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Copper(II) Bromide/Boron Trifluoride Etherate-Cocatalyzed Cyclization of Ketene Dithioacetals and *p*-Quinones: a Mild and General Approach to Polyfunctionalized Benzofurans

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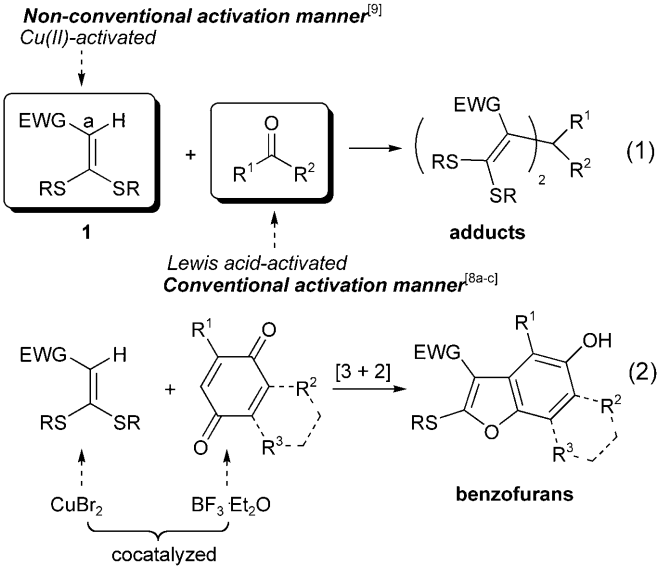
Abstract: A new application of copper(II) bromide-activated ketene dithioacetals as nucleophiles in organic chemistry has been developed. Under the cocatalysis of copper(II) bromide (2.0 mol%) and boron trifluoride etherate (10 mol%), the conjugate addition and sequential cyclization of α-electron-withdrawing group-substituted ketene dithioacetals with *p*-quinones in acetonitrile at room temperature gave a variety of benzofurans. This formal [3+2] cycloaddition provides a general method for catalytic synthesis of polyfunctionalized benzofurans with the advantages of readily available starting materials, cheap catalysts, mild reaction conditions, good yields and wide range of synthetic potential for the benzofuran products. Further transformations of the resulting benzofurans to 2-aminobenzofurans and benzofuro[2,3-*d*]pyrimidine derivatives are also investigated.

Keywords: active alkenes; benzofurans; cocatalysis; copper; cyclization

Introduction

The frequent occurrence of benzofurans in natural products and pharmaceutical molecules[1] has led to the development of numerous synthetic methods for their preparation.[2–5] The predominant strategy involves the assembly of the furan nucleus on a benzenoid scaffold, for example, *via* a cyclization reaction of *o*-functionalized phenols or phenyl ethers,[2–4] and growing interest has been focused on the transition metal-catalyzed processes.[3,4] Nevertheless, the method based on the conjugate addition and sequential cyclization of quinones with active alkenes in the presence of an over-stoichiometric amount of Lewis or Brønsted acids provides an alternative route to the benzofuran skeleton.[5a–f] The $Yb(OTf)_3$-catalyzed conjugate addition of β-keto esters to activated 1,4-naphthoquinones was developed for the facile synthesis of benzofurans recently.[5g] While each of the above approaches[2–5] represents an important advance towards the objective of an efficient method for the construction of benzofurans, the synthesis of densely functionalized benzofurans is limited and remains a challenge. Herein we disclose a $CuBr_2/BF_3{\cdot}Et_2O$-cocatalyzed reaction of *p*-quinones with active alkenes, which allows the efficient construction of a variety of polyfunctionalized benzofurans under mild reaction conditions.

As a part of our ongoing interest in synthetic applications of functionalized ketene dithioacetals,[6,7] the C–C bond-forming reaction at their α-position was examined to extend their synthetic potential.[8,9] Our previous results show that the adducts of α-EWG ketene dithioacetals **1** with aldehydes/simple ketones can be obtained in the presence of either over-stoichiometric amounts of $TiCl_4$ [Scheme 1, Eq. (1), conventional activation manner][8a–c] or catalytic amounts of $CuBr_2$ [10 mol%, Scheme 1, Eq. (1), non-conventional activation manner].[9] It was found that a wider range of reaction partners, both α-EWG ketene dithioacetals and electrophiles (including aldehydes, ketones, and allyl iodide), are promising substrates in this type of coupling reaction when $CuBr_2$ was employed as the catalyst[9] and thus this novel non-conventional activation manner is expected to open a new version of the applications of versatile functionalized ketene dithioacetals in organic chemistry. In the present work, we envisioned a confluence of this cata-



Scheme 1. Activation manners on α-EWG ketene dithioacetals **1**.

lytic topic as a straightforward means for the synthesis of benzofurans[1–5] by a conjugate addition/cyclization sequence, a formal [3+2]cycloaddition, between $CuBr_2$-activated α-EWG ketene dithioacetals as active alkenes and $BF_3{\cdot}Et_2O$-activated *p*-quinones [Scheme 1, Eq. (2)].

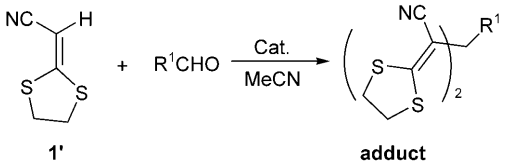
Results and Discussion

Exploration on Cooperative Catalysis[10] of $CuBr_2$ and $BF_3{\cdot}Et_2O$ in the Reaction of α-EWG Ketene Dithioacetals and Aldehydes

With the aim of obtaining further evidence of the catalytic activation of $CuBr_2$ on ketene dithioacetals, we carried out the reaction of 2-(1,3-dithiolan-2-ylidene)acetonitrile **1′** with aldehydes catalyzed by $CuBr_2$ in the presence of a catalytic amount of $BF_3{\cdot}Et_2O$ (an oxophilic Lewis acid for carbonyl activation) as described in Table 1.

According to the results in our previous work,[9] the reaction of **1′** with 4-chlorobenzaldehyde catalyzed by 0.1 equivalent of $CuBr_2$ at room temperature for 12 h to yield adduct **a** in 98% yield (Table 1, entry 1). By comparison, in this work, when 0.1 equivalent of $BF_3{\cdot}Et_2O$ was taken as catalyst to activate aldehydes for this process, 35 h was required to provide **a** with a lower yield (Table 1, entry 2). Notably, with 0.1 equivalent of $CuBr_2$ and 0.1 equivalent of $BF_3{\cdot}OEt_2$ as cooperative catalyst, the reaction was significantly accelerated (Table 1, entry 3). Similarly, in the case of other aldehydes as electrophiles, all the tested $CuBr_2$/$BF_3{\cdot}Et_2O$-cocatalyzed reactions were completed within shorter reaction times (Table 1, entries 5, 7, 9 and 11) than those reactions only with $CuBr_2$ as catalyst (Table 1, entries 4, 6, 8 and 10). Clearly, the experimental results provide strong evidence that $CuBr_2$ plays a key role in increasing the nucleophilicity of the α-carbon atom of ketene dithioacetals (Table 1, entries 1–3) and suggest that the cooperative catalysis of $CuBr_2$ and $BF_3{\cdot}Et_2O$ contributes to the higher reaction efficiency.

Table 1. $CuBr_2$ and $BF_3{\cdot}Et_2O$-cocatalyzed reactions of **1′** with aldehydes.[a]



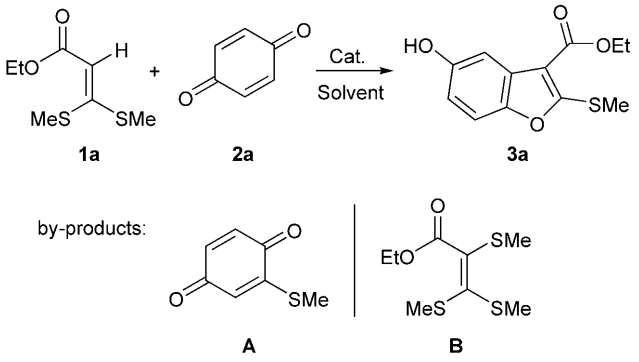
Entry	$CuBr_2$:$BF_3{\cdot}Et_2O$ [equiv.]:[equiv.]	R^1	*t* [h]	Yield[b] of adduct [%]
1	0.1:0	4-ClC_6H_4	12	**a**: 98[9]
2	0:0.1	4-ClC_6H_4	35	**a**: 70
3	0.1:0.1	4-ClC_6H_4	2.0	**a**: 98
4	0.1:0	4-$NO_2C_6H_4$	18	**b**: 96[9]
5	0.1:0.1	4-$NO_2C_6H_4$	4.0	**b**: 95
6	0.1:0	Ph	12	**c**: 93[9]
7	0.1:0.1	Ph	2.5	**c**: 94
8	0.1:0	4-$MeOC_6H_4$	15	**d**: 97[9]
9	0.1:0.1	4-$MeOC_6H_4$	2.0	**d**: 97
10	0.1:0	2-furyl	9.0	**e**: 88[9]
11	0.1:0.1	2-furyl	0.8	**e**: 98

[a] *Reaction conditions:* **1′** (2.0 mmol), aldehydes (1.0 mmol), MeCN (8.0 mL), room temperature.
[b] Isolated yield.

