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An Efficient Catalytic Method for Regioselective Sulfenylation of Electron-Rich Aza-Aromatics at Room Temperature

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Dedicated to Professor Alfredo Ricci on the occasion of his retirement

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Electron-rich aza-aromatic compounds such as indoles and pyrroles are structures of particular interest and importance in organic chemistry. A useful methodology for the regioselective introduction of the sulfenyl group into electron-rich aza-aromatics using *S*-alkyl- and *S*-arylthiophthalimides as sulfenylating agents is described. Catalytic amounts of $CeCl_3 \cdot 7H_2O$/NaI are crucial to the promotion of this regioselective carbon–sulfur-bond-forming electrophilic aromatic substitution reaction. The reaction occurred under mild conditions, and the products were obtained in good to excellent yields. The method represents an efficient preparation of sulfenyl aza-aromatics, which are useful intermediates for important organic transformations, due to the great importance of functionalized indoles among natural compounds and pharmaceutical products.

Introduction

The Friedel–Crafts reaction is one of the most important reactions in organic synthesis, and it provides a useful method for the direct introduction of a functional group into heteroarene compounds.[1] The Friedel–Crafts reaction of electron-rich aza-aromatic rings such as indoles and pyrroles is an interesting challenge in organic chemistry, due to the strong tendency of these compounds to polymerize.[2] Thus, useful modifications in bond-forming Friedel–Crafts-type reactions for the preparation of heterocyclic polyfunctionalized molecules have been realized.[3] Recent studies by us and by others have shown that cerium(III) chloride also promotes the reaction of indoles and pyrroles with several electrophiles, and new reactions for the formation of carbon–nitrogen, carbon–oxygen, and carbon–carbon bonds have been developed.[4] $CeCl_3$ has emerged as a cheap, nontoxic, and water-tolerant Lewis acidic promoter, and the reactivity of commercially available $CeCl_3 \cdot 7H_2O$ increases dramatically in the presence of an iodide source, such as NaI.[5] In recent years, the 3-sulfenylation of indoles with disulfides catalyzed by copper(I) and iron(III) salts have been shown to give similarly excellent improvements over existing Friedel–Crafts-type reactions.[6] Among the numerous aza-aromatic derivatives known, 3-thioindoles have recently attracted considerable attention from both industry and academia, due to their therapeutic value against a variety of diseases.[7] In the public domain, examples of complex small molecules (Figure 1) containing 3-thioindole moieties include MK-886 (**A**), an inhibitor of 5-lipoxygenase,[8] and 3-(arylsulfenyl)indole **B**, an inhibitor of tubulin polymerization that is also capable of inhibiting the growth of human breast cancer cells.[9] 3-Thioindole derivatives are also often used as synthetic intermediates in the preparation of heterocyclic compounds of higher complexity, such as L-737,126 (**C**), which is known to have potent anti-HIV properties.[10] Considering the synthetic utility of 3-thioindoles, methods to insert sulfide moieties into polyfunctionalized aza-aromatic molecules[11] are important, and the development of new procedures that can also be used for this purpose would be desirable.

Many strategies have been developed for the 3-sulfenylation of electron-rich heterocycles, and sulfenylating agents such as thiols,[12] sulfenyl halides,[13] and quinone mono-*O*,*S*-acetals[14] have been used. However, these methods are very difficult to use because of the severe reaction conditions required together with the limited stability of the

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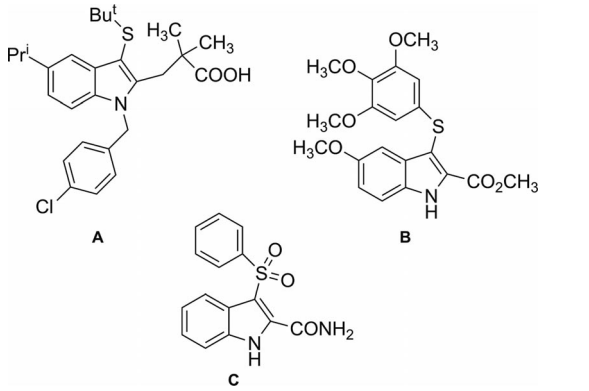


