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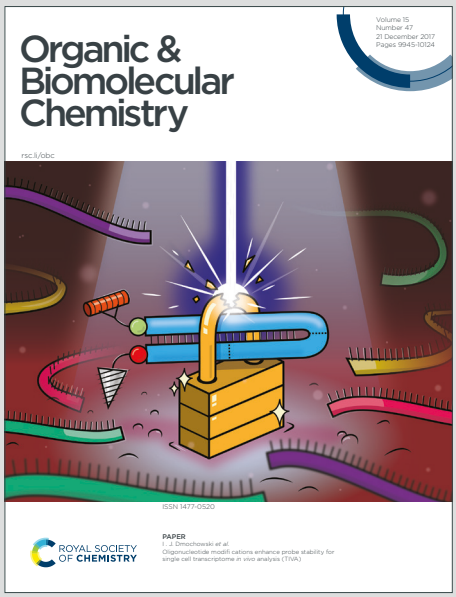

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Palladium-catalyzed three-component cascade arylthiolation with aryldiazonium salts as S-arylation sources

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A novel and efficient palladium-catalyzed three-component cascade cyclization/arylthiolation for the assembly of diverse 3-sulfenylindoles and 3-sulfenylbenzofurans derivatives from 2-alkynylamines and 2-alkynylphenols, aryldiazonium salts, and $Na_2S_2O_3$ under aerobic conditions with PEG-200 as an environmentally benign medium has been developed. The current study features exceptional functional group tolerance, without additional ligand or oxidant or silver salt, eco-friendly, and mild reaction conditions. Ionic liquids [C_2OHmim]Cl as the environmental friendliness additive plays crucial roles in this protocol. Notably, this procedure represents the first example for the use of aryldiazonium salts as the direct S-arylation sources in this type chemical transformation.

Introduction

Organosulfur heterocyclic scaffolds are considered as versatile and important privileged architecture in numerous pharmaceuticals, advanced materials, and biologically active molecules because of these building blocks have unique versatility and availability.[1] In this regard, transition-metal-catalyzed sulfenylation reaction have witnessed considerable attention in the recent years, which can effective assemble structurally diverse sulfur-containing frameworks in a rather straightforward, atom- and step-economical manners.[2] Correspondingly, a number of sulfenylating agents, such as thiols, disulfides, arylsulfonyl chlorides, sulfonyl hydrazides, and *N*-thioarylphthalimides, have been investigated as the sulfur sources. However, all of these elegant developments suffer from certain limitations such as repulsive odor, air or water sensitivity, instability and toxic. As the another green, and highly efficient sulfenylation process, transition metal-free synthetic methods for the preparation of high value-added sulfur-containing structural motifs have also been well established.[3] Alternative inorganic sulfenylating reagents such as S_8, Na_2S, K_2S, sodium sulfinates, sodium thiosulfate, and sulfourea, have also been exploited in recent years. Particularly, a wide array of cascade *S*-arylation reaction for the rapid synthesis of structural complexity. Jiang,[4] Willis,[5] Wu,[6] Deng,[7] Tang,[8] and our group[9] have established a number of cascade *S*-arylation methodologies for the construction of unconventional and more elaborated heterocyclic organosulfur frameworks by employing aryl halides, arylboronic acid, arylhydrazines, and organosilicon reagents as the aryl sources. Nevertheless, the direct cascade *S*-arylation reagents have remained relatively rare. Therefore, it is highly desirable to explore new type S-arylation reagents and catalytic system for the direct S-arylation reaction under eco-friendly conditions.

In addition, as one of important heterocyclic building blocks, highly substituted indoles derivatives exhibit remarkable biological activities and pharmaceuticals activities.[10] It is worth noting that 3-sulfenylindoles display a broad spectrum of biological activities, which can be employed as the drugs assessed for the treatment of heart diseases, bacterial infection, obesity, and cancer diseases.[11] As a result, a wide array of outstanding methodologies have been studied for the construction of these organosulfur heterocyclic frameworks. Generically, there are three representative methods are typically employed in this field. Transition-metal-catalyzed sulfenylation of indoles with various sulfurating reagents have been identified as the most efficient and direct synthetic approach for constructing these heterocyclic scaffolds (Scheme 1a).[12] For instance, Yuan and co-workers developed a novel approach for the synthesis of 3-sulfenylindoles via cobalt-catalyzed aerobic cross-dehydrogenative coupling in water with thiols as the sulfenylating agents.[12d] Moreover, metal free procedure for the direct assembly of 3-sulfenylindoles from indoles with sulfurating reagents have also been developed.[13] For example, Iida and co-workers performed a novel organocatalyst systems flavin-iodine-catalysed sulfenylation of indoles with thiols under mild conditions.[13e] On the other hand, transition-metal-catalyzed cascade electrophilic annulation/arylthiolation reaction using 2-alkynylanilines as the readily accessible starting materials to prepare structurally diverse 3-sulfenylindoles derivatives (Scheme 1b).[14] Using this strategy, Li and Zhang described a metal-involved annulations approach from 2-(1-alkynyl)benzenamines and disulfides.[14b] Especially, our group also demonstrated an unprecedented palladium-catalyzed cascade annulation/arylthiolation reaction the rapid assembly of 3-sulfenylindole derivatives from readily available 2-alkynylamines in

