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Two-Step, Practical, and Diversity-Oriented Synthesis of Multisubstituted Benzofurans from Phenols through Pummerer Annulation Followed by Cross-coupling

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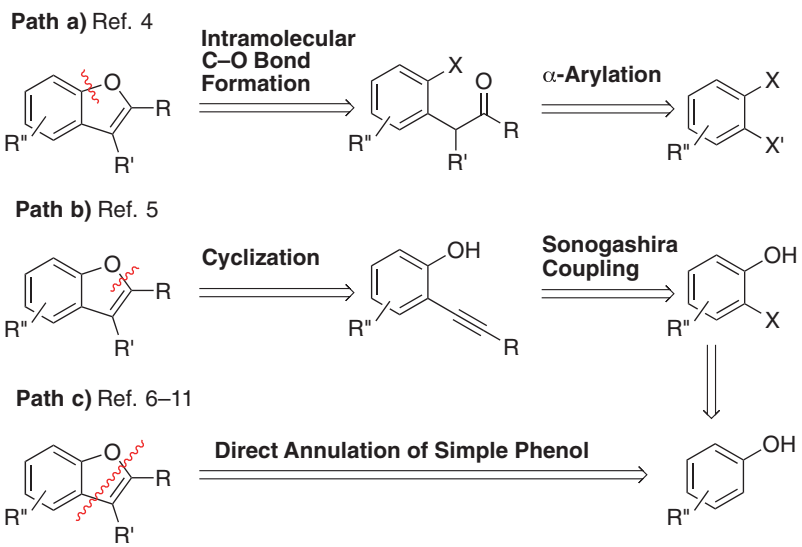
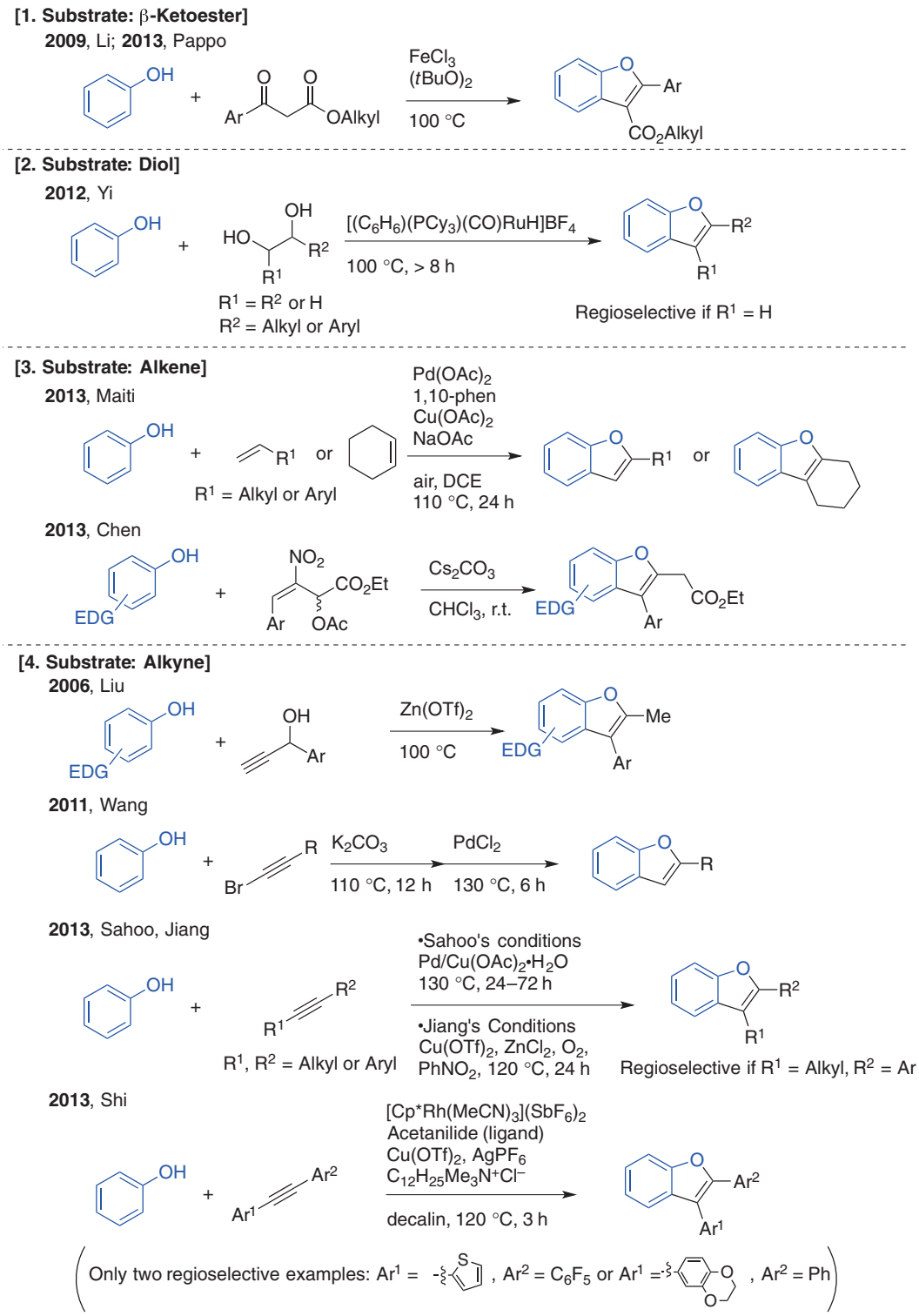
Practical and diversity-oriented synthesis of multisubstituted benzofurans has been accomplished from simple phenols through a Pummerer annulation/cross-coupling sequence. Operationally simple and rapid reactions of phenols with ketene dithioacetal monoxides (KDMs) with the aid of trifluoroacetic anhydride provide the corresponding 2-methylsulfanylbenzo[*b*]furans. The scope of the reaction encompasses phenols and KDMs having a broad range of substituents. The remaining methylsulfanyl group in the annulation products is converted to various aryl groups through cross-coupling reactions that we improved specially to this end. This two-step approach to multisubstituted benzofurans is powerful enough to synthesize highly fluorescent benzofuran derivatives as well as the naturally occurring Eupomatenoid family.

Since a wide variety of benzofuran-containing drugs,[1] natural products,[2] and organic functional materials[3] have been reported, new methodologies for constructing benzofurans have been studied extensively in recent years.[4–15] Mainly, the recent approaches to benzofurans can be categorized into three paths according to the starting materials (Scheme 1): a) α-arylation/intramolecular C–O bond formation sequence from 1,2-dihalogenated arenes,[4] b) Sonogashira/cyclization sequence from 2-halophenols,[5] and c) direct annulation of simple phenols.[6–11] Although the stepwise approaches through Path a) or b) have been regarded as the most reliable and versatile routes to benzofurans, tedious preparations of the precursors (1,2-dihalobenzene derivatives or 2-halophenols) weaken their synthetic utility, especially in synthesizing multisubstituted benzofurans.

Recent development of direct two-component annulations has enabled straightforward syntheses of benzofurans from

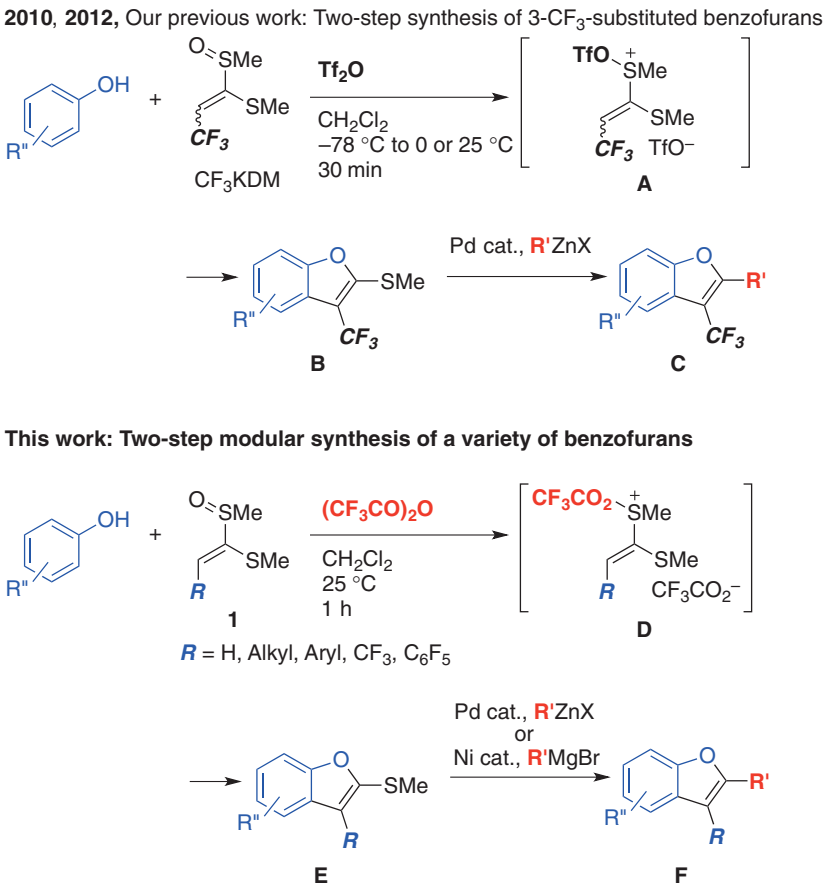


Scheme 1. Categorization of recent approaches to benzofurans.



Scheme 2. Recent examples of direct annulation of phenol to construct benzofuran frameworks (Path c).

phenols (Path c). For example, Li and Pappo reported iron-catalyzed oxidative annulation reactions with β-ketoesters (Scheme 2-1).[6] While the reactions were useful and applicable to synthesize coumestrols,[2a] substituents at the 3 position of the products are strictly limited to alkoxycarbonyls. Annulation with diols[7] or alkenes[8] also directly provided benzofurans (Schemes 2-2 and 2-3). However, regioselectivity was hardly controllable except for the reactions with terminal 1,2-diols,[7] terminal alkenes,[8a] or specially designed alkenes.[8b] Alkynes are also suitable substrates for annulation of phenols (Scheme 2-4). Liu reported annulation of phenols with propargyl alcohols.[9a] However, this Lewis acid-catalyzed annulation limits the scope of substrates to electron-rich phenols and aryl-substituted propargyl alcohols to afford an insufficient variety of benzo-



Scheme 3. Our approach through direct annulation of phenol with KDM (Path c).

furans. Wang utilized addition of phenols onto 1-bromoalkynes followed by palladium-catalyzed intramolecular C–H/C–Br coupling to lead to one-pot syntheses of 2-substituted benzofurans.[9b] Although this two-step strategy is attractive in regard to its modularity at the 2 position and the phenolic substituents, no substituent can be installed at the 3 position in principle. Recently, efficient oxidative annulation reactions with simple alkynes were reported by Sahoo,[9c] Jiang,[9d] and Shi.[9e] Although the scope of these reactions is wide, the regioselectivity of the reactions heavily depends on the electronics of the substituents of alkynes. It is additionally noteworthy that most of the annulation reactions of phenols require harsh conditions. Therefore, it is still difficult to achieve concise and tailor-made syntheses of substituted benzofurans from simple phenols under mild conditions. Development of an easy and divergent strategy for constructing benzofuran frameworks is indispensable for a rapid screening of biologically active molecules or organic functional materials.

In 2010, we reported direct transformation of phenols into 3-trifluoromethylbenzofurans[10] with CF_3-substituted ketene dithioacetal monoxide CF_3KDM[16] through an extended Pummerer reaction[10,16–18] (Scheme 3, Top). The reaction accomplished metal-free, rapid, and regioselective annulation of simple phenols. We proposed that trifluoromethanesulfonic anhydride (Tf_2O) strongly activates CF_3KDM to give reactive monocationic intermediate **A**, which reacts with phenols to furnish 3-trifluoromethyl-2-methylsulfanylbenzo[*b*]furan **B**. Product **B** is transformable by means of cross-coupling with arylzinc reagents to provide 3-trifluoromethyl-2-arylbenzofuran **C**. Two major drawbacks of the reaction are that the scope of ketene dithioacetal monoxide (KDM) is limited to CF_3KDM and that cryogenic conditions are required. We therefore envisioned that the development of a new Pummerer annulation, which proceeds with a wide range of KDMs at ambient temperature, would provide a practical and diversity-oriented route to multisubstituted benzofurans.