Synthesis of Benzofurans by the $CuBr_2$/$BF_3{\cdot}Et_2O$-Cocatalyzed Cyclization of Ketene Dithioacetals with *p*-Quinones

On the basis of the above experimental results, we turned to explore the application of this catalytic process as a novel entry to benzofurans. The substrates α-EWG ketene dithioacetals **1a–g** were conveniently prepared following the procedures reported previously.[7e,8e,f,9] Initially, we chose *p*-benzoquinone **2a** as the electrophile to try the reaction of ethyl 3,3-bis(methylthio)acrylate **1a** and **2a** in the presence of 10 mol% of $CuBr_2$. However, no reaction was detected upon treatment of **1a** and **2a** with $CuBr_2$ in MeCN at room temperature for 24 h (Table 2, entry 1). This result indicates that *p*-benzoquinone is not active enough to react with $CuBr_2$-activated **1a** in this nonconventional activation process. Then, $CuBr_2$ together with $BF_3{\cdot}Et_2O$ were selected as cooperative catalysts for the reaction. To our delight, benzofuran **3a** was obtained in 49% yield by treatment of **1a** (1.0 mmol)

Table 2. Optimization of reaction conditions.[a]



Entry	$CuBr_2$ [equiv.]	$BF_3{\cdot}Et_2O$ [equiv.]	Solvent	T [°C]	t [h]	Yield [%][b]
1	0.1	0	MeCN	r.t.	24	nr[c]
2	0.1	0.1	MeCN	r.t.	2.5	49[d]
3	0.05	0.1	MeCN	r.t.	1.5	73[e]
4	***0.02***	***0.1***	***MeCN***	***r.t.***	1.0	***80***[f]
5	0	0.1	MeCN	r.t.	0.7	38[g]
6	0.02	0.05	MeCN	r.t.	3.0	65
7[h]	0.02	0.1	MeCN	r.t.	1.5	53
8	0.02	0.1	MeCN	50	0.8	54
9	0.02	0.1	MeCN	reflux	0.7	56
10	0.02	0.1	CH_2Cl_2	r.t.	1.5	55
11	0.02	0.1	THF	r.t.	24	nr[c]

[a] *Reaction conditions:* **1a** (1.0 mmol), **2a** (1.5 mmol), solvent (4.0 mL).
[b] Isolated yields.
[c] No reaction.
[d] **A** was obtained in 5.0% yield with the formation of **B** in 23% yield.
[e] **A** was obtained in 5.0% yield with the formation of **B** in 12% yield.
[f] **A** was obtained in 3.0% yield with the formation of **B** in 8.0% yield.
[g] **A** was obtained in 30% yield and no **B** was detected.
[h] **1a** (1.5 mmol), **2a** (1.0 mmol), MeCN (4.0 mL).

with **2a** (1.5 mmol) in MeCN (4.0 mL) in the presence of $CuBr_2$ (0.1 mmol) and $BF_3{\cdot}Et_2O$ (0.1 mmol) under ambient atmosphere for 2.5 h (Table 2, entry 2). In this case, by-products **A** and **B**[11] were isolated in 5.0% and 23% yields, respectively.

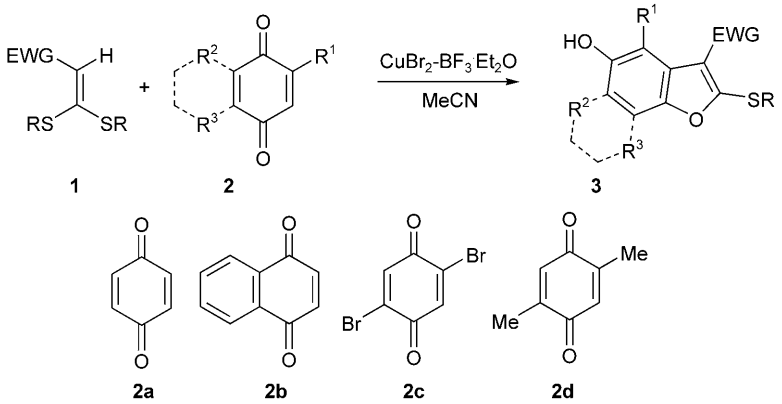
Then, the optimization of the reaction conditions was performed carefully with respect to the amount of catalysts, the ratio of **1a** to **2a**, the reaction temperature and the reaction solvent. As described in Table 2, entries 2–4, the formation of two by-products, especially by-product **B**, could be restrained *via* decreasing the amount of $CuBr_2$. However, when the reaction of **1a** and **2a** was performed without $CuBr_2$, the reaction resulted in complex product mixtures and **3a** was only isolated in 38% yield along with the formation of by-product **A** in 30% yield under identical conditions (Table 2, entry 5). It was also found that excess **1a** (Table 2, entry 7) or higher temperature (Table 2, entries 8 and 9) seemed not acceptable for this procedure. In comparison, the reaction under otherwise the same conditions in CH_2Cl_2 gave **3a** in a lower yield (Table 2, entry 10) and no reaction was detected in THF (Table 2, entry 11). As a result, the best reaction conditions were found to be 2.0 mol% of $CuBr_2$ and 10 mol% of $BF_3{\cdot}Et_2O$ as catalysts (in 4.0 mL MeCN), with the 1.0:1.5 ratio of **1a** to **2a** and at room temperature (Table 2, entry 4).

Subsequently, the scope of this catalytic benzofuran synthesis was studied under the optimized reaction conditions described in Table 2, entry 4, and some representative results are listed in Table 3. Clearly, ketene dithioacetals **1** with a wide range of functional groups at the α-position, including alkoxy carbonyl, acetyl, cyano, benzoyl, and cinnamoyl (Table 3, entries 1–5), could react with *p*-benzoquinone **2a** smoothly to give the desired benzofurans **3a**–**e** in 46–80% yields. On the other hand, to test the generality of the method to the quinone component, selected *p*-quinones **2** were investigated. Pleasingly, as described in Table 3, all the reactions of ketene dithioacetals **1a**–**e** with 1,4-naphthoquinone **2b** could give the corresponding benzofurans **3f**–**j**, respectively, in good to high yields under identical conditions (Table 3, entries 6–10). *p*-Quinones **2c** and **2d** containing either electron-withdrawing or electron-donating substituents were also proved to be effective and gave benzofurans **3k**–**n** in good yields (Table 3, entries 11–14). Similarly, when substrates **1f** and **1g** with ethylthio functionality were selected to react with **2a**–**c**, the desired benzofurans **3o**–**r** were afforded in 48–74% yields, respectively (Table 3, entries 15–18). By contrast, *o*-quinone proved not to be a suitable substrate toward this cyclization and the reaction of 3,5-di-*tert*-butyl-*o*-quinone with **1a** afforded a complex mixture under the identical conditions.

In order to show the synthetic utility of this catalyst system, the synthesis of benzofurans was also expanded to a gram-scale. Catalyzed by 2.0 mol% $CuBr_2$ and 10 mol% $BF_3{\cdot}Et_2O$, **3a** could be obtained in 65% yield (3.27 g) *via* the reaction of **1a** (3.84 g, 20 mmol) with **2a** (3.24 g, 30 mmol) in MeCN (20 mL) at room temperature for 3.0 h.