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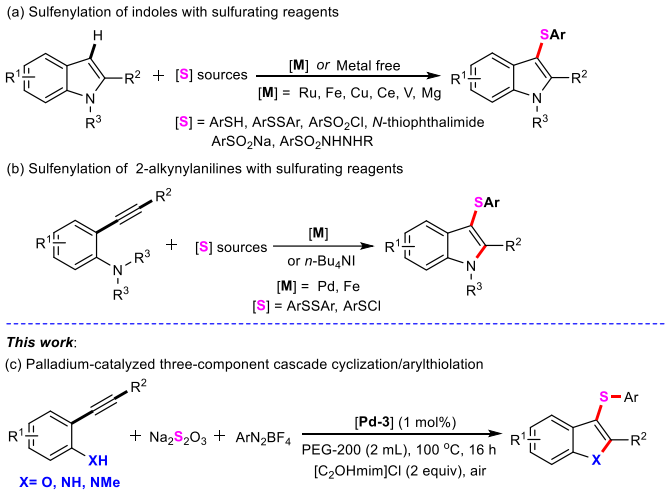
ionic liquids with elemental sulfur as the ideal sulfur sources.[9a] Recently, our group have also successfully discovered an elegant palladium-catalyzed three-component cascade *S*-transfer reaction of acetylinic oximes with aryl halides using readily available $Na_2S_2O_3$ as an odorless sulfenylation reagent under aerobic conditions in ionic liquids for the assembly of 4-sulfenylisoxazole derivatives.[15] To our knowledge, there are no examples disclosed the direct arylation of indoles using aryldiazonium salts as the *S*-aryl sources. Inspired by our previous studies for the synthesis of organosulfur frameworks,[16] and our longstanding interest in Pd-catalyzed cross-coupling reactions of alkynes,[17] herein we describe an efficient and novel palladium-catalyzed three-component cascade *S*-arylation reaction for the assembly of structurally diverse 3-sulfenylindoles and 3-sulfenylbenzofurans derivatives from 2-alkynylamines and 2-alkynylphenols, aryldiazonium salts, and $Na_2S_2O_3$ under aerobic conditions with PEG-200 as an environmentally benign medium (Scheme 1c).

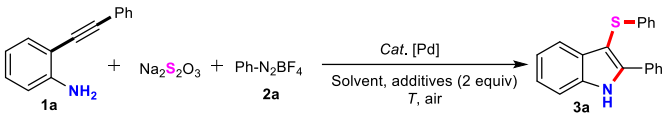


Scheme 1 Representative strategies for the synthesis of 3-sulfenylindoles

Results and discussion

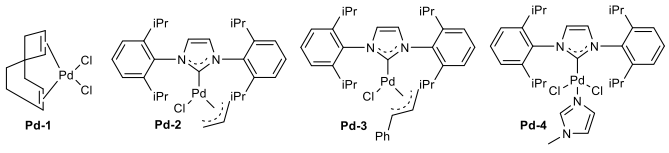
We commenced our investigation by choosing 2-(phenylethynyl)aniline (**1a**), phenyldiazonium salts (**2a**), and sodium thiosulfate ($Na_2S_2O_3$) as the model substrates to optimize the reaction conditions, and the representative results are summarized in Table 1.[18] Initially, no the desired product **3a** was detected in the presence of conventional palladium catalysts such as $Pd(OAc)_2$ and $PdCl_2$ in DMF at 100 °C for 16 h (Entries 1-2). Further investigation on the complex palladium catalysts showed that **Pd-3** was the optimal catalyst for this chemical transformation, and the desired **3a** could be detected in 57% GC yield (Entry 7). In light of our previously observed results, we found that ionic liquids as the additive showed apparent positive effects for the cascade annulation process. [17b] Various ionic liquids additives were next tested, and the ionic liquid $[C_2OHmim]Cl$ was superior to the others under the same conditions (Entry 11). Subsequently, different type solvents were also estimated such as DMSO, Toluene, PEG-200, and PEG-400, it was revealed that PEG-200 was found to be the best choice (Entry 13). In addition, when the reaction was performed at 110 °C for 16 h, the desired product **3a** was still obtained in 89% GC yield (Entry 15). However, the yield decreased dramatically when the temperature was used at 80 °C under the similar condition (Entry 14). Gratifyingly, when the reaction was performed with 1 mol% dosage of the **Pd-3** catalyst, the desired product **3a** was still obtained in 89% GC yield (Entry 16). Finally, in the absence of any palladium catalysts, neither of the starting materials were consumed (Entry 17).

Table 1. Optimization of reaction conditions.[a]



Entry	Catalyst	Additive	Solvent	Yield (%)[b]
1	$Pd(OAc)_2$	nBu_4NBr	DMF	0
2	$PdCl_2$	nBu_4NBr	DMF	trace
3	$Pd(PhCN)_2Cl_2$	nBu_4NBr	DMF	11
4	$[Pd(allyl)Cl]_2$	nBu_4NBr	DMF	34
5	**Pd-1**	nBu_4NBr	DMF	28
6	**Pd-2**	nBu_4NBr	DMF	45
7	**Pd-3**	nBu_4NBr	DMF	57
8	**Pd-4**	nBu_4NBr	DMF	35
9	**Pd-3**	nBu_4NI	DMF	40
10	**Pd-3**	[Bmim]Cl	DMF	50
11	**Pd-3**	$[C_2OHmim]Cl$	DMF	68
12	**Pd-3**	$[C_2OHmim]Cl$	Toluene	26
13	**Pd-3**	$[C_2OHmim]Cl$	PEG-	89 (82)
14[c]	**Pd-3**	$[C_2OHmim]Cl$	PEG-	67
15[d]	**Pd-3**	$[C_2OHmim]Cl$	PEG-	89
16[e]	**Pd-3**	$[C_2OHmim]Cl$	PEG-	89
17	-	$[C_2OHmim]Cl$	PEG-	0

