Regiospecific Synthesis of 5- and 6-Acylated Naphtho[1,2-b]benzofurans via Intramolecular Alkyne Carbonyl Metathesis

Maloy Nayak  
Dileep Kumar Singh  
Ikyon Kim*

College of Pharmacy and Yonsei Institute of Pharmaceutical Sciences, Yonsei University, 85 Songdogwahak-ro, Yeongu-gu, Incheon, 21983, Republic of Korea  
ikyonkim@yonsei.ac.kr

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Abstract  
Straightforward access to various 5- and 6-acylated naphtho[1,2-b]benzofurans was achieved by successive Sonogashira coupling and intramolecular alkyne carbonyl metathesis to assemble the central aromatic C ring of naphtho[1,2-b]benzofurans regiospecifically substituted with an acyl group at the C5 or C6 position.

Key words  
naphtho[1,2-b]benzofuran, Sonogashira coupling, alkyne carbonyl metathesis, intramolecular reaction, regiospecific reaction

Intramolecular alkyne carbonyl metathesis (IACM) of an alkyne and a carbonyl spatially arranged within one molecular skeleton provides an efficient way to make carbo- or heterocycles with an enone functional group (Scheme 1, a). Recently, we have employed this strategy for the synthesis of benzo-fused indolizines, pyrrolo[1,2-a]quinolines, as well as natural products, such as brasiliin, deguelin, and munduserone, constructing the pyridine ring in the former and 3- or 4-acylchromene in the latter.

As an extension, we decided to investigate IACM-based modular synthesis of polyaromatic heterocycles, an important class of chemicals in the area of pharmaceuticals and functional materials. Since IACM typically allows the regiospecific introduction of an acyl moiety in the newly formed ring systems, we hoped to construct polyheterocycles with an acyl group positioned at a specific site, which is quite difficult to achieve by any other synthetic methods such as intermolecular Friedel–Crafts acylation. As part of our continued interest in polyfunctionalized benzofurans we wish to describe here a synthetic approach to naphtho[1,2-b]benzofurans with an acyl unit at the C5 or C6 position through IACM (Scheme 1, b). As 2-arylnaphthalene, 1-acylnaphthalene, and 2-acylnaphthalene have been employed as key pharmacophores in the area of small-molecule drug discovery, we expected that these two hybrid structures would be useful in the discovery of new interesting biological activities.

Retrosynthetically, 2-arylbenzofurans, 2 and 5, having both alkyne and aldehyde groups were required for this purpose. In turn, we expected that Sonogashira cross-coupling of 3 and 6 with terminal alkynes would give rise to 2 and 5, respectively.

Scheme 1  
Synthetic plans
To validate our proposal, preparation of the requisite 3 was first attempted. After several unsuccessful attempts, we finally resorted to Chi’s protocol (Scheme 2). First, ethyl (2-hydroxyphenyl)acetate was coupled with 2-iodobenzoic acid under modified Steglich esterification conditions to give ester 7. Exposure of 7 to excess t-BuOK resulted in β-keto ester 8 in its enol form in excellent yield, which was smoothly converted into methyl 2-(2-iodophenyl)benzofuran-3-carboxylate (9) by treatment of MeOH and concentrated H2SO4. The ester moiety in 9 was transformed into the desired aldehyde to furnish 3 in good overall yield by a three-step sequence: hydrolysis, NaBH4 reduction of the mixed anhydride formed in situ, and IBX oxidation.

When 3 was subjected to Sonogashira coupling conditions with phenylacetylene, 2a was isolated in 94% yield (Scheme 3). After screening of several ACM catalyst conditions, we were pleased to find that heating of 2a in TFA/DCE at 80 °C for 1 hour deliver the desired product 1a in excellent yield.

With these optimized conditions in hand, substrate scope was examined with different terminal alkynes (Table 1). Sonogashira cross-coupling of 3 with several (hetero)aryalkynes proceeded well to give the corresponding alkynes 2 in excellent yields. Subsequent IACM of 2 under the optimized conditions furnished the desired 5-acylnaphtho[1,2-b]benzofurans 4 in good yields except for 2f (entry 5). The formation of 1f can be interpreted as a consequence of domino alkyne carbonyl metathesis/Nazarov cyclization.

Next, 6 was synthesized for the synthesis of 6-acylnaphtho[1,2-b]benzofurans 4 (Scheme 4). Sonogashira coupling of 1-ethyl-2-methoxybenzene with 2-iodobenzaldehyde afforded the corresponding product 12 in 78% yield. To our disappointment, however, no desired 3-iodobenzofuran 6 was observed from the reaction of 12 under several iodocyclization conditions, which might be ascribed to the competitive participation of the formyl group in iodine
Table 1  Synthesis of Diverse 5-Acynaphtho[1,2-b]benzofurans

