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Catalytic Friedel–Crafts/Lactonization Domino Reaction: Facile Access to 3-Hydroxybenzofuran-2-one Scaffold

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A valuable Lewis-acid-catalysed domino reaction involving a Friedel–Crafts alkylation of variously substituted phenols followed by a direct lactonization has been successfully developed (22 examples, yields up to 98 %). This protocol tolerates not only opposite electron demand substituents on the starting materials, but also drastic modifications of the alkylating agents, and gives direct access to the corresponding 3-hydroxy-benzofuran-2-ones, which could easily undergo further chemical transformation. The relevance of our method was further confirmed by the straightforward synthesis of *rac*-BHFF, the recently discovered and extremely promising positive allosteric modulator of the $GABA_B$ receptor.

Introduction

The 3-substituted 3*H*-benzofuran-2-one framework is a common feature of a plethora of remarkably medicinally effective natural products,[1] and it is also found in key intermediates in the synthesis of valuable biologically active molecules.[2] Noteworthy examples are Abiesinols A–F (**1**),[3] which have shown anti-tumor-initiating activity, and (–)-fumimycin (**2**),[4] a mycotoxin isolated from *Aspergillus fumisynnematus* F746, which showed promising antibacterial properties (Figure 1).

Similarly, 3-hydroxybenzofuran-2-ones have piqued curiosity in both medicinal and pharmaceutical fields due to their wide range of biocidal properties. Specifically, as a result of in vivo studies on Sardinian rats, a striking activity as a positive allosteric modulator (PAM) of the metabotropic $GABA_B$ receptor has been ascribed to (*R*,*S*)-5,7-di-*tert*-butyl-3-hydroxy-3-trifluoromethyl-3*H*-benzofuran-2-one (*rac*-BHFF, **3**; Figure 1),[5] which makes molecules of this class attractive compounds with potential therapeutic applications against alcoholism.[6]

Although several elegant strategies for the construction of the 3*H*-benzofuran-2-one scaffold have been reported,[7–10] the number of approaches to the corresponding 3-hydroxy derivatives is much more limited. The synthesis of this latter class of compounds still suffers from narrow substrate scope, harsh reaction conditions, and tedious functional group manipulations.[2b,2c] Consequently, the need for alternative short, practical, and atom-economical synthetic routes to 3-hydroxy-3*H*-benzofuran-2-ones remains a challenging endeavour of great interest.

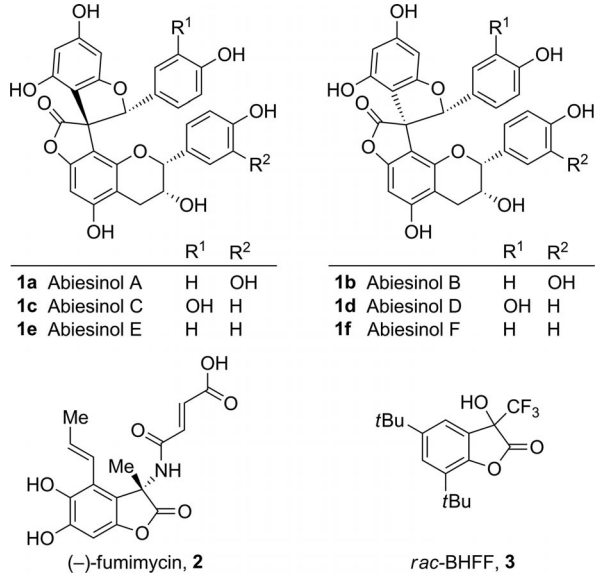

Figure 1. Examples of natural products and biologically active compounds containing a 3-substituted 3*H*-benzofuran-2-one motif.

During the 1980s, Casiraghi[11] and Citterio[12] independently envisaged the possibility of obtaining benzofuran-2-one derivatives by a two-step protocol, which should have basically involved a Lewis-acid-promoted Friedel–Crafts alkylation of phenols and a subsequent ring-closure reaction triggered by the strongly acidic conditions. However, the predicted compounds were never isolated or characterized by either research group. The use of considerably activated phenols and alkylating agents (polyfluorocarbonyl

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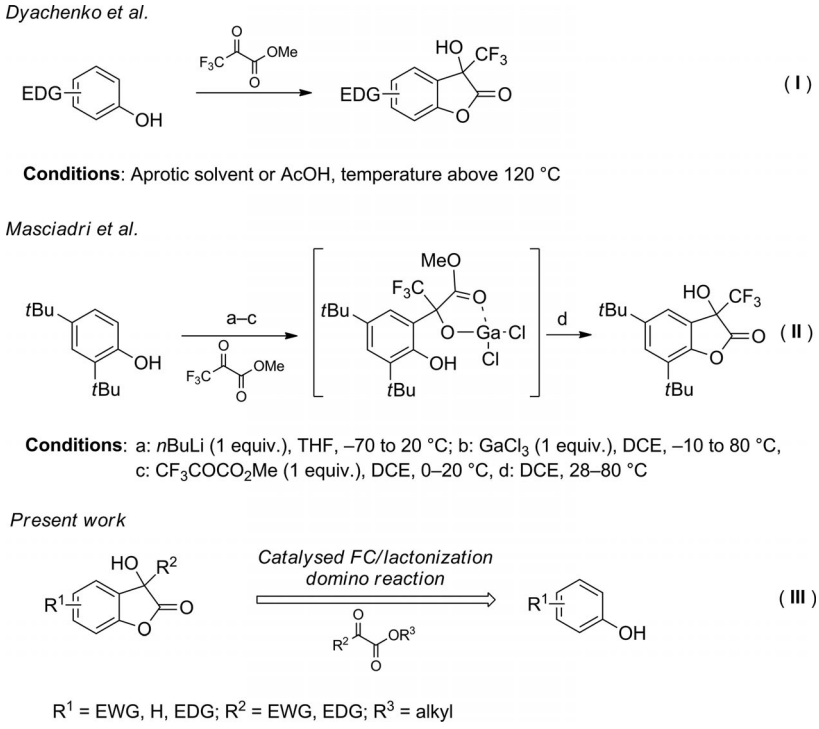


Scheme 1. Previous protocols and our retrosynthetic approach to 3-substituted-3-hydroxybenzofuranone derivatives. EWG = electron-withdrawing group; EDG = electron-donating group; FC = Friedel–Crafts; DCE = 1,2-dichloroethane.

