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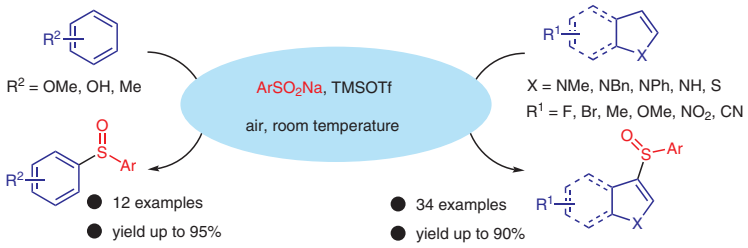
TMSOTf-Promoted Sulfinylation of Electron-Rich Aromatics with Sodium Arylsulfinates

Yuan-Zhao Ji[a]
Hui-Jing Li[*a,b]
Hao-Ran Yang[a]
Zheng-Yan Zhang[a]
Li-Jun Xie[a]
Yan-Chao Wu[*a,b]

[a] School of Marine Science and Technology, Harbin Institute of Technology, 2 Wenhuaxi Road, Weihai 264209, P. R. of China
[b] Weihai Institute of Marine Biomedical Industrial Technology, Wendeng District, Weihai 264400, P. R. of China
lihuijing@iccas.ac.cn
ycwu@iccas.ac.cn



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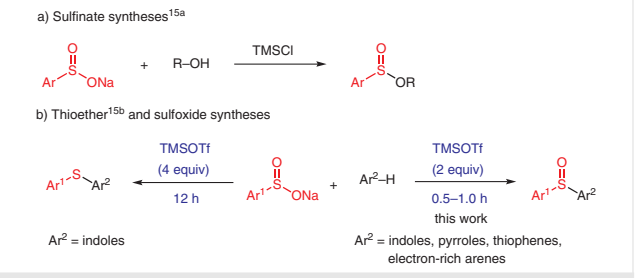
Abstract A new transition-metal-free route for the direct sulfinylation of electron-rich aromatics with sodium arylsulfinates in the presence of TMSOTf is reported. Various electron-rich aromatics, including pyrroles, thiophenes, indoles, and electron-rich arenes, with sodium arylsulfinates are converted into the corresponding sulfoxides in moderate to excellent yields. This protocol possesses many advantages such as readily available and stable starting materials, broad substrate scopes, and transition-metal-free reaction conditions.

Key words sulfinylation, pyrroles, indoles, sulfoxides, sodium arylsulfinates

Sulfoxides are prevalent in important and high-value chemical structures[1] such as the natural products,[2] pharmaceutically active compounds,[3] ligands,[4] organocatalysis,[5] and functional materials.[6] Traditionally, sulfoxides could be prepared by oxidation of sulfides[7] or nucleophilic substitution of sulfinyl derivatives with organometallic reagents.[8] In addition, other synthetic approaches to sulfoxides, such as transition-metal-catalyzed arylation of sulfenate anions,[9] have also been reported.[10] In recent years, direct sulfinylation of electron-rich arenes and heteroarenes has been developed by using sulfinic acids,[11] sulfinates,[12] and sulfinamides[13] as the sulfinylating reagents. Despite these advances, the direct synthesis of the sulfoxides, using easy-to-handle reagents under mild reaction conditions, remains in demand.

On the other hand, sodium arylsulfinates are stable, odorless, and easy-to-handle sulfur compounds, and thus have been widely used as desirable starting materials for the synthesis of organosulfur compounds.[14,15] We have reported the advantages of using sodium arylsulfinates/TMSCl system with oxygenated nucleophiles for obtaining sulfinates under mild conditions (Scheme 1a).[15a] Subsequently, we reported a TMSOTf-promoted thiolation of indoles with sodium arylsulfinates by in situ overreduction of the new generated, sulfinylated intermediates (Scheme 1b, left).[15b] We envisioned that the sulfoxide reduction process might be obviated by carefully controlling the reaction conditions, and thus could facilitate a practical sulfoxide synthesis. We report herein the realization of this strategy by shortening the reaction time (i.e., 12 h vs. 0.5–1 h) and simultaneously decreasing the amount of TMSOTf (i.e., 4 equiv vs. 2 equiv), which provide a facile synthetic protocol to sulfoxides from electron-rich arenes and heteroarenes with sodium arylsulfinates (Scheme 1b, right).