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkyne</th>
<th>2 (yield, b%)</th>
<th>Product</th>
<th>1 (yield, b%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≡C[Me]</td>
<td>2b (98)</td>
<td><img src="image1" alt="Product" /></td>
<td>1b (97)</td>
</tr>
<tr>
<td>2</td>
<td>≡C[O-Me]</td>
<td>2c (96)</td>
<td><img src="image2" alt="Product" /></td>
<td>1c (90)</td>
</tr>
<tr>
<td>3</td>
<td>≡C[O-Me]</td>
<td>2d (94)</td>
<td><img src="image3" alt="Product" /></td>
<td>1d (93)</td>
</tr>
<tr>
<td>4</td>
<td>≡C[O-C3-H]</td>
<td>2e (98)</td>
<td><img src="image4" alt="Product" /></td>
<td>1e (93)</td>
</tr>
<tr>
<td>5</td>
<td>≡C(Me)</td>
<td>2f (75)</td>
<td><img src="image5" alt="Product" /></td>
<td>1f (68)</td>
</tr>
<tr>
<td>6</td>
<td>≡C[S]</td>
<td>2g (95)</td>
<td><img src="image6" alt="Product" /></td>
<td>1g (87)</td>
</tr>
</tbody>
</table>

*Reaction conditions: 1. 3 (0.14 mmol), terminal alkyne (0.16 mmol), (Ph₃P)₂PdCl₂ (0.1 equiv), Cul (0.05 equiv), Et₃N (2 mL), 70 °C, 12 h; 2. 2 (0.1 mmol), TFA/DCE (1:2, 3 mL); 80 °C 1 h.

b Isolated yield.
mediated cyclization. These difficulties in preparing 6 were overcome by replacing the coupling partner by 2-iodobenzyl acetate (13). Thus, when 1-ethynyl-2-methoxybenzene was treated with 13 in the presence of (Ph3P)2PdCl2 (0.1 equiv) and CuI (0.05 equiv) in Et3N at room temperature, the cross-coupled product 14 was obtained in excellent yield. Smooth iodocyclization took place upon exposure of 14 to I2 (4 equiv), affording the cyclized product 15 in 98% yield. Deacetylation of 15 and subsequent PCC oxidation gave 6, setting the stage for sequential Sonogashira coupling/IACM for the synthesis of 6-acylnaphtho[1,2-b]benzofuran.

As shown in Table 2, Sonogashira coupling of 6 with phenylacetylene under the similar reaction conditions employed for the synthesis of 2 led to 5a in 92% yield (entry 1). Again, subjection of 5a in TFA/DCE at 80 °C for 1 hour produced the desired product 4a in excellent yield. The reaction scope was also investigated with different (hetero)aryl- and alkylalkynes under the same reaction sequence. Various 6-acylnaphtho[1,2-b]benzofurans 4 were synthesized in good overall yields. The IACM reaction with a substrate bearing an electron-deficient aryl group on the alkyne 5f also worked well under these conditions to give 4f in 90% yield (entry 6). When 5g having a cyclohex-1-enyl group was exposed to TFA at 80 °C, hexacyclic compound 4g' was obtained as the major product due to Nazarov reaction after IACM (entry 7).

### Table 2  Synthesis of Diverse 6-Acylnaphtho[1,2-b]benzofurans

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkyne</th>
<th>5 (yield, %)</th>
<th>Product</th>
<th>4 (yield, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>5a (92)</td>
<td><img src="image1.png" alt="Image" /></td>
<td>4a (90)</td>
</tr>
<tr>
<td>2</td>
<td>-Me</td>
<td>5b (85)</td>
<td><img src="image2.png" alt="Image" /></td>
<td>4b (95)</td>
</tr>
<tr>
<td>3</td>
<td>-OMe</td>
<td>5c (83)</td>
<td><img src="image3.png" alt="Image" /></td>
<td>4c (90)</td>
</tr>
<tr>
<td>4</td>
<td>-OMe</td>
<td>5d (85)</td>
<td><img src="image4.png" alt="Image" /></td>
<td>4d (88)</td>
</tr>
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</table>
In summary, we have established an expeditious route to 5- and 6-acylated naphtho[1,2-b]benzofurans, hybrid structures of 2-arylbenzofuran and 1- or 2-acynaphtha-
lene, by utilizing a sequential Sonogashira coupling/intra-
molecular alkyne carbonyl metathesis reaction where the benzene ring C of this scaffold was formed with an acyl substituent at the specific position. Both aryl- and alkylal-
kyynes were employed in this sequence to generate a wide variety of new 6-acylnaphtho[1,2-b]benzofurans, exhibiting good functional group tolerance. Application of this protocol for the synthesis of other polyaromatic heterocy-
cycles as well as evaluation of these compounds in biomedical sciences are underway in our laboratory.

