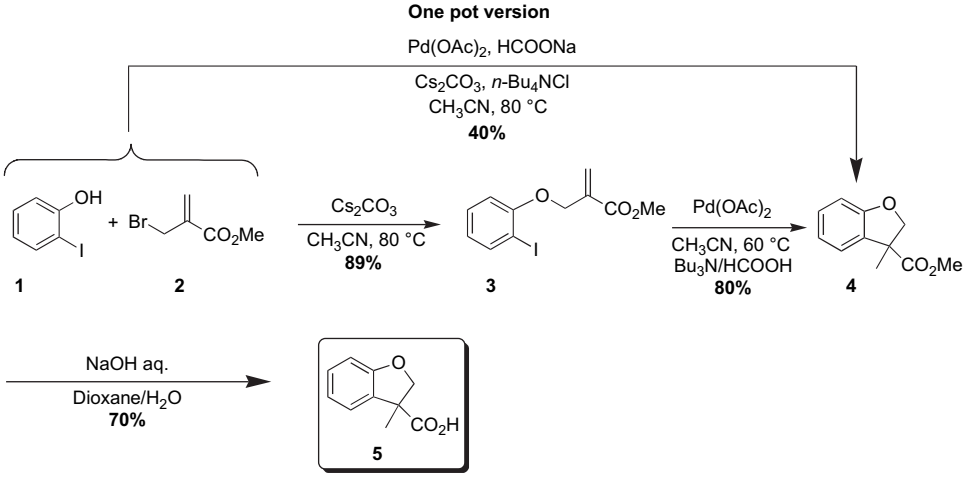
Scheme 1. General strategy for the synthesis of 3,3-disubstituted-2,3-dihydrobenzofuran derivatives.

2. Results and discussion

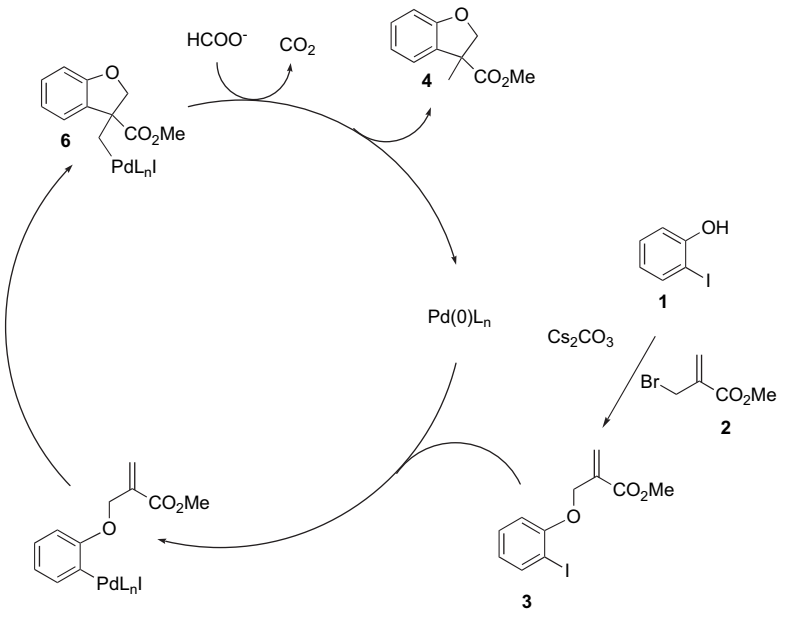
2.1. Pd-catalyzed tandem cyclization-hydride capture

The allylic alkylation of 2-iodophenol **1** using methyl bromomethylacrylate **2**, and Cs_2CO_3 as a base was performed in acetonitrile at 80 °C, leading to the corresponding alkylated compound **3** in 89% yield (Scheme 2). Pd-catalyzed tandem cyclization-hydride capture was achieved using a mixture of tributylamine and formic acid as a hydride source, and $Pd(OAc)_2$ as catalyst, in acetonitrile at 60 °C. Thus, the 3,3-disubstituted-2,3-dihydrobenzofuran **4** was obtained in 80% yield from a 5-*exo*-trig cyclization followed by trapping of the resulting alkylpalladium complex with a hydride (Scheme 2). To get the corresponding carboxylic acid, compound **4** was hydrolyzed with aqueous sodium hydroxide in a mixture of dioxane/water (9/1) providing **5** in 70% yield (Scheme 2).

This sequence (alkylation, cyclization/hydride capture, and saponification) was performed on a gram scale with an overall yield of 45%. Furthermore, we decided to realize this reaction sequence in a one-pot version, starting from **1** and **2**. Compound **4** was obtained in 40% yield with the advantage of avoiding intermediate purification using sodium formate as a hydride source, $Pd(OAc)_2$ as a catalyst and Cs_2CO_3 as base in the presence of tetrabutylammonium chloride (n-Bu_4NCl), in acetonitrile, at 80 °C. Initial reduction of $Pd(OAc)_2$ with HCOONa generates the active Pd(0) species denoted $Pd(0)L_n$ in Scheme 3. The reaction proceeded firstly via alkylation of the phenoxide by allylic bromide **2**,[20] providing **3**. Oxidative addition of **3** to Pd(0)



Scheme 2. Synthesis of compound **4** by Pd-catalyzed tandem cyclization/hydride capture in one or two steps.



Scheme 3. One-pot version of the tandem alkylation/cyclization/hydride capture.

followed by cyclic carbopalladation of the olefin provided alkylpalladium **6**. Hydride trapping, followed by reductive elimination generated the final product **4** and recycled Pd(0).

Following these results, we introduced an additional source of structural diversity, without changing the starting materials, in order to decorate the basic scaffold with more complicated functionalities than a methyl group. The idea was to trap the intermediate alkylpalladium by various nucleophiles rather than a hydride, which would offer a diversity source. The major challenge was to obtain the correct chronology for the successive steps and avoid direct coupling before the cyclization.

2.2. Pd-catalyzed tandem cyclization/Heck reaction

We studied the cyclization step followed by an intermolecular Heck reaction, using methyl acrylate **7** as a model substrate, avoiding direct coupling reaction leading to **9**.

No ideal conditions were found to obtain title compound **8** as the sole product of the reaction. In fact, the best results were obtained by using Et_3N as a base, DMF as solvent, in the presence of *n*-Bu_4NCl. Under these reaction conditions, and after 18 h of reaction, we obtained only a mixture of the desired compounds **8** (64%), the product **9**, resulting from the direct coupling reaction (25%), compound **4**, resulting from the hydride capture (10%) and some iodophenol **1**, resulting from degradation of **3** (Scheme 4).