compounds) as well as harsh reaction conditions such as high temperatures (always over 120 °C) and a strong organic acid as solvent, allowed Dyachenko et al. to accomplish the preparation of few 3-hydroxy-3-(trifluoromethyl)benzofuran-2-ones [Equation (I), Scheme 1].[13] More recently, Masciadri et al. reported quite an interesting one-pot synthesis of **3**, which, in addition to the use of a slight excess of all of the reagents, as well as a stoichiometric amount of the metal activating species, requires several changes concerning temperature and solvents [Equation (II), Scheme 1].[14] To date, neither a catalytic version of such a strategy nor systematic studies involving different substrates and various alkylating agents, both of them bearing opposite electron demanding substituents, have been reported. The main challenges in the development of a catalytic version of this method are: (i) to overcome the complete complexion of the Lewis acid by any oxygen atom present in the reaction mixture, which would result in deactivation of the catalyst; (ii) to promote the ring-closure reaction by increasing the nucleophilicity of the phenolic hydroxy group.

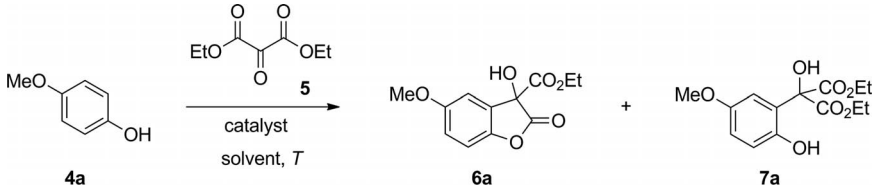
In this paper, we report our successful investigations into the construction of a 3-hydroxybenzofuran-2-one core bearing a quaternary centre at the C-3 position. Starting from inexpensive and abundant phenols, we used the activation ability of Lewis acids to form the desired products in a domino reaction[15] [Equation (III), Scheme 1]. Moreover, we report the use of drastically modified alkylating agents, and also the application of the developed methodology to synthesize *rac*-BHFF (**3**) and its analogues.

Results and Discussion

In the light of the previous syntheses of 3*H*-benzofuran-2-ones involving metal-catalysed protocols, we first tested catalytic amounts of acetic acid and a few of the Lewis acids most widely used in Friedel–Crafts alkylations.[16] We used the cheap diethyl ketomalonate (**5**) as the alkylating agent, and *p*-methoxyphenol (**4a**) as the test substrate (Table 1). The initial trials allowed us to achieve the formation of the target lactone (i.e., **6a**), which was easily separated from the Friedel–Crafts product (i.e., **7a**). In more detail, as shown in Table 1, a catalytic amount of acetic acid in dichloromethane did not promote any reaction (Table 1, entry 1), and even after 96 h, the starting material was recovered almost quantitatively. Moreover, contrary to the reported literature,[11,12,14] there was no need to use a stoichiometric amount of the activating agent to promote the process under investigation. $BF_3{\cdot}Et_2O$ and $AlCl_3$ were neither effective nor efficient (Table 1, entries 2 and 3). The best results were observed with $GaCl_3$ (Table 1, entry 4) and $TiCl_4$ (Table 1, entry 5), both of which gave product **6a** in reasonable overall yields after reasonable reaction times. As these two catalysts produced comparable results, further optimization of the reaction conditions was performed with the much less expensive and much more convenient $TiCl_4$.

Having identified the best Lewis acid catalyst, our efforts were devoted to the development of a protocol that could overcome the main observed drawback, i.e., the formation of intermediate **7a**, and that would thus lead to the desired lactone (i.e., **6a**) in higher yields. Preliminary tests in dichlo-

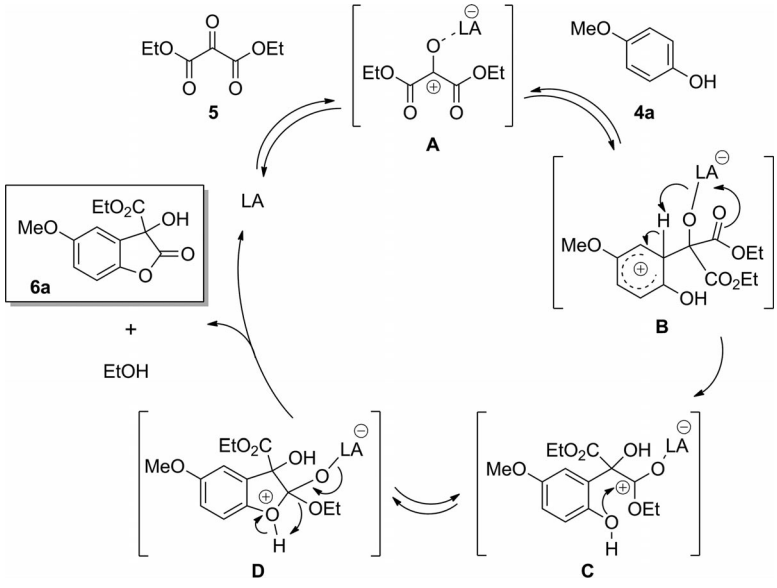
Table 1. Optimization of the Lewis-acid-catalysed Friedel–Crafts/lactonization domino reaction of *p*-methoxyphenol (**4a**) with diethyl ketomalonate (**5**).



Entry[a]	Catalyst	Amount [mol-%]	Solvent	Temp. [°C]	Time [h]	Yield of **6a** [%][b]	Yield of **7a** [%][b]
1	AcOH	30	CH_2Cl_2	r.t.	96	n.d.	n.d.
2	$BF_3{\cdot}Et_2O$	30	CH_2Cl_2	r.t.	24	36	trace
3	$AlCl_3$	30	CH_2Cl_2	r.t.	72	11	15
4	$GaCl_3$	30	CH_2Cl_2	r.t.	24	45	21
5	$TiCl_4$	30	CH_2Cl_2	r.t.	8	40	20
6	$TiCl_4$	20	CH_2Cl_2	r.t.	3	45	17
7[c]	$TiCl_4$	20	CH_2Cl_2	r.t.	3	40	20
8	$TiCl_4$	20	CH_2Cl_2	40	6	55	20
9[c]	$TiCl_4$	20	CH_2Cl_2	40	5.5	37	44
10[d]	$TiCl_4$	20	CH_2Cl_2/toluene	r.t./120	3/5	45	trace
11	$TiCl_4$	20	toluene	120	5	46	trace
12	$TiCl_4$	20	$CHCl_3$	60	6	80	trace
13	$TiCl_4$	20	THF	70	10	trace	20
14[c]	$TiCl_4$	20	$CHCl_3$	60	4.5	64	trace
15	$TiCl_4$	10	$CHCl_3$	60	6	84	trace
16[e]	$TiCl_4$	10	$CHCl_3$	60	7	65	trace