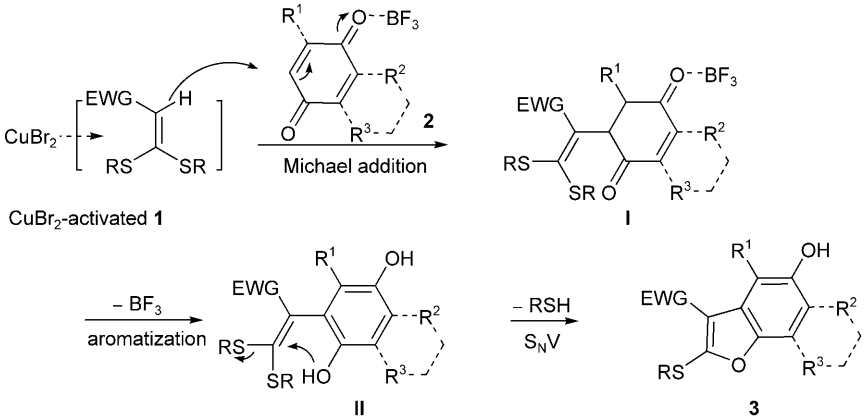
Although the mechanism for the catalytic activation of $CuBr_2$ on α-EWG ketene dithioacetals **1** is not yet clear at this stage, all the above experimental results provide obvious proof of this catalysis. Together with related research results,[5,9,12] clearly, the construction of benzofurans undergoes a formal [3+2]cycloaddition, which is initiated by the conjugate addition of $CuBr_2$-activated ketene dithioacetal **1** with $BF_3{\cdot}Et_2O$-activated quinone **2** (to give the diketone intermediate **I**), followed by aromatization (to give the diphenol intermediate **II**) and subsequent intramolecular S_NV reaction[7a,e,9] as described in Scheme 2.

Table 3. $CuBr_2$ and $BF_3{\cdot}Et_2O$ cocatalyzed synthesis of benzofurans **3**.[a]



Entry	1	EWG	R	2	3	*t* [h]	Yield **3** [%][b]
1	**1a**	CO_2Et	Me	**2a**	**3a**	1.0	80
2	**1b**	MeCO	Me	**2a**	**3b**	5.0	65
3	**1c**	CN	Me	**2a**	**3c**	7.0	46
4	**1d**	PhCO	Me	**2a**	**3d**	2.0	64
5	**1e**	PhCH=CHCO	Me	**2a**	**3e**	3.5	55
6	**1a**	CO_2Et	Me	**2b**	**3f**	0.2	88
7	**1b**	MeCO	Me	**2b**	**3g**	4.0	75
8	**1c**	CN	Me	**2b**	**3h**	12	60
9	**1d**	PhCO	Me	**2b**	**3i**	3.5	58
10	**1e**	PhCH=CHCO	Me	**2b**	**3j**	6.0	51
11	**1a**	CO_2Et	Me	**2c**	**3k**	4.0	64
12	**1d**	PhCO	Me	**2c**	**3l**	8.0	59
13	**1a**	CO_2Et	Me	**2d**	**3m**	5.0	57
14	**1d**	PhCO	Me	**2d**	**3n**	10	52
15	**1f**	CO_2Et	Et	**2a**	**3o**	3.0	74
16	**1f**	CO_2Et	Et	**2b**	**3p**	3.0	65
17	**1f**	CO_2Et	Et	**2c**	**3q**	4.5	60
18	**1g**	PhCO	Et	**2b**	**3r**	15	48

[a] *Reaction conditions:* **1** (1.0 mmol), **2** (1.5 mmol), $CuBr_2$ (0.02 mmol), $BF_3{\cdot}Et_2O$ (0.1 mmol), MeCN (4.0 mL), room temperature.
[b] Isolated yields.

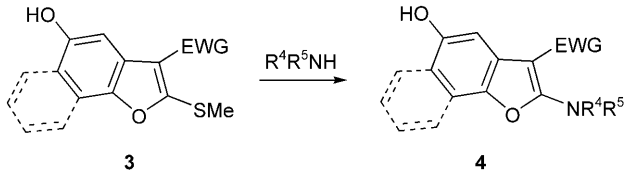


Scheme 2. Proposed mechanism for the cyclization of **1** with **2**.

Applications of the Resulting Polyfunctionalized Benzofurans

Compared with the acid-promoted formal [3+2] cycloaddition of active alkenes with quinones toward the benzofuran motif, we here developed a novel catalytic method, which is one of the most efficient and general known to date. Notably, this catalytic cyclization strategy provides a facile access to a wide variety of benzofurans containing rich functionality, such as 2-alkylthio, 3-EWG, and 5-hydroxy. These functional groups can provide opportunities for further elaboration of these benzofurans.[4g] As an example to introduce more structural diversity, the transformation of benzofurans **3** into 2-aminobenzofurans[13] was firstly examined by direct substitution of the 2-methylthio group of **3** with an amine. As summarized in Table 4, aliphatic primary (Table 4, entries 1 and 2) and secondary amines (Table 4, entries 3–5) are suitable nucleophiles for this S_NV reaction and lead to the 2-aminobenzofurans **4** in high yields. In contrast, the less nucleophilic aniline was found to be inert under identical conditions (Table 4, entry 6).

Table 4. Synthesis of 2-aminobenzofurans **4** from **3**.[a]



3 **4**

Entry	**3**	R^4R^5NH	T [°C]	t [h]	**4**	Yield [%][b]
1	**3d**	*n*-$BuNH_2$	reflux	5.0	**4a**	88
2	**3d**	$BnNH_2$	reflux	7.0	**4b**	82
3	**3d**		r.t.	1.0	**4c**	90
4	**3d**		r.t.	2.0	**4d**	85
5	**3i**		r.t.	3.0	**4e**	80
6	**3d**	$PhNH_2$	reflux	24	–	nr[c]

[a] *Reaction conditions:* **3** (1.0 mmol), amine (3.0 mmol), EtOH (5.0 mL).
[b] Isolated yields.
[c] No reaction.

Additionally, compounds **3** possess the structural characters of ketene monothioacetals which may be used as versatile synthetic intermediates in the construction of fused heterocycles. Thus, an attempt to the synthesis of furo[2,3-*d*]pyrimidines, which exhibit widely valuable biological activities,[14] was carried out *via* the condensation reactions of **3** with guanidine or acetimidamide. As expected, **5a** and **5b** containing the furo[2,3-*d*]pyrimidine motif were easily obtained in high yield, respectively, upon treatment of methylated **3b** (1.0 mmol) with guanidine/acetimidamide (2.0 mmol) at reflux in EtOH (5.0 mL) in the presence of KOH (4.0 mmol) (Scheme 3).

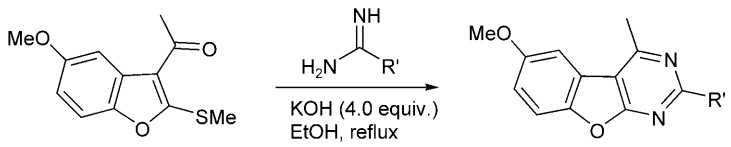
Conclusions

In summary, we have developed a new $CuBr_2$ and $BF_3{\cdot}Et_2O$ cocatalyzed cyclization of α-EWG ketene dithioacetals with *p*-quinones, which provides a simple and general method for the synthesis of polyfunctionalized benzofurans. This protocol is associated with readily available starting materials, cheap catalysts, mild reaction conditions, good yields and wide range of synthetic potential of the resulting products. Furthermore, the novel non-conventional activation of ketene dithioacetals is more valuable in creating new opportunities for the synthetically versatile functionalized ketene dithioacetals. Further studies are in progress.

Experimental Section

General Methods

All reagents were purchased from commercial sources and used without further treatment, unless otherwise indicated. Melting points were uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded at 25 °C at 500 MHz and 125 MHz, respectively, using TMS as internal standard. IR spectra (KBr) were recorded on an FT-IR spectrophotometer in the range of 400–4000 cm^{-1}. Mass spectra were recorded on an LCMsD mass spectrometer.



Scheme 3. Synthesis of furo[2,3-*d*]pyrimidine derivatives.