Scheme 1 Synthetic application of sodium arylsulfinates

Reaction of sodium *p*-toluenesulfinate (**1a**) with *N*-Me-pyrrole (**2a**) was used as a probe for evaluating the reaction conditions (Table 1). Following our previous procedure (2 equiv of TMSCl, CH_2Cl_2, rt),[15a] reaction of sodium *p*-toluenesulfinate (**1a**) with *N*-Me-pyrrole (**2a**, 1.5 equiv) afforded 2-sulfinylpyrrole **3a** and 3-sulfinylpyrrole **4a** in 6% and 55% yields, respectively (Table 1, entry 1). Subsequently, DMSCl, TIPSCl, TBDMSCl, TMSOTf, $BF_3{\cdot}Et_2O$, CF_3SO_3H, *p*-TsOH·H_2O, and AcOH were further investigated for this reaction, and TMSOTf is found to be the most efficient promoter for this reaction (Table 1, entries 1–9). The reaction did not work when it was performed in DMF, DMSO, H_2O (Table 1, entries

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10–12). With the use of $MeNO_2$, MeCN, THF, 1,4-dioxane, and toluene in comparison to $(ClCH_2)_2$, lower yields were found (Table 1, entries 13–18). No reaction took place in the absence of TMSOTf (Table 1, entry 19). Further parameters optimization identified the most effective TMSOTf loading as 2.0 equiv (Table 1, entries 13 and 20–24). The reaction was also performed under argon atmosphere, and the same yield was observed (Table 1, entries 13 and 25), which indicated that noble gas atmosphere is not necessary for this reaction.

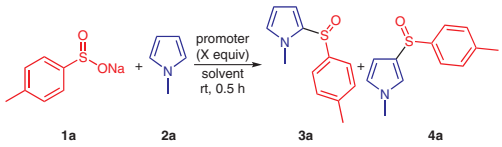
The optimized sulfinylation reaction conditions proved to be effective for various sodium arylsulfinates **1** and pyrroles/thiophenes **2** (Scheme 2). With the aromatic ring bearing hydrogen atoms, electron-withdrawing and electron-donating groups, sodium arylsulfinates **1** reacted smoothly with *N*-Me-pyrrole (**2a**) in the presence of TMSOTf (2 equiv) in $(ClCH_2)_2$ at 25 °C to afford sulfoxides **4a–l** in 31–84% yields within 0.5 h. 1-Naphthyl-, 2-naphthyl-, 2-thienyl-, and cyclopropyl-substituted sodium sulfinates reacted with pyrrole **2a** to generate the sulfoxides **4m–p** in 45–77% yields. *N*-Substituted pyrroles with benzyl and phenyl reacted with sodium *p*-toluenesulfinate (**1a**) to afford the sulfoxides **4q** and **4r** in 90% and 89% yields, respectively. Treatment of 1-tosyl-1*H*-pyrrole with sodium arylsulfinate **2a** failed to give the desired sulfoxide **4s**. The reaction of 1*H*-pyrrole and 2,5-dimethyl-1*H*-pyrrole with sodium arylsulfinate **2a** went smoothly to generate the desired sulfoxides **4t** and **4u** in 41% and 36% yields, respectively.