Unless specified, all reagents and starting materials were purchased from commercial sources and used as received without purification. ‘Concentrated’ refers to the removal of volatile solvents via distillation using a rotary evaporator. ‘Dried’ refers to pouring onto, or passing through, anhyd MgSO4 followed by filtration. Flash chromatography was performed using silica gel (230–400 mesh) with hexanes, EtOAc, and CH2Cl2 as eluent. All reactions were monitored by TLC on 0.25-
mesh silica plates (F-254) visualizing with UV light. Melting points were measured using a capillary melting point apparatus. 1H and 13C NMR spectra were recorded on 400 MHz NMR spectrometer. HRMS were measured with electrospary ionization (ESI) and Q-TOF mass analyzer.
2-(2-Ethoxy-2-oxoethyl)phenyl 2-Iodobenzoyl (7)

To a stirred solution of ethyl (2-hydroxyphenyl)acetate (1.2 g, 6.66 mmol) in anhyd CHCl₃ (25 mL) were added 2-iodobenzoic acid (1.98 g, 7.99 mmol), EDC·HCl (1.53 g, 7.99 mmol), and DMAP (163 mg, 1.33 mmol) at rt and the mixture was stirred overnight. The mixture was washed with 1 M HCl and water followed by sat. aq NaHCO₃ solution. The organic layer was dried (MgSO₄) and concentrated in vacuo to yield the crude product which was purified by flash chromatography (silica gel, hexanes/EtOAc, 9:1) to give 7 (2.33 g, 85%) as a colorless liquid.

\[ \text{1H NMR} \left(400 \text{ MHz}, \text{CDCl}_3\right): \delta = 8.09 \left(t, J = 8.1 \text{ Hz}, 2 \text{ H}\right), 7.49 \left(t, J = 7.6 \text{ Hz}, 1 \text{ H}\right), 7.35–7.39 \left(m, 2 \text{ H}\right), 7.21–7.30 \left(m, 3 \text{ H}\right), 4.08 \left(q, J = 7.1 \text{ Hz}, 2 \text{ H}\right), 3.64 \left(s, 2 \text{ H}\right), 1.14 \left(t, J = 7.1 \text{ Hz}, 3 \text{ H}\right). \]

\[ \text{13C NMR} \left(100 \text{ MHz}, \text{CDCl}_3\right): \delta = 173.4, 171.2, 149.2, 141.9, 139.3, 133.7, 133.4, 131.7, 131.5, 128.7, 126.8, 126.5, 122.6, 94.9, 61.1, 36.7, 14.2. \]


3-[Hydroxy(2-iodophenyl)methylene]benzofuran-2(3H)-one (8)

To a mixture of KOT-Bu (862 mg, 7.68 mmol) in anhyd THF (40 mL) under an N₂ atmosphere was dropwise added a solution of 7 (2.1 g, 5.12 mmol) in THF (5 mL) at 78 °C. The mixture was stirred for 10 min at 78 °C, and then it was warmed to 0 °C and stirred for 2 h at this temperature. The mixture was quenched with 1 M HCl (5 mL). The solution was added dropwise NaBH₄ (200 mg, 5.30 mmol) dissolved in water (0.5 mL). The mixture was stirred for 5 min at 0 °C, and then it was quenched with water (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (MgSO₄) and concentrated in vacuo to yield the product (1.81 g, 97%) as a greenish yellow solid, which was used for the next step without further purification; mp 129.4–131.5 °C.

\[ \text{1H NMR} \left(400 \text{ MHz}, \text{CDCl}_3\right): \delta = 8.04 \left(d, J = 8.0 \text{ Hz}, 1 \text{ H}\right), 7.75 \left(t, J = 7.6 \text{ Hz}, 1 \text{ H}\right), 7.45 \left(d, J = 7.6 \text{ Hz}, 1 \text{ H}\right), 7.30 \left(d, J = 7.6 \text{ Hz}, 1 \text{ H}\right), 7.16–7.23 \left(m, 2 \text{ H}\right), 6.93 \left(t, J = 7.2 \text{ Hz}, 1 \text{ H}\right), 6.31 \left(d, J = 7.2 \text{ Hz}, 1 \text{ H}\right). \]

\[ \text{13C NMR} \left(100 \text{ MHz}, \text{CDCl}_3\right): \delta = 173.4, 171.2, 151.1, 140.3, 138.1, 132.3, 129.3, 128.9, 127.6, 124.2, 121.9, 119.3, 110.1, 100.1, 94.5. \]


Methyl 2-(2-Iodophenyl)benzofuran-3-carboxylate (9)

To a stirred solution of (1.3 g, 3.57 mmol) in anhyd MeOH (40 mL) were added 2-iodobenzoic acid (1.98 g, 8.13 mmol) and NaOH·H₂O (2.4 g, 40 mmol). The mixture was stirred for 3 h, and then it was cooled to r.t. and the mixture was filtered through a pad of Celite, and washed with water (2 × 10 mL) and sat. aq NaHCO₃ solution (2 × 10 mL). The filtrate was washed with water (0.5 mL). The mixture was stirred for 5 min at 0 °C, and then it was quenched with water (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (MgSO₄) and concentrated in vacuo to yield the crude product which was purified by flash chromatography (silica gel, hexanes/EtOAc, 9:1) to afford 9 (905 mg, 98%) as an off-white solid; mp 98 °C.