Typical Procedure for $CuBr_2/BF_3{\cdot}Et_2O$-Cocatalyzed Reaction of 2-(1,3-Dithiolan-2-ylidene)acetonitrile 1′ with Aldehydes

To a well-stirred solution of 2-(1,3-dithiolan-2-ylidene)acetonitrile **1′** (286 mg, 2.0 mmol) and 4-chlorobenzaldehyde (140 mg, 1.0 mmol) in MeCN (8.0 mL) was added $BF_3{\cdot}Et_2O$-MeCN solution (0.1 mL, prediluted by MeCN, M = 1.0 mol/L, 0.1 mmol) and $CuBr_2$ (22.1 mg, 0.1 mmol) at room temperature. The reaction mixture was stirred for 2.0 h. After the starting material **1′** had been consumed as indicated by TLC, the resulting mixture was poured into ice-water (30 mL) and neutralized with aqueous $NaHCO_3$. The precipitate was collected by filtration, washed with water (3 × 20 mL), and dried under vacuum to afford adduct **a** as a white solid; yield: 400 mg (98%). For characterization data of adducts **a**, **b**, **c** and **d**, please see ref.[9]

Typical Procedure for the Synthesis of Benzofurans 3 (with 3a as an Example)

To a well-stirred solution of ethyl 3,3-bis(methylthio)acrylate **1a** (192 mg, 1.0 mmol) and *p*-benzoquinone **2a** (162 mg, 1.5 mmol) in MeCN (4.0 mL) was added $BF_3{\cdot}Et_2O$-MeCN solution (0.1 mL, prediluted by MeCN, M = 1.0 mol/L, 0.1 mmol) and $CuBr_2$ (4.5 mg, 0.02 mmol) at room temperature. The reaction mixture was stirred for 1.0 h. After the starting material **1a** had been consumed as indicated by TLC, the resulting mixture was poured into saturated aqueous NaCl (20 mL), neutralized with aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was washed with water (3 × 20 mL), dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by silica gel chromatography (silica gel, petroleum ether:-diethyl ether = 6:1, v/v) to give ethyl 5-hydroxy-2-(methylthio)benzofuran-3-carboxylate **3a** as a white solid; yield: 202 mg (80%). By-products **A** and **B** were isolated in 3.0% and 8.0% yields, respectively. The product **3a** was often recrystallized to give purer material.

Physical Data of Compounds Isolated

3a: White solid; mp 158–160 °C; ^{1}H NMR (500 MHz, DMSO): δ = 1.34 (t, J = 7.5 Hz, 3H), 2.66 (s, 3H), 4.29 (q, J = 7.0 Hz, 2H), 6.69 (dd, J = 2.5, 9.0 Hz, 1H), 7.18 (d, J = 2.5 Hz, 1H), 7.39 (d, J = 9.0, 1H), 9.43 (s, 1H); ^{13}C NMR (125 MHz, DMSO): δ = 13.2, 14.8, 60.6, 105.7, 107.3, 111.6, 112.4, 127.4, 149.2, 155.1, 163.3, 163.5; IR (KBr): ν = 3321, 2980, 1681, 1263, 970, 836 cm^{-1}; MS (ESI): m/z = 253.1 $[(M+1)]^+$; anal. calcd. for $C_{12}H_{12}O_4S$: C 57.13, H 4.79; found: C 57.34, H 4.71.

A: Yellow solid; mp 144–146 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.33 (s, 3H), 6.35 (s, 1H), 6.73 (d, J = 10.0 Hz, 1H), 6.81 (d, J = 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.6, 124.6, 136.0, 137.5, 153.9, 183.7, 183.8; IR (KBr): ν = 3043, 2992, 1642, 1012 cm^{-1}; MS (ESI): m/z = 155.0 $[(M+1)]^+$; anal. calcd. for $C_7H_6O_2S$: C 54.53, H 3.92; found: C 54.34; H 3.82.

B: Yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.39 (t, J = 7.5 Hz, 3H), 2.31 (s, 3H), 2.32 (s, 3H), 2.42 (s, 3H), 4.34 (t, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.2, 16.1, 16.3, 18.5, 61.7, 132.8, 135.8, 164.7; IR (KBr): ν = 2981, 2922, 1722, 1235, 1056 cm^{-1}; MS (ESI): m/z = 239.0 $[(M+1)]^+$; anal. calcd. for $C_8H_{14}O_2S_3$: C 40.31, H 5.92; found: C 40.52, H 5.84.

3b: White solid; mp 202–204 °C; ^{1}H NMR (500 MHz, DMSO): δ = 2.52 (s, 3H), 2.66 (s, 3H), 6.71 (dd, J = 2.5, 9.0 Hz, 1H), 7.20 (d, J = 2.5 Hz, 1H), 7.40 (d, J = 9.0 Hz, 1H), 9.50 (s, 1H); ^{13}C NMR (125 MHz, DMSO): δ = 13.1, 30.3, 105.5, 111.2, 111.9, 116.4, 126.7, 148.8, 154.7, 162.8, 192.0; IR (KBr): ν = 3204, 2986, 1623, 1259, 979, 878 cm^{-1}; MS (ESI): m/z = 223.0 $[(M+1)]^+$; anal. calcd. for $C_{11}H_{10}O_3S$: C 59.44, H 4.53; found: C 59.21, H 4.43.

3c: White solid; mp 184–186 °C; ^{1}H NMR (500 MHz, DMSO): δ = 2.74 (s, 3H), 6.81–6.84 (m, 2H), 7.48 (d, J = 8.5 Hz, 1H), 9.74 (s, 1H); ^{13}C NMR (125 MHz, DMSO): δ = 14.8, 91.0, 102.9, 112.2, 112.9, 114.3, 126.8, 148.5, 155.1, 162.8; IR (KBr): ν = 3338, 3015, 2224, 1608, 1508, 640 cm^{-1}; MS (ESI): m/z = 206.0 $[(M+1)]^+$; anal. calcd. for $C_{10}H_7NO_2S$: C 58.52, H 3.44, N 6.82; found: C 58.75, H 3.57, N 6.86.

3d: Yellow solid; mp 212–214 °C; ^{1}H NMR (500 MHz, DMSO): δ = 2.63 (s, 3H), 6.56 (d, J = 2.0 Hz, 1H), 6.70 (dd, J = 2.0, 9.0 Hz, 1H), 7.43 (d, J = 9.0 Hz, 1H), 7.56 (t, J = 7.5 Hz, 2H), 7.65–7.70 (m, 3H), 9.37 (s, 1H); ^{13}C NMR (125 MHz, DMSO): δ = 13.5, 105.1, 111.3, 112.4, 116.1, 127.0, 128.2 (2C), 128.7 (2C), 132.3, 139.1, 148.9, 154.3, 163.3, 189.7; IR (KBr): ν = 3261, 3021, 1604, 1444, 1219, 908 cm^{-1}; MS (ESI): m/z = 285.0 $[(M+1)]^+$; anal. calcd. for $C_{16}H_{12}O_3S$: C 67.59, H 4.25; found: C 67.23, H 4.34.

3e: Yellow solid; mp 234–236 °C; ^{1}H NMR (500 MHz, DMSO): δ = 2.69 (s, 3H), 6.73 (dd, J = 2.0, 8.5 Hz, 1H), 7.29 (d, J = 2.0 Hz, 1H), 7.43–7.48 (m, 4H), 7.56 (d, J = 16.0 Hz, 1H), 7.67 (d, J = 16.0 Hz, 1H), 7.77–7.78 (m, 2H), 9.65 (s, 1H); ^{13}C NMR (125 MHz, DMSO): δ = 14.4, 106.3, 112.3, 113.1, 118.0, 125.3, 127.3, 129.3 (2C), 130.0 (2C), 131.5, 135.3, 143.1, 149.8, 155.4, 164.2, 184.9; IR (KBr): ν = 3261, 2923, 1637, 1433, 1183, 962 cm^{-1}; MS (ESI): m/z = 311.1 $[(M+1)]^+$; anal. calcd. for $C_{18}H_{14}O_3S$: C 69.66, H 4.55; found: C 69.45, H 4.43.