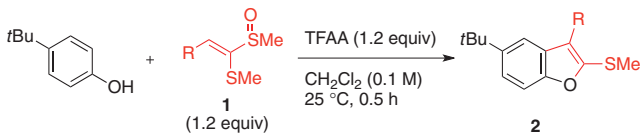
Very recently, we communicated such general annulation to furnish multisubstituted benzofurans **E** (Scheme 3, Bottom).[11] Trifluoroacetic anhydride (TFAA) acts successfully as the milder activator of KDMs to form monocationic intermediate **D** having a sufficiently long lifetime, which is thus able to react with phenol to furnish benzofuran **E**.[19] The reactions are so practical that neither distilled solvents, inert atmospheres, nor low temperatures are required. Moreover, the annulation reactions complete within 1 h at ambient temperature. The following cross-coupling of **E** with arylmagnesium reagents under nickel catalysis or with arylzinc reagents under palladium catalysis can replace the methylsulfanyl group with a variety of aryl groups, thereby increasing the diversity of multisubstituted benzofurans. Our approach to multisubstituted benzofurans is powerful enough to synthesize highly fluorescent molecules and natural products. We report herein the details of our benzofuran synthesis, with an emphasis on the scope and reaction mechanism of the improved Pummerer annulation.

Results and Discussion

Synthesis of Starting Materials. Various KDMs can be obtained from commercially available FAMSO[20] in one or two steps.[21] Electronically neutral and donating aromatic aldehydes were directly converted to aryl-substituted KDMs in high yields via the Knoevenagel condensation (Scheme 4, Method A).[21c,21d] Since Method A was not applicable to aliphatic aldehydes, electron-deficient aromatic aldehydes, and aldehydes having a labile silyl protecting group, an alternative two-step method was invented[21a,21b] to provide an access to a range of KDMs on gram scales (Method B). Usually, *E* isomers were obtained as major products in Method B and these *E*/*Z* stereoisomers were separable on silica gel. The reactivity of each isomer toward the Pummerer annulation is described in Table 4 (vide infra).

Scope and Limitations. In contrast to the previous Tf_2O-mediated Pummerer annulation where only CF_3KDM could be used,[10] the TFAA-mediated reactions of 4-*tert*-butylphenol with variously substituted KDMs **1** proceeded to completion in 30 min at 25 °C in most cases (Table 1). Unsubstituted KDM **1b** was smoothly transformed to 3-unsubstituted benzofuran **2b** in high yield (Entry 2). In addition to phenyl KDM **1a**, methyl KDM **1c** and rather bulky alkyl KDM **1d** also participated to give 3-substituted benzofurans in good yields (Entries 1, 3, and 4). The reaction with 4-trifluoromethylphenyl-substituted KDM **1e** afforded **2e** in high yield while the yield of **2f** bearing an electron-donating substituent was moderate (Entries 5 and 6). Other aryl groups such as 4-halophenyl, bulky 1-naphthyl, and heteroaromatic thienyl provided **2g**, **2h**, and **2i** in 96%, 78%, and 85% yields, respectively (Entries 7–9). KDMs having a perfluorinated substituent also reacted to yield the corresponding products **2j** and **2k** (Entries 10 and 11).[22]

Table 1. Scope of KDMs

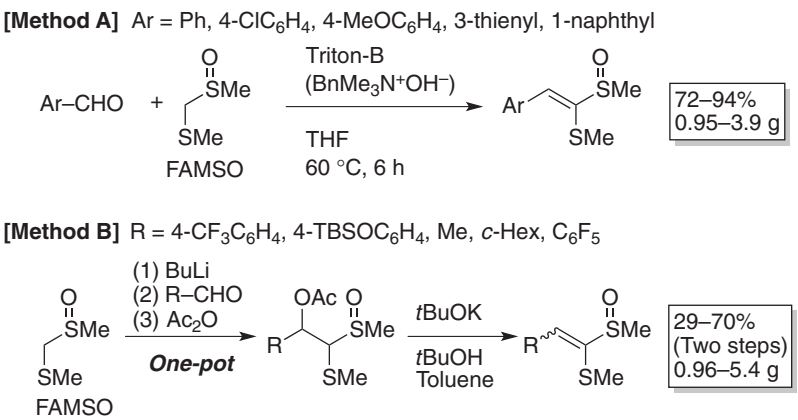


Entry	**1**: R	**2**	Yield/%
1	**1a**: Ph	**2a**	87
2[a)]	**1b**: H	**2b**	67
3	**1c**: Me	**2c**	78
4	**1d**: Cyclohexyl	**2d**	63
5	**1e**: 4-$CF_3C_6H_4$	**2e**	95
6	**1f**: 4-$MeOC_6H_4$	**2f**	51
7	**1g**: 4-ClC_6H_4	**2g**	96
8	**1h**: 1-Naphthyl	**2h**	78
9	**1i**: 3-Thienyl	**2i**	85
10[a),b)]	**1j**: C_6F_5	**2j**	54
11[a),b)]	CF_3KDM: CF_3[c)]	**2k**	61

a) **1** (1 equiv), TFAA (2 equiv), 4-*tert*-butylphenol (2 equiv). b) 40 °C, 1.5 h. c) The *E*/*Z* ratio of CF_3KDM was 4/1.

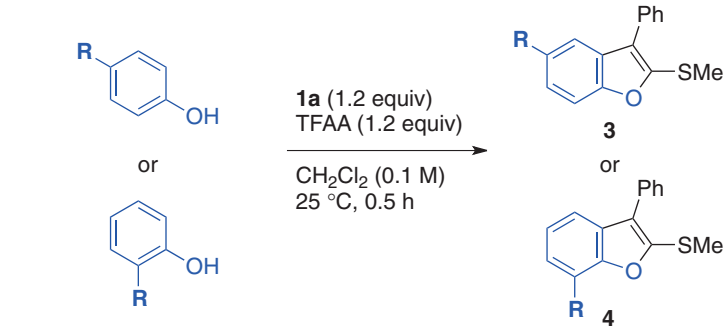
We then studied the scope of *para*- and *ortho*-substituted phenols (Table 2). The reaction of 4-ethoxycarbonylphenol provided **3a** in 77% yield with its ester group intact and no acid-catalyzed transesterification with the unavoidably resulting methanethiol by-product was observed. Thanks to the transition-metal-free conditions, halogenated phenols such as 4-iodophenol and 4-bromophenol were also transformed efficiently to the corresponding benzofurans **3b** and **3c**. The pinacolatoboryl group in **3d** was also tolerable albeit under the acidic conditions. Naturally, further transformations through Suzuki–Miyaura-coupling of **3d** would be viable. Electron-withdrawing trifluoromethyl or electron-donating methoxy groups did not suppress the reaction to yield **3e** and **3f**. Unfortunately, an acetyl or formyl group was not compatible under the original conditions since the resulting trifluoroacetic acid catalyzed dithioacetalization of the carbonyl moieties with methanethiol to yield **3g′** and **3h′**.[23] Further optimization revealed that an addition of K_2CO_3 suppressed this dithioacetalization to afford **3g** and **3h** in good yields. A bulky triisopropylsiloxy group remained unreacted to give **3i** in high yield. Bulky substituents at the *ortho* position did not hamper the reactions and **4a**–**4c** were obtained in good to high yields.

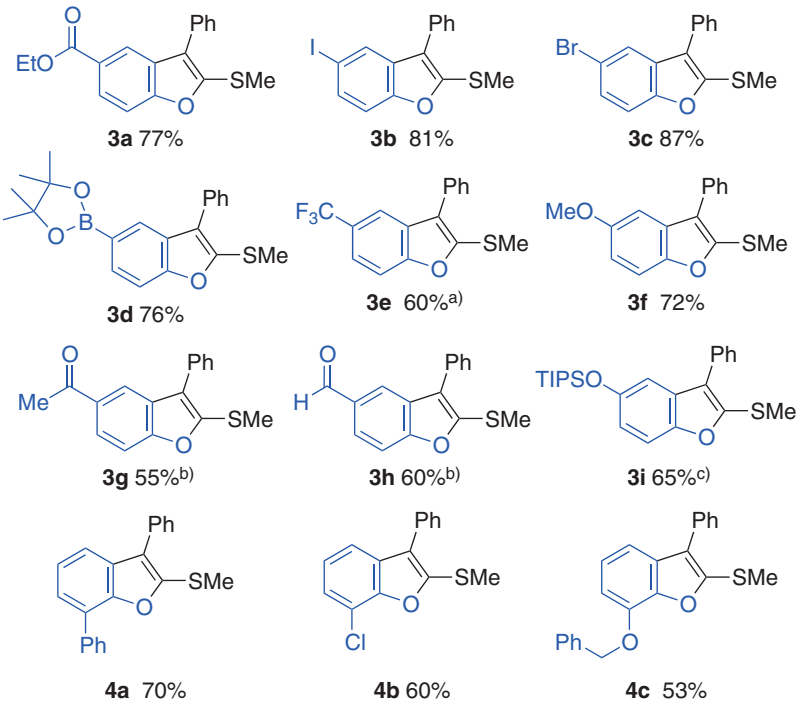
The regioselectivity of the reactions of *meta*-substituted phenols was studied (Table 3). The reaction of 3-*tert*-butylphenol resulted in exclusive formation of **5a** in 80% yield due to the bulky *t*Bu substituent (Entry 1). The reaction of 3-methoxyphenol proceeded exclusively at the 6 position (Entry 2). Unfortunately, the reactions of 3-trifluoromethyl- and iodophenol did not show regioselectivity to yield mixtures of **5** and **5′** (Entries 3 and 4). We proposed that the reaction



Scheme 4. Practical and rapid syntheses of KDMs (Ref. 21).

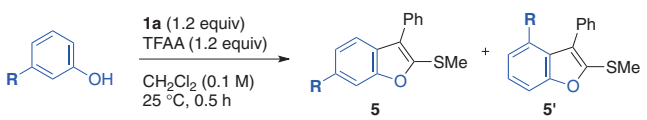
Table 2. Scope of *para*- and *ortho*-Substituted Phenols





a) **1a** (1 equiv), TFAA (1.2 equiv), 4-trifluoromethylphenol (1.2 equiv). b) **1a** (1 equiv), TFAA (2 equiv), phenol (2 equiv), K_2CO_3 (2 equiv), 1 h. c) **1a** (1 equiv), TFAA (2 equiv), phenol (2 equiv).