[a] Unless otherwise stated, the reactions were performed with *p*-methoxyphenol (**4a**; 2.0 mmol) and diethyl ketomalonate (**5**; 2.2 mmol) in solvent (9 mL). [b] Yield of the isolated product. [c] Addition of 4 Å MS. [d] The reaction was performed in two steps. [e] The reaction was performed with an excess of **4a** (1.2 equiv.) with respect to alkylating agent **5**.

romethane showed the benefit of decreasing the catalyst loading and increasing the reaction temperature (Table 1, entries 6 and 8). The temperature could be increased further by using solvents with higher boiling points (Table 1, entries 9–13). Finally, using 10 mol-% of $TiCl_4$ and performing the reaction at 60 °C in anhydrous $CHCl_3$ gave only the desired 3*H*-benzofuran-2-one (i.e., **6a**) in high yield (84%) after a short reaction time (Table 1, entry 15). Neither the addition of 4 Å MS (Table 1, entries 7, 9, and 14) nor starting with a slight excess of *p*-methoxyphenol (**4a**; Table 1, entry 16) gave a better result. Similarly, the catalyst removal after the substrate disappearance upon the usual aqueous workup and the subsequent heating of the reaction mixture solved in toluene, led to the complete conversion of the intermediate **7a** with a considerable loss of the product **6a** (Table 1, entry 10).



Scheme 2. Major catalytic cycle.

Although no exhaustive mechanistic study was undertaken, we were aware of the possible alternative reaction pathways, and of the complexation equilibria between the catalyst and all the other species involved in the reaction.[17] However, we hypothesized that the experimental evidence could be explained by assuming that the reaction, for the most part, followed the catalytic cycle shown in Scheme 2. This catalytic cycle partially resembles recent proposal regarding the synthesis of *rac*-BHFF.[14] The complex mechanistic pathway should involve: (i) an initial coordination between the Lewis Acid (LA) and the alkylating agent **5** to give complex **A**, which promotes (ii) a regioselective Friedel–Crafts alkylation at the *ortho* position of substrate **4a** to give key intermediate **C** after rearomatization of σ complex **B**; and (iii) a subsequent Lewis-acid-assisted intramolecular transesterification to deliver the expected 3-hydroxylactone (i.e., **6a**) and regenerate the catalyst.

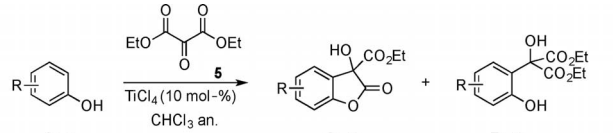
The optimized conditions were evaluated using phenols **4a**–**4n**, which were decorated on the aromatic ring with various substituents with different electronic and steric properties. The results are summarized in Table 2.

In almost all cases, the desired product was successfully formed in quite good yield. With strongly electron-donating groups (in **4a**, **4b**, and **4i**) or a weakly activating alkyl substituent (in **4f**), the corresponding 3-hydroxylactones were formed smoothly in yields (up to 85%) and reaction times comparable to the reference substrate (i.e., **4e**). Unfortunately, the presence in the *para* position of a weakly deactivating group (in **4c**) led to the slow formation of only the uncyclized intermediate (i.e., **7c**; 53%). The strongly deactivating influence of a NO_2 group (in **4d**) led to a complex reaction mixture without any trace of the target compound (i.e., **6d**). Conversely, the introduction of either a further fused aromatic ring (in **4j**–**4n**) or substitution with two hindered alkyl groups (in **4g** and **4h**) in the *ortho* and *para* positions dramatically enhanced the overall reactivity. Indeed, to our extreme delight, with such substrates, the reactions proceeded quickly to give the corresponding 3-hydroxy-2(3*H*)-benzofuranones (i.e., **6g**, **6h**, and **6k**–**6n**) in good to excellent yields (up to 98%). The only surprising result was observed with α-naphthol (**4j**), which required a higher temperature and a longer reaction time than its isomer β-naphthol (**4k**) to be fully converted into the corresponding lactone (i.e., **6j**). The presence of electron-withdrawing groups on the second aromatic ring (in **4m** and **4n**) marginally influenced the general reactivity; the reactions were sluggish, but the expected products (i.e., **6m** and **6n**) were isolated in good yields.

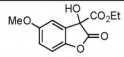
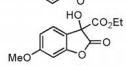
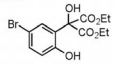
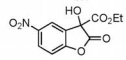
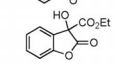
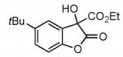
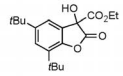
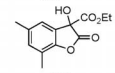
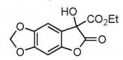
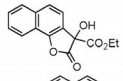
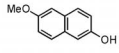
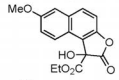
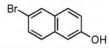
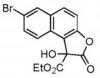
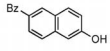
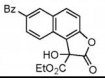
The efficiency of the developed procedure was further validated by testing different alkylating agents. As clearly shown in Scheme 3, the presence of a more strongly electron-withdrawing group (in **8a**, $R^1 = CF_3$), did not influence the outcome, and the well-known biologically active *rac*-BHFF (**3**) was straightforwardly obtained in very good yield (81%) after an exceptionally short time (3 h) compared to the tedious procedure previously reported. In contrast, the presence of an electron-donating group (in **8b**, R^1 = Me; or **8c**, R^1 = Ph) directly bonded to the carbonyl moiety significantly reduced the reactivity. Only after heating the reaction mixture to 60 °C did we observe the slow formation of the desired benzofuran-2-ones (i.e., **9** and **10**), which were isolated in moderate to good yields (Scheme 3).