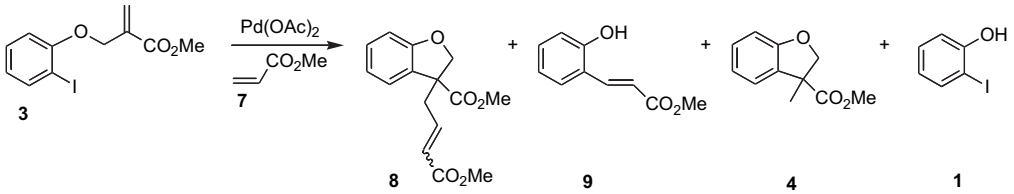
2.3. Pd-catalyzed tandem cyclization/cross-coupling

Different nucleophiles were studied, such as organometallic compounds, to end the synthetic sequence by a cross-coupling reaction in order to improve the structural complexity of the resulting compounds. Since it has been shown in the literature that the cascade could be controlled by the transmetalating reagent, we studied the Stille coupling with tin, known to be slower than with other metals.

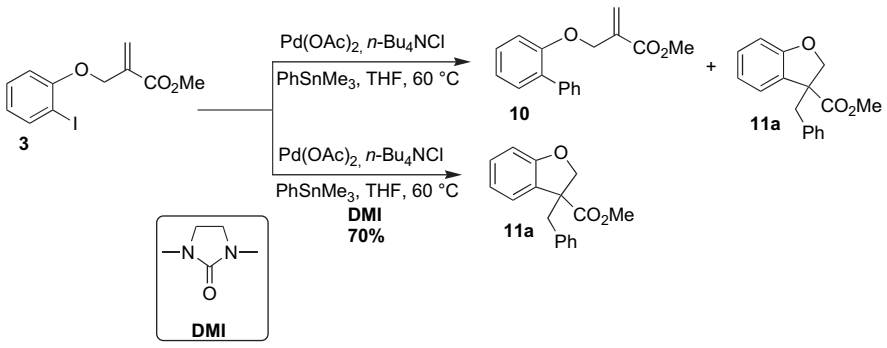
Stille coupling: Conditions of introduction of a phenyl group by a Pd-catalyzed tandem cyclization/Stille coupling sequence were studied, involving trimethyl(phenyl)tin ($PhSnMe_3$) (Scheme 5).

The reaction was performed, in the presence of *n*-Bu_4NCl, and $Pd(OAc)_2$ in THF at 60 °C overnight leading to a mixture of the desired compound **11a** (50%) and of the compound **10** (50%) due to the direct coupling reaction. The 1,3-dimethyl-1-2-imidazolidinone (DMI) was added to this system as a co-solvent. In this case, no direct coupling was observed, only the desired compound **11a** was obtained in 70% yield.

Following these promising results, other organometallics were used to introduce a structural diversity, employing diverse terminating cross-coupling reactions. The best results were obtained with the Suzuki coupling.

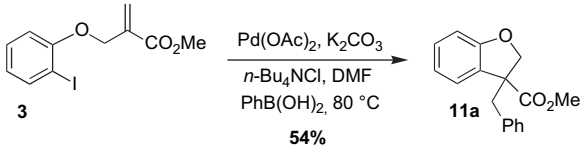


Scheme 4. Pd-catalyzed tandem cyclization/Heck reaction.



Scheme 5. Pd-catalyzed tandem cyclization/Stille coupling.

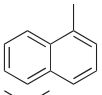
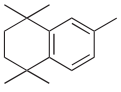
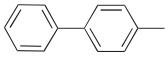
Suzuki coupling: The major advantage of this sequence is the existence of a large variety of commercially available boronic acid derivatives, especially aromatic derivatives. To compare the Suzuki coupling with the results previously obtained with the Stille coupling, we used the phenylboronic acid ($PhB(OH)_2$). Usual conditions for the Suzuki coupling had to be adapted. Indeed, to perform cyclization/Suzuki coupling most catalytic systems include the presence of phosphines. In our study, the reaction rate was dramatically reduced when triphenylphosphine was used as a ligand. Furthermore, an aqueous medium, which is considered as a standard condition for the Suzuki cross-coupling of arylboronic acids, had to be avoided due to the potential hydrolysis of the methyl ester. Phosphine-free system in the presence of a tretraalkylammonuim salt was efficient in this reaction, previously reported for the Heck reaction[21] and the Suzuki coupling.[22] It has been shown that the combination of $Pd(OAc)_2$ with *n*-Bu_4NCl in the presence of a base generated colloidal palladium nanoparticles, which are involved in the catalytic cycle.[22] These conditions allowed us to get the title compound **11a** in 54% yield (Scheme 6).



Scheme 6. Pd-catalyzed tandem cyclization/Suzuki coupling using $PhB(OH)_2$.

This result, associated with the very simple reaction conditions, led us to test the parallel synthesis of the dihydrobenzofurans using an organic synthesizer (Argonaut Quest 210 Parallel Synthesizer) and different arylboronic acids (Scheme 7). Table 1 reports the yields of 3,3-disubstituted-2,3-dihydrobenzofurans obtained. Electron donating, withdrawing or bulky substituents can be present on the aromatic ring.

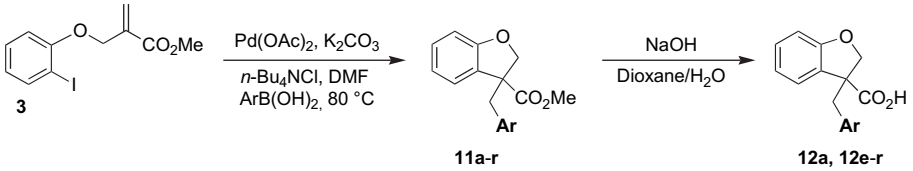
Table 1. 3,3-Disubstituted-2,3-dihydrofurans **11**

Compound	Ar	Yield of **11**(%)[a]	Yield of **12**(%)[a]
a	C_6H_5–	54	70
b	4-MeO–C_6H_4–	56	—[b]
c	3-NO_2–C_6H_4–	56	—[b]
d	2-Me–C_6H_4–	60	—[b]
e	3,4-$(OMe)_2$–C_6H_3–	71	64
f	3,4,5-$(OMe)_3$–C_6H_2–	73	71
g	2-Cl–C_6H_4–	66	70
h	3-Cl–C_6H_4–	82	78
i	4-Cl–C_6H_4–	68	65
j	3,4-$(Cl)_2$–C_6H_3–	85	69
k	2-CF_3–C_6H_4–	49	55
l	4-CF_3O–C_6H_4–	66	73
m	4-AcO–C_6H_4–	73	71
n	4-$CH_3O(CH_2)_2OCH_2O$–C_6H_4–	79	91
o	4-CH_2=CH–C_6H_4–	53	95
p		78	50
q		81	88
r		71	—[b]

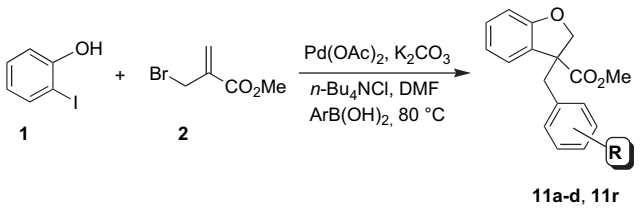
[a] Yield of isolated compounds.
[b] The hydrolysis was not performed.

Thus, 18 products were obtained using this methodology, in moderate to good yields. Most of them were converted into their corresponding carboxylic acid derivatives **12a** and **12e–q**, using the conditions described for the synthesis of **5**.[23]

This sequence was performed in a one-pot version, starting from **1** and **2**, with different arylboronic acids (Scheme 8).