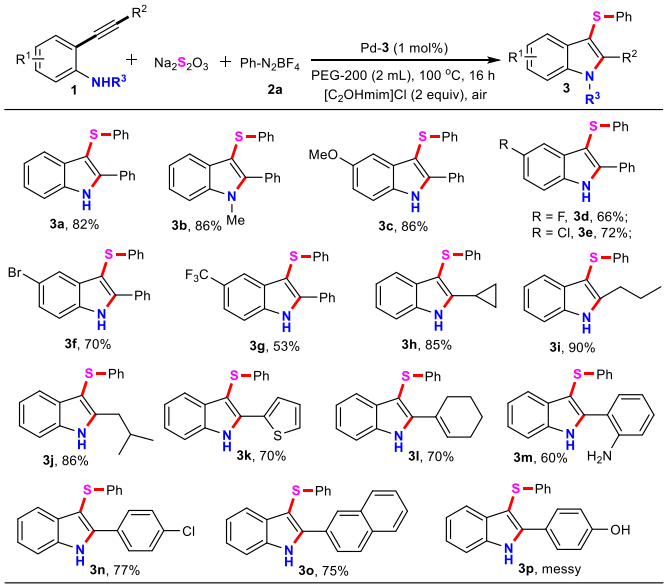
[a] Reactions were performed with **1a** (0.10 mmol), **2a** (0.12 mmol), $Na_2S_2O_3$ (0.20 mmol), catalyst (2 mol %), additives (0.20 mmol), solvent (1 mL) at 100 °C under air for 16 h; [b] Determined by GC using dodecane as the internal standard. The value in parentheses is the yield of isolated product. [c] At 80 °C; [d] At 110 °C. [e] 1 mol% **Pd-3** was used.



With the optimized conditions in hand, we then explored the substrate scope of various 2-alkynylamines, and the representative results are presented in Table 2. As anticipated, both electron-donating and electron-withdrawing substituents on the phenyl ring were perfectly accommodated with the current catalytic system, furnishing the corresponding 3-sulfenylindole derivatives in moderate to good yields. It is worth mentioning that substrates bearing electron-donating groups can give better yields than the ones with electron-withdrawing groups. Specifically, various

halogen atom such as F, Cl, and Br group were compatible with this chemical transformation, giving the corresponding products **3c**, **3d**, and **3e** in 66%, 72%, and 70% yields, respectively. Moreover, the obtained products can allow for further synthetic transformations by transition metal-catalyzed cross-coupling reactions. Delightfully, strong electron-withdrawing group such as CF_3 group on the benzene ring was well tolerated, producing the desired product **3f** in 53% yield. Additionally, the 2-thienyl and 2-vinyl group were amenable to this transformation, and offered the corresponding products **3j** and **3k** in 70% and 71% yields, respectively. Notably, amino substituted 2-alkynylamine **1l** was also perfectly tolerated, and gave the desired **3l** in 60% yield. Substrates bearing hydroxyl group was compatible with the current protocol, however, only a messy mixture **3o** was obtained.

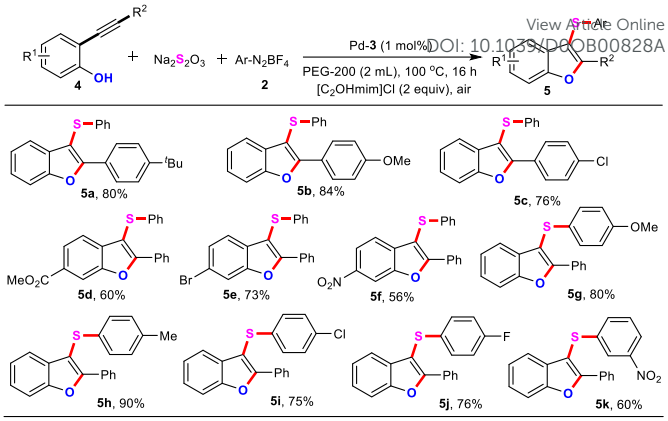
Table 2. Substrate scope of various 2-alkynylamines [a]



[a] Reaction conditions: **1** (0.20 mmol), **2a** (0.24 mmol), $Na_2S_2O_3$ (0.40 mmol), **Pd-3** (1 mol %), [C_2OHmim]Cl (0.4 mmol), PEG-200 (1 mL) at 100 °C under air for 16 h; Yields referred to isolated yield.

Encouraged by the above sulfenylation results, we next investigated the scope of various structurally diverse 2-alkynylphenols and different diazonium salts under the optimal conditions, and the experimental results are illustrated in Table 3. Various 2-alkynylphenols with electron-donating substituents (*t*Bu, OMe) and electron-withdrawing groups (Cl, Br, CO_2Me, NO_2) on the benzene ring, reacted with phenyldiazonium salts (**2a**) facilely to produce the desired products **5a**-**5f** in 56%-84% yields. As for aryl diazonium salts, substituents on the benzene ring such as -Me, -OMe, -F, -Cl, and -NO_2 groups were also well accommodated, providing the expected sulfenylation products **5g**, **5h**, **5i**, **5j**, and **5k** in 80%, 90%, 75%, 76%, and 60% yields, respectively.