Reaction of 3-ethyl-2,5-dimethyl-1*H*-pyrrole with sodium arylsulfinate **2a** is complex under the standard conditions and the expected sulfoxides **4v** was not observed. Interestingly, treatment of 1-(1-benzyl-1*H*-pyrrol-2-yl)ethan-1-one, an electron-deficient pyrrole, with sodium arylsulfinate **2a** under the standard conditions did not afford the corresponding thermodynamic product 3-sulfinylpyrrole. Instead, kinetic product 2-sulfinylpyrrole **3w** was obtained in 13% yield, whose structure has been determined from the observed different chemical shifts and coupling constant between H_a/H_b (δ_a = 5.54 ppm, δ_b = 5.50 ppm, $J_{ab} = J_{ba}$ = 15.0 Hz, Scheme 2). Ethyl 1-benzyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylate, an electron-deficient pyrrole with its 3-positions possessing substituents, was also investigated, which reacted with sodium arylsulfinate **2a** to generate the overreduction product **5x** in 47% yield. The reaction of thiophene, 3-hexylthiophene with sodium arylsulfinate **2a** went smoothly to afford sulfoxides **4y** and **4z** in 23% and 63% yields, respectively.

To prove the synthetic utility of this synthetic method, gram-scale reaction was carried out under the standard sulfinylation conditions (Scheme 3). The reaction of sodium sulfinate **1a** (30 mmol, 5.34 g) reacted smoothly with pyrrole **2a** (45 mmol) in the presence of TMSOTf (60 mmol) in $(ClCH_2)_2$ at 25 °C to afford sulfoxides **4a** (5.32 g) in 81% yield within 0.5 h. This result showed the great potential of this sulfinylation reaction in practical synthesis.

To glean insight into the sulfinylation reaction mechanism, a control experiment was carried out in Scheme 4. By treating of 2-substituted sulfoxide product **3a** in the presence of TMSOTf (2 equiv) in $(ClCH_2)_2$ at 25 °C, 3-substituted sulfoxide product **4a** was generated in 90% yield. This result

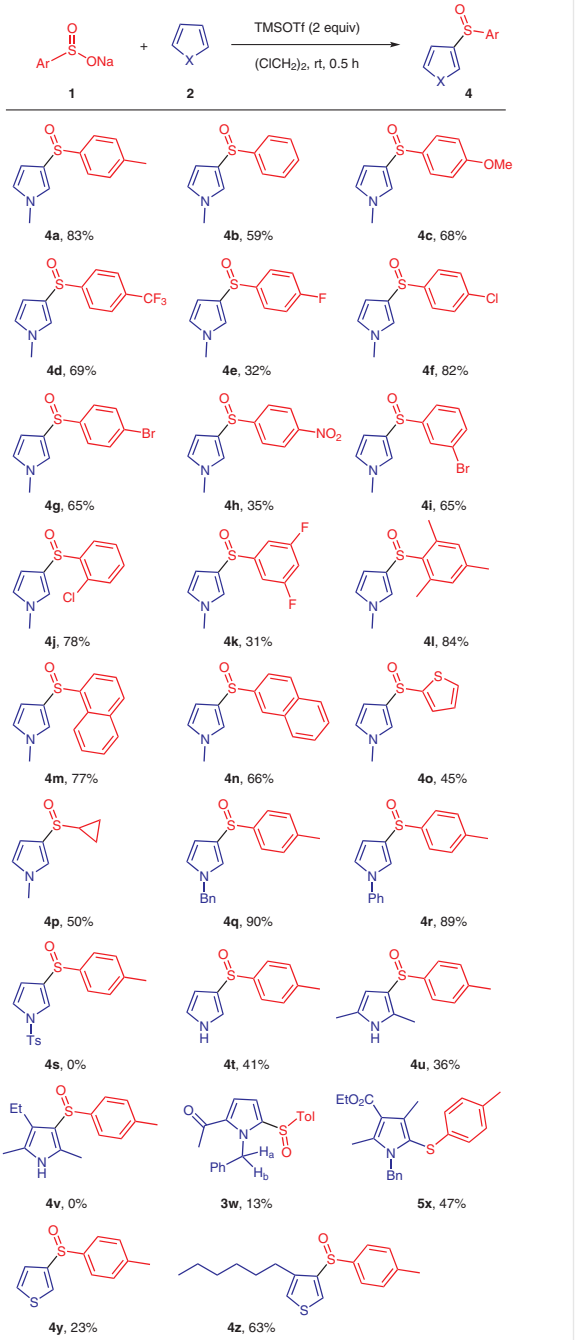
Table 1 Optimization of the Reaction Conditions[a]