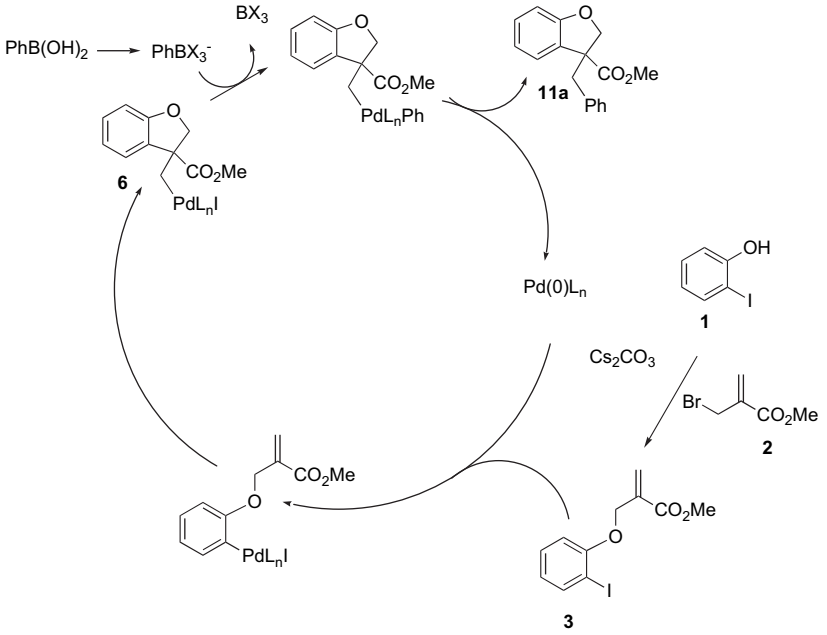


Scheme 7. Pd-catalyzed tandem cyclization/Suzuki coupling using various arylboronic acids followed by a saponification reaction.



Scheme 8. One-pot allylation/cyclization/Suzuki coupling cascade.

In the catalytic cycle, the formation of the alkylpalladium **6** was followed by a transmetallation step with phenylboronate (from the reaction of $PhB(OH)_2$ with the base and/or anions present in the reaction medium). Finally, the reductive elimination generates the title compound **11a** and recycles Pd(0) (Scheme 9).



Scheme 9. Cascade allylation/cyclization/Suzuki coupling.

To our knowledge, only few examples of allylations combined with a Pd-catalyzed process are described in the literature.[18,19,24–28]

Table 2 reports the yields of 3,3-disubstituted-2,3-dihydrobenzofurans obtained from five different arylboronic acids, $ArB(OH)_2$. As observed before, electron donating and withdrawing substituents can be present on the aromatic ring. However, substitution at the *ortho* position led to lower yields.

Table 2. One-pot synthesis of 3,3-disubstituted-2,3-dihydrofurans

11	R	Yield (%)[a]
a	H	45[b]
b	4-OMe	50
c	3-NO_2	40
d	2-Me	28
r	4-Ph	57

[a] Yield of isolated compounds.
[b] Compound **11a** was obtained as the sole product (74% NMR yield).

3. Conclusion

We have developed a very simple and an efficient method for the synthesis of a wide range of functionalized 3,3-disubstituted-2,3-dihydrobenzofurans, from commercially available 2-iodophenol, and methyl bromomethylacrylate via Pd-catalyzed tandem cyclization/Suzuki cross-coupling. Those conditions could be directly applied to automated synthesis leading to libraries of functionalized heterocyclic building blocks. This strategy will now be extended to more functionalized phenols and other 1,1-disubstituted alkenes, to introduce additional diversity and structural complexity. Finally, an asymmetric version of this reaction is currently underway, in order to control the configuration of the newly created stereogenic center.

4. Experimental section

4.1. General

All reagents were commercially available and used without purification. IR spectra were recorded on Perkin Elmer FT Paragon 1000 spectrometer. ^1H and ^{13}C NMR analyses were performed with a Brüker AC 400 MHz and 200 MHz. IR spectra were recorded on Perkin Elmer FT Paragon 1000 spectrometer. Mass spectra were recorded on JEOL JSM DX300-SX 102 spectrometer, with 3-nitrobenzyl alcohol (NBA) or a mixture glycerol/thioglycerol (50/50, v/v) (GT) as matrix.

4.1.1. 2-(3-Methoxycarbonylallyloxyl)-iodobenzene (3). To a solution of methyl-2-bromomethacrylate **2** (3.52 g, 16.67 mmol) in CH_3CN (160 mL) were added Cs_2CO_3 (4.47 g, 13.36 mmol) and 2-iodophenol **1** (2.1 g, 9.54 mmol). The resulting mixture was stirred for 5 h at 80 °C, cooled to room temperature, diluted with Et_2O, and filtered over Celite. The organic layer was washed with

brine, dried over $MgSO_4$, filtered, and concentrated. Column chromatography (silica gel, hexane/CH_2Cl_2: 1/1) afforded 2.71 g (89%) of **3**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.78 (s, 3H), 4.76 (d, 2H, J=1.7 Hz), 6.23 (d, 1H, J=1.2 Hz), 6.42 (d, 1H, J=1.3 Hz), 6.70 (td, 1H, J=7.6 Hz, J=1.1 Hz), 6.80 (d, 1H, J=8.2 Hz), 7.26 (td, 1H, J=8.6 Hz, J=1.5 Hz), 7.74 (dd, 1H, J=7.8 Hz, J=1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.46, 67.30, 86.87, 112.83, 123.41, 127.26, 129.95, 135.43, 139.9, 157.12, 166.19; IR (film) ν 3024, 3000, 2949, 2844, 1717, 1636.5, 1581, 1475, 1438, 1396, 1313, 1278, 1250, 1195, 1155, 1121, 1056, 1036, 1018, 956, 868, 817, 748, 642 cm^{-1}; MS (FAB$^+$, GT) m/z=319 (MH^+), 233, 149, 131; HRMS for $C_{11}H_{12}O_3I$ (MH^+): calcd 318.9831 found 318.9843.

4.1.2. 3-Methyl-3-methoxycarbonyl-2,3-dihydrobenzofuran (4). To a solution of Bu_3N (2.77 mL, 11.62 mmol) in acetonitrile (60 mL) was added HCOOH (0.219 mL, 5.81 mmol). The resulting mixture was stirred for 10 min at room temperature. To this mixture were then added a solution of **3** (1.68 g, 5.28 mmol) in CH_3CN (10 mL), and a solution of $Pd(OAc)_2$ (118.5 mg, 0.528 mmol) in CH_3CN (2 mL). The resulting mixture was stirred for 17 h at 60 °C, cooled to room temperature and concentrated. The residue was dissolved in Et_2O, and the resulting organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was dissolved finally in hexane and filtered over alumina and concentrated affording 811 mg (80%) of **4**.