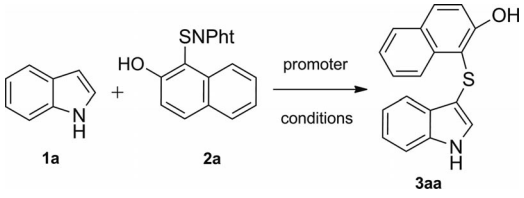
Figure 1. Examples of biologically active 3-thioindole derivatives.

reagents, and the observed yields are relatively low. Furthermore, some of the catalysts used are expensive, toxic, and air/moisture sensitive. Thus, a mild and efficient general method for the sulfenylation of aza-aromatics is still necessary. Given that some of us have experience in electrophilic sulfur-transfers, we focused our attention on *N*-thiophthalimides. It is well known that these reagents are useful sulfur-transfer reagents that have been used for many years for the formation of new sulfur–sulfur[15] and sulfur–nitrogen[16] bonds. In particular, they have been used in the synthesis of complex natural products, such as in the introduction the methyl trisulfide moiety into the calicheamicin skeleton.[17] Generally, *N*-thiophthalimides are commonly prepared by reacting potassium phthalimide with the appropriate sulfenyl halide.[18] However, this procedure suffers from several limitations due to the high reactivity, low stability, and difficulties in storing and handling of many sulfenyl halides. We have developed an optimized procedure in which phthalimidesulfenyl chloride (PhtNSCl, Pht = Phthaloyl), a crystalline solid that can be easily prepared and stored for months without decomposition, reacts with nucleophiles, such as alkynes,[19] enolizable ketones,[20] phenols,[21] and other electron-rich arenes,[22] to form a variety of *N*-thiophthalimides as potential sulfur-transfer reagents useful for the formation of carbon–sulfur bonds.[19–23] For all these reasons, we report in this paper the results of a study on the potential of different substituted *S*-aryl- and *S*-alkylthiophthalimides as sulfur-transfer reagents towards indoles and pyrroles, a reaction of particular interest bearing in mind the biological relevance of the products obtained. In this context, recently, Silveira et al. have found that 3-sulfenyl indoles are obtained by using *N*-thiophthalimides and dry $CeCl_3$ in DMF at 80 °C.[24] We have repeated the reaction without $CeCl_3$, and the corresponding 3-sulfenyl indole was recovered in similar yield (72%). The same formation of indole dimer or trimer by-products, whose separation from the desired product by liquid chromatography is very difficult, was also observed. This result provides evidence that the $CeCl_3$ is not necessary in Silveira's conditions. Thus, a general electrophilic aromatic substitution reaction of indoles and pyrroles with this type of sulfur electrophile reagents under mild conditions of $CeCl_3{\cdot}7H_2O$/NaI catalysis seemed an attractive proposition. Indeed, our efforts have allowed us to develop a new general procedure that proceeds under mild catalytic reaction conditions, and unlike the method reported by Tudge et al.,[25] we have developed a sulfenylation protocol that proceeds at room temperature.

Results and Discussion

First, the reaction of indole (**1a**) with *S*-arylthiophthalimide **2a** was carried out using $CeCl_3{\cdot}7H_2O$ (1 equiv.) and NaI (1 equiv.) as promoter, in acetonitrile at room temperature, the desired 3-sulfenylindole (i.e., **3aa**) was produced in 75% yield after 24 h (Table 1, entry 1). Changing the temperature to 70 °C, only traces of the desired product were recovered, along with several by-products (Table 1, entry 2).

Table 1. Sulfenylation of indole **1a** under different reaction conditions.[a]



Entry	$CeCl_3{\cdot}7H_2O$ [equiv.]	NaI [equiv.]	Conditions/time	Yields [%][b]
1	1.00	1.00	CH_3CN, r. t./4 h	75
2	1.00	1.00	CH_3CN, reflux/2 h	trace[c]
3	1.00	1.00	SiO_2, r. t./2 h	trace[c]
4	0.30	0.30	CH_3CN, r. t./4 h	95
5	0.30	–	CH_3CN, r. t./4 h	trace[d]
6	–	0.30	CH_3CN, r. t./4 h	trace[d]

[a] All reactions were carried out by stirring mixtures of **1a** (2 mmol), *N*-thiophthalimide **2a** (2 mmol), and catalyst for the reaction times shown. [b] Yields of products isolated by column chromatography. [c] Complex reaction mixture analyzed by GC/MS. [d] Starting material recovered after reaction.