\[ \text{1H NMR} \left(400 \text{ MHz}, \text{CDCl}_3\right): \delta = 8.00 \left(d, J = 7.9 \text{ Hz}, 1 \text{ H}\right), 7.81 \left(d, J = 7.2 \text{ Hz}, 1 \text{ H}\right), 7.54 \left(d, J = 8.0 \text{ Hz}, 1 \text{ H}\right), 7.44–7.48 \left(m, 2 \text{ H}\right), 7.31–7.39 \left(m, 2 \text{ H}\right), 7.17–7.20 \left(m, 1 \text{ H}\right), 4.75 \left(s, 2 \text{ H}\right), 1.81 \left(s, 1 \text{ H}\right). \]

\[ \text{13C NMR} \left(100 \text{ MHz}, \text{CDCl}_3\right): \delta = 154.5, 154.3, 139.8, 135.6, 132.2, 131.2, 128.2, 125.1, 123.2, 120.6, 117.0, 111.6, 99.1, 56.4. \]


2-(2-Iodophenyl)benzofuran-3-carboxaldehyde (3)

To a stirred solution of (11) (990 mg, 2.83 mmol) in EtOAc (20 mL) was added IBX (2.4 g, 8.49 mmol). The mixture was refluxed for 3 h, and then it was cooled to r.t., filtered through a pad of Celite, and washed with EtOAc. The filtrate was washed with sat. aq NaHCO₃ (3 × 10 mL) and water (2 × 10 mL). The combined organic layers were dried (MgSO₄) and concentrated in vacuo to give the crude product which was purified by flash chromatography (silica gel, hexanes/EtOAc, 9:1) to afford 3 (914 mg, 93%) as a white solid; mp 104.9–106.9 °C.

\[ \text{1H NMR} \left(400 \text{ MHz}, \text{CDCl}_3\right): \delta = 9.98 \left(s, 1 \text{ H}\right), 8.29 \left(d, J = 8.0 \text{ Hz}, 1 \text{ H}\right), 8.05–8.07 \left(m, 1 \text{ H}\right), 7.59–7.61 \left(m, 1 \text{ H}\right), 7.53–7.54 \left(m, 2 \text{ H}\right), 7.41–7.47 \left(m, 2 \text{ H}\right), 7.26–7.30 \left(m, 3 \text{ H}\right). \]

\[ \text{13C NMR} \left(100 \text{ MHz}, \text{CDCl}_3\right): \delta = 186.6, 166.8, 154.4, 140.3, 133.9, 132.6, 132.3, 128.3, 127.2, 124.4, 122.9, 118.9, 111.6, 98.2. \]


2-(2-Iodophenyl)benzofuran-3-carbaldehyde (2a); Typical Procedure

To a mixture of (3) (50 mg, 0.14 mmol) in Et,N (2 mL) were added phenylacetylene (0.018 ml, 0.16 mmol), (Ph,P)₂PdCl₂ (10 mg, 0.014 mmol), and Cul (1.33 mg, 0.007 mmol). The mixture was stirred at 70 °C for 12 h, and then it was concentrated in vacuo to yield the
crude product. Purification by flash chromatography (silica gel, hexanes/EtOAc, 9:1) afforded 2a (43.5 mg, 94%) as an off-white solid; mp 102.3–104.6 °C.

1H NMR (400 MHz, CDCl3): δ = 10.26 (s, 1 H), 8.31–8.32 (m, 1 H), 7.70–7.75 (m, 2 H), 7.49–7.58 (m, 3 H), 7.40–7.42 (m, 2 H), 7.31–7.33 (m, 2 H), 7.25–7.27 (m, 3 H).

13C NMR (100 MHz, CDCl3): δ = 180.7, 164.2, 154.7, 133.6, 131.7, 130.8, 130.4, 128.9, 128.6, 128.5, 126.2, 125.1, 124.9, 124.1, 122.9, 122.4, 118.7, 111.4, 94.0, 87.4.


2-{2-[((3-Methoxyphenyl)ethynyl]phenyl}benzofuran-3-carbaldehyde (1a)

2-{2-[((4-Methoxyphenyl)ethynyl]phenyl}benzofuran-3-carbaldehyde (1b)

2-{2-[p-Tolyethynyl]phenyl}benzofuran-3-carbaldehyde (2b)

White solid; yield: 47.5 mg (98%); mp 112.2–114.4 °C.

1H NMR (400 MHz, CDCl3): δ = 10.28 (s, 1 H), 8.33–8.34 (m, 1 H), 7.72–7.76 (m, 2 H), 7.40–7.46 (m, 3 H), 7.42–7.43 (m, 2 H), 7.23 (d, J = 7.6 Hz, 2 H), 7.08 (d, J = 7.6 Hz, 2 H), 2.32 (s, 3 H).

13C NMR (100 MHz, CDCl3): δ = 180.7, 164.2, 154.7, 139.2, 133.4, 131.6, 130.8, 130.7, 130.3, 129.3, 128.4, 126.1, 125.2, 124.9, 124.3, 122.9, 119.3, 111.3, 94.3, 86.9, 217.


2-{2-[(4-Methoxyphenyl)ethynyl]phenyl}benzofuran-3-carbaldehyde (2c)

Pale yellow solid; yield: 35.0 mg (75%); mp 103.1–105.2 °C.