3f: White solid; mp 208–210 °C; ^{1}H NMR (500 MHz, DMSO): δ = 1.38 (t, J = 7.0 Hz, 3H), 2.78 (s, 3H), 4.33 (q, J = 7.0 Hz, 2H), 7.34 (s, 1H), 7.48 (t, J = 8.0 Hz, 1H), 7.63 (t, J = 7.5 Hz, 1H), 8.11 (d, J = 8.0 Hz, 1H), 8.20 (d, J = 8.5 Hz, 1H), 10.26 (s, 1H); ^{13}C NMR (125 MHz, DMSO): δ = 13.4, 14.9, 60.7, 100.1, 108.7, 119.5, 120.7, 122.6, 123.0, 123.8, 124.8, 127.9, 144.4, 151.2, 160.8, 163.6; IR (KBr): ν = 3290, 3002, 1662, 1379, 1134, 995 cm^{-1}; MS (ESI): m/z = 303.1 $[(M+1)]^+$; anal. calcd. for $C_{16}H_{14}O_4S$: C 63.56, H 4.67; found: C 63.23, H 4.55.

3g: White solid; mp 250–252 °C; ^{1}H NMR (500 MHz, DMSO): δ = 2.59 (s, 3H), 2.80 (s, 3H), 7.39 (s, 1H), 7.48–7.51 (m, 1H), 7.62–7.65 (m, 1H), 8.13 (d, J = 8.0 Hz, 1H), 8.20 (d, J = 8.5 Hz, 1H), 10.25 (s, 1H); ^{13}C NMR (125 MHz, DMSO): δ = 13.6, 30.3, 99.8, 118.0, 119.1, 120.1, 122.0, 122.1, 123.2, 124.4, 127.4, 144.0, 150.8, 160.0, 192.3; IR (KBr): ν = 3187, 2998, 1616, 1251, 959, 763 cm^{-1}; MS (ESI): m/z = 273.0 $[(M+1)]^+$; anal. calcd. for $C_{15}H_{12}O_3S$: C 66.16, H 4.44; found: C 66.35, H 4.36.

3h: White solid; mp 222–224 °C; ^{1}H NMR (500 MHz, DMSO): δ = 2.83 (s, 3H), 6.91 (s, 1H), 7.58 (s, 1H), 7.71 (s, 1H), 8.18 (d, J = 8.0 Hz, 1H), 8.24 (d, J = 8.0 Hz, 1H), 10.6 (s, 1H); ^{13}C NMR (125 MHz, DMSO): δ = 16.2, 93.8, 97.1, 113.6, 119.9, 120.9, 123.0, 123.9, 124.0, 126.1, 128.7, 144.9, 152.1, 160.9; IR (KBr): ν = 3305, 3013, 2226, 1665, 1249,

765 cm^{-1}; MS (ESI): $m/z=256.0$ $[(M+1)]^+$; anal. calcd. for $C_{14}H_9NO_2S$: C 65.87, H 3.55, N 5.49; found: C 65.68, H 3.42, N 5.46.

3i: Yellow solid; mp 228–230 °C; ^{1}H NMR (500 MHz, DMSO): $\delta=2.74$ (s, 3H), 6.77 (s, 1H), 7.51 (t, $J=7.5$ Hz, 1H), 7.58 (t, $J=7.5$ Hz, 2H), 7.66 (t, $J=7.5$, 1H), 7.70 (t, $J=7.5$, 1H), 7.76 (d, $J=7.5$ Hz, 2H), 8.19 (d, $J=8.5$ Hz, 2H), 10.15 (s, 1H); ^{13}C NMR (125 MHz, DMSO): $\delta=14.5$, 99.8, 118.4, 119.7, 120.7, 122.9 (2C), 123.7, 125.1, 128.0, 129.0 (2C), 129.2 (2C), 133.1, 139.4, 144.7, 150.9, 160.6, 190.3; IR (KBr): $\nu=3185$, 3035, 1602, 1589, 917, 761 cm^{-1}; MS (ESI): $m/z=335.1$ $[(M+1)]^+$; anal. calcd. for $C_{20}H_{14}O_3S$: C 71.84, H 4.22; found: C 71.69, H 4.11.

3j: Yellow solid; mp 242–244 °C; ^{1}H NMR (500 MHz, DMSO): $\delta=2.84$ (s, 3H), 7.46 (s, 1H), 7.50–7.54 (m, 4H), 7.66–7.69 (m, 2H), 7.74 (d, $J=15.5$ Hz, 1H), 7.82 (d, $J=7.0$ Hz, 2H), 8.18 (d, $J=8.5$ Hz, 1H), 8.22(d, $J=8.5$ Hz, 1H), 10.32 (s, 1H); ^{13}C NMR (125 MHz, DMSO): $\delta=14.1$, 99.7, 119.0, 119.2, 120.2, 122.1, 122.3, 123.3, 124.6, 124.8, 127.5, 128.6 (2C), 129.2 (2C), 130.7, 134.6, 142.4, 144.3, 150.9, 160.2, 184.4; IR (KBr): $\nu=3152$, 2930, 1638, 1556, 1251, 765 cm^{-1}; MS (ESI): $m/z=361.1$ $[(M+1)]^+$; anal. calcd. for $C_{22}H_{16}O_3S$: C 73.31, H 4.47; found: C 73.10, H 4.39.

3k: White solid; mp 186–188 °C; ^{1}H NMR (500 MHz, DMSO): $\delta=1.33$ (t, $J=7.0$ Hz, 3H), 2.65 (s, 3H), 4.32 (q, $J=7.0$ Hz, 2H), 7.14 (s, 1H), 10.54 (s, 1H); ^{13}C NMR (125 MHz, DMSO): $\delta=14.6$, 14.7, 61.6, 98.6, 102.0, 112.6, 115.4, 127.5, 146.2, 152.8, 160.5, 162.5; IR (KBr): $\nu=3242$, 2985, 1637, 1370, 1169, 865 cm^{-1}; MS (ESI): $m/z=409.0$ $[(M+1)]^+$; anal. calcd. for $C_{12}H_{10}Br_2O_4S$: C 35.15, H 2.46; found: C 35.33, H 2.37.

3l: White solid; mp 214–216 °C; ^{1}H NMR (500 MHz, DMSO): $\delta=2.55$ (s, 3H), 7.20 (s, 1H), 7.53 (t, $J=7.5$ Hz, 2H), 7.69 (t, $J=7.0$ Hz, 1H), 7.82 (d, $J=7.0$ Hz, 2H), 10.58 (s, 1H); ^{13}C NMR (125 MHz, DMSO): $\delta=15.9$, 97.9, 101.7, 115.8, 121.5, 128.5, 129.0 (2C), 129.4 (2C), 134.1, 137.8, 145.9, 151.9, 154.4, 189.6; IR (KBr): $\nu=3148$, 2992, 1599, 1461, 1159, 887 cm^{-1}; MS (ESI): $m/z=440.9$ $[(M+1)]^+$; anal. calcd. for $C_{16}H_{10}Br_2O_3S$: C 43.47, H 2.28; found: C 43.29, H 2.36.

3m: White solid; mp 178–180 °C; ^{1}H NMR (500 MHz, DMSO): $\delta=1.32$ (t, $J=7.0$ Hz, 3H), 2.34 (s, 6H), 2.63 (s, 3H), 4.28 (d, $J=7.0$ Hz, 2H), 6.62 (s, 1H), 9.08 (s, 1H); ^{13}C NMR (125 MHz, DMSO): $\delta=13.4$, 13.8, 14.7 (2C), 60.9, 110.2, 113.0, 113.6, 117.9, 125.6, 148.3, 152.4, 161.1, 163.7; IR (KBr): $\nu=3355$, 2985, 1638, 1369, 1152, 858 cm^{-1}; MS (ESI): $m/z=281.1$ $[(M+1)]^+$; anal. calcd. for $C_{14}H_{16}O_4S$: C 59.98, H 5.75; found: C 59.76, H 5.63.

3n: White solid; mp 220–222 °C; ^{1}H NMR (500 MHz, DMSO): $\delta=1.74$ (s, 3H), 2.40 (s, 3H), 2.52 (s, 3H), 6.70 (s, 1H), 7.54 (t, $J=7.5$ Hz, 2H), 7.68 (t, $J=7.5$ Hz, 1H), 7.78 (d, $J=7.0$ Hz, 2H), 9.12 (s, 1H); ^{13}C NMR (125 MHz, DMSO): $\delta=13.2$, 15.0, 16.1, 112.1, 114.7, 118.5, 121.6, 127.0, 129.5 (2C), 129.7 (2 C), 134.2, 138.6, 148.4, 152.0, 154.0, 191.8; IR (KBr): $\nu=3284$, 2969, 1592, 1460, 1190, 887 cm^{-1}; MS (ESI): $m/z=313.1$ $[(M+1)]^+$; anal. calcd. for $C_{18}H_{16}O_3S$: C 69.21, H 5.16; found: C 69.38, H 5.23.