Then we moved to a solvent-free approach, which we had used previously in the development of a new strategy for the Michael reaction,[26] but this strategy was unsuccessful, and only traces of 3-sulfenylindole **3aa** were recovered (Table 1, entry 3). In general, an equimolar ratio of cerium trichloride and NaI in acetonitrile was found to give the best results, and in optimizing the reaction conditions, we tested several different stoichiometries of $CeCl_3{\cdot}7H_2O$/NaI relative to the starting materials, while keeping these two reagents in an equimolar ratio. Our results in Table 1 indicate that 0.3 equiv. cerium salt and 0.3 equiv. NaI were the most appropriate for this type of reaction. Hence in this process, the $CeCl_3{\cdot}7H_2O$/NaI system works as a catalyst rather than a stoichiometric promoter of this sulfenylating reaction. Undoubtedly, the presence of NaI is essential for the efficient preparation of 3-sulfenylindole **3aa** by our

methodology, but all previous efforts to structurally characterize our $CeCl_3 \cdot 7H_2O$/NaI system have been unsuccessful. For a possible understanding of the mechanistic role of NaI, we analyzed the interaction between $CeCl_3 \cdot 7H_2O$ and NaI by X-ray Photoelectron Spectroscopy (XPS).[27] The $CeCl_3 \cdot 7H_2O$/NaI system was treated with acetonitrile for 4 h at room temperature, and then the solvent was removed by rotary evaporation and the resulting mixture was analyzed. From this study, it may be inferred that the introduction of the NaI into the system does not alter the degree of the hybridization of the f states with the conduction states. This suggests that there is no direct interaction between the Ce^{III} center and the iodide ion. Given that it is known that the activity of $CeCl_3 \cdot 7H_2O$/NaI system is mainly exerted in the heterogeneous phase, we believe that a chloride-bridged oligomeric structure of $CeCl_3 \cdot 7H_2O$[28] could be broken by donor species such as iodide ion, and that the resulting monomeric $CeCl_3 \cdot 7H_2O$/NaI complex would be a more active Lewis acid catalyst. After optimization of the amounts of $CeCl_3 \cdot 7H_2O$ and NaI used in the reaction, we also observed that neither $CeCl_3 \cdot 7H_2O$ (Table 1, entry 5) nor NaI (Table 1, entry 6) alone could accomplish the sulfenylation reaction, even after 1 week. It is also worth noting that the sulfenylation is not catalyzed by water alone: no trace of 3-sulfenyl indole was observed following the simple addition of water to a mixture of indole (**1a**) and *N*-thiophthalimide **2a**.

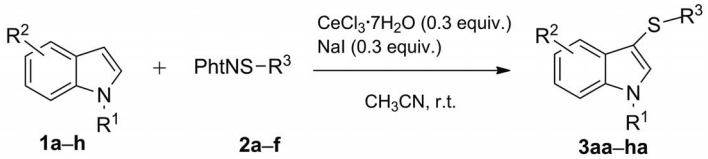
A variety of solvents were examined, and the efficiency based on the yields of **3aa** showed that acetonitrile was the solvent of choice. In fact, the order, in terms of efficiency, was as follows (yields in parentheses): acetonitrile (95%), EtOH (64%), THF (60%), DMF (55%), CH_2Cl_2 (45%), and Et_2O (40%). Then we examined several substrates using a variety of functionalized indoles and *S*-alkyl- and *S*-arylthiophthalimides. The results are shown in Table 2. The substitution on the indole nucleus occurred exclusively at the 3-position, and the indole nitrogen did not require prior protection. Under our conditions, the indole moieties are reactive substrates, and even indolyl rings bearing electron-withdrawing groups gave the corresponding 3-sulfenylindoles in satisfactory yields (Table 2, entries 5, 7, 8, and 11). We also investigated the electronic effects of substituents on the nitrogen of the indole ring, and here, the presence of an electron-donating group (in **1d**) resulted in the formation of the corresponding product **3da** in a shorter reaction time than when an electron-withdrawing group was present (in **1f**) (Table 2, entries 6 and 10, respectively). It can, therefore, safely be asserted that the reaction proceeded in good yield, even for less reactive indoles, and, interestingly, also for an indole derivative containing a hydroxy group (i.e., **1b**). It is known that direct Lewis-acid-promoted reactions of hydroxyindole substrates are generally problematic, and normally result in low yields due to the interaction of the indolyl hydroxy group with the Lewis acid catalyst.[29] With our system, this problem with hydroxyindoles was much reduced (Table 2, entries 2 and 3). In short, the conditions of our methodology are such that they provide high compatibility with a wide range of functional groups.