1H NMR (400 MHz, CDCl3): δ = 10.20 (s, 1 H), 8.30–8.31 (m, 1 H), 7.67 (d, J = 7.2 Hz, 1 H), 7.64–7.62 (d, J = 7.5 Hz, 1 H), 7.55–7.57 (m, 1 H), 7.40–7.51 (m, 4 H), 6.08 (s, 1 H), 2.02–2.06 (m, 4 H), 1.49–1.61 (m, 4 H).

13C NMR (100 MHz, CDCl3): δ = 187.1, 164.3, 154.6, 136.8, 133.3, 130.6, 130.1, 128.0, 126.0, 125.1, 124.8, 124.6, 122.9, 120.3, 118.5, 111.3, 96.0, 84.9, 28.7, 25.9, 22.1, 21.4.


2-{2-[(Thiophen-3-ylthynyl)phenyl]benzofuran-3-carbaldehyde (2g)

Off-white solid; yield: 45.0 mg (95%); mp 93.5–95.8 °C.

1H NMR (400 MHz, CDCl3): δ = 10.29 (s, 1 H), 8.33–8.34 (m, 1 H), 7.72–7.74 (m, 2 H), 7.52–7.59 (m, 3 H), 7.40–7.43 (m, 3 H), 7.23 (s, 1 H), 7.01 (d, J = 4.6 Hz, 1 H).

13C NMR (100 MHz, CDCl3): δ = 187.1, 164.0, 154.7, 133.3, 130.7, 130.3, 129.7, 129.7, 128.5, 126.2, 125.6, 125.1, 124.9, 124.1, 122.9, 121.5, 118.6, 111.3, 89.3, 87.0.


Naphtho[1,2-b]benzofuran-5-yl(phenyl)methanone (1a)

To a solution of 2a (32 mg, 0.1 mmol) in DCE (2.0 mL) was added TFA (1.0 mL) and the resulting solution was stirred at 80 °C for 1 h. Then the mixture was cooled down to r.t. and concentrated in vacuo to yield the crude product. Purification by flash chromatography (silica gel, hexanes/EtOAc, 9:1) afforded 1a (31 mg, 97%) as an off-white solid; mp 167.4–168.9 °C.

1H NMR (400 MHz, CDCl3): δ = 8.56 (d, J = 8.0 Hz, 1 H), 8.33 (d, J = 8.2 Hz, 1 H), 8.17 (s, 1 H), 7.94–7.95 (m, 5 H), 7.69–7.77 (m, 2 H), 7.59–7.66 (m, 2 H), 7.51–7.52 (m, 3 H), 7.39–7.43 (m, 1 H).

13C NMR (100 MHz, CDCl3): δ = 197.8, 156.5, 138.9, 133.3, 132.0, 131.2, 130.7, 128.6, 127.5, 127.2, 127.0, 126.9, 124.7, 123.6, 122.1, 121.7, 121.4, 120.6, 117.8, 112.2.


Naphtho[1,2-b]benzofuran-5-yl(p-toly)methanone (1b)

Off-white solid; yield: 33.0 mg (97%); mp 163.4–165.6 °C.

1H NMR (400 MHz, CDCl3): δ = 8.55 (d, J = 7.2 Hz, 1 H), 8.28 (d, J = 8.4 Hz, 1 H), 8.15 (s, 1 H), 7.95 (d, J = 7.2 Hz, 1 H), 7.84 (d, J = 7.6 Hz, 2 H), 7.68–7.76 (m, 2 H), 7.50–7.61 (m, 2 H), 7.40 (t, J = 7.2 Hz, 1 H), 7.30 (d, J = 7.6 Hz, 2 H), 2.46 (s, 3 H).

13C NMR (100 MHz, CDCl3): δ = 197.5, 156.4, 144.3, 136.3, 132.4, 131.1, 130.8, 129.4, 127.4, 127.1, 126.9, 126.9, 124.8, 123.5, 121.7, 121.5, 121.4, 120.56, 117.8, 112.2, 21.9.
HRMS (ESI-QTOF): m/z [M + Na]+ calcd for C_{21}H_{12}O_{3}: 359.0942; found: 359.0943.

(4-Methoxyphenyl)naphtho[1,2-b]benzofuran-5-yl)methanone (1e)
White solid; yield: 31.5 mg (90%); mp 154.2–156.4 °C.

1H NMR (400 MHz, CDCl3): δ = 8.54 (d, J = 8.4 Hz, 1 H), 8.25–8.28 (m, 1 H), 7.97 (d, J = 6.1 Hz, 1 H), 7.92 (s, 1 H), 7.68–7.75 (m, 3 H), 7.48–7.65 (m, 2 H), 7.39–7.44 (m, 2 H).

13C NMR (100 MHz, CDCl3): δ = 191.0, 156.4, 153.7, 143.6, 135.4, 132.8, 130.8, 128.6, 127.5, 127.2, 126.9, 126.7, 126.6, 124.7, 123.6, 121.8, 121.4, 121.2, 120.5, 117.7, 112.2.