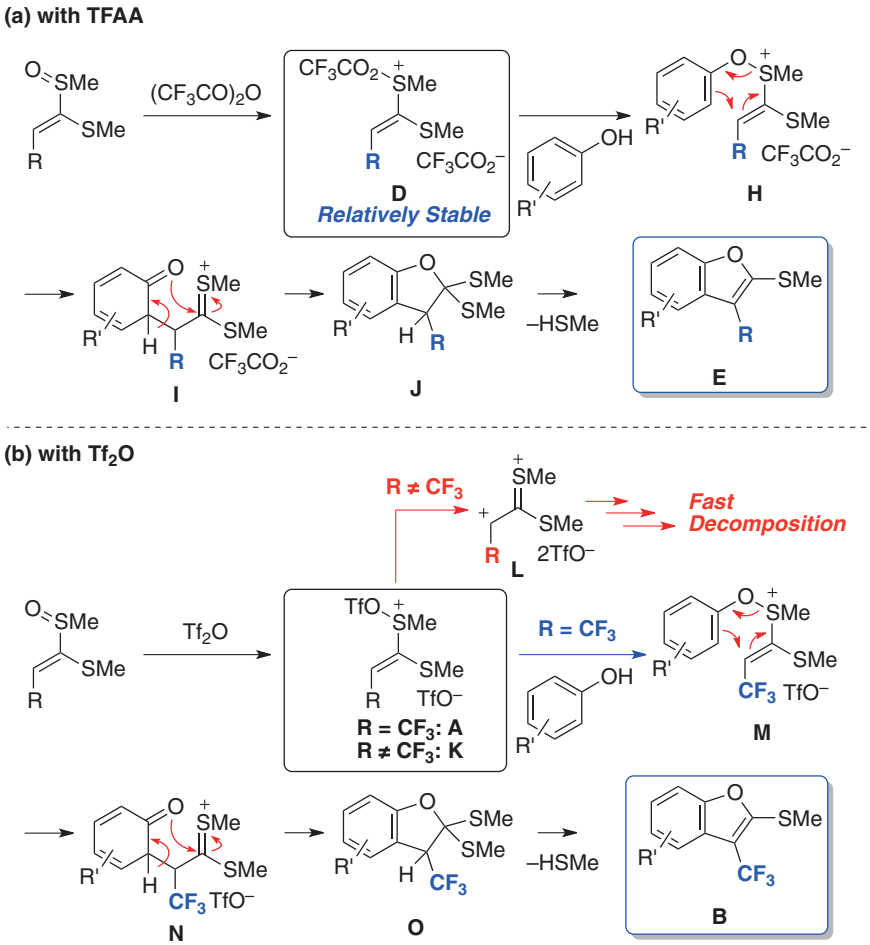
Table 3. Regioselectivity of *meta*-Substituted Phenols



Entry	R	5	5:5′	Yield/%
1	*t*Bu	**5a**	>99:1	80
2	MeO	**5b**	>99:1	63
3	CF_3	**5c**	65:35	53
4	I	**5d**	59:41	87

would take place through [3,3]-sigmatropic rearrangement, wherein the more electron-rich *ortho* position predominantly attacks the electron-deficient vinylic carbon of **H** (vide infra, Scheme 5). On the basis of our proposal, these regioselectivities observed can be roughly rationalized by the Kohn–Sham HOMO analysis of these *meta*-substituted phenols (Figure 1).[24] Because of the 3-methoxy group, the HOMO of 3-methoxyphenol has a node across the 2 and 5 positions, which indicates no reactivity at the 2 position of 3-methoxyphenol. In contrast, judging from the HOMOs of 3-*t*Bu, CF_3, and I-substituted phenols, the 2 and 6 positions should have similar reactivity from an electronic viewpoint although the 2 position of 3-*tert*-butylphenol is likely to be sterically shielded.

The reactions were applicable to various phenol derivatives (Table 4). The reactions of 2-naphthol proceeded to give **6a** and **6b** with perfect regioselectivity. Although the reactivity of the more sterically congested (*Z*)-**1e** was lower than that of (*E*)-**1e**, **6a** was obtained in a good yield of 51%. Other 2-naphthols having a triisopropylsiloxy substituent reacted with **1a** to provide **6c** and **6d** without loss of the TIPS group. Vanillin was converted to the corresponding benzofuran **6e** in 45% yield, along with unaromatized **6e′** in 22% yield, in the presence of K_2CO_3. Phenolphthalein, which is mostly insoluble in dichloromethane, reacted in CH_2Cl_2/MeCN (5:1) co-solvent to



Scheme 5. Proposed mechanism of Pummerer annulation with a) TFAA and b) Tf_2O.

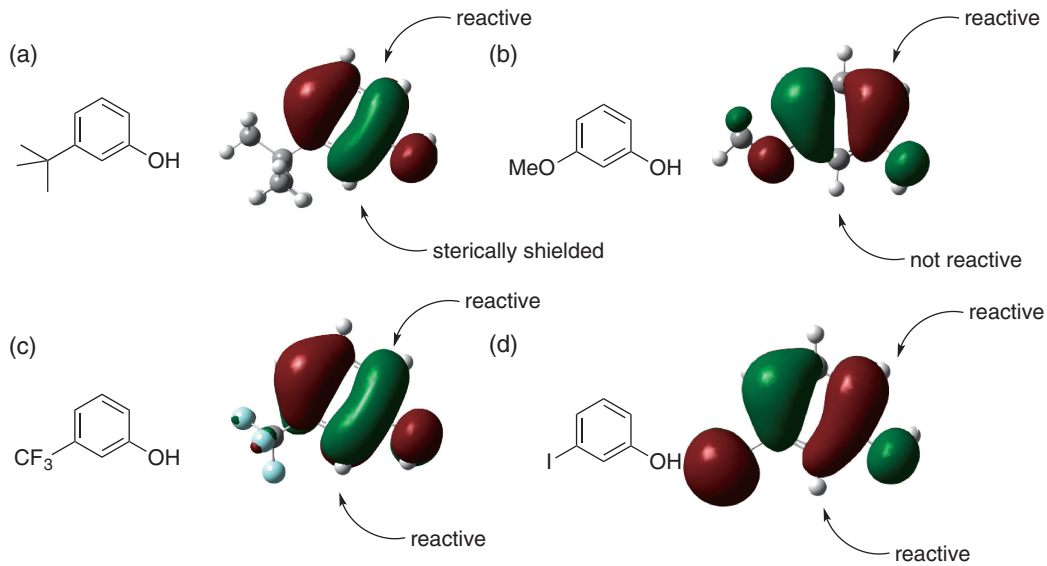
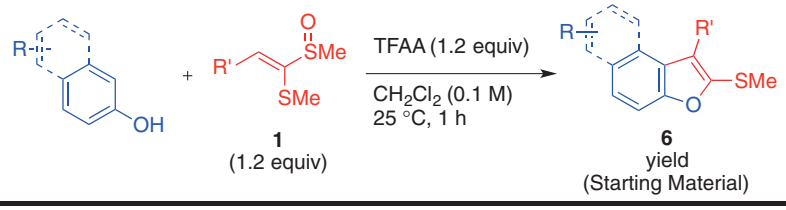
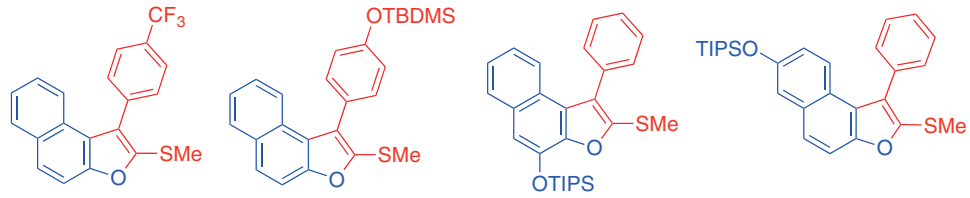


Figure 1. Kohn–Sham HOMOs of *meta*-substituted phenols: (a) 3-*tert*-butylphenol; (b) 3-methoxyphenol; (c) 3-trifluoromethylphenol; (d) 3-iodophenol.

afford **6f** in 54% yield. Gratifyingly, the reaction of 1,3-dihydroxybenzene (resorcinol) afforded the corresponding benzodifuran **6g** regioselectively in one shot. The positions of two hydroxy groups are important: 2-*tert*-butylhydroquinone, an arene having two hydroxy groups at the 1,4-positions, failed to react. Alternatively, 4-siloxyphenol engaged in the Pummerer

Table 4. Reactions of Various Hydroxyaromatics



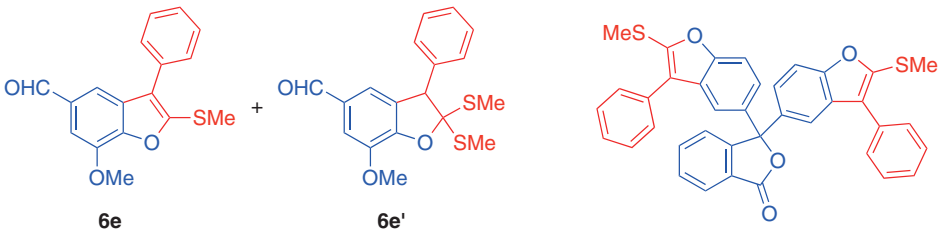


6a 92%
(51%: reaction with (*Z*)-**1e**)
(2-Naphthol)

6b 74%[a),b)]
(2-Naphthol)

6c 62%[c)]
(3-TIPSO-2-naphthol)

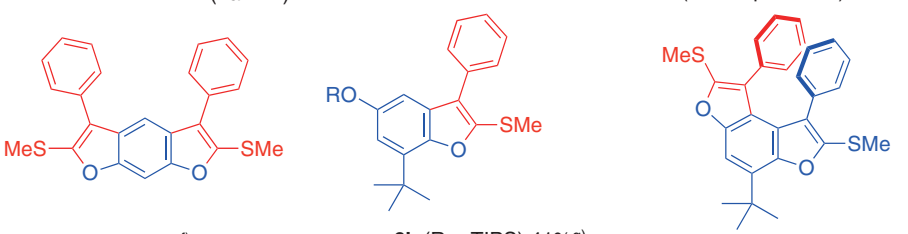
6d 83%[a)]
(6-TIPSO-2-naphthol)



6e **6e'**

67%[d)] (**6e**:45%, **6e'**:22%)
(Vanillin)

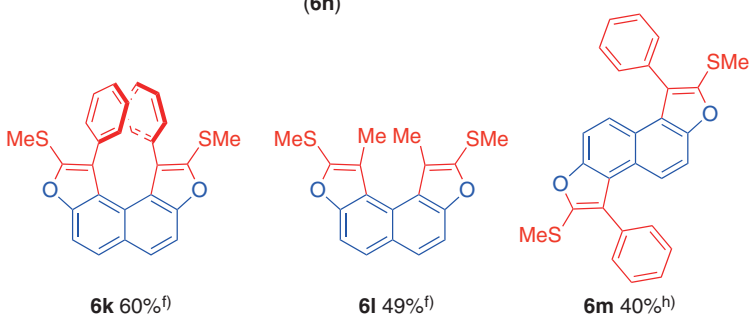
6f 54%[e)]
(Phenolphthalein)



6g 49%[f)]
(Resolcinol)

TBAF → **6h** (R = TIPS) 41%[g)]
(2-*t*Bu-4-TIPSO-phenol)
→ **6i** (R = H) 96%
(**6h**)

6j 66%[a)] (**6i**)
6j 0% (2-*t*Bu-hydroquinone)



6k 60%[f)]
(2,7-naphthalenediol)

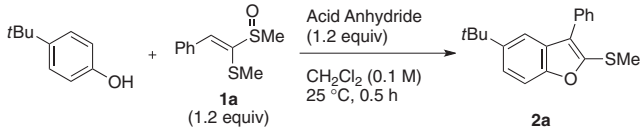
6l 49%[f)]
(2,7-naphthalenediol)

6m 40%[h)]
(2,6-naphthalenediol)

a) Alcohol (1 equiv), **1** (2 equiv), TFAA (2 equiv). b) *E*/*Z* ratio of **1** was 4/1. c) Alcohol (2 equiv), **1** (1 equiv) TFAA (2 equiv). d) Vanillin (2 equiv), **1a** (1 equiv), TFAA (2 equiv), K_2CO_3 (2 equiv). e) Phenolphthalein (1 equiv), **1a** (3 equiv), TFAA (3 equiv), CH_2Cl_2/MeCN (5/1). f) Diol (1 equiv), **1** (3 equiv), TFAA (3 equiv). g) **1a** (2.5 equiv), TFAA (3 equiv). h) Diol (2 equiv), **1a** (1 equiv), TFAA (1.5 equiv).

annulation to afford **6h**, which was then deprotected with TBAF to give 5-hydroxybenzofuran **6i**. The second Pummerer annulation was then performed to give benzodifuran **6j**. The reactions of 2,7- or 2,6-naphthalenediol gave the corresponding naphthodifurans **6k**–**6m** directly. The structures of **6k** and **6m** were unambiguously determined by X-ray crystallographic analyses.[11] Finally, we performed a gram-scale synthesis of **6k** to demonstrate the robustness of the Pummerer annulation

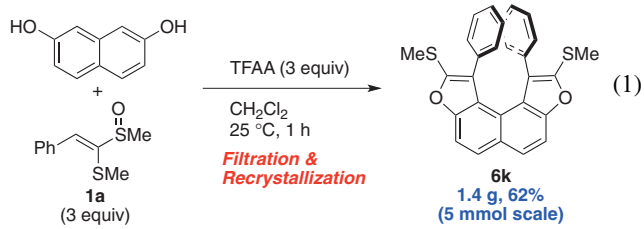
Table 5. Comparison of Acid Anhydride



Entry	Acid anhydride	pK_a[a)]	Yield[b)]/% (**2a**)	Recovery[b)]/% (**1a**)
1	Tf_2O	−14	25	8
2	Ts_2O	−2.8	12	22
3	Ms_2O	−2.6	5	9
4	**TFAA [$(CF_3CO)_2O$]**	**−0.25**	**87**[c)]	**0**
5	Ac_2O	4.8	0	>99
6	TFA [CF_3CO_2H]	−0.25	0	92

a) pK_a Value of the corresponding acid in water.[25] b) Determined by ^{1}H NMR. c) Isolated yield.