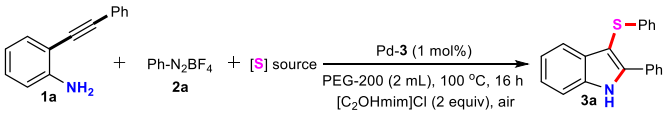
Table 3. Substrate scope of various 2-alkynylphenols and different diazonium salts [a]



[a] Reaction conditions: **4** (0.20 mmol), **2** (0.24 mmol), $Na_2S_2O_3$ (0.40 mmol), **Pd-3** (1 mol %), [C_2OHmim]Cl (0.4 mmol), PEG-200 (1 mL) at 100 °C under air for 16 h; Yields referred to isolated yield.

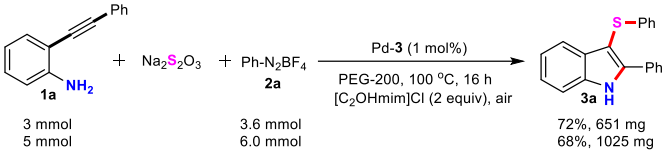
Furthermore, we turned our attention to the different sulfur sources under the standard reaction conditions. As illustrated in Table 4, other easily available inorganic sulfur sources such as Na_2S, S_8, and $Na_2S_2O_5$ were not compatible with the current protocol, and failed to offer the desired product **3a**. In contrast, when PhSH was employed as a sulfenylating agents, the desired product **3a** was detected in 26% GC yield. Unfortunately, no desired product **3a** was observed when PhSSPh was applied as the sulfenylating agent.

Table 4. Investigation of different sulfur sources



[S] Source	Na_2S	PhSH	S_8	PhSSPh	$Na_2S_2O_5$
GC yields	-	26%	-	-	-

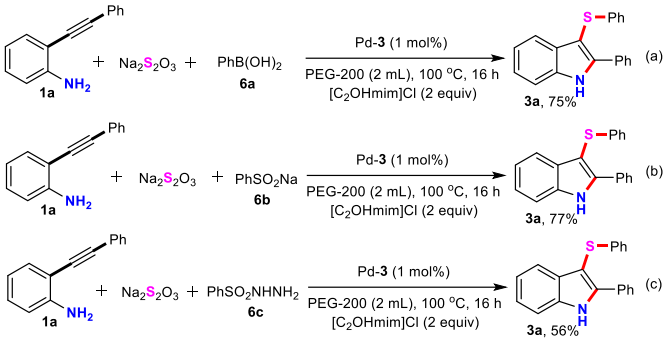
Subsequently, a gram-scale synthesis of **3a** was performed under the optimized reaction conditions (Scheme 2). When 3 mmol of **1a** was utilized, 0.651 g of the desired product **3a** was obtained in 72% yield. Notably, when 5 mmol of **1a** was explored, the product **3a** was also generated in 68% yield.



Scheme 2 Scale-up experiment

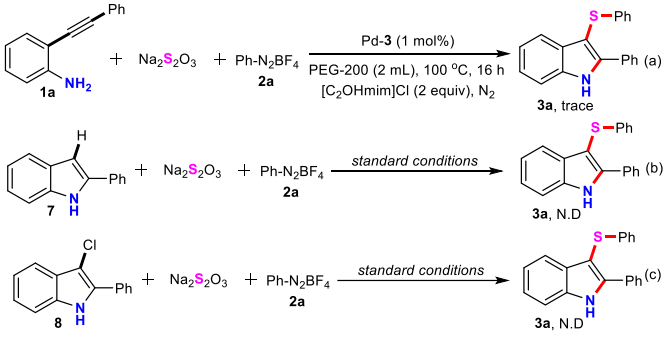
Satisfied with the obtained results, various aryl reagents were then observed under the standard conditions. For instance, the cascade Suzuki-type/annulation/arylthiolation cross-coupling of phenylboric acid (**6a**), 2-(phenylethynyl)aniline (**1a**), and $Na_2S_2O_3$ proceeded smoothly to give the product **3a** in 75% yield (Scheme 3a). Similarly, the desulfitative coupling of **6b** occurred uneventfully as well, thus providing the target product **3a** in 77% yield (Scheme

3b). Particularly noteworthy was that the desulfitative-denitrogenative arylation cascade approach of arylsulfonyl hydrazides **6c** allowed successfully to produce the desired **3a** in 56% yield (Scheme 3c).



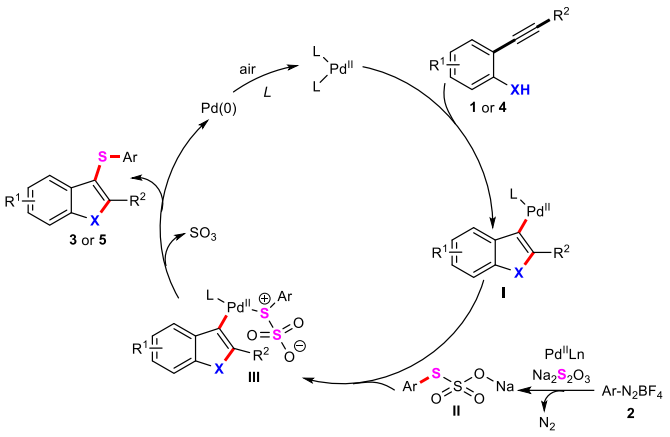
Scheme 3 Investigation of different aryl sources

To gain preliminary insights into this cascade sulfenylation pathway, several control experiments were further conducted (Scheme 4). First, only a trace amount of the desired product **3a** was observed when this cascade three-component tandem cyclization reaction was performed under an N_2 atmosphere (Scheme 4a). Thus, this control reaction suggests that an aerobic oxidative condition was irreplaceable for this chemical process. Subsequently, when treated with 2-phenyl-1H-indole (**7**) and 3-chloro-2-phenyl-1H-indole (**8**) with phenyl diazonium salts (**2a**), and $Na_2S_2O_3$ under the standard conditions, no desired product **3a** was detected by GC-MS analysis (Scheme 4b and 4c). This observation suggested that 2-phenyl-1H-indole (**7**) and 3-chloro-2-phenyl-1H-indole (**8**) are not possible intermediates in this cascade sulfenylation procotol.