In the light of this, and due to the great importance of functionalized indoles[30] among natural compounds and pharmaceutical products, we used our methodology for the synthesis of a heterocyclic compound with five fused rings (i.e., **3ha**) (Table 2, entry 13). The optimized reaction conditions were successfully applied to *tert*-butyl 1*H*-indole-2-carboxylate **1h** too. This compound was easily prepared from the corresponding 2-carboxylic acid indole,[31] and then, after reaction with arylthiophthalimide **2a**, we isolated the corresponding oxathiepinoindole (i.e., **3ha**) in good yield, and with none of the 3-sulfenylindole adduct isolated. We believe that the formation of the lactone moiety in **3ha** could occur through intramolecular transesterification arising from the selective deprotection of a *tert*-butyl ester catalyzed by the $CeCl_3 \cdot 7H_2O$/NaI system.[32] It is also noteworthy that an ethyl ester does not undergo deprotection (Table 2, entry 4), and although we cannot exclude an interaction of the Ce^{III} Lewis acid with the β-keto ester moiety[33] of **2c**, this is neither productive nor an obstacle to the sulfenylation reaction.

The results show that the combination of NaI and $CeCl_3$ is essential for the sulfenylation, and the fact that the adducts (i.e., **3**) were obtained in high yields without formation of any of the oligomeric by-products normally observed under the influence of strong acids[34] excludes the possibility that sites may contain simultaneously Brønsted and Lewis acidic sites.[35] To confirm this, following Spencer's approach,[36] we found that the reaction worked well in the presence of a strongly hindered base, 2,6-di-*tert*-butyl-4-methylpyridine, which only binds to protons and is unable to coordinate to the cerium center, due to the bulky *tert*-butyl groups.[37] Analogously, we also obtained high yields of the desired products in the presence of a radical inhibitor such as 2,6-di-*tert*-butyl-4-methylphenol,[38] which demonstrates that the reaction has not occurred following an electron-transfer pathway. Finally, we also carried out the reaction with other cerium salts such as CAN [Cerium(IV) ammonium nitrate], $Ce(OTf)_3$, and $Ce(NO_3)_3$. Among these, $CeCl_3$ was found to be the most effective reagent, and gave the best results. The reactivity observed in all cases indicates that the reaction was being catalyzed by Lewis acidic cerium rather than the counter-ion in $CeCl_3$.[25] Thus, even though it would be premature to speculate on the exact nature of the mechanism, our findings can be rationalized by assuming that under these conditions,[19c,22b] an initial coordination of a cerium(III) Lewis acid species occurs at the oxygen of the imidic group (Scheme 1).

Unfortunately, it was impossible to follow the course of the reaction by NMR spectroscopy,[39] owing to the presence of paramagnetic Ce^{III} species.[40] In fact, when we tried to study the complexation of reagents with $CeCl_3$ by ^{13}C NMR spectroscopy, the signals observed were very broad, and no identifiable species could be discerned from the spectra. An attempt to study the process in the more expensive [D_3]acetonitrile (rather than $CDCl_3$ or CD_3OD) gave more complicated results. Therefore, we propose that a nucleophilic substitution of the indole C-3 at the sulfur of the sulfenyl group moiety gave intermediates **4** and **5**.