(eq 1). Treatment of 2,6-naphthalenediol (5 mmol) with **1a** afforded 1.4 g of **6k** after filtration over a pad of silica gel and recrystallization from CH_2Cl_2/MeOH.

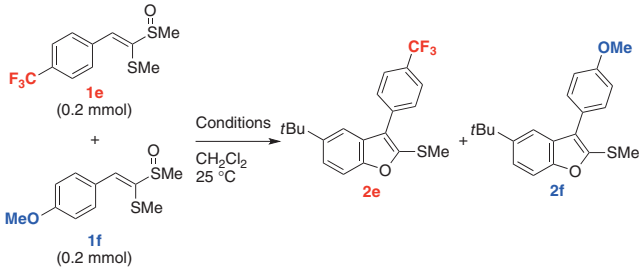


(1)

Comparison of Activators. We compared the reactivity of acid anhydrides as activators in the reaction of 4-*tert*-butylphenol with **1a** (Table 5). Employment of Tf_2O afforded **2a** in 25% yield and **1a** was barely recovered (Entry 1). We assumed that the monocationic intermediate that is generated through activation of **1a** with Tf_2O is too unstable and has insufficient lifetime to react with 4-*tert*-butylphenol due to the strong Lewis acidity of Tf_2O (pK_a of TfOH is −14 in water). We envisaged that the use of a less Lewis acidic activator would give a more stable monocationic intermediate that has enough lifetime to react with phenol before it decomposes. While the reaction in the presence of less acidic sulfonic anhydrides such as Ts_2O or Ms_2O (pK_a of TsOH = −2.8, MsOH = −2.6) gave **2a** in only low yields (Entries 2 and 3), employment of TFAA (pK_a of CF_3CO_2H = −0.25) furnished **2a** in 87% yield (Entry 4). Since acetic anhydride (pK_a of AcOH = 4.8) was not acidic enough to activate KDM, **1a** was recovered quantitatively (Entry 5). Interestingly, the corresponding Brønsted acid CF_3CO_2H was ineffective for activation of **1a** to promote the reaction, and 92% of **1a** was recovered (Entry 6). The careful choice of an activator is critical in terms of the reactivity and stability of monocationic intermediates.

Mechanistic Studies. A proposed mechanism of the Pummerer annulation with TFAA is shown in Scheme 5a. KDM is activated with TFAA to give relatively stable monocationic intermediate **D**. Intermediate **D** reacts with phenol to provide **H** before unproductive decomposition of **D** proceeds. [3,3]-Sigmatropic rearrangement of **H** provides **I** that readily cyclizes into **J**. Elimination of MeSH from **J** smoothly proceeds to afford

Table 6. Comparison of the Reactivity

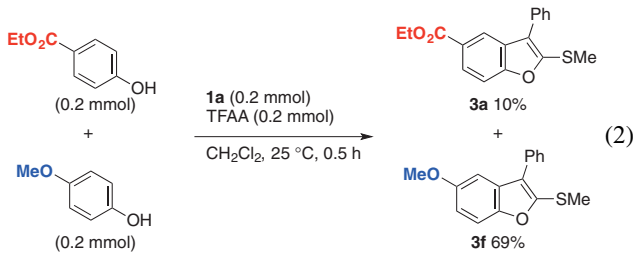


Entry	Conditions	Yield/% **2e**	Yield/% **2f**
1	4-*t*BuC_6H_4OH (0.2 mmol), then TFAA (**0.2 mmol**), 0.5 h	0	44
2	4-*t*BuC_6H_4OH (0.2 mmol), then TFAA (**0.48 mmol**), 0.5 h	41	36
3	TFAA (**0.48 mmol**), 0.25 h then 4-*t*BuC_6H_4OH (0.2 mmol), 0.5 h	78	trace

the corresponding benzofuran **E**. This mechanism is similar to that of the reaction with Tf_2O (Scheme 5b).[10] The key of the Pummerer annulation is the stability of monocationic intermediate **D**, **A**, or **K**. When the reactions of KDMs bearing *no* CF_3 group are performed in the presence of more Lewis acidic Tf_2O, monocationic intermediate **K** would readily decompose probably via dicationic intermediate **L**. A strongly electron-withdrawing CF_3 group would suppress the formation of a dicationic intermediate to circumvent these decomposition pathways.[16d]

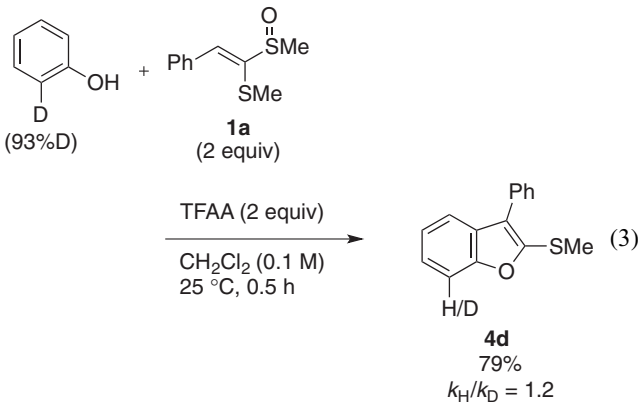
We compared the reactivities of KDMs having electronically different aryl groups (4-$CF_3C_6H_4$ and 4-$MeOC_6H_4$) (Table 6). Treatment of a 1:1 mixture of **1e** and **1f** (0.2 mmol each) with 4-*tert*-butylphenol (0.2 mmol) in the presence of *1 equiv* of TFAA (0.2 mmol) afforded a 44% yield of **2f** without formation of **2e**. Obviously, electron-rich **1f** was selectively activated by TFAA because of the higher nucleophilicity of its sulfoxide oxygen. When the reaction was performed in the presence of 2.4 equiv of TFAA (0.48 mmol), both **2e** and **2f** were obtained in 41% and 36% yield, respectively. We are interested in the stability of activated **1e** and **1f** and the following experiment was performed to briefly determine the lifetimes of these activated KDMs. After treatment of **1e** and **1f** with TFAA (0.48 mmol) for 0.25 h, 4-*tert*-butylphenol (0.2 mmol) was then added to the mixture. As a result, benzofuran **2e** was obtained exclusively in 78% yield and only a trace of **2f** was obtained. This contrastive result indicates that most of the activated **1f** decomposed within 0.25 h and that more than 78% of the activated **1e** survived for 0.25 h. We thus conclude that activation of electron-rich KDM occurs faster than that of electron-poor KDM but that activated monocationic intermediate derived from electron-rich KDM is less stable than that derived from electron-poor KDM.

The reactivity of phenol derivatives was studied. A mixture of 4-ethoxycarbonylphenol (0.2 mmol) and 4-methoxyphenol (0.2 mmol) was treated with **1a** (0.2 mmol) in the presence of TFAA (0.2 mmol) to afford **3f** as a major product (eq 2). The more electron-rich and thus more nucleophilic phenol showed higher reactivity toward the activated KDM.



(2)

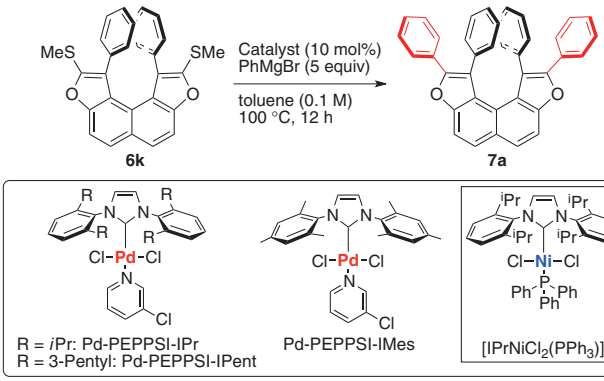
A deuterium labeling experiment showed a very small kinetic isotope effect of 1.2 (eq 3), indicating that C–H bond cleavage is not involved in the rate-determining step.[18n]



(3)

Ni–NHC-Catalyzed Cross-Coupling Reactions of Bulky 3-Aryl-2-methylsulfanylbenzofurans with Arylmagnesium Reagents. We reported efficient cross-coupling reactions of 3-trifluoromethyl-2-methylsulfanylbenzofuran[10b] with arylzinc reagents by using Organ's Pd–PEPPSI–IPr catalyst.[26] In the report, we found that a newly introduced 2-aryl substituent remarkably affects the photophysical properties of the benzofurans. This fact drove us to develop more efficient reactions to transform the methylsulfanyl group at the crowded 2 position of benzofurans. Despite its low chemoselectivity, cross-coupling reaction with organomagnesium reagents still remains as a highly efficient transformation[27] and has been widely applied for the syntheses of natural products[28] and organic materials.[29] In this full paper, we disclose the details of modified reaction conditions for cross-coupling reactions of bulky 3-aryl-2-methylsulfanylbenzofurans with organomagnesium reagents.[30–32] The optimization of the reaction conditions is summarized in Table 7. The reactions of bulky substrate **6k** were sluggish with a nickel catalyst having PPh_3[30b–30e] or dppe[30d–30f] while they are known as efficient ligands for the reactions of thioethers with Grignard reagents (Entries 1 and 2). [$PdCl_2$(dppf)] (dppf: 1,1′-bis(diphenylphosphino)ferrocene) was also less effective, which was efficient for our previously reported transformation of 3-trifluoromethyl-2-methylsulfanylbenzofurans[10b] (Entry 3). Pd–PEPPSI–IPr showed higher catalytic activity to afford **7a** in 54% yield (Entry 4). Less bulky Pd–PEPPSI–IMes or more sterically congested Pd–PEPPSI–IPent yielded complex mixtures (Entries 5 and 6). Finally, a nickel catalyst that has an IPr ligand[33] gave the highest yield of 68% (Entry 7). A large-scale reaction was performed on a 4-mmol scale to give 1.5 g of **7a** in 62% yield, which was easily purified through successive filtration and recrystallization (Entry 8).