One-pot version: To a solution of **2** (58.3 mg, 0.326 mmol) in CH_3CN (5 mL) were added Cs_2CO_3 (318.8 mg, 0.979 mmol), **1** (51.2 mg, 0.233 mmol), HCOONa (21.9 mg, 0.326 mmol), $Pd(OAc)_2$ (5.23 mg, 0.023 mmol), and n-Bu_4NCl (77.4 mg, 0.280 mmol). The resulting mixture was stirred for 17 h at 80 °C, cooled to room temperature and concentrated. The residue was dissolved in Et_2O, and the resulting organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was dissolved in hexane and filtered over alumina and concentrated affording 18 mg (40%) of **4**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.57 (s, 3H), 3.69 (s, 3H), 4.21 (d, 1H, J=9 Hz), 5.02 (d, 1H, J=9 Hz), 6.76–6.89 (m, 2H), 7.14 (td, 1H, J=7.7 Hz, J=1.4 Hz), 7.28 (dd, 1H, J=7.5 Hz, J=1.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.95, 52.71, 53.12, 80.38, 110.42, 121.22, 124.68, 129.75, 130.40, 159.79, 174.62; IR (film) ν 3030, 2952, 2896, 2849, 2796, 1732, 1597, 1482, 1462, 1222, 1137, 1107, 1068, 1017, 987 cm^{-1}; MS (FAB$^+$, NBA) m/z=192 (M^+), 149, 133 (M^+-CO_2Me), 97, 81, 72, 55, 43, 29; HRMS for $C_{11}H_{12}O_3$ (M^+): calcd 192.0786 found 192.0787.

4.1.3. 3-Methyl-2,3-dihydrobenzofuran-3-carboxylic acid (5). To a solution of **4** (1.15 g, 5.99 mmol) in a mixture of dioxane/H_2O (9/1) (50 mL) was added aqueous solution of NaOH (2 M) (13.5 mL, 26.95 mmol). The resulting mixture was stirred for 4 h at room temperature and concentrated. The residue was dissolved in H_2O, and the aqueous layer was extracted three times with Et_2O, acidified by adding HCl (1 N) until pH=1–3 and extracted three times with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated affording 746 mg (70%) of **5**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.60 (s, 3H), 4.21 (d, 1H, J=9.2 Hz), 5.02 (d, 1H, J=9.2 Hz), 6.78 (d, 1H, J=8.1 Hz), 6.87 (td, 1H, J=7.5 Hz, J=0.8 Hz), 7.16 (td, 1H, J=7.7 Hz, J=1.3 Hz), 7.31 (dd, 1H, J=7.5 Hz, J=1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.54, 52.60, 79.98, 110.54, 121.36, 124.76, 129.68, 130.05, 159.80, 180.37; IR (film) ν 3084, 3020, 2973, 2929, 2849, 1704, 1597, 1482, 1462, 1410, 1296, 1238, 1177, 1154, 1068, 1017, 988, 833, 752, 685, 622 cm^{-1}; MS (FAB$^+$, NBA) m/z=178 (M^+), 133 (M^+-CO_2H), 105, 89, 77; HRMS for $C_{10}H_{10}O_3$ (M^+): calcd 178.0630 found 178.0624.

4.1.4. 3-Methylacrylate-3-methoxycarbonyl-2,3-dihydrobenzofuran (8). To a solution of **3** (60.3 mg, 0.19 mmol) in DMF (4 mL) were added Et_3N (53 μL, 0.38 mmol), n-Bu_4NCl (63.3 mg, 0.228 mmol), a solution of $Pd(OAc)_2$ (4.4 mg, 0.019 mmol) in DMF (1 mL), and methyl acrylate **7** (18.9 μL, 0.209 mmol). The resulting mixture was stirred for 16 h at 80 °C, cooled to room temperature, diluted with Et_2O, and filtered over Celite. This organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated affording a mixture of **8**, as a major compound (64% by NMR), **9**, **4**, and **1**.

4.1.5. 3-Benzyl-3-methoxycarbonyl-2,3-dihydrobenzofuran (11a). *Stille conditions*: To a solution of **3** (200.4 mg, 0.629 mmol) and DMI (0.240 mL, 2.2 mmol) in THF (12 mL) were added n-Bu_4NCl (209.75 mg, 0.755 mmol), a solution of $Pd(OAc)_2$ (14.12 mg, 0.063 mmol) in THF (1 mL), and Me_3PhSn (0.137 mL, 0.755 mmol). The resulting mixture was stirred for 17 h at 60 °C, cooled to room temperature, diluted with Et_2O, and filtered over Celite. This organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. Column chromatography (silica gel, hexane/CH_2Cl_2: 1/1) afforded 118 mg (70%) of **11a**.

Suzuki conditions: To a solution of **3** (106.6 mg, 0.335 mmol) in DMF (6 mL) were added K_2CO_3 (92.6 mg, 0.670 mmol), n-Bu_4NCl (111.7 mg, 0.402 mmol), a solution of $Pd(OAc)_2$ (7.5 mg, 0.0335 mmol) in DMF (1 mL), and a solution of $Ph(BOH)_2$ (44.9 mg, 0.368 mmol) in DMF (2 mL). The resulting mixture was stirred for 15 h at 80 °C, cooled to room temperature filtered over Celite and concentrated. Column chromatography (silica gel, hexane/CH_2Cl_2: 1/1) afforded 48.5 mg (54%) of **11a**.

One-pot version: To a solution of **2** (48.9 mg, 0.273 mmol) in DMF (3 mL) were added K_2CO_3 (110.15 mg, 0.955 mmol), **1** (50.1 mg, 0.228 mmol), n-Bu_4NCl (76 mg, 0.274 mmol), a solution of $Pd(OAc)_2$ (5.12 mg, 0.0273 mmol) in DMF (1 mL), and $Ph(BOH)_2$ (30.54 mg, 0.3 mmol). The resulting mixture was stirred for 15 h at 80 °C, cooled to room temperature filtered over Celite and concentrated. Column chromatography (silica gel, hexane/CH_2Cl_2: 1/1) afforded 27.5 mg (45%) of **11a**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.12 (d, 1H, J=13.7 Hz), 3.50 (d, 1H, J=13.7 Hz), 3.76 (s, 3H), 4.53 (d, 1H, J=9.5 Hz), 4.91 (d, 1H, J=9.5 Hz), 6.81 (d, 1H, J=8 Hz), 6.94 (td, 1H, J=7.5 Hz, J=0.9 Hz), 7.03–7.07 (m, 2H), 7.19–7.30 (m, 4H), 7.41 (dd, 1H, J=7.5 Hz, J=1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.46, 52.93, 58.10, 77.01, 110.48, 121.09, 125.52, 127.51, 128.84, 129.99, 130.01, 136.59,

159.94, 173.28; IR (film) ν 3030, 2953, 2923, 2849, 1733, 1596, 1480, 1459, 1436, 1315, 1293, 1226, 1098, 1088, 1022, 979, 877, 834, 798, 753, 701 cm^{-1}; MS (FAB^+, NBA) m/z=268 (M^+), 209 (M^+-CO_2Me), 177 (M^+-CH_2Ph), 149, 105, 91, 69, 55, 43, 41, 29; HRMS for $C_{17}H_{16}O_3$ (M^+): calcd 268.1099 found 268.1081.