Table 2. 3-Sulfenylation of indoles **1** catalyzed by $CeCl_3 \cdot 7H_2O$/NaI in acetonitrile at room temp.[a]



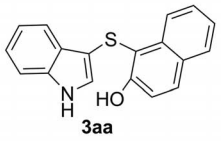
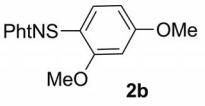
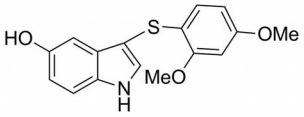
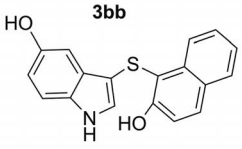
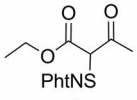
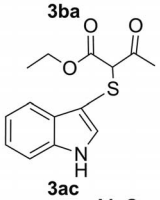
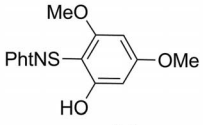
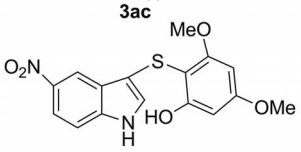
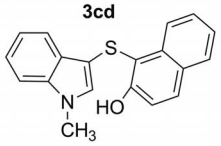
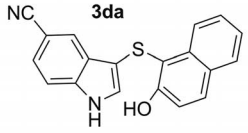
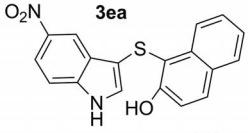
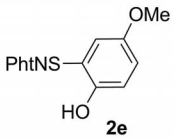
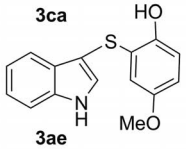
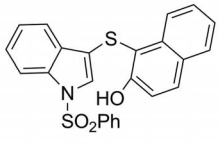
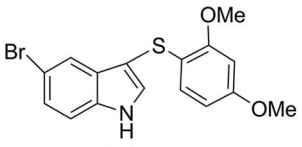
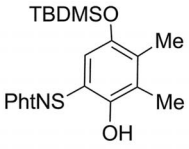
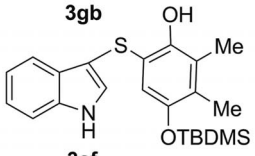
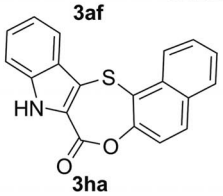
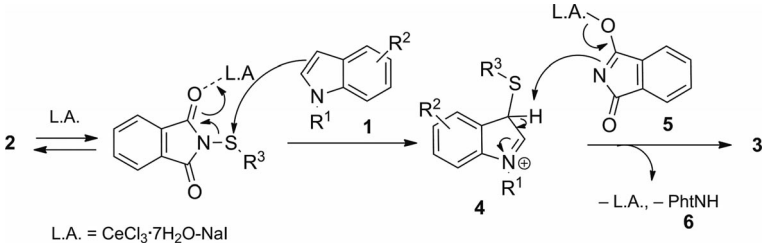
Entry	R^1, R^2	2	Product[b]	Time (h)	Yield (%)[c]
1	R^1 = H R^2 = H **1a**	**2a**	 **3aa**	4	95
2	R^1 = H R^2 = 5-OH **1b**	 **2b**	 **3bb**	24	78
3	**1b**	**2a**	 **3ba**	6	76
4	**1a**	 **2c**	 **3ac**	1	79
5	R^1 = H R^2 = 5-NO_2 **1c**	 **2d**	 **3cd**	2.5	75
6	R^1 = CH_3 R^2 = H **1d**	**2a**	 **3da**	1	90
7	R^1 = H R^2 = 5-CN **1e**	**2a**	 **3ea**	1	70
8	**1c**	**2a**	 **3ca**	1	73
9	**1a**	 **2e**	 **3ae**	1.5	82
10	R^1 = H R^2 = 1-SO_2Ph **1f**	**2a**	 **3fa**	3	85

Table 2. *(continued)*

Entry	R^1, R^2	2	Product[b]	Time (h)	Yield (%)[c]
11	R^1 = H R^2 = 5-Br **1g**	**2b**	 **3gb**	24	88
12	**1a**	 **2f**	 **3af**	24	77
13	R^1 = H R^2 = 2-CO_2Bu^t **1h**	**2a**	 **3ha**	1	80[d]

[a] All products were identified by their IR, NMR, and mass spectra. [b] Regioselectivity estimated from ^{1}H NMR spectroscopic analysis. [c] Yields of products after isolation by flash chromatography. [d] Only the product of cyclization was isolated. TBDMS = *tert*-butyldimethylsilyl.