3o: White solid; mp 154–156 °C; ^{1}H NMR (500 MHz, DMSO): $\delta=1.31$–1.36 (m, 6H), 3.20 (q, $J=7.0$ Hz, 2H), 4.27 (q, $J=7.5$ Hz, 2H), 6.69 (dd, $J=2.0$, 9.0 Hz, 1H), 7.16 (d, $J=2.0$ Hz, 1H), 7.38 (d, $J=9.0$, 1H), 9.57 (s, 1H); ^{13}C NMR (125 MHz, DMSO): $\delta=15.1$, 16.2, 25.5, 61.1, 106.1, 108.2, 112.0, 113.0, 127.6, 149.6, 155.3, 163.0, 163.9; IR (KBr): $\nu=3357$, 2998, 1659, 1232, 1058, 797 cm^{-1}; MS (ESI): $m/z=267.0$ $[(M+1)]^+$; anal. calcd. for $C_{13}H_{14}O_4S$: C 58.63, H 5.30; found: C 58.49, H 5.18.

3p: White solid; mp 174–176 °C; ^{1}H NMR (500 MHz, DMSO): $\delta=1.38$ (t, $J=7.0$ Hz, 3H), 1.43 (t, $J=7.0$ Hz, 3H), 3.35 (q, $J=7.5$ Hz, 2H), 4.33 (q, $J=7.5$ Hz, 2H), 7.35 (s, 1H), 7.49 (t, $J=7.5$ Hz, 1H), 7.63 (t, $J=7.0$ Hz, 1H), 8.11 (d, $J=8.0$ Hz, 1H), 8.20 (d, $J=8.0$ Hz, 1H), 10.27 (s, 1H); ^{13}C NMR (125 MHz, DMSO): $\delta=14.9$, 15.9, 25.6, 60.8, 100.2, 109.5, 119.5, 120.7, 122.8, 123.0, 123.9, 124.9, 128.0, 144.5, 151.3, 160.1, 163.6; IR (KBr): $\nu=3278$, 3005, 1663, 1376, 1129, 989 cm^{-1}; MS (ESI): $m/z=317.1$ $[(M+1)]^+$; anal. calcd. for $C_{17}H_{16}O_4S$: C 64.54, H 5.10; Found: C 64.68, H 5.19.

3q: White solid; mp 178–180 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=1.42$–1.48 (m, 6H), 3.22 (q, $J=7.0$ Hz, 2H), 4.33 (q, $J=7.0$ Hz, 2H), 6.42 (s, broad, 1H), 7.17 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=14.3$, 15.1, 26.3, 61.3, 98.9, 102.9, 111.7, 114.8, 126.7, 147.1, 150.7, 162.2, 162.6; IR (KBr): $\nu=3241$, 2983, 2927, 1636, 1171, 867 cm^{-1}; MS (ESI): $m/z=423.0$ $[(M+1)]^+$; anal. calcd. for $C_{13}H_{12}Br_2O_4S$: C 36.82, H 2.85; found: C 36.63, H 2.71.

3r: White solid; mp 182–184 °C; ^{1}H NMR (500 MHz, DMSO): $\delta=1.36$ (t, $J=7.0$ Hz, 3H), 3.27 (q, $J=7.0$ Hz, 2H), 6.78 (s, 1H), 7.52 (t, $J=8.0$ Hz, 1H), 7.58 (t, $J=7.5$ Hz, 2H), 7.66–7.72 (m, 2H), 7.77 (d, $J=7.5$ Hz, 2H), 8.19 (d, $J=8.5$ Hz, 2H), 10.17 (s, 1H); ^{13}C NMR (125 MHz, DMSO): $\delta=15.8$, 27.0, 99.8, 119.8, 120.0, 120.9, 123.0, 123.2, 123.9, 125.4, 128.2, 129.3 (2C), 129.4 (2C), 133.4, 139.3, 144.9, 151.1, 158.9, 190.6; IR (KBr): $\nu=3202$, 2967, 1594, 1429, 1148, 912 cm^{-1}; MS (ESI): $m/z=349.1$ $[(M+1)]^+$; anal. calcd. for $C_{21}H_{16}O_3S$: C 72.39, H 4.63; found: C 72.58, H 4.74.

General Procedure for the Synthesis of 4 (with 4a as an Example)

To a solution of **3d** (284 mg, 1.0 mmol) in 5.0 mL of ethanol, was added butan-1-amine (0.03 mL, 3.0 mmol). The resulting mixture was stirred under reflux. After completion of the reaction as indicated by TLC, the reaction mixture was poured into saturated aqueous NaCl (20 mL), neutralized with dilute HCl, and extracted with CH_2Cl_2 (3×20 mL). The combined organic phase was washed with water (3×20 mL), dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash chromatography (silica gel, petroleum ether:diethyl ether = 5:1) to give **4a** as yellow crystals; yield: 271 mg (88%).

Physical Data of Compounds Isolated

4a: Yellow crystals; mp 202–204 °C; ^{1}H NMR (500 MHz, DMSO): $\delta=0.92$ (t, $J=7.0$ Hz, 3H), 1.32–1.38 (m, 2H), 1.60–1.65 (m, 2H), 3.51 (d, $J=5.5$ Hz, 2H), 6.07 (d, $J=2.5$ Hz, 1H), 6.39 (dd, $J=6.0$, 8.5 Hz, 1H), 7.15 (d, $J=8.5$ Hz, 1H), 7.51–7.58 (m, 5H), 9.02 (s, broad, 1H), 9.11 (s, 1H); ^{13}C NMR (125 MHz, DMSO): $\delta=14.1$, 20.0, 32.2, 41.8, 93.2, 104.9, 108.9, 110.8, 127.4 (2C), 127.6, 129.0 (2C), 130.9, 141.8, 143.0, 154.5, 167.0, 188.5; IR (KBr): $\nu=3196$, 2958, 1657, 1531, 1366, 1171, 751 cm^{-1}; MS (ESI): $m/z=310.1$ $[(M+1)]^+$; anal. calcd. for $C_{19}H_{19}NO_3$: C 73.77, H 6.19, N 4.53; found: C 73.59, H 6.27, N 4. 59.

4b: Yellow crystals; mp 176–178 °C; ^{1}H NMR (500 MHz, DMSO): δ = 4.72 (d, J = 6.5 Hz, 2H), 6.08 (d, J = 2.0 Hz, 1H), 6.39 (dd, J = 2.0, 8.5 Hz, 1H), 7.13 (d, J = 8.5 Hz, 1H), 7.29 (d, J = 7.5 Hz, 1H), 7.37 (t, J = 7.5 Hz, 2H), 7.42 (d, J = 7.0 Hz, 2H), 7.52–7.58 (m, 5H), 9.03 (s, 1H), 9.52 (t, J = 6.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO): δ = 45.5, 93.5, 105.0, 109.0, 110.9, 127.4 (2C), 127.6, 127.9 (3C), 129.0 (2C), 129.2 (2C), 131.0, 139.0, 141.7, 143.0, 154.5, 166.6, 188.8; IR (KBr): ν = 3196, 2963, 1641, 1582, 1455, 747 cm^{-1}; MS (ESI): m/z = 344.1 [(M+1)]$^+$; anal. calcd. for $C_{22}H_{17}NO_3$: C 76.95, H 4.99, N 4.08; found: C 76.83, H 4.90, N 4.12.

4c: Yellow crystals; mp 218–220 °C; ^{1}H NMR (500 MHz, DMSO): δ = 1.39–1.48 (m, 6H), 3.27 (s, 4H), 6.45 (dd, J = 2.0, 8.5 Hz, 1H), 6.53 (d, J = 1.5 Hz, 1H), 7.14 (d, J = 8.5 Hz, 1H), 7.51 (t, J = 7.5 Hz, 2H), 7.59 (t, J = 7.5 Hz, 1H), 7.67 (d, J = 7.5 Hz, 2H), 9.06 (s, 1H); ^{13}C NMR (125 MHz, DMSO): δ = 32.8, 34.3 (2C), 59.0 (2C), 104.0, 114.3, 118.6, 119.4, 137.9 (2C), 138.2 (2C), 139.6, 141.3, 150.1, 151.7, 163.4, 173.4, 198.5; IR (KBr): ν = 3440, 2920, 1559, 1462, 1140, 999 cm^{-1}; MS (ESI): m/z = 322.1 [(M+1)]$^+$; anal. calcd. for $C_{20}H_{19}NO_3$: C 74.75, H 5.96, N 4.36; found: C 74.54, H 5.88, N 4.31.