4.1.6. 3-Benzyl-2,3-dihydrobenzofuran-3-carboxylic acid (12a). To a solution of **11a** (28 mg, 0.104 mmol) in a mixture of dioxane/H_2O (9/1) (10 mL) was added aqueous solution of NaOH (2 M) (0.235 mL, 0.470 mmol). The resulting mixture was stirred for 4 h at room temperature and concentrated. The residue was dissolved in H_2O, and the aqueous layer was extracted three times with Et_2O, acidified with 1 N HCl until pH=1–3 and extracted three times with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated affording 18.5 mg (70%) of **10a**: ^1H NMR (250 MHz, $CDCl_3$) δ 3.09 (d, 1H, J=13.8 Hz), 3.47 (d, 1H, J=13.8 Hz), 4.46 (d, 1H, J=9.6 Hz), 4.84 (d, 1H, J=9.6 Hz), 6.75 (d, 1H, J=8 Hz), 6.90 (t, 1H, J=7.4 Hz), 7.01–7.05 (m, 2H), 7.14–7.21 (m, 4H), 7.38 (d, 1H, J=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.00, 57.95, 76.64, 110.59, 121.24, 125.51, 127.64, 128.24, 128.93, 130.04, 130.31, 136.28, 159.97, 178.29; IR (film) ν 3082, 3030, 2959, 2926, 2850, 1702, 1596, 1480, 1460, 1410, 1315, 1291, 1276, 1239, 1099, 1088, 1022, 973, 834, 751, 701 cm^{-1}; MS (FAB^-, NBA) m/z=253 ($M^\bullet-H$), 209 ($M^\bullet-CO_2H$), 46; HRMS for $C_{16}H_{13}O_3$ ($M^\bullet-H$): calcd 253.0865 found 253.0860.

4.1.7. 3-(4-Methoxybenzyl)-3-methoxycarbonyl-2,3-dihydrobenzofuran (11b). Synthesized according to the procedure described for the preparation of **11a**, using 4-methoxyphenylboronic acid, followed by column chromatography (silica gel, hexane/CH_2Cl_2: 2/3) afforded **11b** (56% and 50% one-pot version): ^1H NMR (250 MHz, $CDCl_3$) δ 3.00 (d, 1H, J=13.8 Hz), 3.36 (d, 1H, J=13.8 Hz), 3.70 (s, 3H), 3.73 (s, 3H), 4.45 (d, 1H, J=9.5 Hz), 4.83 (d, 1H, J=9.5 Hz), 6.74 (d, 3H, J=8.6 Hz), 6.84–7.00 (m, 3H), 7.15 (td, 1H, J=7.8 Hz, J=1.3 Hz), 7.34 (dd, 1H, J=7.5 Hz, J=1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.68, 52.90, 55.59, 58.26, 77.00, 110.44, 114.21, 121.04, 125.55, 128.58, 128.81, 129.94, 131.02, 159.09, 159.95, 173.37; IR (film) ν 3065–2998, 2952, 2924, 2849, 1732, 1610, 1596, 1583, 1513, 1480, 1461, 1440, 1291, 1274, 1247, 1179, 1114, 1097, 1035, 980, 936, 835, 793, 755 cm^{-1}; MS (FAB^+, NBA) m/z=299 (MH^+), 239 (M^+-CO_2Me), 214, 121, 177 (M^+-CH_2Ar), 69, 57, 41, 29; HRMS for $C_{18}H_{19}O_4$ (MH^+): calcd 299.1283 found 299.1283.

4.1.8. 3-(3-Nitrobenzyl)-3-methoxycarbonyl-2,3-dihydrobenzofuran (11c). Synthesized according to the procedure described for the preparation of **11a**, using 3-nitrophenylboronic acid, followed by column chromatography (silica gel, hexane/CH_2Cl_2: 2/3) afforded **11c** (56% and 40% one-pot version): ^1H NMR (250 MHz, $CDCl_3$) δ 3.26 (d, 1H, J=13.6 Hz), 3.48 (d, 1H, J=13.6 Hz), 3.80 (s, 3H), 4.48 (d, 1H, J=9.6 Hz), 4.89 (d, 1H, J=9.6 Hz), 6.77 (d, 1H, J=8 Hz), 6.97 (t, 1H, J=7.5 Hz), 7.19–7.45 (m, 4H), 7.88 (br s, 1H), 8.11 (d, 1H, J=8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.83, 53.24, 57.86, 76.84, 110.69, 121.36, 122.67, 124.96, 125.36, 127.82, 129.63, 130.45, 136.27, 138.47, 148.52, 159.92, 172.80; IR (film) ν 3056, 2955, 2927, 2850, 1732, 1583, 1531, 1481, 1461, 1436, 1353, 1266, 1230, 1101, 1024, 986, 894, 806, 737 cm^{-1}; MS (FAB^+, GT) m/z=314 (MH^+), 254 (M^+-CO_2Me), 242, 177 (M^+-CH_2Ar), 147, 136, 110; HRMS for $C_{17}H_{16}O_5N$ (MH^+): calcd 314.1028 found 314.1039.

4.1.9. 3-(2-Methylbenzyl)-3-methoxycarbonyl-2,3-dihydrobenzofuran (11d). Synthesized according to the procedure described for the preparation of **11a**, using 2-methylphenylboronic acid, followed by column chromatography (silica gel, hexane/CH_2Cl_2: 1/1) afforded **11d** (60% and 28% one-pot version): ^1H NMR (250 MHz, $CDCl_3$) δ 2.05 (s, 3H), 3.13 (d, 1H, J=14.7 Hz), 3.45 (d, 1H, J=14.7 Hz), 3.71 (s, 3H), 4.38 (d, 1H, J=9.4 Hz), 4.92 (d, 1H, J=9.4 Hz), 6.77 (d, 1H, J=8 Hz), 6.81–6.88 (m, 2H), 7.03–7.11 (m, 2H), 7.15 (dd, 1H, J=7.8 Hz, J=1.4 Hz), 7.19–7.23 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.10, 40.76, 53.02, 57.63, 77.62, 110.46, 121.09, 125.75, 126.36, 127.35, 128.91, 129.13, 129.96, 130.93, 135.20, 137.55, 159.87, 173.68; IR (film) ν 3054, 2988, 2954, 2844, 1734, 1596, 1481, 1461, 1459, 1436, 1266, 1228, 1022, 986, 896, 739, 705 cm^{-1}; MS (FAB^+, NBA) m/z=283 (MH^+), 223 (M^+-CO_2Me), 177 (M^+-CH_2Ar), 105, 77, 39, 27; HRMS for $C_{18}H_{19}O_3$ (MH^+): calcd 283.1334 found 283.1318.