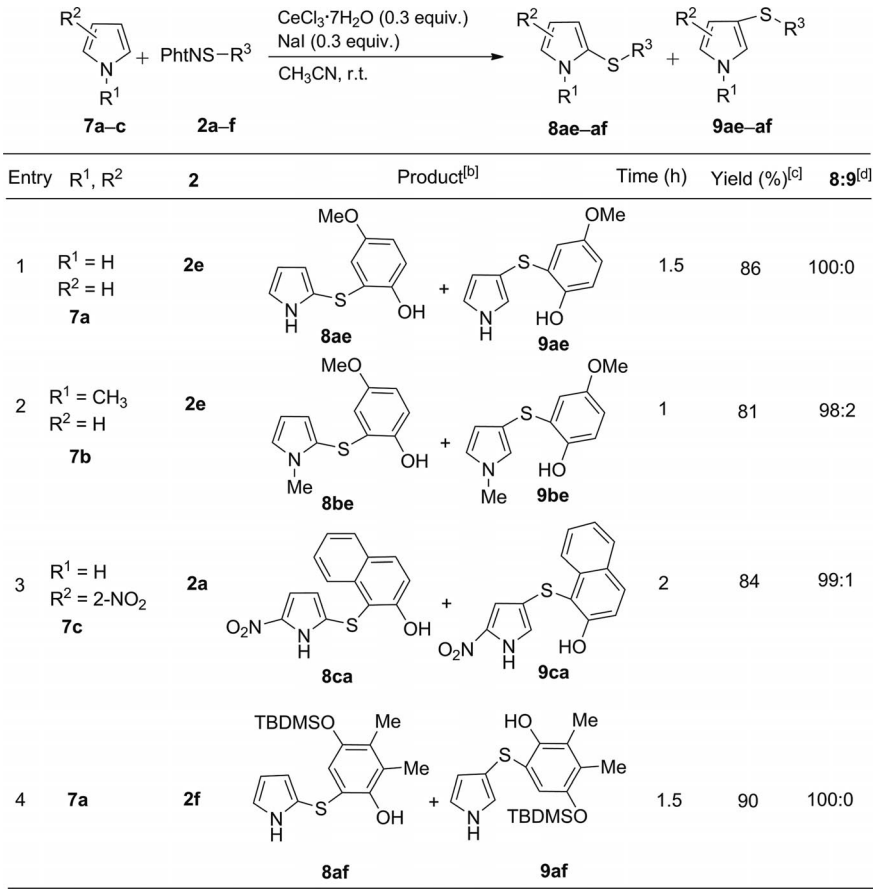


Scheme 1. Proposed reaction mechanism.

Finally aromatization of **4** to reform the indole ring (in **3**) occurs by deprotonation of **4** by the nitrogen atom of **5**, releasing the catalyst and resulting in the formation of phthalimide **6** and sulfenyl indole target **3**. Of course, various other mechanistic hypothesis have been proposed to explain the formation of the 3-sulfonylindoles in other sulfenylation reaction systems.[4,41] However, all these interpretations are ruled out in our system by some unequivocal experimental evidence. We observed that our $CeCl_3$·$7H_2O$/NaI system failed to promote some intramolecular electrophilic cyclizations of *N*-thiophthalimides that occur using, for example, $AlCl_3$ as Lewis acid. It is difficult to rationalize how these reactions could fail if a very reactive sulfenyl iodide was formed as intermediate. Certainly, we cannot definitely rule out the possibility of the formation of a transient sulfenyl iodide as the actual sulfur-transfer reagent, as in the mechanism described by Tudge.[25] However, the high lability of sulfenyl iodides, compared to those of other halides,[42] and their fast disproportionation to give disulfides, which were never isolated or observed as by-products in our experiments, seem to suggest that the actual sulfur-transfer species is a Lewis-acid-activated *N*-thiophthalimide, as shown in Scheme 1, and not a sulfenyl iodide. Further confirmation of such a mechanism comes from the fact that no diaryl disulfide was observed when *S*-arylthiophthalimide **2a** was treated with $CeCl_3$·$7H_2O$/NaI system without the addition of indole (**1a**).