Scheme 4 Control experiments for mechanism study

Based on the current experiment results and previous literature precedents, the postulated mechanism is illustrated in Scheme 5. Initially, nucleopalladation of 2-alkynylphenols or 2-alkynylamines gives vinyl palladium intermediate **I**.[17c] Meanwhile, in the presence of palladium catalyst, aryl diazonium salts reacted with thiosulfate affords thiosulfate complex **II** along with releasing nitrogen gas. Then, ligand exchange between intermediate **I** and thiosulfate intermediate **II** affords palladium thiosulfate intermediate **III**.[19] Subsequently, the sequential release of SO_3 and the reductive elimination process generates the desired products.[17] Finally, the palladium(0) species is additionally oxidized to the palladium(II) active catalyst by air to complete this catalytic cycle.[20]



Scheme 5. Possible Mechanism

Conclusions

In summary, we have successfully demonstrated a novel and efficient palladium-catalyzed three-component cascade cyclization/arylthiolation for the assembly of diverse 3-sulfenylindoles and 3-sulfenylbenzofurans derivatives in moderate to good yields from readily available 2-alkynylamines and 2-alkynylphenols under aerobic conditions. This procedure represents the first example for the use of aryldiazonium salts as a unique aryl source in this type chemical transformation. Prominently, the ionic liquids [C_2OHmim]Cl as the optimal additive makes this transformation green and high efficiency. Notably, the current study demonstrates exceptional functional group tolerance, ligands free, no additional oxidant or silver salt, eco-friendly, and operation simplicity.

Experimental section

Materials and methods

Melting points were measured using a melting point instrument and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz NMR spectrometer. The chemical shifts are referenced to signals at 7.24 and 77.0 ppm, respectively, and chloroform was used as a solvent with TMS as the internal standard. GC-MS data were obtained using electron ionization. HRMS was carried out on a high-resolution mass spectrometer (LCMS-IT-TOF). TLC was performed using commercially available 100–400 mesh silica gel plates (GF_{254}). Unless otherwise noted, purchased chemicals were used without further purification.

Typical procedure for the preparation of 3-sulfenylindoles and 3-sulfenylbenzofurans

A 15 mL vial was charged with 2-alkynylamines or 2-alkynylphenols **1** (0.20 mmol), aryldiazonium salts **2** (0.24 mmol), $Na_2S_2O_3$ (0.40 mmol), Pd catalyst **Pd-3** (1.0 mol %), [C_2OHmim]Cl (2 equiv), and PEG-200 (2 mL). After being heated at 100 °C under air for 16 h, the reaction was quenched by water and extracted with CH_2Cl_2 three times. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by flash column chromatography on silica gel (hexanes/ethyl acetate) to afford the desired products **3** or **5**.

2-Phenyl-3-(phenylthio)-1H-indole (3a).[14a] Yield: 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.73 (d, J = 7.6 Hz, 2H), 7.64 (d, J = 7.6 Hz, 1H), 7.36 (dt, J = 21.2, 6.8 Hz, 4H), 7.25 (t, J = 7.6 Hz, 1H), 7.12 (dt, J = 15.6, 7.2 Hz, 5H), 7.02 (t, J = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 139.4, 135.9, 131.4, 131.2, 128.9, 128.8, 128.6, 128.2, 125.6, 124.6, 123.4, 121.2, 120.0, 111.2, 99.4 ppm; HRMS-ESI (m/z): calcd for $C_{20}H_{15}NNaS$, $[M+Na]^+$: 324.0817, found 324.0823.

1-Methyl-2-phenyl-3-(phenylthio)-1H-indole (3b).[9a] Yield: 86%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.0 Hz, 1H), 7.44 - 7.36 (m, 6H), 7.30 (t, J = 7.6 Hz, 1H), 7.22 - 7.15 (m, 1H), 7.11 (t, J = 7.6 Hz, 2H), 7.04 (d, J = 7.6 Hz, 2H), 6.96 (t, J = 7.2 Hz, 1H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.8, 140.1, 137.6, 130.7, 130.6, 129.8, 128.8, 128.7, 128.4, 125.6, 124.5, 122.8, 121.1, 119.8, 109.8, 99.8, 31.8 ppm; HRMS-ESI (m/z): calcd for $C_{21}H_{18}NS$, $[M+H]^+$: 316.1154, found 316.1148.

5-Methoxy-2-phenyl-3-(phenylthio)-1H-indole (3c).[9a] Yield: 86%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.68 (d, J = 7.6 Hz, 2H), 7.43 - 7.32 (m, 3H), 7.25 (d, J = 8.4 Hz, 1H), 7.19 - 7.00 (m, 6H), 6.90 (d, J = 8.4 Hz, 1H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 142.6, 139.3, 132.2, 131.4, 130.7, 128.9, 128.8, 128.6, 128.1, 125.5, 124.7, 113.8, 112.2, 101.2, 98.9, 55.9 ppm; HRMS-ESI (m/z): calcd for $C_{21}H_{17}NNaOS$, $[M+Na]^+$: 354.0923, found 354.0927.