4.1.10. 3-(3,4-Dimethoxybenzyl)-2,3-dihydrobenzofuran-3-carboxylic acid (12e). Synthesized using 3,4-dimethoxyphenylboronic acid to afford **11e** (71%). Compound **11e** was transformed according to the procedure described for preparation of **12a** to afford **12e** (64%): ^1H NMR (250 MHz, $CDCl_3$) δ 3.07 (d, 1H, J=13.8 Hz), 3.33 (d, 1H, J=13.8 Hz), 3.58 (s, 3H), 3.78 (s, 3H), 4.45 (d, 1H, J=9.5 Hz), 4.83 (d, 1H, J=9.5 Hz), 6.39 (d, 1H, J=1.7 Hz), 6.61 (dd, 1H, J=8.0 Hz, J=1.6 Hz), 6.71 (t, 2H, J=8.0 Hz), 6.89 (t, 1H, J=7.4 Hz), 7.17 (t, 1H, J=7.4 Hz), 7.39 (d, 1H, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.65, 55.97, 56.20, 58.09, 76.50, 110.65, 111.42, 113.06, 121.18, 122.30, 125.54, 128.09, 128.59, 130.31, 148.60, 149.04, 160.13, 179.36; IR (film) ν 3076, 3004, 2931, 2832, 1705, 1592, 1515, 1478, 1460, 1415, 1315, 1261, 1238, 1152, 1139, 1026, 971, 749 cm^{-1}; MS (FAB^-, NBA) m/z=313 ($M^\bullet-H$), 314 ($M^\bullet$), 46; HRMS for $C_{18}H_{17}O_5$ ($M^\bullet-H$): calcd 313.1076 found 313.1066.

4.1.11. 3-(3,4,5-Trimethoxybenzyl)-2,3-dihydrobenzofuran-3-carboxylic acid (12f). Synthesized according to the procedure described for the preparation of **11a**, using 3,4,5-dimethoxyphenylboronic acid to afford **11f** (73%). Compound **11f** was transformed according to the procedure described for preparation of **12a** to afford **12f** (71%): ^1H NMR (250 MHz, $CDCl_3$) δ 3.13 (d, 1H, J=13.8 Hz), 3.38 (d, 1H, J=13.8 Hz), 3.68 (s, 6H), 3.81 (s, 3H), 4.51 (d, 1H, J=9.5 Hz), 4.91 (d, 1H, J=9.5 Hz), 6.23 (s, 2H), 6.80 (d, 1H, J=8.0 Hz), 6.96 (t, 1H, J=7.5 Hz), 7.23 (t, 1H, J=7.9 Hz), 7.44 (d, 1H, J=7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.21, 56.33, 58.00, 61.26, 76.49, 107.13, 110.67, 121.20, 125.51, 128.07, 130.37, 131.80, 137.51, 153.39, 160.09, 178.95; IR (film) ν 3079, 3000, 2940, 2838, 1731, 1704, 1592, 1510, 1482, 1462, 1423, 1337, 1239, 1128, 1004, 977, 833, 755 cm^{-1}; MS (FAB^-, NBA)

m/*z*=343 (M•−H), 299, 46; HRMS for $C_{19}H_{19}O_6$ (M•−H): calcd 343.1182 found 343.1194.

4.1.12. 3-(2-Chlorobenzyl)-2,3-dihydrobenzofuran-3-carboxylic acid (12g). Synthesized according to the procedure described for the preparation of **11a**, using 2-chlorophenylboronic acid to afford **11g** (66%). Compound **11g** was transformed according to the procedure described for preparation of **12a** to afford **12g** (70%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.36 (d, 1H, *J*=14.4 Hz, H), 3.63 (d, 1H, *J*=14.4 Hz, H), 4.48 (d, 1H, *J*=9.6 Hz), 4.90 (d, 1H, *J*=9.6 Hz), 6.74 (d, 1H, *J*=8.0 Hz), 6.87–6.92 (m, 2H), 7.00–7.18 (m, 3H), 7.27–7.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.96, 57.59, 76.56, 110.65, 121.27, 125.63, 127.21, 127.86, 128.96, 130.22, 130.43, 131.30, 134.30, 135.43, 160.10, 179.21 (CO); IR (film) ν 3064, 3024, 2961, 2850, 1703, 1595, 1480, 1461, 1443, 1317, 1288, 1239, 1162, 1131, 1022, 975, 834, 751, 678 cm^{-1}; MS (FAB$^-$, NBA) *m*/*z*=287 (M•−H), 243 (M•−CO_2H), 223, 46; HRMS for $C_{16}H_{12}O_3{}^{35}Cl$ (M•−H): calcd 287.0475 found 287.0468.

4.1.13. 3-(3-Chlorobenzyl)-2,3-dihydrobenzofuran-3-carboxylic acid (12h). Synthesized according to the procedure described for the preparation of **11a**, using 3-chlorophenylboronic acid to afford **11h** (78%). Compound **11h** was transformed according to the procedure described for preparation of **12a** to afford **12h** (78%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.08 (d, 1H, *J*=13.8 Hz), 3.41 (d, 1H, *J*=13.8 Hz), 4.44 (d, 1H, *J*=9.6 Hz), 4.85 (d, 1H, *J*=9.6 Hz), 6.76 (d, 1H, *J*=8.0 Hz), 6.91 (t, 2H, *J*=7.5 Hz), 7.00 (s, 1H), 7.09–7.19 (m, 3H), 7.33 (d, 1H, *J*=6.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.50, 57.82, 76.53, 110.70, 121.37, 125.41, 127.83, 127.89, 128.32, 130.14, 130.25, 130.52, 134.69, 138.22, 159.97, 178.56; IR (film) ν 3080, 3022, 2959, 2926, 2851, 1704, 1596, 1573, 1481, 1462, 1430, 1409, 1316, 1277, 1239, 1209, 1082, 1022, 976, 833, 793, 752, 684 cm^{-1}; MS (FAB$^-$, NBA) *m*/*z*=287 (M•−H), 243 (M•−CO_2H), 223, 46; HRMS for $C_{16}H_{12}O_3{}^{35}Cl$ (M•−H): calcd 287.0475 found 287.0474.

4.1.14. 3-(4-Chlorobenzyl)-2,3-dihydrobenzofuran-3-carboxylic acid (12i). Synthesized according to the procedure described for the preparation of **11a**, using 4-chlorophenylboronic acid to afford **11i** (65%). Compound **11i** was transformed according to the procedure described for preparation of **12a** to afford **12i** (65%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.13 (d, 1H, *J*=13.8 Hz), 3.43 (d, 1H, *J*=14.0 Hz), 4.47 (d, 1H, *J*=9.6 Hz), 4.88 (d, 1H, *J*=9.6 Hz), 6.80 (d, 1H, *J*=8.1 Hz), 6.91–7.00 (m, 3H), 7.15–7.26 (m, 3H), 7.40 (d, 1H, *J*=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.21, 57.89, 76.51, 110.70, 121.35, 125.44, 127.78, 129.07, 130.49, 131.39, 133.66, 134.64, 159.96, 179.03; IR (film) ν 3084, 3028, 2952, 2925, 2884, 1704, 1596, 1481, 1462, 1408, 1317, 1296, 1238, 1094, 1016, 975, 835 cm^{-1}; MS (FAB$^-$, NBA) *m*/*z*=287 (M•−H), 243 (M•−CO_2H), 223, 46; HRMS for $C_{16}H_{12}O_3{}^{35}Cl$ (M•−H): calcd 287.0475 found 287.0475.