Similarly to what was observed with diethyl ketomalonate (**5**), remarkable results were achieved with methyl 3,3,3-trifluoropyruvate (**8a**). This compound not only proved to be the most reactive alkylating agent, but it could also give easy access to a library of promising medicinally active compounds (Scheme 4). Starting from the most activated substrates (i.e., **4h**, **4k**–**4n**), the domino Friedel–Crafts/lactonization reaction proceeded smoothly to give the expected lactone derivatives **11a**–**11e**. It was not necessary to increase

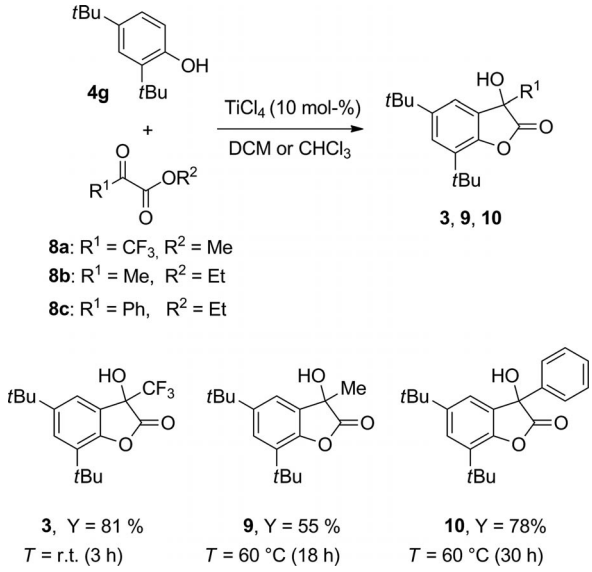
Table 2. Substrate scope and limitations of the Friedel–Crafts/lactonization domino reaction.



4a–n 6a–n 7a–n

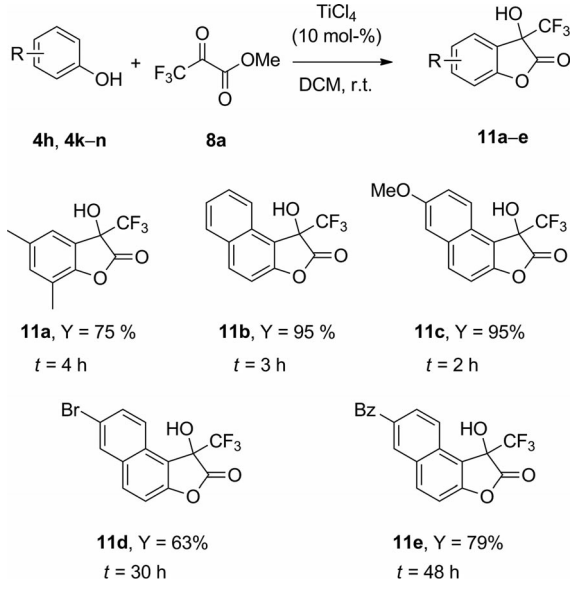
Substrate[a]		Temp. [°C]	Time [h]	Product		Y [%][b]
4a		60	6	**6a**		84
4b		60	5	**6b**		85
4c		60	12	**7c**		53
4d		60	2	**6d**		n.d.
4e		60	6	**6e**		87
4f		60	7	**6f**		83
4g[c]		r.t.	3	**6g**		88
4h[c]		r.t.	3	**6h**		90
4i		60	6	**6i**		84
4j		60	4	**6j**		95
4k[c]		r.t.	2	**6k**		98
4l[c]		r.t.	3	**6l**		85
4m[c]		r.t.	6	**6m**		60
4n		r.t.	12	**6n**		87

[a] Unless otherwise stated, the reactions were performed with phenols **4a**–**4n** (2.0 mmol) and diethyl ketomalonate (**5**; 2.2 mmol) in the presence of $TiCl_4$ (10 mol-%) in anhydrous $CHCl_3$ (9 mL). [b] Yield of the isolated product. [c] Anhydrous CH_2Cl_2 was used as solvent.



Scheme 3. The reactions were performed with phenol **4g** (2.0 mmol) and various alkylating agents (2.2 mmol) in the presence of $TiCl_4$ (10 mol-%) in anhydrous solvents (9 mL; CH_2Cl_2 for **3**, $CHCl_3$ for **9** and **10**) at the reported temperature.

the reaction temperature, even when moderately deactivating substituents were introduced onto the second aromatic ring (in **4m** and **4n**).



Scheme 4. The reactions were performed with phenols **4h** and **4k**–**4n** (2.0 mmol) with 3,3,3-trifluoromethyl pyruvate (**8a**) as the alkylating agent (2.2 mmol) in the presence of $TiCl_4$ (10 mol-%) in anhydrous CH_2Cl_2 (9 mL) at room temperature.

Conclusions

In summary, we have presented the development of a domino Friedel–Crafts/lactonization reaction that enables the synthesis of numerous new 3-hydroxy-3-substituted benzofuran-2-ones in a one-step procedure starting from the corresponding readily available phenols. The protocol relies on: (i) the unprecedented use of a catalytic amount of $TiCl_4$ (10 mol-%) as the activating species, which, despite several possibilities for interaction with oxygen atoms present in the reaction mixture, promotes the initial alkylation as well as the subsequent intramolecular transesterification; (ii) the use of mild heating to induce the lactonization when necessary (with poorly reactive or unreactive systems). This systematic study not only confirmed Dyachenko's results concerning highly activated and hindered substrates and reagents,[13] but also suggests that our method tolerates the introduction of opposite electron demand substituents on the alkylating agents and on most of the phenols tested. Indeed, except for compounds **4c** and **4d**, which did not gave the desired products, all the other substrates tested were successfully transformed in the corresponding target benzofuran-2-one derivatives. This route offers an attractive alternative to the system recently developed by Zhou for the synthesis of such natural product building blocks.[10b] Indeed, the lactone products are undeniably valuable building blocks for total synthesis, since the functional groups connected to the newly introduced quaternary carbon centre could subsequently undergo further chemical transformation. The developed method provides a highly efficient and effective one-pot synthesis of the well-known biologically active (*R*,*S*)-5,7-di-*tert*-butyl-3-hydroxy-3-trifluoromethyl-3*H*-benzofuran-2-one (*rac*-BHFF, **3**), and also opens the possibility for the synthesis of libraries of compounds for medicinal evaluation. The extension of the optimized procedure to the corresponding nitrogen derivatives and the development of an asymmetric version of this reaction are underway, and the results will be reported in due course.