5-Fluoro-2-phenyl-3-(phenylthio)-1H-indole (3d).[9a] Yield: 66%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.64 (d, J = 7.2 Hz, 2H), 7.30 (dd, J = 16.4, 7.6 Hz, 3H), 7.25 - 7.16 (m, 2H), 7.06 (t, J = 7.2 Hz, 2H), 6.97 (dd, J = 14.8, 7.6 Hz, 3H), 6.88 (t, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9 (d, J = 235.6 Hz), 143.9, 138.8, 132.4 (d, J = 2.5 Hz), 132.1, 129.0, 128.9, 128.7, 128.1, 125.7, 124.9, 112.2 (d, J = 9.5 Hz), 111.9 (d, J = 21.3 Hz), 105.0 (d, J = 24.0 Hz), 99.6 (d, J = 4.5 Hz) ppm; HRMS-ESI (m/z): calcd for $C_{20}H_{14}FNNaS$, $[M+Na]^+$: 342.0723, found 342.0720.

5-Chloro-2-phenyl-3-(phenylthio)-1H-indole (3e).[9a] Yield: 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.72 (d, J = 7.2 Hz, 2H), 7.51 (d, J = 8.4 Hz, 1H), 7.48 - 7.34 (m, 4H), 7.18 - 7.11 (m, 3H), 7.08 - 7.00 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7, 138.9, 136.3, 131.0, 129.8, 129.4, 129.2, 128.9, 128.8, 128.1, 125.8, 124.9, 122.0, 120.9, 111.2, 100.0 ppm; HRMS-ESI (m/z): calcd for $C_{20}H_{14}ClNNaS$, $[M+Na]^+$: 358.0428, found 358.0434.

5-Bromo-2-phenyl-3-(phenylthio)-1H-indole (3f).[9a] Yield: 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.68 (s, 1H), 7.66 (d, J = 6.8 Hz, 2H), 7.34 (dd, J = 15.6, 7.2 Hz, 3H), 7.25 (d, J = 8.8 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 7.09 (t, J = 7.2 Hz, 2H), 7.00 (d, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 138.9, 134.5, 133.1, 130.9, 129.1, 128.9, 128.8, 128.2, 126.4, 125.6, 124.9, 122.5, 114.7, 112.7, 99.3 ppm; HRMS-ESI (m/z): calcd for $C_{20}H_{14}BrNNaS$, $[M+Na]^+$: 401.9923, found 401.9928.

2-Phenyl-3-(phenylthio)-5-(trifluoromethyl)-1H-indole (3g). [9a] Yield: 53%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 7.95 (s, 1H), 7.74 (d, J = 7.2 Hz, 2H), 7.48 (s, 2H), 7.46 - 7.34 (m, 3H), 7.15 (t, J = 7.2 Hz, 2H), 7.11 - 7.00 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 138.5, 137.2, 130.9, 130.6, 129.2, 129.0, 128.8, 128.2, 125.6 (q, J = 256.4 Hz), 125.0, 123.4 (q, J = 41.8 Hz), 120.2 (q, J = 3.5 Hz), 111.6 (q, J = 4.2 Hz), 111.6, 100.7 ppm; HRMS-ESI (m/z): calcd for $C_{21}H_{14}F_3NNaS$, $[M+Na]^+$: 392.0691, found 392.0695.

2-Cyclopropyl-3-(phenylthio)-1H-indole (3h).[12c] Yield: 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.27 (d, J = 7.6 Hz, 1H), 7.18 - 7.08 (m, 6H), 7.02 (t, J = 6.8 Hz, 1H), 2.41 - 2.27 (m, 1H), 1.02 (d, J = 7.6 Hz, 2H), 0.84 (d, J = 4.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.0, 139.7, 135.0, 130.7, 128.6, 125.6, 124.6, 122.2, 120.7, 118.6, 110.8, 99.4, 8.3, 7.9 ppm; HRMS-ESI (m/z): calcd for $C_{17}H_{15}NNaS$, $[M+Na]^+$: 288.0817, found 288.0820.

3-(Phenylthio)-2-propyl-1H-indole (3i).[9a] Yield: 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.16 - 7.08 (m, 3H), 7.08 - 6.99 (m, 3H), 2.86 (t, J = 7.2 Hz, 2H), 1.79 - 1.54 (m, 2H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 139.5, 135.5, 130.3, 128.8, 125.4, 124.6, 122.2, 120.7, 119.1, 110.8, 99.1, 28.6, 23.0, 14.0 ppm; HRMS-ESI (m/z): calcd for $C_{17}H_{17}NNaS$, $[M+Na]^+$: 290.0974, found 290.0978.

2-Isobutyl-3-(phenylthio)-1H-indole (3j).[9a] Yield: 86%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.12 (dd, J = 9.6, 4.8 Hz, 3H), 7.03 (dd, J = 14.8, 7.6 Hz, 3H), 2.75 (d, J = 7.2 Hz, 2H), 1.98 (m, 1H), 0.90 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 139.5, 135.5, 130.3, 128.6, 125.5, 124.5, 122.3, 120.6, 119.2, 111.0, 99.8, 35.6, 29.3, 22.5 ppm; HRMS-ESI (m/z): calcd for $C_{18}H_{19}NNaS$, $[M+Na]^+$: 304.1130, found 304.1133.