4d: Yellow crystals; mp 216–218 °C; ^{1}H NMR (500 MHz, DMSO): δ = 3.34 (d, J = 4.0 Hz, 4H), 3.53 (d, J = 4.0 Hz, 4H), 6.45 (s, 1H), 6.48 (t, J = 8.5 Hz, 1H), 7.17 (d, J = 8.5 Hz, 1H), 7.53 (t, J = 7.5 Hz, 2H), 7.62 (d, J = 7.5 Hz, 1H), 7.70 (d, J = 7.5 Hz, 2H), 9.07 (s, 1H); ^{13}C NMR (125 MHz, DMSO): δ = 48.7 (2C), 65.8 (2C), 95.8, 105.4, 110.0, 110.5, 128.9 (2C), 129.1 (2C), 130.2, 132.4, 140.8, 142.7, 154.4, 163.9, 189.5; IR (KBr): ν = 3199, 2993, 2863, 1554, 1111, 805 cm^{-1}; MS (ESI): m/z = 324.1 [(M+1)]$^+$; anal. calcd. for $C_{19}H_{17}NO_4$: C 70.58, H 5.30, N 4.33; found: C 70.33, H 5.41, N 4.37.

4e: Yellow crystals; mp 232–234 °C; ^{1}H NMR (500 MHz, DMSO): δ = 1.41–1.44 (m, 4H), 1.45–1.48 (m, 2H), 3.34 (t, J = 5.0 Hz, 4H), 6.88 (s, 1H), 7.34 (t, J = 7.5 Hz, 1H), 7.52–7.56 (m, 3H), 7.62 (t, J = 7.5 Hz, 1H), 7.74–7.75 (m, 2H), 7.99 (d, J = 8.0 Hz, 1H), 8.11 (d, J = 8.5 Hz, 1H), 9.87 (s, 1H); ^{13}C NMR (125 MHz, DMSO): δ = 23.8, 25.2 (2C), 50.1 (2C), 96.8, 100.6, 118.9, 120.4, 121.5, 123.2, 123.7, 125.5, 127.4, 129.1 (2C), 129.2 (2C), 132.4, 136.4, 140.7, 150.4, 163.5, 189.7; IR (KBr): ν = 3440, 2928, 1539, 1392, 1127, 675 cm^{-1}; MS (ESI): m/z = 372.1 [(M+1)]$^+$; anal. calcd. for $C_{24}H_{21}NO_3$: C 77.61, H 5.70, N 3.77; found: C 77.46, H 5.57, N 3.79.

General Procedure for the Synthesis of 5 (with 5a as an Example)

To a solution of **3b** (222 mg, 1.0 mmol) and CH_3I (0.09 mL, 1.5 mmol) in 4.0 mL of DMF was added K_2CO_3 (138 mg, 1.0 mmol). The resulting mixture was stirred at room temperature. After completion of the reaction as indicated by TLC, the reaction mixture was poured into saturated aqueous NaCl (20 mL) and neutralized with dilute HCl. The white precipitate was collected by filtration, washed with water (30 mL) and dried under vacuum to afford 1-(5-methoxy-2-(methylthio)benzofuran-3-yl)ethanone **3b′** as a white solid; yield: 214 mg (95%).

Then, **3b′** (118 mg, 0.5 mmol) was redissolved in 5.0 mL of ethanol and treated with guanidine hydrochloride (95.5 mg, 1.0 mmol) and KOH (112 mg, 2.0 mmol) under reflux. After completion of the reaction as indicated by TLC, the reaction mixture was poured into saturated aqueous NaCl (10 mL) and neutralized with dilute HCl. The resulting precipitate was collected by filtration, washed with water (10 mL) and dried under vacuum to afford **5a** as a white solid; yield: 103 mg (90%).

Physical Data of Compounds Isolated

3b′: White solid; mp 86–88 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.63 (s, 3H), 2.71 (s, 3H), 3.88 (s, 3H), 6.84 (dd, J = 2.5, 8.5 Hz, 1H), 7.34 (d, J = 8.5 Hz, 1H), 7.39 (d, J = 2.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.7, 30.5, 55.9, 103.8, 110.9, 111.5, 117.3, 127.2, 150.1, 157.0, 163.2, 192.7; IR (KBr): ν = 3110, 2996, 2932, 1649, 1496, 1162, 859 cm^{-1}; MS (ESI): m/z = 237.1 [(M+1)]$^+$; anal. calcd. for $C_{12}H_{12}O_3S$: C 61.00, H 5.12; found: C 61.21, H 5.23.

5a: White solid; mp 276–278 °C; ^{1}H NMR (500 MHz, DMSO): δ = 2.67 (s, 3H), 3.84 (s, 3H), 6.95 (d, J = 8.0 Hz, 1H), 7.04 (s, 2H), 7.32 (s, 1H), 7.51 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO): δ = 22.7, 56.3, 103.1, 105.6, 112.3, 112.6, 123.3, 146.6, 156.7, 163.0, 163.8, 171.0; IR (KBr): ν = 3355, 3166, 2996, 1656, 1577, 1183, 788 cm^{-1}; MS (ESI): m/z = 230.1 [(M+1)]$^+$; anal. calcd. for $C_{12}H_{11}N_3O_2$: C 62.87, H 4.84, N 18.33; found: C 62.68, H 4.75, N 18.38.

5b: White solid; mp 136–138 °C; ^{1}H NMR (500 MHz, DMSO): δ = 2.65 (s, 3H), 2.81 (s, 3H), 3.86 (s, 3H), 7.13 (d, J = 8.0 Hz, 1H), 7.45 (s, 1H), 7.64 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO): δ = 22.7, 26.1, 56.4, 106.7, 110.8, 113.1, 116.2, 121.4, 147.5, 156.9, 162.5, 165.2, 168.9; IR (KBr): ν = 3165, 2973, 2839, 1593, 1485, 1183, 788 cm^{-1}; MS (ESI): m/z = 229.1 [(M+1)]$^+$; anal. calcd. for $C_{13}H_{12}N_2O_2$: C 68.41, H 5.30, N 12.27; found: C 68.53, H 5.39, N 12.21.

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References

[1] For representative examples on bioactivities of benzofurans, see: a) B. L. Flynn, E. Hamel, M. J. Katherine, *J. Med. Chem.* **2002**, *45*, 2670–2673; b) S. Pautus, S. W. Yee, M. Jayne, M. P. Coogan, C. Simons, *Bioorg. Med. Chem.* **2006**, *14*, 3643–3653; c) M. Dixit, B. K. Tripathi, A. K. Tamrakar, A. K. Srivastava, B. Kumar, A. Goel, *Bioorg. Med. Chem.* **2007**, *15*, 727–734; d) Y. Chen, X. Wei, H. Xie, H. Deng, *J. Nat. Prod.* **2008**, *71*, 929–932; e) N. T. Dat, X. Jin, K. Lee, Y.-S. Hong, Y. H. Kim, J. J. Lee, *J. Nat. Prod.* **2009**, *72*, 39–43.

[2] For selected reviews of the chemistry and synthesis of benzofurans, see: a) X.-L. Hou, Z. Yang, H. N. C. Wong, in: *Progress in Heterocyclic Chemistry*, Vol. 14, (Eds.: G. W. Gribble, T. L. Gilchrist), Pergamon, Oxford, England, **2002**, pp 139–179; b) X.-L. Hou, Z. Yang, K. S. Yeung, H. N. C. Wong, in: *Progress in Heterocyclic Chemistry*, Vol. 17, (Eds.: G. W. Gribble, T. L.

Gilchrist), Pergamon, Oxford, England, **2005**, pp 142–171; c) L. De Luca, G. Nieddu, A. Porcheddu, G. Giacomelli, *Curr. Med. Chem.* **2009**, *16*, 1–20.