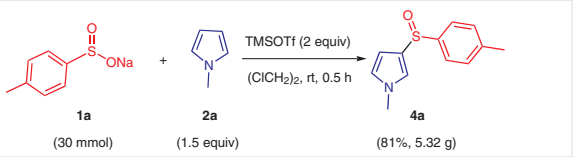
1a 2a 3a 4a

Entry	Promoter (X equiv)	Solvent	Yield of **3a** (%)[b]	Yield of **4a** (%)[b]
1	TMSCl (2.0)	CH_2Cl_2	6	55
2	DMSCl (2.0)	CH_2Cl_2	4	22
3	TIPSCl (2.0)	CH_2Cl_2	2	20
4	TBDMSCl (2.0)	CH_2Cl_2	3	62
5	TMSOTf (2.0)	CH_2Cl_2	0	76
6	$BF_3{\cdot}Et_2O$ (2.0)	CH_2Cl_2	0	60
7	CF_3SO_3H (2.0)	CH_2Cl_2	0	66
8	*p*-TsOH·H_2O (2.0)	CH_2Cl_2	0	23
9	AcOH (2.0)	CH_2Cl_2	N.D.	N.D.
10	TMSOTf (2.0)	DMF	N.D.	N.D.
11	TMSOTf (2.0)	DMSO	N.D.	N.D.
12	TMSOTf (2.0)	H_2O	N.D.	N.D.
13	TMSOTf (2.0)	$(ClCH_2)_2$	0	88 (83[c])
14	TMSOTf (2.0)	$MeNO_2$	0	60
15	TMSOTf (2.0)	MeCN	0	81
16	TMSOTf (2.0)	THF	0	74
17	TMSOTf (2.0)	1,4-dioxane	0	50
18	TMSOTf (2.0)	toluene	0	77
19	–	$(ClCH_2)_2$	N.R.	N.R.
20	TMSOTf (0.5)	$(ClCH_2)_2$	6	10
21	TMSOTf (1.0)	$(ClCH_2)_2$	4	38
22	TMSOTf (1.5)	$(ClCH_2)_2$	0	73
23	TMSOTf (3.0)	$(ClCH_2)_2$	0	74
24	TMSOTf (4.0)	$(ClCH_2)_2$	0	64
25[d]	TMSOTf (2.0)	$(ClCH_2)_2$	0	88

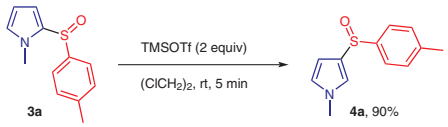
[a] General conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), and promoter (0–0.8 mmol) in solvent (1.0 mL) at rt for 0.5 h. DMS = dimethylsilyl; TIPS = triisopropylsilyl; TBDMS = *tert*-butyldimethylsilyl; N.D. = no detection; N.R. = no reaction.
[b] The yield was determined by ^1H NMR spectroscopy using 0.2 mmol of CH_2Br_2 as a standard.
[c] Isolated yield.
[d] Under argon.



Scheme 2 TMSOTf-promoted sulfinylation of pyrroles/thiophenes **2** with sodium sulfinates **1**. *Reagents and conditions*: **1** (0.2 mmol), **2** (0.3 mmol), and TMSOTf (0.4 mmol) in $(ClCH_2)_2$ (1.0 mL) at rt for 0.5 h. Isolated yields are given.