3-(Phenylthio)-2-(thiophen-2-yl)-1H-indole (3k).[14a] Yield: 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.77 (s, 1H), 7.64 (d, J = 7.6 Hz, 1H), 7.57 (d, J = 4.8 Hz, 1H), 7.45- 7.31 (m, 2H), 7.24 - 7.19 (m, 1H), 7.13 (dt, J = 14.4, 7.6 Hz, 5H), 7.02 (t, J = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 137.7, 135.6, 132.1, 131.4, 128.8, 126.5, 126.3, 125.6, 124.6, 123.7, 123.4, 121.3, 119.7, 111.2, 99.1 ppm; HRMS-ESI (m/z): calcd for $C_{18}H_{13}NNaS_2$, $[M+Na]^+$: 330.0382, found 330.0386.

2-(Cyclohex-1-en-1-yl)-3-(phenylthio)-1H-indole (3l).[9a] Yield: 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.35 (d, J = 7.6 Hz, 1H), 7.24 - 6.93 (m, 8H), 6.35 (s, 1H), 2.63 - 2.54 (m, 2H), 2.25 - 2.19 (m, 2H), 1.78 - 1.72 (m, 2H), 1.68 - 1.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 139.8, 135.0, 131.2, 130.2, 129.3, 128.6, 125.5, 124.4, 122.8, 120.8, 119.5, 110.8, 97.9, 27.4, 25.7, 22.6, 21.9 ppm; HRMS-ESI (m/z): calcd for $C_{20}H_{19}NNaS$, $[M+Na]^+$: 328.1130, found 328.1126.

2-(3-(Phenylthio)-1H-indol-2-yl)aniline (3m).[9b] Yield: 60%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 7.2 Hz, 2H), 7.22 - 7.14 (m, 4H), 7.08 (d, J =

7.2 Hz, 2H), 7.04 (t, *J* = 7.0 Hz, 1H), 6.83 - 6.74 (m, 2H), 3.55 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 140.5, 138.8, 136.0, 131.4, 130.3, 130.2, 128.7, 125.7, 124.6, 123.2, 121.0, 119.7, 118.8, 117.4, 116.5, 111.2, 101.0 ppm; HRMS-ESI (m/z): calcd for $C_{20}H_{17}N_2S$, $[M+H]^+$: 317.1107, found 317.1105.

2-(4-Chlorophenyl)-3-(phenylthio)-1H-indole (3n).[9b] Yield: 77%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.64 (t, *J* = 6.8 Hz, 3H), 7.45 - 7.34 (m, 3H), 7.27 (t, *J* = 7.6 Hz, 1H), 7.16 (dd, *J* = 14.4, 7.2 Hz, 3H), 7.05 (dd, *J* = 15.6, 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9, 138.8, 135.8, 134.6, 131.2, 129.8, 129.2, 129.0, 128.8, 125.6, 124.8, 123.7, 121.4, 120.1, 111.2, 100.2 ppm; HRMS-ESI (m/z): calcd for $C_{20}H_{14}ClNNaS$, $[M+Na]^+$: 358.0428, found 358.0433.

2-(Naphthalen-2-yl)-3-(phenylthio)-1H-indole (3o).[21] Yield: 75%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.16 (s, 1H), 7.92 - 7.85 (m, 2H), 7.81 (m, 2H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.52 - 7.45 (m, 2H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.28 (t, *J* = 7.2 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.14 - 7.10 (m, 4H), 7.04 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 139.2, 136.1, 133.2, 133.2, 131.4, 128.8, 128.5, 128.4, 127.9, 127.5, 126.8, 126.6, 125.8, 125.6, 124.7, 123.5, 121.3, 120.0, 111.1, 100.2 ppm; HRMS-ESI (m/z): calcd for $C_{24}H_{18}NS$, $[M+H]^+$: 352.1154, found 352.1158.

2-(4-(*tert*-Butyl)phenyl)-3-(phenylthio)benzofuran (5a).[9a] Yield: 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 7.6 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 3H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.25 - 7.18 (m, 5H), 7.13 - 7.08 (m, 1H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 153.8, 152.6, 136.4, 130.8, 129.0, 127.3, 127.0, 126.4, 125.8, 125.6, 125.0, 123.4, 120.3, 111.3, 103.9, 34.9, 31.3 ppm; HRMS-ESI (m/z): calcd for $C_{24}H_{22}NaOS$, $[M+Na]^+$: 381.1284, found 381.1287.

2-(4-Methoxyphenyl)-3-(phenylthio)benzofuran (5b).[14a] Yield: 84%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.24 - 7.16 (m, 5H), 7.13 - 7.06 (m, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 157.8, 153.7, 136.5, 131.2, 129.2, 129.0, 126.3, 125.4, 124.8, 123.4, 122.4, 120.1, 114.2, 111.3, 102.6, 55.5 ppm; HRMS-ESI (m/z): calcd for $C_{21}H_{16}NaO_2S$, $[M+Na]^+$: 355.0763, found 355.0766.

2-(4-Chlorophenyl)-3-(phenylthio)benzofuran (5c).[22] Yield: 76%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.2 Hz, 2H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.43 (d, *J* = 7.2 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.25 - 7.18 (m, 5H), 7.15 - 7.09 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 153.8, 135.7, 135.4, 130.7, 129.2, 128.8, 128.6, 128.3, 126.7, 125.6, 125.5, 123.5, 120.5, 111.6, 105.5 ppm; HRMS-ESI (m/z): calcd for $C_{20}H_{13}ClNaOS$, $[M+Na]^+$: 359.0268, found 359.0265.