HRMS (ESI-QTOF): m/z [M + H]+ calcd for C_{19}H_{12}O_{3}S: 329.0631; found: 329.0635.

(2-(2-Methoxyphenyl)ethyl)benzaldehyde (12)
To a solution of 2-iodobenzaldehyde (250 mg, 1.08 mmol) in MeCN (3 mL) were added 1-ethyl-2-methoxybenzene (157 mg, 1.19 mmol), (Ph3P)2PdCl2 (76 mg, 0.108 mmol), CuI (10 mg, 0.054 mmol), and Et3N (0.45 mL, 3.24 mmol). The mixture was stirred at 70 °C for 2 h, and then it was concentrated in vacuo to yield the crude product. Purification by flash chromatography (silica gel, hexanes/EtOAc, 9:1) afforded 12 (198 mg, 78%) as a white solid; mp 80.7–83.2 °C.

1H NMR (400 MHz, CDCl3): δ = 7.10 (t, J = 7.6 Hz, 1 H), 7.62–7.67 (m, 2 H), 7.57 (s, 1 H), 7.45–7.46 (m, 2 H), 6.92–6.98 (m, 2 H), 3.93 (s, 3 H).

13C NMR (100 MHz, CDCl3): δ = 192.7, 160.5, 136.0, 133.8, 133.4, 131.3, 130.7, 128.5, 127.5, 127.1, 120.7, 111.7, 110.8, 93.2, 89.2, 55.9.

HRMS (ESI-QTOF): m/z [M + H]+ calcd for C_{17}H_{14}O_{3}: 237.0910; found: 237.0914.

(2-(2-Methoxyphenyl)ethyl)benzyl Acetate (14)
To a mixture of 13 [500 mg, 1.81 mmol] in Et3N (5 mL) were added 1-ethyl-2-methoxybenzene (251 mg, 1.90 mmol), (Ph3P)2PdCl2 (127 mg, 0.181 mmol), and CuI (17 mg, 0.091 mmol). The mixture was stirred at r.t. for 2 h, and then it was concentrated in vacuo to yield the crude product. Purification by flash chromatography (silica gel, hexanes/EtOAc, 9:1) afforded 14 (440 mg, 88%) as a colorless oil.

1H NMR (400 MHz, CDCl3): δ = 7.58 (d, J = 6.8 Hz, 1 H), 7.49 (d, J = 7.8 Hz, 1 H), 7.42–7.43 (m, 3 H), 7.29–7.35 (m, 3 H), 6.87–6.96 (m, 2 H), 5.41 (s, 2 H), 3.93 (s, 3 H), 2.13 (s, 3 H).

13C NMR (100 MHz, CDCl3): δ = 171.1, 160.3, 137.5, 133.3, 132.1, 130.6, 130.1, 128.4, 128.2, 121.3, 121.0, 120.6, 112.4, 110.8, 77.4, 65.2, 55.9, 21.1.

HRMS (ESI-QTOF): m/z [M + H]+ calcd for C_{17}H_{14}O_{3}: 281.0912; found: 281.1176.

(2-Iodobenzofuran-2-yl)benzyl Acetate (15)
To a stirred solution of 14 (440 mg, 1.57 mmol) in CH2Cl2 (10 mL) was added 1g (1.59 g, 6.28 mmol) and the resulting mixture was stirred at r.t. for 12 h. Then sat. aq. Na2S2O3 solution was added to the mixture and extracted with CH2Cl2 (3 × 15 mL). The combined organic layers were washed with brine, dried (MgSO4), and concentrated in vacuo to yield the crude product. Purification by flash chromatography (silica gel, hexanes/EtOAc, 9:1) afforded 15 (604 mg, 98%) as a colorless gum.

1H NMR (400 MHz, CDCl3): δ = 7.68 (d, J = 7.7 Hz, 1 H), 7.45–7.57 (m, 5 H), 7.33–7.41 (m, 2 H), 5.23 (s, 2 H), 1.97 (s, 3 H).

13C NMR (100 MHz, CDCl3): δ = 170.8, 154.7, 154.6, 136.0, 131.7, 131.4, 130.3, 129.3, 129.1, 128.2, 125.9, 123.8, 121.9, 111.5, 65.4, 64.6, 20.9.

HRMS (ESI-QTOF): m/z [M + H]+ calcd for C_{17}H_{14}O_{3}: 392.9982; found: 392.9981.
2-(3-Iodobenzofuran-2-yl)benzaldehyde (6)

To a stirred solution of 15 (600 mg, 1.53 mmol) in MeOH (50 mL) was added K₂CO₃ (1.06 g, 7.65 mmol) and the resulting mixture was stirred at rt. for 30 min. Then the solvent was removed in vacuo. Water was added to the mixture and it was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine, dried (Na₂SO₄), and concentrated in vacuo to yield the crude product. To the crude product dissolved in CH₂Cl₂ (50 mL) was added PCC (493 mg, 2.29 mmol) and the mixture was stirred at rt. for 2 h. Purification by flash chromatography (silica gel, hexanes/EtOAc, 9:1) afforded 6 (439 mg, 82%) as an off-white solid; mp 77.4–79.2 °C.