Scheme 3 Gram-scale synthesis



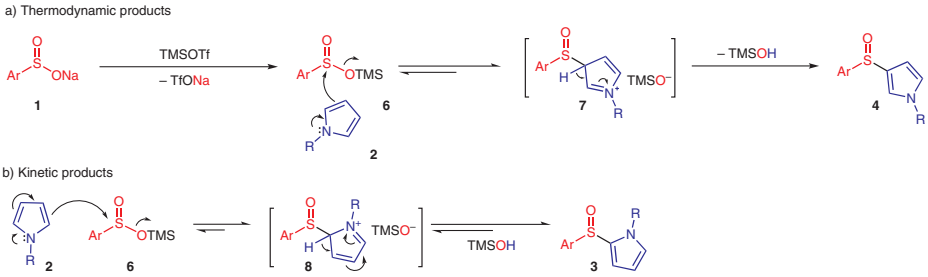
Scheme 4 The control experiment

indicated that the sulfinylation reaction probably underwent a rearrangement from C2-sulfinylpyrroles **3** to C3-sulfinylpyrroles **4**.

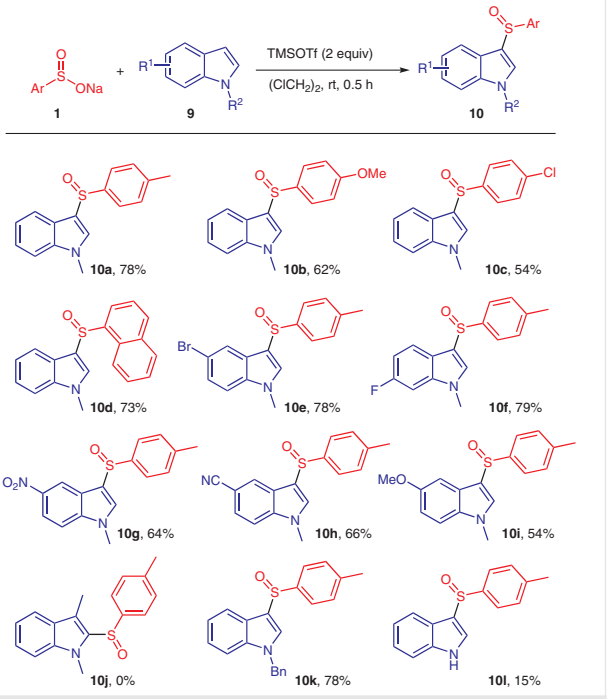
Based on the experimental results and literature reports,[15,16] the possible reaction pathway for the sulfinylation of pyrroles is depicted in Scheme 5. Reaction of sodium arylsulfinates **1** with TMSOTf generated trimethylsilyl sulfinates **6**, which underwent electrophilic substitution reaction with pyrroles **2** at the C3 position to form thermodynamic intermediates **7**. Finally, intermediates **7** were converted into thermodynamic products **4** with the release of TMSOH (Scheme 5, a). On the other hand, electrophilic substitution reaction of trimethylsilyl sulfinates **6** with pyrroles **2** at the C2 position generated kinetic intermediates **8**, which were converted into kinetic products **3** with the release of TMSOH (Scheme 5, b). When electron-rich pyrroles were used as the substrates, thermodynamic products **4** were obtained as the major products under our standard reaction conditions. When electron-deficient pyrroles were used as the substrates, kinetic products, such as 2-sulfinylpyrrole **3w**, or the related overreduction products, such as thioether **5x**, might be obtained.