4.1.15. 3-(3,4-Dichlorobenzyl)-2,3-dihydrobenzofuran-3-carboxylic acid (12j). Synthesized according to the procedure described for the preparation of **11a**, using 3,4-dichlorophenylboronic acid to afford **11j** (85%). Compound **11j** was transformed according to the procedure described for preparation of **12a** to afford **12j** (69%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.09 (d, 1H, *J*=13.8 Hz), 3.35 (d, 1H, *J*=13.8 Hz), 4.42 (d, 1H, *J*=9.6 Hz), 4.85 (d, 1H, *J*=9.6 Hz), 6.72–6.85 (m, 2H), 6.92 (t, 1H, *J*=7.4 Hz), 7.09 (d, 1H, *J*=2.0 Hz), 7.18–7.27 (m, 2H), 7.35 (d, 1H, *J*=7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.85, 57.73, 76.44, 110.79, 121.45, 125.34, 127.47, 129.40, 130.67, 130.79, 131.93, 132.06, 132.85, 136.35, 159.95, 178.69; IR (film) ν 3065, 2993, 2954, 2929, 1704, 1595, 1481, 1462, 1398, 1316, 1279, 1238, 1134, 1032, 977, 834, 756 cm^{-1}; MS (FAB$^-$, NBA) *m*/*z*=321 (M•−H), 277 (M•−CO_2H), 46; HRMS for $C_{16}H_{11}O_3{}^{35}Cl_2$ (M•−H): calcd 321.0085 found 321.0076.

4.1.16. 3-(2-Trifluoromethylbenzyl)-2,3-dihydrobenzofuran-3-carboxylic acid (12k). Synthesized according to the procedure described for the preparation of **11a**, using 2-(trifluoromethyl)phenylboronic acid to afford **11k** (49%). Compound **11k** was transformed according to the procedure described for preparation of **12a** to afford **12k** (55%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.42 (d, 1H, *J*=15.8 Hz), 3.78 (d, 1H, *J*=15.6 Hz), 4.26 (d, 1H, *J*=9.7 Hz), 5.02 (d, 1H, *J*=9.7 Hz), 6.77 (d, 1H, *J*=8.1 Hz), 6.93 (t, 2H, *J*=7.4 Hz), 7.18–7.25 (m, 1H), 7.29–7.32 (m, 2H), 7.39 (d, 1H, *J*=7.6 Hz), 7.63 (d, 1H, *J*=6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.78, 56.90, 76.68, 110.74, 121.42, 126.05, 126.87, 126.93, 127.53, 128.01, 130.07, 130.36, 130.67, 132.28, 135.41, 160.04, 179.37 (CO); IR (film) ν 3073, 3007, 2954, 2908, 1704, 1608, 1596, 1482, 1462, 1312, 1240, 1167, 1120, 1062, 1039, 1022, 975, 837, 769, 755 cm^{-1}; MS (FAB$^-$, NBA) *m*/*z*=321 (M•−H), 277 (M•−CO_2H), 46; HRMS for $C_{17}H_{12}O_3F_3$ (M•−H): calcd 321.0739 found 321.0749.

4.1.17. 3-(4-Trifluoromethoxybenzyl)-2,3-dihydrobenzofuran-3-carboxylic acid (12l). Synthesized according to the procedure described for the preparation of **11a**, using 4-(trifluoroacetyl)phenylboronic acid to afford **11l** (66%). Compound **11l** was transformed according to the procedure described for preparation of **12a** to afford **12l** (73%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.11 (d, 1H, *J*=13.9 Hz), 3.43 (d, 1H, *J*=13.9 Hz), 4.43 (d, 1H, *J*=9.6 Hz), 4.85 (d, 1H, *J*=9.6 Hz), 6.75 (d, 1H, *J*=8.0 Hz), 6.91 (t, 1H, *J*=7.5 Hz), 7.03 (s, 4H), 7.17 (td, 1H, *J*=7.6 Hz, *J*=1.3 Hz), 7.34 (d, 1H, *J*=6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.08, 57.87, 76.53, 110.71, 121.29, 121.36, 125.37, 127.81, 128.89, 130.52, 131.42, 134.91, 148.86, 159.95, 178.88; IR (film) ν 3046–2931, 1704, 1596, 1510, 1482, 1462, 1416, 1258, 1222, 1166, 1111, 1021, 976, 835, 753 cm^{-1}; MS (FAB$^-$, NBA) *m*/*z*=337 (M•−H), 293 (M•−CO_2H), 46; HRMS for $C_{17}H_{12}O_4F_3$ (M•−H): calcd 337.0688 found 337.0679.

4.1.18. 3-(4-Acetylbenzyl)-2,3-dihydrobenzofuran-3-carboxylic acid (12m). Synthesized according to the procedure described for the preparation of **11a**, using 4-acetylphenylboronic acid to afford **11m** (73%). Compound **11m** was transformed according to the procedure described for preparation of **12a** to afford **12m** (70%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.57 (s, 3H), 3.22 (d, 1H, *J*=13.7 Hz), 3.52 (d, 1H, *J*=13.7 Hz), 4.48 (d, 1H, *J*=9.6 Hz), 4.89 (d, 1H,

J=9.6 Hz), 6.78 (d, 1H, J=8.1 Hz), 6.95 (t, 1H, J=7.2 Hz), 7.14 (d, 2H, J=8.2 Hz), 7.22 (t, 1H, J=7.6 Hz), 7.41 (d, 1H, J=7.6 Hz), 7.83 (d, 2H, J=8.2 Hz,); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.98, 43.79, 57.75, 76.58, 110.70, 121.37, 125.43, 127.85, 128.89, 128.96, 130.37, 130.50, 136.37, 141.99, 159.95, 178.11, 198.70; IR (film) ν 3054–2931, 1731, 1704, 1682, 1607, 1571, 1481, 1461, 1415, 1360, 1268, 1238, 1186, 1119, 1021, 973, 835, 753, 737, 703 cm^{-1}; MS (FAB$^-$, NBA) m/z=295 (M•−OH).

4.1.19. 3-[4-(1,3,6-Trioxaheptane)benzyl]-2,3-dihydrobenzofuran-3-carboxylic acid (12n). Synthesized according to the procedure described for the preparation of **11a**, using 4-(1,3,6-trioxaheptane)phenylboronic acid to afford **11n** (79%). Compound **11n** was transformed according to the procedure described for preparation of **12a** to afford **12n** (91%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.09 (d, 1H, J=13.9 Hz), 3.37 (s, 3H), 3.45 (d, 1H, J=13.9 Hz), 3.54–3.57 (m, 2H), 3.79–3.83 (m, 2H), 4.50 (d, 1H, J=9.5 Hz), 4.88 (d, 1H, J=9.5 Hz), 6.79 (d, 1H, J=8.0 Hz), 6.90–7.01 (m, 5H), 7.22 (td, 1H, J=7.8 Hz, J=1.4 Hz), 742 (dd, 1H, J=7.5 Hz, J=1.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.18, 58.05, 59.36, 68.01, 72.01, 76.59, 93.85, 110.54, 116.63, 116.68, 121.08, 125.48, 128.34, 129.64, 129.69, 130.22, 131.12, 156.82, 159.96, 178.48; IR (film) ν 3165, 3015, 2923, 2908, 2822, 1731, 1704, 1610, 1596, 1511, 1481, 1461, 1398, 1367, 1314, 1224, 1180, 1165, 1098, 1003, 836 cm^{-1}; MS (FAB$^-$, NBA) m/z=357 (M•−H), 313 (M•−CO_2H), 46; HRMS for $C_{20}H_{21}O_6$ (M•−H): calcd 357.1338 found 357.1340.