1H NMR (400 MHz, CDCl₃): δ = 10.09 (s, 1 H), 8.12 (d, J = 7.5 Hz, 1 H), 7.82 (d, J = 7.5 Hz, 1 H), 7.74 (t, J = 7.5 Hz, 1 H), 7.64 (t, J = 7.2 Hz, 1 H), 7.39–7.51 (m, 4 H).

13C NMR (100 MHz, CDCl₃): δ = 191.3, 154.96, 152.4, 134.8, 133.6, 132.6, 131.6, 131.5, 130.3, 128.2, 126.5, 124.1, 122.2, 111.7, 67.9.

HRMS (ESI-QTOF): m/z [M + H]+ calcd for C₂₄H₁₇O₂: 337.1226; found: 337.1225.

2-(3-[(4-Methoxyphenyl)ethynyl]benzofuran-2-yl)benzaldehyde (5d)

Yellow solid; yield: 42.8 mg (76%); mp 161.1–163.0 °C.

1H NMR (400 MHz, CDCl₃): δ = 10.46 (s, 1 H), 8.15 (d, J = 7.8 Hz, 1 H), 8.03 (d, J = 7.8 Hz, 1 H), 7.97 (s, 1 H), 7.86 (d, J = 7.1 Hz, 1 H), 7.69–7.78 (m, 3 H), 7.58–7.63 (m, 2 H), 7.52 (d, J = 8.4 Hz, 1 H), 7.39–7.47 (m, 2 H), 7.17 (d, J = 8.4 Hz, 1 H), 7.12 (s, 1 H), 3.94 (s, 3 H).

13C NMR (100 MHz, CDCl₃): δ = 191.6, 158.6, 154.6, 154.2, 134.5, 134.2, 133.6, 132.4, 131.5, 130.1, 129.8, 129.6, 129.2, 128.9, 128.6, 128.3, 127.1, 126.3, 123.98, 121.1, 119.7, 117.6, 111.7, 105.98, 105.1, 96.6, 79.3, 55.5.

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1H NMR (400 MHz, CDCl₃): δ = 10.32 (s, 1 H), 8.09 (dd, J = 0.8, 7.8 Hz, 1 H), 7.79 (d, J = 7.8 Hz, 1 H), 7.68–7.72 (m, 2 H), 7.52–7.59 (m, 2 H), 7.33–7.41 (m, 2 H), 2.45 (t, J = 7.0 Hz, 2 H), 1.57–1.61 (m, 2 H), 1.43–1.48 (m, 2 H), 0.94 (t, J = 7.3 Hz, 2 H).

13C NMR (100 MHz, CDCl₃): δ = 191.5, 154.5, 153.7, 133.97, 133.4, 132.5, 129.9, 129.6, 129.5, 128.0, 120.6, 123.7, 120.9, 111.6, 105.5, 97.7, 97.6, 30.6, 22.1, 19.5, 13.7.


(3-Methoxyphenyl)(naphtho[1,2-b]benzofuran-6-yl)methanone

Brown solid, yield: 31.0 mg (88%); mp 137.9–139.5 °C.

1H NMR (400 MHz, CDCl₃): δ = 8.53 (d, J = 8.2 Hz, 1 H), 8.06 (d, J = 7.8 Hz, 1 H), 7.98–8.00 (m, 2 H), 7.73–7.77 (m, 2 H), 7.47–7.53 (m, 2 H), 7.41 (t, J = 7.9 Hz, 1 H), 7.32 (t, J = 7.5 Hz, 1 H), 7.21 (d, J = 8.1 Hz, 1 H), 3.89 (s, 3 H).

13C NMR (100 MHz, CDCl₃): δ = 196.2, 159.9, 156.5, 152.8, 139.3, 131.4, 131.1, 129.6, 129.5, 128.6, 127.2, 127.1, 126.9, 129.7, 123.8, 123.2, 122.8, 121.3, 120.0, 117.5, 114.4, 111.7, 55.7.


6-Methoxynaphthalen-1-yl(naphtho[1,2-b]benzofuran-6-yl)methanone

Off-white solid; yield: 35.8 mg (89%); mp 161.3–162.6 °C.

1H NMR (400 MHz, CDCl₃): δ = 8.56 (d, J = 7.9 Hz, 1 H), 8.36 (s, 1 H), 8.16 (d, J = 8.4 Hz, 1 H), 7.99–8.01 (m, 3 H), 7.85 (d, J = 8.5 Hz, 1 H), 7.73–7.77 (m, 3 H), 7.62–7.66 (m, 1 H), 7.47 (t, J = 7.8 Hz, 1 H), 7.29 (d, J = 7.8 Hz, 1 H), 7.18–7.22 (m, 2 H), 3.97 (s, 3 H).

13C NMR (100 MHz, CDCl₃): δ = 196.2, 160.1, 156.5, 152.8, 137.6, 133.1, 133.0, 131.6, 131.4, 129.4, 128.4, 127.8, 127.5, 127.1, 126.8, 126.6, 124.0, 123.8, 123.3, 122.7, 121.3, 119.8, 117.7, 111.7, 105.98, 55.6.