Table 7. Optimization of Cross-Coupling Reaction with Phenylmagnesium Bromide



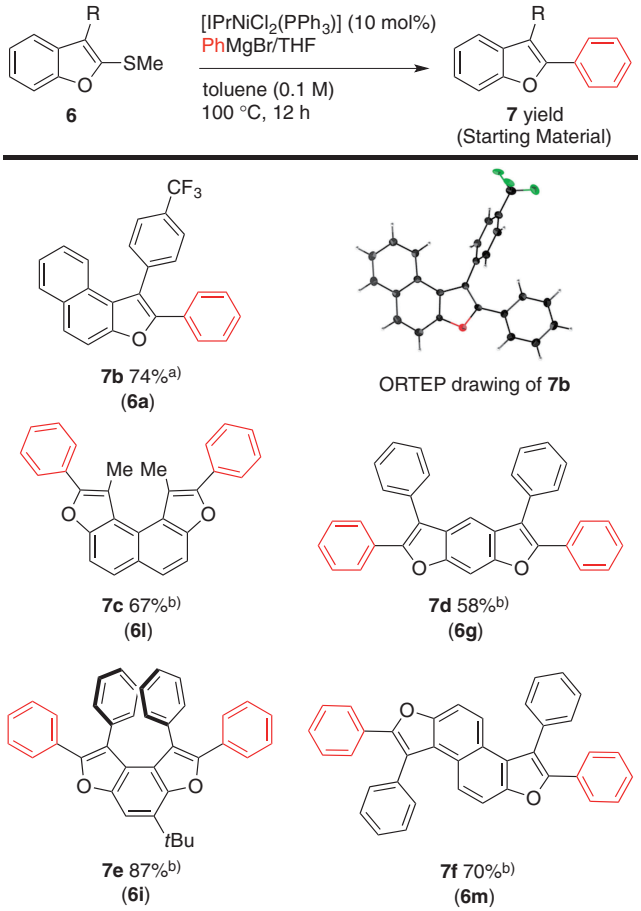
Entry	Catalyst	Isolated yield/%
1	[$NiCl_2(PPh_3)_2$]	(22)[a]
2	[$NiCl_2$(dppe)]	(14)[a]
3	[$PdCl_2$(dppf)]	(14)[a]
4	Pd–PEPPSI–IPr	54
5	Pd–PEPPSI–IMes	cm[b]
6	Pd–PEPPSI–IPent	cm[b]
7	[$IPrNiCl_2(PPh_3)$]	68
8[c]	[$IPrNiCl_2(PPh_3)$]	62 (1.5 g)

a) Determined by ^{1}H NMR. b) Complex mixture. c) 4-mmol scale.

The new catalytic conditions were effective for the transformations of other Pummerer annulation products (Table 8). Phenylation of **6a** gave **7b** in 74% yield, the structure of which was confirmed by X-ray crystallographic analysis. Employing the highly active catalytic system, diphenylation also proceeded smoothly to afford densely phenylated π-extended difurans **7c**–**7f**. Notably, the products were isolated by recrystallization without silica gel column chromatography.

Rational synthesis of multisubstituted difurans was accomplished through our iterative Pummerer annulation/cross-coupling strategy over 5 steps from a siloxyphenol (Table 9).[34] Siloxy-substituted 2-methylsulfanylfuran **3** or **6**, which is prepared through Pummerer annulation of the corresponding siloxyphenol, is converted through nickel-catalyzed cross-coupling with an organomagnesium reagent. The siloxy group on **8** is then deprotected with TBAF to give **9**. Subsequent Pummerer annulation takes place to construct the second furan ring with KDM **1**. Cross-coupling of the resulting difuran **10** with an organometallic reagent furnishes tetrasubstituted difuran **11**. For example, we firstly converted 2-methylsulfanylnaphthofuran **6k** with 4-biphenylylmagnesium bromide in the presence of the nickel catalyst to yield 6-siloxy-2,3-diarylnaphthofuran **8a**. Subsequent deprotection of the siloxy group with TBAF gave **9a** in 85% yield over 2 steps. The regioselective Pummerer annulation of **9a** with naphthyl-substituted KDM **1h** followed by the second nickel-catalyzed reaction with 2-naphthylmagnesium bromide provided **11a** in 51% overall yield. The tetraarylated structure of **11a** was unambiguously confirmed by X-ray crystallographic analysis.[11] Another multisubstituted naphthodifuran **11b** having an ester moiety was easily synthesized from **6k** in 44% overall yield

Table 8. Further Transformations



a) PhMgBr (2.5 equiv). b) PhMgBr (5 equiv).

employing a 4-ethoxycarbonylphenylzinc reagent under our coupling conditions.[10b,36] Triphenylene- and phenanthrene-type difurans **11c**[37] and **11d**[38] were also systematically prepared from **6i** and **3i**, respectively. The strategy provides a simple and easy access to a variety of multisubstituted difurans via a direct and intuitive route.

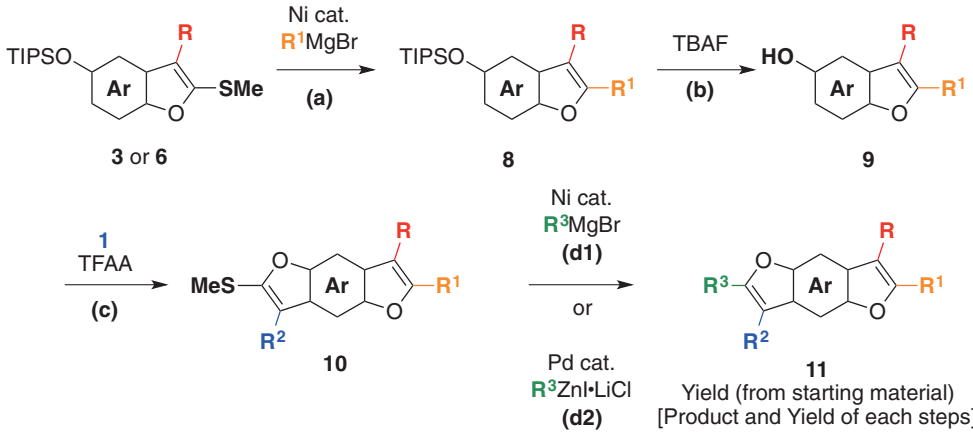
Photophysical Properties of Benzofurans. Table 10 represents the photophysical properties of furan derivatives **7** and **11**, including their absorption and emission properties and fluorescence quantum yields. Generally, substituted furans showed bright blue fluorescence with high quantum yields. Benzodifurans **7d**, **7e** and naphthofurans **7f**, **11a** having tetraaryl groups showed mirror images of their absorption bands in the fluorescence spectra with small Stokes shifts (See SI). In contrast, compounds **11b**–**11d** having an electron-withdrawing ethoxycarbonyl moiety on an aryl group showed small overlap between their absorption and emission bands. For comparison, the UV–vis absorption and emission spectra of compounds **7f**, **11a**, and **11b** having the same naphtho[2,1-*b*:6,5-*b*′]difuran core are shown in Figure 2. Since an electron-withdrawing ethoxycarbonyl group is likely to have some effect on the significantly red-shifted and broad emission spectrum of **11b**, further theoretical investigations and evaluations of the substituent effect are ongoing in our laboratory. Compared with naphtho*mono*furan **7a** ($\Phi_F = 0.31$), difurans **7b**–**7f** and **11a**–**11e** generally showed higher quantum yields ($\Phi_F = 0.45$–0.93) with various substituents, which highlights the usefulness of our iterative annulation/cross-coupling strategy for screening of naphthodifurans toward new organic materials.

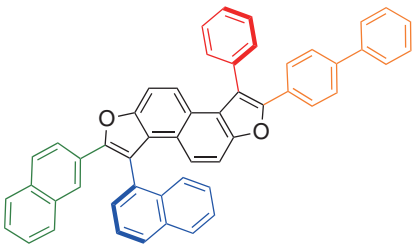
Syntheses of Eupomatenoids. Eupomatenoids[39] were first isolated from *Eupomatia laurina* in 1972,[39a] and were shown to have interesting biological activities such as anticancer[40a] or anti-*Trypanosoma cruzi* activity.[40b] There are several reports on the synthesis of Eupomatenoids.[41] In recent reports by Bach et al.,[41b,41c] the linear syntheses of Eupomatenoids from 2,3,5-tribromobenzo[*b*]furan (**13**), the key common intermediate was derived from commercially available 5-bromobenzo[*b*]furan (**12**) in three steps (Scheme 6). They elegantly installed the three substituents, aryl, propenyl, and then methyl groups, to tribromobenzofuran **13** in four or five steps. However, the aryl group at the 2 position must be installed in the first step of the synthesis. Since the Eupomatenoid family has variety on the aryl group, late-stage arylation would be highly desirable for diversity-oriented synthesis of Eupomatenoids.

As a proof-of-principle, we applied the Pummerer annulation/coupling strategy toward diversity-oriented synthesis of Eupomatenoids. In contrast to Bach's linear synthesis, our convergent strategy includes the concise synthesis of **14** as the key common intermediate (Scheme 7): the reaction of 4-[(*E*)-1-propenyl]phenol, which is readily available from 4-hydroxybenzaldehyde, with methyl-substituted KDM **2d** proceeded smoothly in the presence of TFAA to give **14** in 79% yield. Notably, the reaction was clean enough to perform further transformation without silica gel column chromatography. Nickel-catalyzed arylation of **14** with 3,4-methylenedioxyphenylmagnesium bromide furnished Eupomatenoid-3 in 79% yield. Since methoxy moieties could not survive under the nickel-catalyzed conditions,[33e] attempts to synthesize TBS-Eupomatenoid-5 with an arylmagnesium reagent resulted in forming a complex mixture containing a trace amount of the expected product. We therefore achieved the synthesis of Eupomatenoid-5 by means of the palladium/arylzinc combination of milder reactivity.[10b] Pd-PEPPSI-IPr-catalyzed arylation of **14** with 3-methoxy-4-siloxyphenylzinc reagent provided TBS-Eupomatenoid-5 in 57% yield. Quantitative deprotection with TBAF completed the synthesis of Eupomatenoid-5.

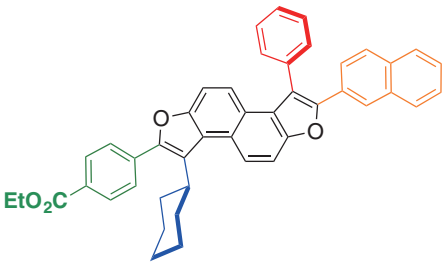
Summary. We developed the Pummerer annulation/coupling strategy toward facile and diversity-oriented syntheses of multisubstituted benzofurans. The transition-metal-free annulation directly constructs benzofuran frameworks in one shot from simple phenols and KDMs with the aid of TFAA as a mild activator. Thanks to the conditions that are orthogonal to transition-metal-catalyzed transformations, wide ranges of phenols and KDMs having reactive functionalities such as boryl and halogens are compatible. Detailed mechanistic study revealed the reactivities of KDMs toward acid anhydrides and of phenols with activated KDMs, supporting our plausible mechanism. Improved nickel-catalyzed cross-coupling reactions with readily available and cheap arylmagnesium reagents[42] were broadly applicable to the bulky benzofuranyl thioethers. While there is a limitation in functional group tolerability,[43] this method would be a good alternative to the reported palladium-catalyzed cross-coupling with arylzinc reagents that needed relatively burdensome procedures for their

Table 9. Rational Synthesis of Difurans[a)]

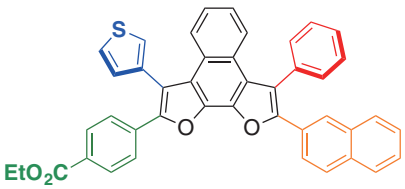




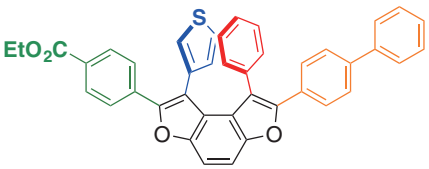
11a: 51% (from **6k**)
[**9a**:85%(a,b),
10a:75%(c), **11a**:80%(d1)]



11b: 44% (from **6k**)
[**10b**:46%(a–c[b)]), **11b**:95%(d2)]



11c: 19% (from **6i**)
[**8c**:71%(a), **10c**:29%(b,c[c)]), **11c**:90%(d2)]



11d: 42% (from **3i**)
[**8d**:89%(a), **9d**:83%(b),
10d:84%(c), **11d**:67%(d2)]

a) Reaction conditions: (a) [$IPrNiCl_2(PPh_3)$] (10 mol %), R^1MgBr/THF (1 M, 2.5 equiv), toluene (0.1 M), 100 °C, 12 h; (b) TBAF/THF (1 M, 3 equiv), THF (0.1 M), 25 °C, 3 h; (c) **1** (2 equiv), TFAA (2 equiv), CH_2Cl_2, 25 °C, 1 h; (d1) [$IPrNiCl_2(PPh_3)$] (10 mol %), R^3MgBr/THF (1 M, 2.5 equiv), toluene (0.1 M), 100 °C, 12 h; (d2) Pd–PEPPSI–IPr (10 mol %), R^3ZnI•LiCl/THF[35] (1 M, 2.5 equiv), toluene/MeCN (1:1, 0.05 M), 60 °C, 12 h. b) *E*/*Z* ratio of **1d** used in this reaction was 3:2. c) CH_2Cl_2/MeCN (5:1, 0.08 M) was used as a solvent.

preparation.[38] This straightforward Pummerer annulation/cross-coupling strategy enabled rational syntheses of highly fluorescent benzofuran molecules and Eupomatenoid natural products having furan cores. The annulation/coupling sequence will therefore make an impact not only for pharmaceutical chemists working on combinatorial lead-structure identification but also for chemists who need libraries for development of functional organic materials.