4.1.20. 3-(4-Vinylbenzyl)-2,3-dihydrobenzofuran-3-carboxylic acid (12o). Synthesized according to the procedure described for the preparation of **11a**, using 4-vinylphenylboronic acid to afford **11o** (53%). Compound **11o** was transformed according to the procedure described for preparation of **12a** to afford **12o** (95%):^{1}H NMR (250 MHz, $CDCl_3$) δ 3.14 (d, 1H, J=13.8 Hz), 3.50 (d, 1H, J=13.8 Hz), 4.51 (d, 1H, J=9.5 Hz), 4.89 (d, 1H, J=9.5 Hz), 5.23 (dd, 1H, J=10.9 Hz, J=0.6 Hz), 5.71 (dd, 1H, J=17.6 Hz, J=0.7 Hz), 6.67 (q, 1H, J=17.6 Hz, J=10.9 Hz), 6.80 (d, 1H, J=8.1 Hz), 6.95 (td, 1H, J=7.5 Hz, J=0.9 Hz), 7.04 (d, 2H, J=8.2 Hz), 7.20–7.31 (m, 3H), 7.43 (dd, 1H, J=7.5 Hz, J=1.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.73, 58.00, 76.60, 110.62, 114.31, 121.27, 125.52, 126.76, 127.00, 128.20, 130.24, 130.33, 135.87, 136.69, 136.78, 136.87, 159.97, 178.97; IR (film) ν 3086, 3023, 2953, 2924, 1704, 1630, 1596, 1512, 1481, 1462, 1407, 1316, 1294, 1239, 1119, 1099, 1021, 974, 912, 835 cm^{-1}; MS (FAB$^-$, NBA) m/z=279 (M•−H), 235 (M•−CO_2H), 46; HRMS for $C_{18}H_{15}O_3$ (M•−H): calcd 279.1021 found 279.1029.

4.1.21. 3-(1-Methylenylnaphtyl)-2,3-dihydrobenzofuran-3-carboxylic acid (12p). Synthesized according to the procedure described for the preparation of **11a**, using 1-naphtylboronic acid to afford **11p** (78%). Compound **11p** was transformed according to the procedure described for preparation of **12a** to afford **12p** (50%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.26 (d, 1H, J=13.8 Hz), 3.64 (d, 1H, J=13.8 Hz), 4.54 (d, 1H, J=9.6 Hz), 4.87 (d, 1H, J=9.6 Hz), 6.76 (d, 1H, J=8.1 Hz), 6.93 (t, 1H, J=7.1 Hz), 7.12–7.24 (m, 2H), 7.39–7.44 (m, 3H), 7.50 (s, 1H), 7.63–7.69 (m, 1H), 7.73–7.77 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.18, 58.07, 76.65, 110.66, 121.31, 125.56, 126.28, 126.60, 128.00, 128.03, 128.12, 128.32, 128.58, 128.99, 130.37, 132.89, 133.75, 133.86, 159.99, 178.93; IR (film) ν 3054–2860, 1704, 1596, 1508, 1481, 1461, 1367, 1315, 1239, 1154, 1099, 1022, 975, 821, 751 cm^{-1}; MS (FAB$^-$, NBA) m/z=303 (M•−H), 259 (M•−CO_2H), 46; HRMS for $C_{20}H_{15}O_3$ (M•−H): calcd 303.1021 found 303.1010.

4.1.22. 3-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-2-methylenylnaphtyl)-2,3-dihydrobenzofuran-3-carboxylic acid (12q). Synthesized according to the procedure described for the preparation of **11a**, using 5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphtylboronic acid to afford **11q** (81%). Compound **11q** was transformed according to the procedure described for preparation of **12a** to afford **12** (88%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.136 and 1.143 (2s, 6H), 1.25 (s, 6H), 1.63 (s, 4H), 3.09 (d, 1H, J=13.8 Hz), 3.46 (d, 1H, J=13.8 Hz), 4.50 (d, 1H, J=9.5 Hz), 4.90 (d, 1H, J=9.5 Hz), 6.80 (d, 1H, J=8.0 Hz), 6.86–6.97 (m, 4H), 7.17–7.19 (m, 1H), 7.44 (dd, 1H, J=7.6 Hz, J=1.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.99, 32.12, 32.23, 32.30, 34.39, 34.47, 35.41, 35.42, 43.76, 58.03, 76.64, 110.52, 121.18, 125.58, 127.03, 127.22, 128.18, 128.39, 130.17, 133.02, 144.08, 145.29, 159.97, 179.16; MS (FAB$^-$, NBA) m/z=363 (M•−H), 319 (M•−CO_2H), 46.

4.1.23. 3-(4-Phenylbenzyl)-3-methoxycarbonyl-2,3-dihydrobenzofuran (11r). Synthesized according to the procedure described for the preparation of **11a**, using 4-biphenylboronic acid, followed by column chromatography (silica gel, hexane/CH_2Cl_2: 1/1) afforded **11r** (71% and 57% one-pot version): ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.20 (d, 1H, J=13.7 Hz), 3.57 (d, 1H, J=13.7 Hz), 3.82 (s, 3H) 4.60 (d, 1H, J=9.5 Hz), 4.98 (d, 1H, J=9.5 Hz), 6.86 (d, 1H, J=8 Hz), 6.99 (td, 1H, J=7.4 Hz, J=0.8 Hz), 7.15 (d, 2H, J=8.2 Hz), 7.27 (td, 1H, J=8.6 Hz, J=1.4 Hz), 7.39–7.56 (m, 6H), 7.62 (d, 2H, J=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.10, 53.00, 58.14, 77.06, 110.54, 121.14, 125.53, 127.41, 127.53, 127.71, 128.82, 129.19, 130.07, 130.44, 135.66, 140.36, 141.05, 159.97, 173.31; IR (film) ν 3063, 3030, 2954, 2928, 2855, 1732, 1596, 1481, 1460, 1435, 1409, 1328, 1314, 1298, 1276, 1228, 1118, 1097, 1076, 1022, 1008, 981, 880, 836, 763, 699 cm^{-1}; MS (FAB$^+$, NBA) m/z=573, 483, 392, 366, 345 (MH$^+$), 344 (M$^+$), 307, 289, 167, 91, 55, 41; HRMS for $C_{23}H_{21}O_3$ (MH$^+$): calcd 345.1491 found 345.1500.

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