(3-Fluorophenyl)(naphtho[1,2-b]benzofuran-6-yl)methanone

Off-white solid; yield: 30.6 mg (90%); mp 130.7–132.6 °C.

1H NMR (400 MHz, CDCl₃): δ = 8.54 (d, J = 8.2 Hz, 1 H), 8.06 (d, J = 7.9 Hz, 1 H), 8.00 (d, J = 8.2 Hz, 1 H), 7.97 (s, 1 H), 7.72–7.80 (m, 4 H), 7.64 (t, J = 7.5 Hz, 1 H), 7.48–7.52 (m, 2 H), 7.31–7.39 (m, 2 H).

13C NMR (100 MHz, CDCl₃): δ = 195.0, 164.1, 161.6, 156.5, 152.9, 140.2, 140.1, 131.4, 130.6, 130.3, 129.5, 128.9, 127.5, 127.3, 127.0, 126.6, 123.95, 123.89, 123.3, 123.0, 121.4, 120.4, 121.2, 117.5, 117.3, 111.7, 111.8, 55.6.


(9cS,13aR)-9c,10,11,12,13,13a-Hexahydro-14H-benzo[3,4]fluoren-2,1-benzofuran-14-one

Colorless oil; yield: 26.8 mg (82%).

1H NMR (400 MHz, CDCl₃): δ = 8.91 (d, J = 7.4 Hz, 1 H), 8.55 (d, J = 8.2 Hz, 1 H), 8.24 (d, J = 8.1 Hz, 1 H), 7.81 (t, J = 7.3 Hz, 1 H), 7.67–7.72 (m, 2 H), 7.52 (t, J = 7.5 Hz, 1 H), 7.45 (t, J = 7.2 Hz, 1 H), 4.02–4.08 (m, 1 H), 3.05 (br s, 1 H), 2.53–2.61 (m, 2 H), 1.82–1.88 (m, 1 H), 1.65–1.76 (m, 2 H), 1.42–1.51 (m, 1 H), 1.22–1.31 (m, 1 H), 1.01–1.11 (m, 1 H).

13C NMR (100 MHz, CDCl₃): δ = 207.1, 156.51, 156.49, 152.1, 129.3, 128.6, 128.4, 127.1, 126.9, 125.41, 125.39, 124.5, 124.3, 123.5, 122.3, 115.1, 111.4, 49.4, 38.6, 33.8, 23.8, 23.0, 22.9.

HRMS (ESI-QTOF): m/z [M + H⁺] calcd for C₂₉H₂₄O₄: 327.1380; found: 327.1384.


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1-Naphtho[1,2-b]benzofuran-6-yl)pentan-1-one (4h)
Off-white solid; yield: 29.3 mg (97%); mp 134.6–136.2 °C.
1H NMR (400 MHz, CDCl3): \( \delta = 8.76 \) (d, \( J = 7.9 \) Hz, 1 H), 8.65 (d, \( J = 7.8 \) Hz, 1 H), 7.76 (d, \( J = 7.8 \) Hz, 1 H), 7.63–7.72 (m, 4 H), 7.49–7.53 (m, 1 H), 2.85 (t, \( J = 7.7 \) Hz, 2 H), 1.66–1.70 (m, 2 H), 1.45–1.51 (m, 2 H), 0.98 (t, \( J = 7.3 \) Hz, 3 H).
13C NMR (100 MHz, CDCl3): \( \delta = 182.98, 156.7, 153.9, 146.1, 137.9, 134.6, 132.9, 130.2, 129.7, 127.6, 127.4, 127.2, 126.6, 125.0, 124.6, 112.2, 110.7, 35.8, 32.1, 23.0, 14.2.

Naphtho[1,2-b]benzofuran-6-yl(thiophen-3-yl)methanone (4i)
Gray solid; yield: 28.6 mg (87%); mp 137.8–139.6 °C.
1H NMR (400 MHz, CDCl3): \( \delta = 8.52 \) (d, \( J = 7.6 \) Hz, 1 H), 8.02–8.09 (m, 4 H), 7.72–7.78 (m, 3 H), 7.64 (t, \( J = 6.8 \) Hz, 1 H), 7.47–7.50 (m, 2 H), 7.33 (t, \( J = 6.8 \) Hz, 1 H).
13C NMR (100 MHz, CDCl3): \( \delta = 189.7, 156.4, 152.8, 142.3, 135.5, 131.96, 131.5, 129.4, 128.63, 128.56, 127.1, 126.9, 126.8, 126.2, 123.9, 123.3, 122.8, 121.3, 117.2, 111.7.

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Supporting Information
Supporting Information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588120. 1H and 13C NMR spectra of synthesized compounds are included.

References
(7) 5- or 6-Acylnaphtho[1,2-b]benzofuran can be viewed as a hybrid molecule consisting of 2-arylbenzofuran and 1- or 2-acylnaphthalene.