Experimental

Instrumentation and Chemicals. ^{1}H NMR (600 MHz), ^{19}F NMR (565 MHz), and ^{13}C NMR (151 MHz) spectra were taken on a JEOL ECA-600 spectrometer and were recorded in $CDCl_3$. Chemical shifts (δ) are in parts per million relative to chloroform at 7.26 ppm for ^{1}H and relative to $CDCl_3$ at 77.2 ppm for ^{13}C. Hexafluorobenzene was used as the external reference for ^{19}F ($\delta = -162.9$ ppm). IR spectra were determined on a JASCO IR-810 spectrometer. Mass spectra were determined on a Bruker micrOTOF II spectrometer. X-ray data were taken at −180 °C with a Rigaku RAXIS-RAPID diffractometer by using graphite monochromated Cu Kα radiation ($\lambda = 1.54187$ Å). The structures were solved by direct method SIR-97 and refined by SHELXL-97 program.[44] Spectroscopic grade solvents were used for all spectroscopic studies without further purification. UV–visible absorption spectra were recorded on a Shimadzu UV-2550 spectrometer. Fluorescence spectra were recorded on a Shimadzu RF-5300PC spectrometer. Absolute fluorescence quantum yields were measured by a photon-counting method by using an integration sphere on a Hamamatsu Photonics C9920-02 spectrometer.

Silica gel (Wakogel 300 mesh) was used for column chromatography. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Phenols were purchased from Wako Pure Chemical Industries, Ltd. and TCI Co., Ltd. and used as received. 2-Deuteriophenol was prepared according to the literature[45] and deuterium content was determined by APCI-MS and ^{1}H NMR. (*E*)-4-(1-Propenyl)phenol was prepared according to the literature.[46] FAMSO and bis(methylsulfanyl)methane were purchased from Wako Pure Chemical Industries, Ltd. Triton-B and [IPrNiCl$_2$(PPh$_3$)] was purchased from TCI Co., Ltd. Pd–PEPPSI–IPr was purchased from Aldrich. Toluene was distilled over CaH$_2$ and stored under nitrogen atmosphere. Anhydrous THF was purchased from Wako Pure Chemical Industries, Ltd. and stored under nitrogen atmosphere. CH$_2$Cl$_2$ was purchased from Wako Pure Chemical Industries, Ltd. and used as is. Reactions of KDMs with phenols were carried out in open air. Transition metal-catalyzed reactions were carried out under

Table 10. Optical Properties of **7a–7f** and **11a–11e** in CH$_2$Cl$_2$

7 or **11**	λ_{max}/nm (ε/10^4 M^{-1} cm^{-1})	λ_{em}/nm	Φ_F
7a	312 (3.1)	386, 402	0.31
	348 (2.6)	387	0.45
7b	330 (2.5)		
	310 (1.9)		
7c	383 (2.0)	373, 402	0.50
	317 (4.8)		
7d	343 (3.9)	390	0.93[3j]
	303 (2.8)		
7e	343 (4.0)	393	0.45
	381 (7.0)	387, 408, 431	0.83
7f	363 (6.8)		
	325 (3.1)		
	311 (2.5)		
	397 (6.4)	406, 430	0.71
11a	378 (6.6)		
	329 (2.5)		
	315 (2.4)		
	374 (5.4)	447	0.81
11b	328 (2.3)		
	315 (2.0)		
11c	390 (3.8)	469	0.71
	310 (2.9)		
11d	368 (4.4)	450	0.62
11e	344 (4.3)	374, 391	0.78

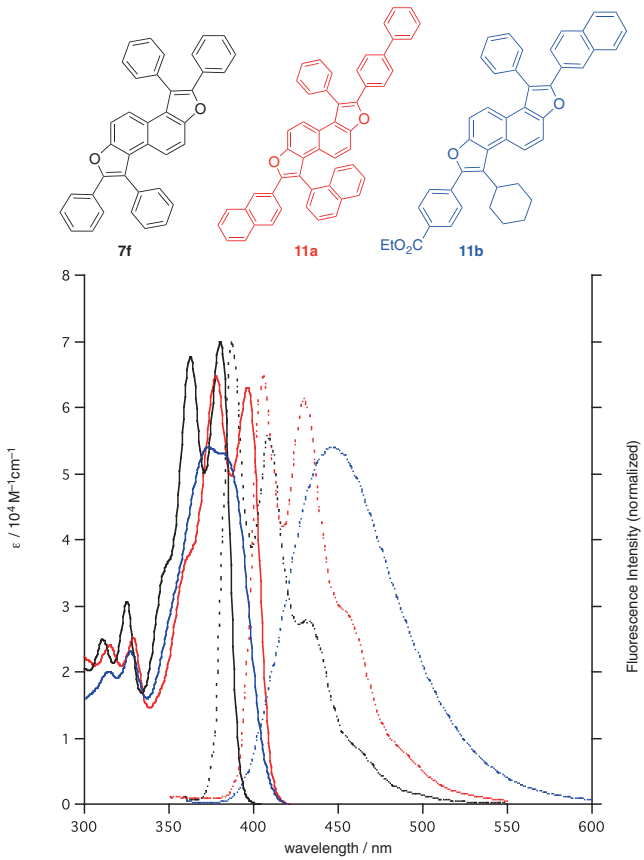
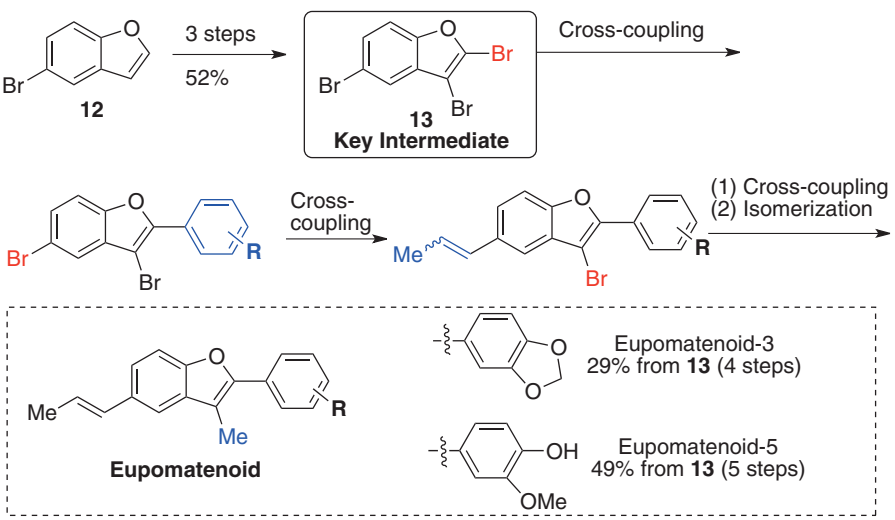
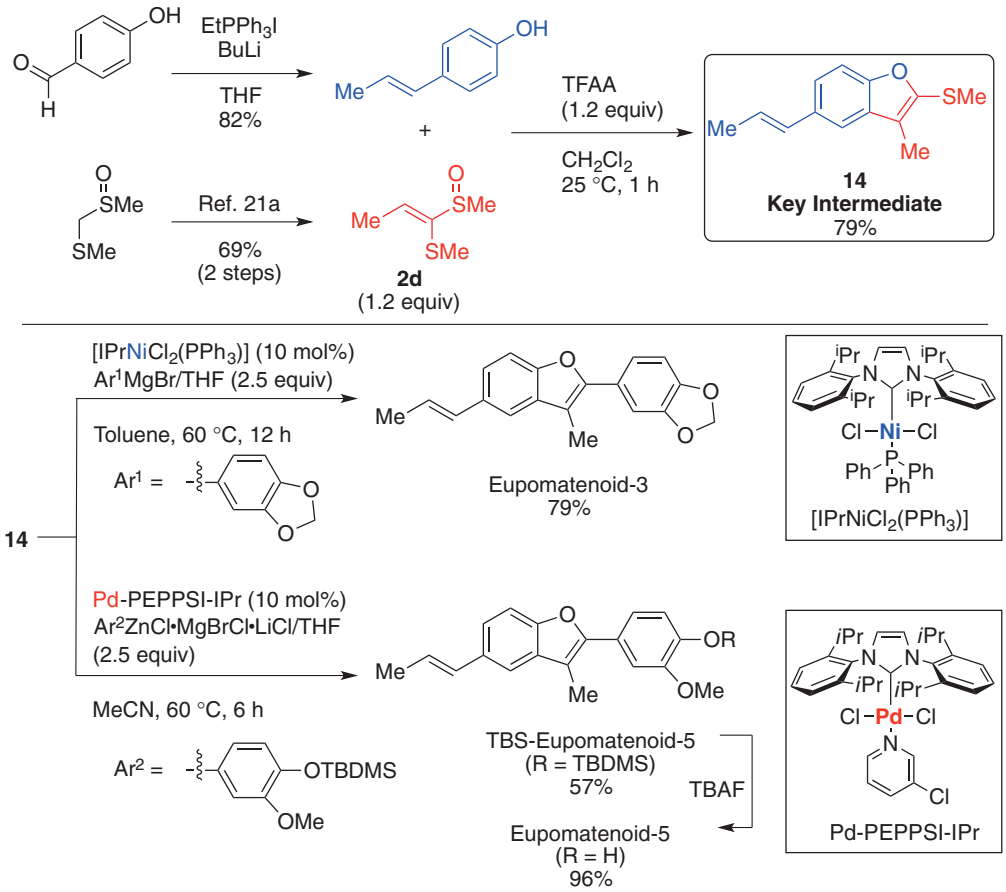


Figure 2. UV–vis absorption (solid line) and fluorescence spectra (dashed line) of **7f** (black), **11a** (red), and **11b** (blue) in CH$_2$Cl$_2$.



Scheme 6. Bach's synthesis of Eupomatenoids.



Scheme 7. Syntheses of Eupomatenoids through the Pummerer annulation/coupling strategy.

nitrogen atmosphere. *Note that the resulting methanethiol after the Pummerer annulations or cross-coupling of 2-methylsulfanylbenzofurans is so malodorous that the reactions and work-up procedures should be performed in a well-ventilated fume hood.*

General Procedures. Typical Procedure for Syntheses of Benzofurans: Preparation of **2a** is representative (Table 1). In a reaction flask, 4-*tert*-butylphenol (30 mg, 0.20 mmol) and **1a** (51 mg, 0.24 mmol) were dissolved in dichloromethane (2 mL). Trifluoroacetic anhydride (33 µL, 0.24 mmol) was added to the solution at 25 °C. After being stirred for 30 min, the mixture was filtered through a pad of alumina and the filtrate was concentrated. Chromatographic purification on silica gel (hexane/CH_2Cl_2 = 5/1) yielded 5-(*tert*-butyl)-2-methylsulfanyl-3-phenylbenzo[*b*]furan (**2a**, 51 mg, 0.17 mmol, 87%).

Typical Procedure for Ni-Catalyzed Cross-Coupling Reactions: Preparation of **7a** is representative (Table 7, Entry 7). Thioether **6k** (45 mg, 0.10 mmol) and [IPrNiCl$_2$-(PPh$_3$)] (7.8 mg, 0.010 mmol) were added to a Schlenk tube under argon. Toluene (1 mL) and PhMgBr (0.5 mL, 0.5 mmol, 1 M in THF) were successively added to the tube and the resulting mixture was heated at 100 °C for 12 h. The mixture was allowed to cool to ambient temperature. The reaction was quenched with HCl aq (1 M, 5 mL). The organic compounds were extracted with CH_2Cl_2 three times. The combined organic part was then washed with brine. The mixture was filtered through a pad of silica gel and Na_2SO_4 and concentrated in vacuo. Recrystallization from CH_2Cl_2/MeOH afforded the corresponding product **7a** in 68% yield (35 mg, 0.068 mmol).