Sulfinylation of indoles **9** with sodium arylsulfinates **1** were subsequently investigated (Scheme 6). With the aromatic ring bearing electron-withdrawing or electron-donating groups (Cl, Me, MeO), sodium sulfinates **1** reacted smoothly with *N*-methylindole (**9a**) in the presence of TMSOTf (2 equiv) in $(ClCH_2)_2$ at 25 °C to afford sulfoxides **10a–c** in 54–78% yields within 0.5 h. Sodium naphthalene-1-sulfinate reacted well with indole **9a** to afford sulfoxide **10d** in 73% yield. A wide variety of indoles with substituent groups such as halogen, nitro, cyano, and methoxyl reacted smoothly with sodium *p*-toluenesulfinate (**1a**) to afford sulfoxides **10e–i** in 54–79% yields. Unfortunately, treatment of 1,3-dimethyl-1*H*-indole with sodium arylsulfinate **2a** failed to provide the desired sulfoxide **10j**. *N*-Substituted indole with benzyl and *N*-unsubstituted indole reacted with sodium *p*-toluenesulfinate (**1a**) to generate sulfoxides **10k** and **10l** in 78% and 15% yields, respectively.

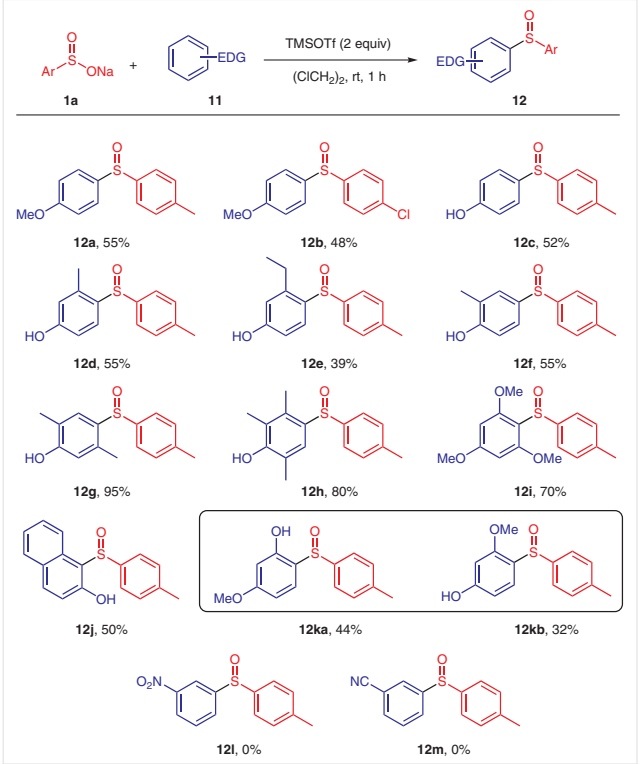
The feasibility of this sulfoxide synthesis was also explored by using various arenes **11** as the substrates (Scheme 7). Arenes **11** bearing electron-donating groups (EDG) such as OMe, OH, and Me reacted with sodium arylsulfinates **1** in the presence of TMSOTf (2 equiv) in $(ClCH_2)_2$ at 25 °C to afford sulfoxides **12a–i** in 39–95% yields within 1 h.



Scheme 5 Proposed mechanism for the sulfinylation of pyrroles **2** with sodium arylsulfinates **1**



Scheme 6 TMSOTf-promoted sulfinylation of indoles **9** with sodium arylsulfinates **1**. *Reagents and conditions*: **1** (0.2 mmol), **9** (0.4 mmol), and TMSOTf (0.4 mmol) in $(ClCH_2)_2$ (1.0 mL) at rt for 0.5 h. Isolated yields are given.



Scheme 7 TMSOTf-promoted sulfinylation of arenes **11** with sodium arylsulfinates **1**. *Reagents and conditions*: **1** (0.2 mmol), **11** (0.4 mmol), and TMSOTf (0.4 mmol) in $(ClCH_2)_2$ (1.0 mL) at rt for 1 h. Isolated yields are given.

Naphthalen-2-ol reacted well with sodium *p*-toluenesulfinate (**1a**) to afford the desired sulfoxide **12j** in 50% yield. Treatment of 3-methoxyphenol with sodium arylsulfinate **1a** afforded the two sulfoxide isomers **12ka** and **12kb** in 44% and 32% yields, respectively. Treatment of nitrobenzene and cyanobenzene with sodium sulfinate **2a** under the standard conditions failed to give the desired sulfoxides **12l** and **12m**; meanwhile, the starting material nitrobenzene and cyanobenzene were recovered in 89% and 86% yields, respectively.