Experimental Section

General Remarks: All reactions were monitored by thin-layer chromatography (TLC), which was carried out on Merck F-254 silica glass plates visualized with UV light, phosphomolybdic acid (5% in ethanol), or ceric ammonium molybdate. Flash chromatography was carried out on Sigma–Aldrich silica gel (60, particle size: 0.040–0.063 mm). ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ (99.8% deuterium) at 25 °C using a Varian Gemini 300 spectrometer (300 MHz). Chemical shifts are expressed in parts per million (δ scale) and are referenced to the residual protons of the NMR solvent ($CDCl_3$: δ = 7.26 ppm). The following abbreviations are used to explain the multiplicities: s = singlet, br. s = broad singlet, d = doublet, t = triplet, dq = doublet of quartets, m = multiplet. Coupling constants (*J*) are expressed in Hz. Infrared spectra (FTIR) were obtained using a Bruker Vector 22 spectrometer, and data are presented as the frequency of absorption (cm^{-1}). HRMS spectra were recorded with a Micromass Q-TOF *micro* Mass Spectrometer (Waters) or a Micromass LCT (ESI) spectrometer with Lock Spray Injector (Injection Loop-Modus in an HPLC system, Waters, Alliance 2695). Melting points were determined with a Mel-Temp apparatus. Solvents and common reagents were purchased from a commercial supplier (Sigma–Aldrich), and were used without further purification. Anhydrous toluene was freshly distilled from sodium immediately before use.

General Procedure: The alkylating agent (2.2 mmol) was added in one portion to a stirred solution of substrate **4** (2.0 mmol) in anhydrous $CHCl_3$ (9 mL), and then $TiCl_4$ (1 M in anhydrous CH_2Cl_2; 0.4 mL, 10 mol-%) was added. The system was kept under an argon atmosphere. The clear reddish solution was stirred at the reported temperature (Table 1) until the substrate had been completely consumed (TLC, hexane/EtOAc, 7:3). Afterwards, the reaction mixture was poured into cold water (18 mL), and the aqueous phase was extracted several times with EtOAc (4× 20 mL). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel to give the products as described below.

Ethyl 3-Hydroxy-5-methoxy-2-oxo-2,3-dihydrobenzofuran-3-carboxylate (6a): The single product was purified by flash chromatography on silica gel (hexane/EtOAc, 7:3), and was obtained as a yellow oil (423 mg, 84%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 3.79 (s, 3 H, OCH_3), 4.16–4.39 (m, 2 H, CH_2CH_3), 4.44 (s, 1 H, OH), 6.84 (s, 1 H, CH_{arom}), 6.95 (d, J = 8.8 Hz, 1 H, CH_{arom}), 7.08 (d, J = 8.8 Hz, 1 H, CH_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 55.9, 64.1, 76.8, 109.3, 112.2, 117.4, 126.0, 148.1, 157.1, 168.5, 172.1 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3492, 3238, 3020, 2934, 2833, 1751, 1718, 1611 cm^{-1}. HRMS: calcd. for $C_{12}H_{12}NaO_6$ 275.0532; found 275.0529.

Diethyl 2-Hydroxy-2-(2-hydroxy-5-methoxyphenyl)malonate (7a): The single product was purified by flash chromatography on silica gel (hexane/EtOAc, 7:3), and was obtained as a white solid (119 mg, 20%), m.p. 112–114 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (t, J = 7.1 Hz, 6 H, CH_2CH_3), 3.76 (s, 3 H, OCH_3), 4.30–4.41 (m, 4 H, CH_2CH_3), 4.57 (s, 1 H, OH), 6.81–6.92 (m, 3 H, CH_{arom}), 7.14 (s, 1 H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (2 C), 55.8, 63.5 (2 C), 80.9, 113.3, 115.8, 119.1, 127.7, 148.8, 153.1, 169.5 (2 C) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3413, 3382, 3020, 2980, 2938, 2907, 1755, 1727, 1601 cm^{-1}. HRMS: calcd. for $C_{14}H_{18}NaO_7$ 321.0950; found 321.0954.

Ethyl 3-Hydroxy-6-methoxy-2-oxo-2,3-dihydrobenzofuran-3-carboxylate (6b): The single product was purified by flash chromatography on silica gel (hexane/EtOAc, 7:3), and was obtained as a yellow oil (428 mg, 85%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 3.84 (s, 3 H, OCH_3), 4.15–4.45 (m, 3 H, CH_2CH_3, OH), 6.71–6.73 (m, 2 H, CH_{arom}), 7.21 (d, J = 9.0 Hz, 1 H, CH_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 55.9, 64.0, 76.4, 98.2, 111.0, 117.3, 125.2, 155.8, 162.8, 168.9, 172.4 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3452, 3244, 3020, 2984, 2912, 1755, 1723, 1605 cm^{-1}. HRMS: calcd. for $C_{12}H_{12}NaO_6$ 275.0532; found 275.0534.

Diethyl 2-(5-Bromo-2-hydroxyphenyl)-2-hydroxymalonate (7c): The single product was purified by flash chromatography on silica gel (hexane/EtOAc, 8:2), and was obtained as a yellow oil (367 mg, 53%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (t, J = 7.1 Hz, 6 H, CH_2CH_3), 4.32–4.40 (m, 4 H, CH_2CH_3), 4.69 (s, 1 H, OH), 6.81 (d, J = 8.6 Hz, 1 H, CH_{arom}), 7.34 (d, J = 8.6 Hz, 1 H, CH_{arom}), 7.49 (s, 1 H, CH_{arom}), 7.90 (s, 1 H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (2 C), 63.7, 63.9, 80.7, 112.2, 120.3, 130.8, 133.4, 149.5, 154.7, 168.6, 169.2 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3496, 3031, 2936, 2901, 1757, 1741, 1624 cm^{-1}. HRMS: calcd. for $C_{13}H_{15}BrNaO_6$ 368.9950; found 368.9947 [referred to the most abundant bromine isotope, Br (78.9183)].

Ethyl 3-Hydroxy-2-oxo-2,3-dihydrobenzofuran-3-carboxylate (6e): The single product was purified by flash chromatography on silica gel (hexane/EtOAc, 7:3), and was obtained as a yellow oil (386 mg, 87%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 4.15–4.35 (m, 2 H, CH_2CH_3), 4.50 (br. s, 1 H, OH), 7.14–7.46 (m, 4 H, CH_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 64.2, 76.4, 111.6, 124.3, 125.2, 125.5, 131.9, 154.5, 168.6, 171.9 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3495, 3034, 2983, 2901, 1751, 1735, 1630 cm^{-1}. HRMS: calcd. for $C_{11}H_{10}NaO_5$ 245.0426; found 245.0423.