Characterization Data. Compounds **2a–2k**, **3a**, **3c–3f**, **3h–3i**, **4a**, **5b**, **6a**, **6c–6e**, **6e′**, **6g**, **6k**, **6m**, **8c**, **8d**, **9a**, **9d**, **10a–10d**, **11a–11d**, **14**, and TBS-Eupomatenoid-3 are reported in the communication.[11] Compounds **4d**,[19] **7d**,[3j] Eupomatenoid-3,[39b] Eupomatenoid-5[39b] are known compounds and showed the identical spectra according to the literature.

5-Iodo-2-methylsulfanyl-3-phenylbenzo[*b*]furan (3b): Oil. IR (neat): 2925, 1432, 1261, 1097, 964, 766, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.55 (s, 3H), 7.25–7.27 (m, 1H), 7.42–7.43 (m, 1H), 7.51–7.53 (m, 2H), 7.56–7.59 (m, 3H), 7.94–7.95 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 16.80, 86.87, 112.97, 121.41, 127.94, 128.56, 128.88, 129.12, 131.17, 131.23, 133.04, 148.92, 154.96; HRMS (APCI-MS, positive): m/z = 365.9573. calcd for $C_{15}H_{11}OIS$: 365.9570 $[M]^+$.

5-Acetyl-2-methylsulfanyl-3-phenylbenzo[*b*]furan (3g): Oil. IR (neat): 2925, 1688, 1251, 1090, 739 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.56 (s, 3H), 2.64 (s, 3H), 7.42–7.44 (m, 1H), 7.51–7.54 (m, 3H), 7.60–7.62 (m, 2H), 7.96–7.98 (m, 1H), 8.23 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 16.92, 27.00, 111.10, 121.05, 122.94, 125.40, 128.11, 128.84, 129.01, 129.26, 131.23, 133.18, 149.65, 158.23, 197.72; HRMS (APCI-MS, positive): m/z = 282.0700. calcd for $C_{17}H_{14}O_2S$: 282.0709 $[M]^+$.

7-Chloro-2-methylsulfanyl-3-phenylbenzo[*b*]furan (4b): Oil. IR (neat): 2927, 1417, 933, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.59 (s, 3H), 7.18–7.20 (m, 1H), 7.31–7.32 (m, 1H), 7.41–

7.43 (m, 1H), 7.50–7.53 (m, 3H), 7.59–7.61 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 17.02, 116.63, 118.39, 123.03, 124.06, 124.75, 127.96, 128.86, 129.21, 130.20, 131.49, 149.05, 151.40; HRMS (APCI-MS, positive): $m/z = 274.0226$. calcd for $C_{15}H_{11}O^{35}ClS$: 274.0219 $[M]^+$.

7-Benzyloxy-2-methylsulfanyl-3-phenylbenzo[*b*]furan (4c): Oil. IR (neat): 2925, 1497, 1274, 728, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.55 (s, 3H), 5.56 (s, 2H), 6.88–6.89 (m, 1H), 7.13–7.15 (m, 1H), 7.23–7.25 (m, 1H), 7.34–7.43 (m, 4H), 7.50–7.54 (m, 4H), 7.62–7.64 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 17.47, 71.36, 109.39, 112.74, 123.43, 123.79, 127.62, 127.72, 128.20, 128.72, 128.76, 129.33, 130.45, 132.03, 137.09, 144.22, 145.44, 147.93; HRMS (APCI-MS, positive): $m/z = 346.1033$. calcd for $C_{22}H_{18}O_2S$: 346.1022 $[M]^+$.

6-(*tert*-Butyl)-2-methylsulfanyl-3-phenylbenzo[*b*]furan (5a): Solid. Mp 105–110 °C; IR (neat): 2929, 2873, 1489, 1313, 1076, 966, 825, 754, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.42 (s, 9H), 2.55 (s, 3H), 7.36–7.38 (m, 1H), 7.40–7.43 (m, 1H), 7.51–7.54 (m, 2H), 7.56 (s, 1H), 7.59–7.60 (m, 1H), 7.65–7.66 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 17.41, 31.82, 35.15, 107.86, 119.33, 120.99, 122.91, 125.89, 127.59, 128.72, 129.22, 132.23, 147.12, 148.85, 156.06; HRMS (APCI-MS, positive): $m/z = 296.1237$. calcd for $C_{19}H_{20}OS$: 296.1229 $[M]^+$.

6-Trifluoromethyl-2-methylsulfanyl-3-phenylbenzo[*b*]-furan (5c) + 4-Trifluoromethyl-2-methylsulfanyl-3-phenyl-benzo[*b*]furan (5c′): Oil. IR (neat): 3060, 1423, 1310, 1110, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.50 (s, 3H $\times$ 0.35), 2.59 (s, 3H $\times$ 0.65), 7.34–7.71 (m, 8H $\times$ 0.35 + 7H $\times$ 0.65), 7.76 (s, 1H $\times$ 0.65); ^{13}C NMR signals are not assigned because the signals are too complicated; ^{19}F NMR ($CDCl_3$): δ −59.12, −62.20; HRMS (APCI-MS, positive): $m/z = 308.0492$. calcd for $C_{16}H_{11}OF_3S$: 308.0483 $[M]^+$.

6-Iodo-2-methylsulfanyl-3-phenylbenzo[*b*]furan (5d) + 4-Iodo-2-methylsulfanyl-3-phenylbenzo[*b*]furan (5d′): Oil. IR (neat): 2924, 1406, 1094, 961, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.48 (s, 3H $\times$ 0.41), 2.54 (s, 3H $\times$ 0.59), 6.99–7.01 (m, 1H $\times$ 0.41), 7.36–7.68 (m, 7H), 7.86 (s, 1H $\times$ 0.59); ^{13}C NMR ($CDCl_3$): δ 16.89, 16.95, 84.04, 88.14, 111.13, 120.30, 121.22, 122.31, 124.66, 125.67, 127.92, 128.27, 128.35, 128.86, 129.14, 129.24, 130.33, 130.73, 131.39, 132.20, 132.25, 134.78, 148.37, 150.78, 155.10, 156.02; HRMS (APCI-MS, positive): $m/z = 365.9591$. calcd for $C_{15}H_{11}OIS$: 365.9575 $[M]^+$.

3-(4-*tert*-Butyldimethylsiloxyphenyl)-2-methylsulfanyl-naphtho[2,1-*b*]furan (6b): Oil. IR (neat) 2928, 1497, 1251, 908, 802, 780 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.33 (s, 6H), 1.07 (s, 9H), 2.48 (s, 3H), 7.02–7.04 (m, 2H), 7.31–7.34 (m, 1H), 7.39–7.43 (m, 3H), 7.65–7.66 (m, 1H), 7.73–7.75 (m, 1H), 7.82–7.84 (m, 1H), 7.91–7.92 (m, 1H); ^{13}C NMR ($CDCl_3$): δ −4.10, 18.08, 18.47, 25.91, 112.19, 120.32, 122.57, 123.38, 124.55, 125.95, 126.04, 126.18, 127.97, 129.02, 130.92, 131.71, 147.44, 153.41, 155.77 (One sp^2 signal was not observed because of overlapping.); HRMS (APCI-MS, positive): $m/z = 421.1662$. calcd for $C_{25}H_{29}O_2SSi$: 421.1652 $[M + H]^+$.

3,3-Bis[5-(2-methylsulfanyl-3-phenylbenzo[*b*]furanyl)]-2-benzofuran-1(3*H*)-one (6f): Yellow solid. Mp 101–115 °C; IR (neat): 1763, 1459, 1097, 962 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.52 (s, 6H), 7.26–7.28 (m, 2H), 7.34–7.37 (m, 2H), 7.41–7.46 (m, 6H), 7.49–7.50 (m, 4H), 7.53–7.55 (m, 1 H), 7.59–7.60 (m, 1H), 7.63 (m, 2H), 7.67–7.69 (m, 1H), 7.93–7.95 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 16.95, 92.45, 111.05, 118.37, 122.60, 124.10, 124.33, 125.59, 126.38, 127.82, 128.56, 128.87, 129.11, 129.55, 131.43, 134.23, 136.63, 149.14, 152.52, 155.39, 169.86; HRMS (APCI-MS, positive): $m/z =$ 611.1338. calcd for $C_{38}H_{27}O_4S_2$: 611.1345 $[M + H]^+$.

7-*tert*-Butyl-5-(triisopropylsiloxy)-2-methylsulfanyl-3-phenylbenzo[*b*]furan (6h): Oil. IR (neat): 2944, 1596, 1404, 1153, 865 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.10–1.12 (s, 18H), 1.24–1.28 (m, 3H), 1.52 (s, 9H), 2.55 (s, 3H), 6.80 (s, 1H), 6.93 (s, 1H), 7.38–7.39 (m, 1H), 7.48–7.51 (m, 2H), 7.57–7.58 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 12.87, 16.96, 18.17, 30.04, 34.50, 106.96, 114.76, 121.89, 127.42, 128.71, 129.15, 129.38, 132.43, 135.00, 147.07, 149.17, 152.17 ppm; HRMS (APCI-MS, positive): $m/z = 468.2520$. calcd for $C_{28}H_{40}O_2SSi$: 468.2513 $[M]^+$.

7-*tert*-Butyl-5-hydroxy-2-methylsulfanyl-3-phenylbenzo-[*b*]furan (6i): Yellow solid. Mp 136–137 °C; IR (neat): 3421, 2955, 1421, 941, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.52 (s, 9H), 2.56 (s, 3H), 4.78 (br, 1H), 6.75 (s, 1H), 6.88 (s, 1H), 7.36–7.38 (m, 1H), 7.46–7.49 (m, 2H), 7.55–7.56 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 16.92, 29.97, 34.54, 102.48, 110.46, 121.74, 127.53, 128.74, 129.16, 129.73, 132.23, 135.68, 147.55, 149.09, 151.77; HRMS (APCI-MS, positive): $m/z =$ 312.1188. calcd for $C_{19}H_{20}O_2S$: 312.1179 $[M]^+$.

7-*tert*-Butyl-2,5-di(methylsulfanyl)-3,4-diphenylbenzo-[1,2-*b*;4,3-*b*′]difuran (6j): Yellow solid. Mp 168–169 °C; IR (neat): 2962, 1482, 962, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.62 (s, 9H), 2.42 (s, 3H), 2.49 (s, 3H), 6.45–6.87 (m, 4H), 6.93–6.96 (m, 2H), 6.98–7.01 (m, 4H), 7.43 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 16.94, 17.32, 30.13, 34.83, 104.81, 118.49, 121.02, 122.76, 123.97, 127.26, 127.33, 127.38, 127.42, 129.69, 131.80, 132.94, 133.17, 147.93, 151.39, 153.22 (Two sp^2 signals were not observed because of overlapping.); HRMS (APCI-MS, positive): $m/z = 458.1365$. calcd for $C_{28}H_{26}O_2S_2$: 458.1369 $[M]^+$.

3,4-Dimethyl-2,5-di(methylsulfanyl)naphtho[2,1-*b*:7,8-*b*′]-difuran (6l): Solid. Gradually decomposed from 99 °C; IR (neat): 2924, 1373, 1256, 899, 816 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.48 (s, 6H), 2.50 (s, 6H), 7.55 (d, $J = 9.0$ Hz, 2H), 7.71 (d, $J = 9.0$ Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 13.03, 17.75, 110.86, 121.51, 121.99, 123.68, 126.36, 128.19, 147.44, 155.47; HRMS (APCI-MS, positive): $m/z = 328.0580$. calcd for $C_{18}H_{16}O_2S_2$: 328.0586 $[M]^+$.