Pyrroles, like indoles, are heteroaromatic structural motifs present in a vast number of natural products,[43] and they are frequently used as building blocks in the construction of more complex heterocycles in medicinal and pharmaceutical chemistry.[44] The importance of sulfenyl pyrroles as valuable building blocks for the assembly of bioactive agents with a broad range of pharmacological activity[45] prompted us to evaluate whether our Lewis-acid-catalyzed sulfenylation reaction could also be used on pyrrole substrates.[46] We tested the optimized reaction conditions, and 2-sulfenylpyrroles were obtained in good yields, in short reaction times, and with complete regioselectivity for C-2-sulfenylation (Table 3).

Table 3. Sulfenylation of pyrroles **7** with thiophthalimides **2** catalyzed by $CeCl_3 \cdot 7H_2O$/NaI at room temp.[a]



Entry	R^1, R^2	2	Product[b]	Time (h)	Yield (%)[c]	8:9[d]
1	R^1 = H, R^2 = H, **7a**	**2e**	**8ae** + **9ae**	1.5	86	100:0
2	R^1 = CH_3, R^2 = H, **7b**	**2e**	**8be** + **9be**	1	81	98:2
3	R^1 = H, R^2 = 2-NO_2, **7c**	**2a**	**8ca** + **9ca**	2	84	99:1
4	**7a**	**2f**	**8af** + **9af**	1.5	90	100:0

[a] All products were identified by their IR, NMR, and mass spectra. [b] Regioselectivity estimated from ^{1}H NMR spectroscopic analysis. [c] Yields of products after isolation by flash chromatography. [d] The regioisomeric ratio was estimated by GC/MS analysis of the crude of reaction mixture. It was not possible to separate the C-3-substituted by-product by column chromatography.

Conclusions

In summary, we have reported a Lewis-acid-catalyzed sulfenylation of electron-rich aza-aromatic compounds with good functional group tolerance, using a $CeCl_3 \cdot 7H_2O$/NaI system. The simplicity of our approach, the low cost of the reagents, and the fact that no particular precautions to exclude moisture or oxygen from the reaction system need to be taken suggest to us that the $CeCl_3 \cdot 7H_2O$/NaI combination could be useful in further reactions for the formation of new heterocycles. In particular, the procedure studied represents an efficient method for the preparation of sulfenyl aza-aromatic compounds, which are of profound importance in organic chemistry. It is clear that the simplicity of this approach represents another example of the attractiveness of $CeCl_3 \cdot 7H_2O$/NaI as catalyst for new bond-forming reactions. Even if the exact nature of the intermediate obtained by the interaction of the reagents with the $CeCl_3 \cdot 7H_2O$/NaI catalyst is not yet known, we believe that this method will find many useful applications in organic synthesis and in medicinal chemistry.[47] The mild reaction conditions described in this paper also suggest that new applications of this sulfenylation method in synthesis should be possible, which will result in the utility of *N*-thiophthalimides, already regarded as useful compounds, being developed further. New schemes of synthesis for the preparation of other biologically important substances are in progress in our laboratories, and the results will be reported subsequently.

Experimental Section

General Remarks: Commercially available reagents were used throughout without purification unless otherwise stated. Solvents (EtOAc and hexanes) for flash chromatography were distilled. Analytical thin-layer chromatography was carried out on pre-coated glass-backed plates (Merck Kieselgel 60 F_{254}), which were visualized under UV light at 254 nm and/or by dipping the plates into iodine vapour and Von's reagent [ceric sulfate (1.0 g) and ammonium molybdate (24.0 g) in sulfuric acid (31 mL) and water (470 mL)]. Solutions were evaporated under reduced pressure with a rotary evaporator, and the residue was purified by chromatography on silica gel 60 (230–400 mesh).

Fully characterized compounds were chromatographically homogeneous. Infrared spectra were recorded with a Perkin–Elmer FTIR Paragon 500 spectrometer as thin films on NaCl plates. Only the characteristic peaks are quoted. NMR spectra were recorded at 400 MHz (^{1}H) or 100 MHz (^{13}C). Chemical shifts are quoted in

ppm, and were referenced to residual H in the deuterated solvent as the internal standard. *J* values are quoted in Hz. Mass spectra were obtained both using electron ionization (EI) at 70 eV, and electrospray ionization (ESI). Fragment ions were separated with a quadrupolar mass analyzer. High-resolution mass-spectra (HRMS) analysis was carried out using ESI, analyzed by time-of-flight (TOF). X-ray Photoelectron Spectroscopy was performed with an A1 anode (A1 K_α: 1487.7 eV). A surface area of 700 × 300 nm was analyzed at a take-off angle of 90°. The analyzer was a VG-Clam 4 hemisperical analyzer, which provided on overall resolution of 0.7 eV for a constant pass energy of 22 eV. All measurements were performed below 10^{-9} Torr.