Ethyl 5-(*tert*-Butyl)-3-hydroxy-2-oxo-2,3-dihydrobenzofuran-3-carboxylate (6f): The single product was purified by flash chromatography on silica gel (hexane/EtOAc, 8:2), and was obtained as a yellow oil (466 mg, 83%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 1.24 [s, 9 H, $C(CH_3)_3$], 4.12–4.27 (m, 2 H, CH_2CH_3), 5.01 (s, 1 H, OH), 7.00 (d, J = 8.5 Hz, 1 H, CH_{arom}), 7.34 (s, 1 H, CH_{arom}), 7.40 (d, J = 8.5 Hz, 1 H, CH_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 31.5, 34.9, 63.8, 76.9, 110.9, 115.0, 121.2, 125.3, 128.8, 148.7, 168.8, 172.5 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3287, 3014, 2870, 1804, 1742, 1614 cm^{-1}. HRMS: calcd. for $C_{15}H_{18}NaO_5$ 301.1052; found 301.1051.

Ethyl 5,7-Di-*tert*-butyl-3-hydroxy-2-oxo-2,3-dihydrobenzofuran-3-carboxylate (6g): The single product was purified by flash chromatography on silica gel (hexane/CH_2Cl_2, 1:1), and was obtained as a white solid (587 mg, 88%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 1.23 [s, 9 H, $C(CH_3)_3$], 1.34 [s, 9 H, $C(CH_3)_3$], 4.07–4.27 (m, 2 H, CH_2CH_3), 4.90 (br. s, 1 H, OH), 7.18 (s, 1 H, CH_{arom}), 7.32 (s, 1 H, CH_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 29.7, 31.6, 34.6, 35.1, 64.0, 76.3, 118.3, 119.9, 125.1, 126.0, 134.3, 148.2, 169.1, 172.3 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3514, 3287, 3014, 2870, 1804, 1742, 1614 cm^{-1}. HRMS: calcd. for $C_{19}H_{26}NaO_5$ 357.1678; found 257.1677.

Ethyl 3-Hydroxy-5,7-dimethyl-2-oxo-2,3-dihydrobenzofuran-3-carboxylate (6h): The single product was purified by flash chromatography on silica gel (hexane/EtOAc, 8:2), and was obtained as a yellow oil (450 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 2.29 (s, 6 H, CCH_3), 4.09–4.38 (m, 2 H, CH_2CH_3), 4.51 (br. s, 1 H, OH), 6.93 (s, 1 H, CH_{arom}), 7.03 (s, 1 H, CH_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 15.0, 21.1, 64.1, 76.9, 121.5, 121.8, 124.9, 133.9, 134.7, 151.0, 168.9, 172.3 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3486, 3262, 3042, 2980, 2922, 1801, 1742, 1629 cm^{-1}. HRMS: calcd. for $C_{13}H_{14}NaO_5$ 273.0739; found 273.0742.

Ethyl 7-Hydroxy-6-oxo-6,7-dihydro-[1,3]dioxolo[4,5-*f*]benzofuran-7-carboxylate (6i): The single product was purified by flash chromatography on silica gel (hexane/EtOAc, 7:3), and was obtained as an orange oil (446 mg, 84%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 4.16–4.36 (m, 2 H, CH_2CH_3), 4.57 (s, 1 H, OH), 6.00 (s, 2 H, OCH_2O), 6.69 (s, 1 H, CH_{arom}), 6.73 (s, 1 H, CH_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 64.3, 76.9, 95.1, 102.1, 104.1, 116.8, 145.2, 149.6, 150.3, 168.9, 172.3 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3353, 3080, 2987, 2898, 2772, 1834, 1758, 1601 cm^{-1}. HRMS: calcd. for $C_{12}H_{10}NaO_7$ 289.0324; found 289.0324.

Ethyl 3-Hydroxy-2-oxo-2,3-dihydronaphtho[1,2-*b*]furan-3-carboxylate (6j): The product was obtained after purification by flash chromatography on silica gel (hexane/EtOAc, 8:2) as a white solid (516 mg, 95%), m.p. 86–88 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 4.16–4.38 (m, 2 H, CH_2CH_3), 4.60 (br. s, 1 H, OH), 7.37 (d, J = 8.4 Hz, 1 H, CH_{arom}), 7.60–7.63 (m, 2 H, CH_{arom}), 7.71 (d, J = 8.4 Hz, 1 H, CH_{arom}), 7.91 (d, J = 8.6 Hz, 1 H, CH_{arom}), 8.08 (d, J = 8.0 Hz, 1 H, CH_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 64.3, 77.4, 119.6, 119.9, 121.6, 125.3, 127.4, 128.1, 128.5, 135.5 (2 C), 151.2, 168.8, 172.3 ppm. IR

($CHCl_3$): $\tilde{\nu}$ = 3407, 3040, 3015, 2981, 2907, 1817, 1738, 1651 cm^{-1}. HRMS: calcd. for $C_{15}H_{12}NaO_5$ 295.0582; found 295.0582.

Ethyl 1-Hydroxy-2-oxo-1,2-dihydronaphtho[2,1-*b*]furan-1-carboxylate (6k): The product was obtained after purification by crystallization (hexane/EtOAc) as a yellow solid (533 mg, 98%), m.p. 128–130 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.11 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 4.17 (dq, J = 10.8, J = 7.2 Hz, 1 H, $CHHCH_3$), 4.31 (dq, J = 10.8, J = 7.2 Hz, 1 H, $CHHCH_3$), 4.62 (s, 1 H, OH), 7.38 (d, J = 8.8 Hz, 1 H, CH_{arom}), 7.48 (ddd, J = 8.3, 7.0, 1.2 Hz, 1 H, CH_{arom}), 7.57 (ddd, J = 8.3, 7.0, 1.2 Hz, 1 H, CH_{arom}), 7.78 (d, J = 8.3 Hz, 1 H, CH_{arom}), 7.90 (d, J = 8.3 Hz, 1 H, CH_{arom}), 7.97 (d, J = 8.8 Hz, 1 H, CH_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 64.4, 77.3, 111.7, 117.5, 122.2, 125.6, 128.8, 129.0, 129.4, 131.3, 133.1, 153.2, 169.1, 172.4 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3408, 3040, 3015, 2980, 2907, 1817, 1738, 1651 cm^{-1}. HRMS: calcd. for $C_{15}H_{12}NaO_5$ 295.0582; found 295.0583.