Methyl 2-phenyl-3-(phenylthio)benzofuran-5-carboxylate (5d).[9a] Yield: 60%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 - 8.22 (m, 3H), 8.08 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.50 - 7.43 (m, 3H), 7.24 - 7.18 (m, 4H), 7.16 - 7.08 (m, 1H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 158.9, 156.6, 135.9, 131.1, 129.8, 129.4, 129.2, 128.7, 127.6, 127.1, 126.7, 126.0, 125.9, 122.8, 111.3, 105.3, 52.2 ppm; HRMS-ESI (m/z): calcd for $C_{22}H_{16}NaO_3S$, $[M+Na]^+$: 383.0712, found 383.0718.

6-Bromo-2-phenyl-3-(phenylthio)benzofuran (5e).[9a] Yield: 73%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.2 Hz, 2H), 7.68 (s, 1H), 7.42 (dq, *J* = 14.0, 6.8 Hz, 3H), 7.35 - 7.27 (m, 2H), 7.20 - 7.15 (m, 4H), 7.14 - 7.08 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 154.1, 135.8, 130.0, 129.8, 129.3, 129.2, 128.7, 127.4, 127.0, 126.9, 125.9, 121.4, 118.7, 114.8, 105.1 ppm; HRMS-ESI (m/z): calcd for $C_{20}H_{13}BrNaOS$, $[M+Na]^+$: 402.9763, found 402.9756.

6-Nitro-2-phenyl-3-(phenylthio)benzofuran (5f).[9a] Yield: 56%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 6.8 Hz, 2H), 8.06 (s, 1H), 7.94 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.51 - 7.38 (m, 6H), 7.36 - 7.32 (m, 1H), 7.25 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 154.2, 148.9, 139.6, 131.8, 130.0, 129.8, 128.9, 127.4, 125.6, 123.8, 120.8, 120.4, 120.0, 111.8, 102.8 ppm; HRMS-ESI (m/z): calcd for $C_{20}H_{13}NNaO_3S$, $[M+Na]^+$: 370.0508, found 370.0505.

3-((4-Methoxyphenyl)thio)-2-phenylbenzofuran (5g).[14a] Yield: 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.6 Hz, 1H), 7.78 (s, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.37 - 7.29 (m, 2H), 7.24 - 7.16 (m, 5H), 7.10 (dt, *J* = 8.4, 4.8 Hz, 1H), 6.96 (dd, *J* = 8.0, 1.6 Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 157.5, 153.8, 136.2, 130.9, 129.8, 129.1, 126.5, 125.8, 125.4, 123.6, 120.5, 120.0, 115.9, 112.4, 111.4, 105.0, 55.4 ppm; HRMS-ESI (m/z): calcd for $C_{21}H_{16}NaO_2S$, $[M+Na]^+$: 355.0763, found 355.0766.

2-Phenyl-3-(*p*-tolylthio)benzofuran (5h).[13b] Yield: 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 7.6 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 7.2 Hz, 2H), 7.36 (d, *J* = 6.8 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 2H), 6.96 (d, *J* = 7.6 Hz, 2H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 154.0, 135.5, 132.5, 131.1, 123.0, 129.8, 129.2, 128.6, 127.4, 127.0, 125.2, 123.3, 120.6, 111.4, 105.4, 21.2 ppm; HRMS-ESI (m/z): calcd for $C_{21}H_{16}NaOS$, $[M+Na]^+$: 339.0814, found 339.0819.

3-((4-Chlorophenyl)thio)-2-phenylbenzofuran (5i).[13b] Yield: 75%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.2 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.48 - 7.36 (m, 4H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.12 (q, *J* = 8.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 154.2, 134.7, 131.5, 130.6, 129.8, 129.5, 129.2, 128.7, 127.8, 127.5, 125.6, 123.7, 120.3, 111.3, 104.2 ppm; HRMS-ESI (m/z): calcd for $C_{20}H_{13}ClNaOS$, $[M+Na]^+$: 359.0268, found 359.0271.

3-((4-Fluorophenyl)thio)-2-phenylbenzofuran (5j).[13b] Yield: 76%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 7.2 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.45 (t, *J* = 7.2 Hz, 3H), 7.40 (d, *J* = 7.2 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.24 - 7.15 (m, 3H), 6.89 (t, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2 (d, *J* = 243.6 Hz), 157.2, 154.0, 131.0 (d, *J* = 3.2 Hz), 130.6, 129.7, 129.4, 128.7 (d, *J* = 8.3 Hz), 128.6, 127.4, 125.4, 123.4, 120.3, 116.3 (d, *J* = 21.2 Hz), 111.4, 105.4 ppm; HRMS-ESI (m/z): calcd for $C_{20}H_{13}FNaOS$, $[M+Na]^+$: 343.0563, found 343.0557.

3-((3-Nitrophenyl)thio)-2-phenylbenzofuran (5k).[13b] Yield: 60%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.6 Hz, 2H), 8.06 (d, *J* = 8.8 Hz, 2H), 7.612 (d, *J* = 8.0 Hz, 1H), 7.49 - 7.38 (m, 5H), 7.24 (t, *J* = 7.6 Hz,

3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 154.2, 146.4, 145.6, 130.0, 129.3, 128.9, 127.4, 125.9, 125.8, 124.2, 123.8, 119.8, 111.8, 102.2 ppm; HRMS-ESI (m/z): calcd for $C_{20}H_{13}NNaO_3S$, $[M+Na]^+$: 370.0508, found 370.0504.

Conflicts of interest

There are no conflicts to declare.

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