[3] For selected reviews on the synthesis of benzofurans by transition metal-catalyzed transformations, see: a) F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* **2004**, *104*, 3079–3160; b) R. E. Ziegert, J. Torang, K. Knepper, S. Brase, *J. Comb. Chem.* **2005**, *7*, 147–169; c) S. Cacchi, G. Fabrizi, A. Goggiamani, *Curr. Org. Chem.* **2006**, *10*, 1423–1455; d) G. Zeni, R. C. Larock, *Chem. Rev.* **2006**, *106*, 4644–4680.

[4] For selected examples on the synthesis of benzofurans by transition metal-catalyzed transformations, see: a) H. Zhang, E. M. Ferreira, B. M. Stoltz, *Angew. Chem.* **2004**, *116*, 6270–6274; *Angew. Chem. Int. Ed.* **2004**, *43*, 6144–6148; b) I. Nakamura, Y. Mizushima, Y. Yamamoto, *J. Am. Chem. Soc.* **2005**, *127*, 15022–15023; c) A. Fürstner, P. W. Davies, *J. Am. Chem. Soc.* **2005**, *127*, 15024–15025; d) J. Oppenheimer, W. L. Johnson, M. R. Tracey, R. P. Hsung, P.-Y. Yao, R. Liu, K. Zhao, *Org. Lett.* **2007**, *9*, 2361–2364; e) B. Lu, B. Wang, Y. Zhang, D. Ma, *J. Org. Chem.* **2007**, *72*, 5337–5341; f) C. Eidamshaus, J. D. Burch, *Org. Lett.* **2008**, *10*, 4211–4214; g) S. G. Newman, V. Aureggi, C. S. Bryan, M. Lautens, *Chem. Commun.* **2009**, 5236–5238.

[5] For selected examples on the synthesis of benzofurans based on quinones, see: a) M. E. Jung, F. Perez, *Org. Lett.* **2009**, *11*, 2165–2167; b) X.-M. Cheng, X.-W. Liu, *J. Comb. Chem.* **2007**, *9*, 906–908; c) G. Z. Stasevich, V. L. Stepanenko, M. V. Kudrevatykh, O. Yu. Avrutina, O. N. Bubel, *Chem. Heterocycl. Compd.* **2003**, *39*, 707–712; d) S. Al-Mousawi, M. M. Abdel-Khalik, S. El-Sherbiny, E. John, M. H. Elnagdi, *J. Heterocycl. Chem.* **2001**, *38*, 949–953; e) H. Takahata, A. Anazawa, K. Moriyama, T. Yamazaki, *J. Chem. Soc. Perkin Trans. 1* **1987**, 1501–1504; f) V. Aggarwat, A. Kumar, H. Ila, H. Junjappa, *Synthesis* **1981**, 157–158; g) N. V. S. Mudiganti, S. Claessens, N. D. Kimpe, *Tetrahedron* **2009**, *65*, 1716–1723.

[6] For selected reviews, see: a) R. K. Dieter, *Tetrahedron* **1986**, *42*, 3029–3096; b) H. Junjappa, H. Ila, C. V. Asokan, *Tetrahedron* **1990**, *46*, 5423–5506.

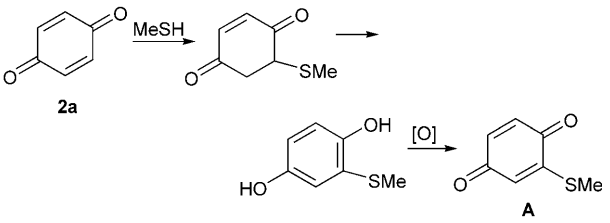
[7] For representative examples, see: a) X. Bi, D. Dong, Q. Liu, W. Pan, L. Zhao, B. Li, *J. Am. Chem. Soc.* **2005**, *127*, 4578–4579; b) J. Liu, M. Wang, B. Li, Q. Liu, Y. Zhao, *J. Org. Chem.* **2007**, *72*, 4401–4405; c) J. Tan, X. Xu, L. Zhang, Y. Li, Q. Liu, *Angew. Chem.* **2009**, *121*, 2912–2916; *Angew. Chem. Int. Ed.* **2009**, *48*, 2868–2872; d) J. Liu, M. Wang, F. Han, Y. Liu, Q. Liu, *J. Org. Chem.* **2009**, *74*, 5090–5092; e) Z. Fu, M. Wang, Y. Dong, J. Liu, Q. Liu, *J. Org. Chem.* **2009**, *74*, 6105–6110.

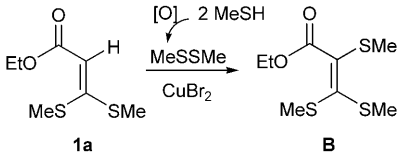
[8] a) Y. Yin, M. Wang, Q. Liu, J. Hu, S. Sun, J. Kang, *Tetrahedron Lett.* **2005**, *46*, 4399–4402; b) S. Sun, Q. Zhang, Q. Liu, J. Kang, Y. Yin, D. Li, D. Dong, *Tetrahedron Lett.* **2005**, *46*, 6271–6274; c) Q. Zhang, Y. Liu, M. Wang, Q. Liu, J. Hu, Y. Yin, *Synthesis* **2006**, 3009–3014; d) Y. Yin, Q. Zhang, J. Li, S. Sun, Q. Liu, *Tetrahedron Lett.* **2006**, *47*, 6071–6074; e) Z. Fu, M. Wang, Y. Ma, Q. Liu, J. Liu, *J. Org. Chem.* **2008**, *73*, 7625–7630; f) Y. Ma, M. Wang, D. Li, B. Bekturhun, J. Liu, Q. Liu, *J. Org. Chem.* **2009**, *74*, 3116–3121.

[9] H.-J. Yuan, M. Wang, Y.-J. Liu, Q. Liu, *Adv. Synth. Catal.* **2009**, *351*, 112–116, and references cited therein.

[10] a) D. H. Paull, C. J. Abraham, M. T. Scerba, E. Alden-Danforth, T. Lectka, *Acc. Chem. Res.* **2008**, *41*, 655–663; b) Y. J. Park, J.-W. Park, C.-H. Jun, *Acc. Chem. Res.* **2008**, *41*, 222–234.

[11] a) Formation of by-product **A** should result from a sequential Michael addition of methanethiol (eliminating product) with benzoquenone **2a**, aromatization, and oxidation. b) Formation of by-product **B** should result from the coupling of $CuBr_2$-activated **1a** and 1,2-dimethyldisulfane (formed by the coupling of two methanethiol).





[12] In order to understand this process, we performed additional two reactions under the cooperative catalysis of $CuBr_2$ (2.0 mol%) and $BF_3{\cdot}Et_2O$ (10 mol%) in MeCN at room temperature for 1.0 h, (i) the reaction of **1a** (1.0 mmol) and **2a** (1.0 mmol) at ambient conditions; (ii) the reaction of **1a** (1.0 mmol) and **2a** (1.0 mmol) under N_2. The former reaction gave benzofuran **3a** in 52% yield and the latter one afforded **3a** in 58% yield. By comparison of the experimental data, no evidence suggests that the coupling of **1a** and **2a** benefits from O_2. Thus, the experimental results do not support a Cu(II)-catalyzed oxidative coupling of ketene dithioacetals and quinones.

[13] Aminobenzofurans are evaluated as either a scaffold in natural product synthesis or useful building blocks in organic synthesis, see: a) T. Benincori, F. Sannicolo, *J. Org. Chem.* **1988**, *53*, 1309–1312; b) M. Gerster, R. Wicki, *Synthesis* **2004**, 249–254; c) T. Ishikawa, T. Miyahara, M. Asakura, S. Higuchi, Y. Miyauchi, S. Saito, *Org. Lett.* **2005**, *7*, 1211–1214.

[14] a) A. Gangjee, R. Devraj, J. J. McGuire, R. L. Kisliuk, *J. Med. Chem.* **1995**, *38*, 3798–3805; b) Y. Maeda, M. Nakano, H. Sato, Y. Miyazaki, S. L. Schweiker, J. L. Smith, A. T. Truesdale, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3907–3911; c) Z. Janeba, J. Balzarini, G. Andrei, R. Snoeck, E. De Clercq, M. J. Robins, *J. Med. Chem.* **2005**, *48*, 4690–4696; d) N. Foloppe, L. M. Fisher, R. Howes, P. Kierstan, A. Potter, A. G. S. Robertson, A. E. Surgenor, *J. Med. Chem.* **2005**, *48*, 4332–4345.