Ethyl 1-Hydroxy-7-methoxy-2-oxo-1,2-dihydronaphtho[2,1-*b*]furan-1-carboxylate (6l): The product was obtained after purification by flash chromatography on silica gel (hexane/EtOAc, 8:2) as an orange solid (513 mg, 85%), m.p. 121–123 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 3.91 (s, 3 H, OCH_3), 4.12–4.35 (m, 2 H, CH_2CH_3), 4.62 (br. s, 1 H, OH), 7.19 (s, 1 H, CH_{arom}), 7.24 (d, J = 10.2 Hz, 1 H, CH_{arom}), 7.33 (d, J = 8.8 Hz, 1 H, CH_{arom}), 7.69 (d, J = 9.0 Hz, 1 H, CH_{arom}), 7.84 (d, J = 8.8 Hz, 1 H, CH_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 55.5, 64.3, 77.3, 107.5, 112.0, 117.8, 121.6, 123.5, 124.3, 131.4, 132.6, 151.6, 157.4, 169.2, 172.5 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3246, 3033, 3024, 2982, 1820, 1746, 1610, 1584 cm^{-1}. HRMS: calcd. for $C_{16}H_{14}NaO_6$ 325.0688; found 325.0687.

Ethyl 7-Bromo-1-hydroxy-2-oxo-1,2-dihydronaphtho[2,1-*b*]furan-1-carboxylate (6m): The product was obtained after purification by flash chromatography on silica gel (hexane/EtOAc, 8:2) as a yellow solid (421 mg, 60%), m.p. 126–128 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.11 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 4.13–4.36 (m, 2 H, CH_2CH_3), 4.65 (br. s, 1 H, OH), 7.40 (d, J = 8.9 Hz, 1 H, CH_{arom}), 7.63 (d, J = 10.2 Hz, 1 H, CH_{arom}), 7.66 (d, J = 10.2 Hz, 1 H, CH_{arom}), 7.87 (d, J = 8.9 Hz, 1 H, CH_{arom}), 8.06 (s, 1 H, CH_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 64.5, 77.1, 112.9, 117.9, 119.5, 123.8, 127.4, 131.4, 132.1, 132.3 (2 C), 153.4, 168.9, 172.0 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3225, 3024, 2986, 1820, 1743, 1575, 1510 cm^{-1}. HRMS: calcd. for $C_{15}H_{11}BrNaO_5$ 372.9688; found 372.9690 [referred to the most abundant bromine isotope, Br (78.9183)].

Ethyl 7-benzoyl-1-hydroxy-2-oxo-1,2-dihydronaphtho[2,1-*b*]furan-1-carboxylate (6n): The product was obtained after purification by flash chromatography on silica gel ($CHCl_3$/MeOH, 98:2) as a yellow solid (654 mg, 87%), m.p. 160–161 °C. ^{1}H NMR [300 MHz, $(CD_3)_2CO$]: δ = 1.02 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 4.16 (ddq, J = 7.1, J = 10.8, J = 35.6 Hz, 2 H, CH_2CH_3), 6.92 (br. s, 1 H, OH), 7.51–7.56 (m, 3 H, CH_{arom}), 7.62 (tt, J = 7.4, J = 1.6 Hz, 1 H, CH_{arom}), 7.77–7.80 (m, 2 H, CH_{arom}), 7.98 (dd, J = 8.7, J = 1.7 Hz, 1 H, CH_{arom}), 8.05 (d, J = 8.8 Hz, 1 H, CH_{arom}), 8.24 (d, J = 8.7 Hz, 1 H, CH_{arom}), 8.36 (d, J = 1.5 Hz, 1 H, CH_{arom}) ppm. ^{13}C NMR [75 MHz, $(CD_3)_2CO$]: δ = 14.2, 63.8, 78.5, 113.5, 120.0, 123.8, 128.9, 129.4 (2 C), 130.7 (2 C), 131.0, 131.6, 133.4, 133.6, 135.3, 135.7, 138.5, 155.2, 168.5, 173.4, 196.1 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3197, 3032, 1820, 1568, 1536, 1370 cm^{-1}. HRMS: calcd. for $C_{22}H_{16}NaO_6$ 399.0845; found 399.0844.

5,7-Di-*tert*-butyl-3-hydroxy-3-(trifluoromethyl)benzofuran-2(3*H*)-one, *rac*-BHFF (3): The single product was purified by flash chromatography on silica gel (hexane/CH_2Cl_2, 1:1), and was obtained as a white solid (534 mg, 81%). All analytical data are consistent with literature values.[5a]

5,7-Di-*tert*-butyl-3-hydroxy-3-methylbenzofuran-2(3*H*)-one (9): The single product was purified by flash chromatography on silica gel (hexane/CH_2Cl_2, 1:1), and was obtained as a white solid (276 mg, 50%), m.p. 103–105 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 [s, 9 H, $C(CH_3)_3$], 1.40 [s, 9 H, $C(CH_3)_3$], 1.71 (s, 3 H, CH_3), 2.87 (br. s, 1 H, OH), 7.29 (s, 1 H, CH_{arom}), 7.34 (s, 1 H, CH_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.8, 29.8, 31.7, 34.5, 35.1, 72.5, 118.2, 124.9, 129.3, 134.0, 148.0, 148.6, 178.4 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3307, 3030, 2965, 1808, 1484, 1365 cm^{-1}. HRMS: calcd. for ($C_{17}H_{21}F_3NaO_5$) 299.1623; found 299.1622.

5,7-Di-*tert*-butyl-3-hydroxy-3-phenylbenzofuran-2(3*H*)-one (10): The single product was purified by flash chromatography on silica gel (hexane/CH_2Cl_2, 1:1), and was obtained as a yellow oil (527 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 [s, 9 H, $C(CH_3)_3$], 1.44 [s, 9 H, $C(CH_3)_3$], 3.08 (br. s, 1 H, OH), 7.19 (d, J = 2.1 Hz, 1 H, CH_{arom}), 7.34–7.43 (m, 6 H, CH_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.8, 31.6, 34.5, 35.0, 76.9, 119.6, 125.1, 125.6 (2 C), 128.7 (2 C), 128.8, 129.3, 134.0, 139.4, 148.2, 149.2, 176.8 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3307, 3030, 2967, 1808, 1480, 1370 cm^{-1}. HRMS: calcd. for ($C_{22}H_{26}NaO_3$) 361.1780; found 361.1781.