In summary, we have developed a facile sulfoxides synthesis via the TMSOTf-promoted sulfinylation of electron-rich aromatics, including pyrroles, thiophenes, indoles, and electron-rich arenes, with sodium arylsulfinates under transition-metal-free conditions.[17] A wide variety of sulfoxides were obtained with moderate to excellent yields. These reactions could take place under mild conditions without the need for using transition-metal catalysts, which offers attractive industrial application prospects.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1691563.

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(17) **General Procedure for the Preparation of Sulfoxides 4**
The mixture of sodium arylsulfinate (0.2 mmol, 1.0 equiv), pyrrole/thiophenes (0.3 mmol, 1.5 equiv), and TMSOTf (0.4 mmol, 2.0 equiv) in $(ClCH_2)_2$ (1.0 mL) was stirred at 25 °C for 0.5 h. After completion of the reaction, water (5 mL) and dichloromethane (10 mL) were added. The two layers were separated, and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed by brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (ethyl acetate–petroleum ether = 1:1) to afford the desired sulfoxides **4**.
Compound **4a**: white solid, mp 84–86 °C; 36.3 mg, 83% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (d, *J* = 8.2 Hz, 2 H), 7.27 (d, *J* = 8.0 Hz, 2 H), 6.95 (t, *J* = 2.0 Hz, 1 H), 6.58 (t, *J* = 2.5 Hz, 1 H), 6.16 (dd, *J* = 3.0, 1.7 Hz, 1 H), 3.64 (s, 3 H), 2.39 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.9, 140.3, 129.3, 126.8, 124.5, 124.3, 123.9, 107.4, 36.4, 21.2. Data are in accordance to those previously reported.[13a]
General Procedure for the Preparation of Sulfoxides 10
The mixture of sodium arylsulfinate (0.2 mmol, 1.0 equiv), indole (0.4 mmol, 2.0 equiv), and TMSOTf (0.4 mmol, 2.0 equiv) in $(ClCH_2)_2$ (1.0 mL) was stirred at 25 °C for 0.5 h. After completion of the reaction, water (5 mL) and dichloromethane (10 mL) were added. The two layers were separated, and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed by brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (ethyl acetate–petroleum ether = 1:1) to afford the desired sulfoxides **10**.
Compound **10a**: white solid, mp 138–139 °C; 42.0 mg, 78% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.2 Hz, 2 H), 7.48 (d, *J* = 8.7 Hz, 2 H),7.34–7.24 (m, 4 H), 7.12–7.08 (m, 1 H), 3.79 (s, 3 H), 2.40 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.9, 140.3, 137.6, 132.5, 129.5, 124.8, 124.3, 123.2, 121.3, 119.8, 116.5, 110.0, 33.2, 21.2. Data are in accordance to those previously reported.[13a]
General Procedure for the Preparation of Sulfoxides 12
The mixture of sodium arylsulfinate (0.2 mmol, 1.0 equiv), arene (0.4 mmol, 2.0 equiv), and TMSOTf (0.4 mmol, 2.0 equiv) in $(ClCH_2)_2$ (1.0 mL) was stirred at 25 °C for 1 h. After completion of the reaction, water (5 mL) and dichloromethane (10 mL) were added. The two layers were separated, and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed by brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (ethyl acetate–petroleum ether = 1:1) to afford the desired sulfoxides **12**.
Compound **12a**: colorless oil, 27.0 mg, 55% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 8.8 Hz, 2 H), 7.49 (d, *J* = 8.1 Hz, 2 H), 7.25 (d, *J* = 7.3 Hz, 2 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 3.81 (s, 3 H), 2.36 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.8, 142.5, 141.2, 136.9, 129.8, 127.0, 124.7, 114.7, 55.4, 21.3. Data are in accordance to those previously reported.[11a]