2,3,4,5-Tetraphenylnaphtho[2,1-*b*:7,8-*b*′]difuran (7a): Yellow solid. Mp >250 °C. IR (neat): 1382, 960, 757, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$ at 60 °C): δ 6.59–6.60 (m, 4H), 6.83–6.86 (m, 4H), 6.99–7.02 (m, 2H), 7.24–7.30 (m, 10H), 7.72–7.74 (m, 2H), 7.89–7.91 (m, 2H); ^{13}C NMR ($CDCl_3$ at 60 °C): δ 111.08, 121.90, 121.98, 123.03, 126.16, 127.02, 127.90, 128.24, 128.32, 128.91 (2C), 129.35, 132.20, 132.65, 150.87, 154.70; HRMS (APCI-MS, positive): $m/z = 512.1753$. calcd for $C_{38}H_{24}O_2$: 512.1771 $[M]^+$; UV–vis (CH_2Cl_2): λ_{max} (ε [M^{-1} cm^{-1}]) = 312 (3.1×10^4) nm; Fluorescence (CH_2Cl_2, $\lambda_{ex} = 280$ nm): $\lambda_{max} = 386$, 402 nm, $\Phi_F = 0.31$.

3-(4-Trifluoromethylphenyl)-2-phenylnaphtho[2,1-*b*]-furan (7b): Yellow solid. Mp 144–145 °C; IR (neat): 1619, 1327, 1103, 805 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.28–7.33 (m, 4H), 7.41–7.52 (m, 4H), 7.71–7.76 (m, 3H), 7.79–7.80 (m, 1H),

7.84–7.86 (m, 2H), 7.94–7.96 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 112.41, 118.26, 122.94, 123.26, 124.44 (q, $J = 271$ Hz), 124.66, 126.44, 126.48, 126.52, 126.60, 128.24, 128.39, 128.76, 129.33, 130.57, 130.65 (q, $J = 32$ Hz), 131.18, 131.36, 139.06, 150.68, 151.80; ^{19}F NMR ($CDCl_3$): δ −63.49; HRMS (APCI-MS, positive): $m/z = 388.1076$. calcd for $C_{25}H_{15}OF_3$: 388.1070 $[M]^+$; UV–vis (CH_2Cl_2): λ_{max} (ε [M^{-1} cm^{-1}]) = 310 (1.9×10^4), 330 (2.5×10^4), 348 (2.6×10^4) nm; Fluorescence (CH_2Cl_2, $\lambda_{ex} = 280$ nm): $\lambda_{max} = 387$ nm, $\Phi_F = 0.45$.

3,4-Dimethyl-2,5-diphenylnaphtho[2,1-*b*:7,8-*b*′]difuran (7c): Yellow solid. Gradually decomposed around 174–185 °C. IR (neat): 1381, 906, 810, 687 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.80 (s, 6H), 7.36–7.38 (m, 2H), 7.51–7.54 (m, 4H), 7.65–7.66 (m, 2H), 7.77–7.78 (m, 2H), 7.95–7.97 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 14.27, 110.89, 114.69, 122.54, 125.09, 126.48, 126.56, 127.84, 128.57, 128.87, 131.58, 151.11, 153.69; HRMS (APCI-MS, positive): $m/z = 388.1466$. calcd for $C_{28}H_{20}O_2$: 388.1458 $[M]^+$; UV–vis (CH_2Cl_2): λ_{max} (ε [M^{-1} cm^{-1}]) = 317 (4.8×10^4), 383 (2.0×10^4) nm; Fluorescence (CH_2Cl_2, $\lambda_{ex} =$ 350 nm): $\lambda_{max} = 373$, 402 nm, $\Phi_F = 0.50$.

7-*tert*-Butyl-2,3,4,5-tetraphenylbenzo[1,2-*b*;4,3-*b*′]difuran (7e): Yellow solid. Mp >250 °C; IR (neat): 2957, 1445, 1068, 687 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.70 (s, 9H), 6.89–7.04 (m, 9H), 7.15–7.25 (m, 11H), 7.54 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 30.28, 34.92, 105.53, 118.92, 120.87, 123.29, 126.80, 126.85, 127.53, 127.70, 127.75, 127.80, 128.26, 128.37, 128.58, 128.60, 130.39, 130.45, 131.30, 132.27, 134.27, 134.54, 149.53, 150.82, 151.20, 151.53 (Two sp^2 signals were not observed because of overlapping.); HRMS (APCI-MS, positive): $m/z =$ 519.2306. calcd for $C_{38}H_{30}O_2$: 519.2319 $[M]^+$; UV–vis (CH_2Cl_2): λ_{max} (ε [M^{-1} cm^{-1}]) = 343 (4.0×10^4) nm; Fluorescence (CH_2Cl_2, $\lambda_{ex} = 280$ nm): $\lambda_{max} = 393$ nm, $\Phi_F = 0.45$.

2,3,7,8-Tetraphenylnaphtho[2,1-*b*:6,5-*b*′]difuran (7f): Solid. Mp >250 °C. IR (neat): 3060, 1559, 1389, 809, 691 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.24–7.27 (m, 6H), 7.51–7.61 (m, 18H); ^{13}C NMR ($CDCl_3$): δ 111.74, 119.59, 120.89, 124.82, 125.67, 126.48, 127.99, 128.45, 128.56, 129.70, 130.88, 131.04, 135.07, 150.39, 150.74 (One sp^2 signal was not observed because of overlapping.); HRMS (APCI-MS, positive): $m/z = 512.1770$. calcd for $C_{38}H_{24}O_2$: 512.1771 $[M]^+$; UV–vis (CH_2Cl_2): λ_{max} (ε [M^{-1} cm^{-1}]) = 311 (2.5×10^4), 325 (3.1×10^4), 363 (6.8×10^4), 381 (7.0×10^4) nm; Fluorescence (CH_2Cl_2, $\lambda_{ex} = 350$ nm): $\lambda_{max} = 387$, 408, 431 nm, $\Phi_F =$ 0.83.

5-Triisopropylsiloxy-2,3-diphenylbenzo[*b*]furan (8e): Oil. IR (neat): 2923, 1497, 1197, 909, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.13–1.15 (m, 18H), 1.27–1.32 (m, 3H), 6.92–6.94 (m, 1H), 7.01 (s, 1H), 7.30–7.34 (m, 3H), 7.40–7.44 (m, 2H), 7.48–7.53 (m, 4H), 7.66–7.67 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 12.83, 18.15, 109.70, 111.34, 117.69, 117.75, 127.21, 127.70, 128.44, 128.55, 129.10, 129.82, 130.99, 133.13, 149.39, 151.49, 152.33 (One sp^2 signal was not observed because of overlapping.); HRMS (APCI-MS, positive): $m/z = 442.2322$. calcd for $C_{29}H_{34}O_2Si$: 442.2323 $[M]^+$.

5-Hydroxy-2,3-diphenylbenzo[*b*]furan (9e): Oil. IR (neat): 3319 (br), 1466, 1148, 759, 691 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.63 (br, 1H), 6.84–6.86 (m, 1H), 6.89–6.90 (m, 1H), 7.29–7.33 (m, 3H), 7.39–7.41 (m, 2H), 7.45–7.49 (m, 4H), 7.63–7.64 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 105.18, 111.75, 113.50, 117.55, 127.12, 127.76, 128.53, 128.57, 129.12, 129.80, 130.80, 131.24, 132.94, 149.22, 151.70, 151.84; HRMS (APCI-MS, positive): $m/z = 286.0988$. calcd for $C_{20}H_{14}O_2$: 286.0986 $[M]^+$.

2-Methylsulfanyl-3,4,5-triphenylbenzo[1,2-*b*;4,3-*b*′]-difuran (10e): Solid. Mp 181–182 °C. IR (neat): 3064, 1502, 1228, 757, 688 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.42 (s, 3H), 6.86–6.90 (m, 4H), 6.95–7.01 (m, 6H), 7.20–7.21 (m, 3H), 7.30–7.32 (m, 2H), 7.49–7.55 (m, 2H); ^{13}C NMR ($CDCl_3$); δ 17.17, 108.08, 119.04, 121.44, 122.21, 124.16, 127.26, 127.66, 127.86, 128.11, 128.33, 128.36, 129.76, 130.33, 131.07, 133.39, 133.73, 149.07, 151.39, 151.79, 152.94 (Two sp^2 signas were not observed because of overlapping.); HRMS (APCI-MS, positive): $m/z = 463.1707$. calcd for $C_{34}H_{20}O_2$: 463.1693 $[M]^+$.

2,3,4,5-Tetraphenylbenzo[1,2-*b*;4,3-*b*′]difuran (11e): Yellow solid. Mp >250 °C. IR (neat): 3049, 1411, 754, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.89–6.92 (m, 4H), 6.97–6.98 (m, 4H), 7.03–7.05 (m, 2H), 7.16–7.18 (m, 6H), 7.23–7.26 (m, 2H), 7.58 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 108.34, 119.14, 122.97, 127.03, 127.70, 127.96, 128.30, 128.59, 130.37, 131.10, 134.23, 151.28, 151.77; HRMS (APCI-MS, positive): $m/z = 463.1707$. calcd for $C_{34}H_{20}O_2$: 463.1693 $[M]^+$; UV–vis (CH_2Cl_2): λ_{max} (ε [M^{-1} cm^{-1}]) = 344 (4.3×10^4) nm; Fluorescence (CH_2Cl_2, $\lambda_{ex} = 300$ nm): $\lambda_{max} = 374$, 391 nm, $\Phi_F =$ 0.78.

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Supporting Information

UV–visible and fluorescence spectra, crystallographic data, and NMR spectra. This material is available electronically on J-STAGE.

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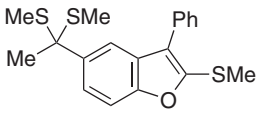
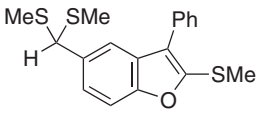
23 Without addition of K_2CO_3, dithioacetals **3g′** and **3h′** were obtained in low yields.



3g'



3h'

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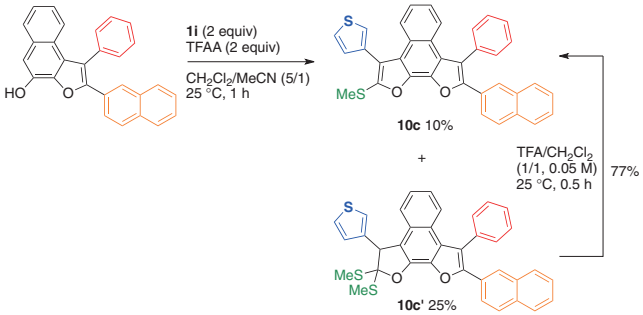
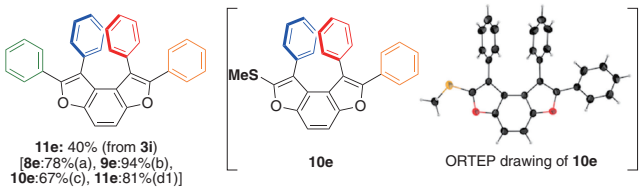


38 The regioselectivity of the reaction of **9d** with **1i** to afford **10d** was determined by analogy to the synthesis of **11e** via **10e** shown below. The structure of intermediate **10e** was unambiguously determined by X-ray crystallographic analysis.



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42 A variety of arylmagnesium reagents are commercially available and are cheaper than the corresponding arylzinc reagent. For instance, a PhMgBr solution in THF costs 6,000 yen for 50 mmol while a PhZnBr solution in THF costs 22,500 yen for 25 mmol from Aldrich).

43 A disadvantage of the nickel-catalyzed reactions is low functional group tolerability. For instance, the IPr/Ni catalyst can often cleave the C(sp^2)–O bonds of anisole derivatives. In such cases, the Pd-PEPPSI-IPr/ArZnX system is the better option because alkoxy groups are compatible under the milder conditions. We recommend employing a readily available arylzinc reagent that was prepared from the corresponding aryl bromide, Mg metal, LiCl, and $ZnCl_2$ (Ref. 35b).

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