3-Hydroxy-5,7-dimethyl-3-(trifluoromethyl)benzofuran-2(3*H*)-one (11a): The single product was purified by flash chromatography on silica gel (hexane/EtOAc, 7:3), and was obtained as a white solid (369 mg, 75%), m.p. 119–120 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.29 (s, 3 H, CH_3), 2.34 (s, 3 H, CH_3), 4.09 (br. s, 1 H, OH), 7.12 (s, 1 H, CH_{arom}), 7.17 (s, 1 H, CH_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.9, 21.1, 77.2 (q, $^2J_{CF3}$ = 25.8 Hz), 120.6, 121.7, 122.5 (q, $^1J_{CF3}$ = 282.3 Hz), 123.8, 135.1, 135.3, 150.8, 170.7 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3309, 3030, 2968, 1808, 1485, 1362 cm^{-1}. HRMS: calcd. for $C_{11}H_9F_3NaO_3$ 269.0401; found 269.0402.

1-Hydroxy-1-(trifluoromethyl)naphtho[2,1-*b*]furan-2(1*H*)-one (11b): The single product was purified by flash chromatography on silica gel ($CHCl_3$/MeOH, 98:2), and was obtained as a white solid (509 mg, 95%). All analytical data are consistent with literature values.[11]

1-Hydroxy-7-methoxy-1-(trifluoromethyl)naphtho[2,1-*b*]furan-2(1*H*)-one (11c): The single product was purified by flash chromatography on silica gel ($CHCl_3$/MeOH, 98:2), and was obtained as a white solid (566 mg, 95%), m.p. 150–151 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.92 (s, 3 H, OCH_3), 4.39 (br. s, 1 H, OH), 7.18 (s, 1 H, CH_{arom}), 7.27 (d, J = 8.2 Hz, 1 H, CH_{arom}), 7.32 (d, J = 8.2 Hz, 1 H, CH_{arom}), 7.89 (d, J = 9.0 Hz, 1 H, CH_{arom}), 8.02 (d, J = 9.0 Hz, 1 H, CH_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.5, 77.5, 107.3, 111.7, 113.5, 121.8, 124.0 (q, $^1J_{CF3}$ = 287.3 Hz), 125.0, 125.3 (q, $^5J_{CF3}$ = 2.8 Hz), 132.9, 133.0, 151.6, 157.5, 171.4 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3189, 3039, 1820, 1587, 1531, 1377 cm^{-1}. HRMS: calcd. for $C_{14}H_9F_3NaO_4$ 321.0351; found 321.0353.

7-Bromo-1-hydroxy-1-(trifluoromethyl)naphtho[2,1-*b*]furan-2(1*H*)-one (11d): The single product was purified by flash chromatography on silica gel ($CHCl_3$/MeOH, 98:2), and was obtained as a yellow solid (437 mg, 63%), m.p.126–128 °C. ^{1}H NMR (300 MHz, CD_3OD): δ = 7.44 (d, J = 8.9 Hz, 1 H, CH_{arom}), 7.69 (dd, J = 2.0, J = 9.0 Hz, 1 H, CH_{arom}), 7.92 (d, J = 8.9 Hz, 1 H, CH_{arom}), 8.02 (d, J = 9.1 Hz, 1 H, CH_{arom}), 8.05 (d, J = 1.5 Hz, 1 H, CH_{arom}) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 78.3, (q, $^2J_{CF3}$ = 25.8 Hz), 113.6, 116.3, 120.3, 124.5 (q, $^1J_{CF3}$ = 285.9 Hz), 126.5 (q, $^5J_{CF3}$ = 2.9 Hz), 129.3, 132.3, 132.7, 133.9, 134.5, 154.4, 171.9 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3196, 3030, 3014, 2981, 1823, 1570, 1536 cm^{-1}.

HRMS: calcd. for $C_{13}H_6BrF_3NaO_3$ 368.9350; found 368.9348 [referred to the most abundant bromine isotope, Br (78.9183)].

7-Benzoyl-1-hydroxy-1-(trifluoromethyl)naphtho[2,1-*b*]furan-2(1*H*)-one (11e): The product was obtained after purification by flash chromatography on silica gel ($CHCl_3$/MeOH, 98:2) as a white solid (587 mg, 79%), m.p. > 270 °C (decomposition). ^{1}H NMR [400 MHz, $(CD_3)_2CO$]: δ = 7.53 (s, 1 H, OH), 7.62 (t, J = 7.6 Hz, 2 H, CH_{arom}), 7.68 (d, J = 8.9 Hz, 1 H, CH_{arom}), 7.73 (tt, J = 7.6, J = 1.5 Hz, 1 H, CH_{arom}), 7.89–7.92 (m, 2 H, CH_{arom}), 8.14 (dd, J = 8.8, J = 1.7 Hz, 1 H, CH_{arom}), 8.36 (d, J = 8.8 Hz, 1 H, CH_{arom}), 8.46 (d, J = 8.9 Hz, 1 H, CH_{arom}), 8.50 (d, J = 1.6 Hz, 1 H, CH_{arom}) ppm. ^{13}C NMR [100 MHz, $(CD_3)_2CO$]: δ = 73.2 (q, $^2J_{CF3}$ = 33 Hz), 113.6, 115.7, 124.3 (q, $^1J_{CF3}$ = 286 Hz), 125.0 ($^5J_{CF3}$ = 2.9 Hz), 128.6, 129.3, 129.6 (2 C), 130.9 (2 C), 131.5, 132.4, 133.6, 135.7, 137.4, 138.6, 155.7, 171.1, 196.1 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3197, 3032, 1820, 1568, 1536, 1370 cm^{-1}. HRMS: calcd. for $C_{20}H_{11}F_3NaO_4$ 395.0507; found 395.0507.

Supporting Information (see footnote on the first page of this article): Full characterization of the known products, and copies of all of the ^{1}H and ^{13}C NMR spectra.

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