Typical Procedure for the $CeCl_3·7H_2O$/NaI-Catalyzed Sulfenylation Reaction of 1-(1*H*-Indol-3-ylthio)naphthalen-2-ol (3aa): $CeCl_3·7H_2O$ (0.26 g, 0.72 mmol) and NaI (0.1 g, 0.72 mmol) were added to a mixture of indole (**1a**; 0.28 g, 2.4 mmol) and 2-(2-hydroxynaphthalen-1-ylthio)isoindoline-1,3-dione (**2a**; 0.76 g, 2.4 mmol) in CH_3CN (25 mL) at room temperature. The reaction mixture was stirred at room temperature for 4 h. After the reaction was complete, as indicated by TLC, the mixture was treated with a solution of CH_3COOH (10% in dist. H_2O; 10 mL) and extracted with CH_2Cl_2 (50 mL). The extract was washed with a saturated solution of $NaHCO_3$ (10 mL) and dried with anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was purified by chromatography on silica gel (eluent: cyclohexane/ethyl acetate = 75:25) to afford 3-sulfenylindole **3aa** (0.66 g, 95%) as a brown oil. ^{1}H NMR (CD_3OD): δ = 6.94 (t, *J* = 8.1 Hz, 1 H), 7.04 (t, *J* = 8.1 Hz, 1 H), 7.16 (d, *J* = 8.9 Hz, 1 H), 7.26–7.28 (m, 2 H), 7.46–7.50 (m, 2 H), 7.64 (d, *J* = 7.7 Hz, 1 H), 7.69–7.72 (m, 2 H), 8.72 (d, *J* = 8.5 Hz, 1 H) ppm. ^{13}C NMR (CD_3OD): δ = 106.0, 112.7, 112.8, 114.1, 118.6, 120.1, 120.7, 124.1, 124.3, 126.2, 128.0, 129.5, 130.3, 132.2, 135.4, 136.9, 137.9, 157.7 ppm. IR (neat): $\tilde{\nu}$ = 3424, 3056, 1593 cm^{-1}. ESI-MS: positive ion mode: *m*/*z* = 292 $[M + H]^+$, 314 $[M + Na]^+$; negative ion mode: *m*/*z* = 290 $[M - H]^-$, 326 $[M + Cl]^-$. HRMS: calcd. for $C_{18}H_{14}NOS$ $[M + H]^+$ 292.0796; found 292.0790.

3-(2,4-Dimethoxyphenylthio)-1*H*-indol-5-ol (3bb): Column chromatography on silica gel (eluent: cyclohexane/ethyl acetate = 75:25) gave product **3bb** in 78% isolated yield as a yellow oil. ^{1}H NMR ($CDCl_3$): δ = 3.75 (d, *J* = 3.1 Hz, 3 H), 3.92 (d, *J* = 8.5 Hz, 3 H), 5.02 (br. s, 1 H), 6.23–6.26 (m, 1 H), 6.45 (d, *J* = 2.1 Hz, 1 H), 6.62 (d, *J* = 8.5 Hz, 1 H), 6.80–6.83 (m, 2 H), 6.99 (s, 1 H), 7.42 (d, *J* = 2.6 Hz, 1 H), 8.37 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 55.7, 56.1, 98.9, 101.7, 104.3, 105.2, 112.6, 112.9, 127.7, 129.9, 130.6, 131.8, 131.9, 150.8, 156.6, 158.9 ppm. IR (neat): $\tilde{\nu}$ = 3391, 1582, 1410 cm^{-1}. ESI-MS: positive ion mode: *m*/*z* = 302 $[M + H]^+$, 324 $[M + Na]^+$; negative ion mode: *m*/*z* = 300 $[M - H]^-$, 335 $[M + Cl]^-$. HRMS: calcd. for $C_{16}H_{16}NO_3S$ $[M + H]^+$ 302.0851; found 302.0847.

3-(2-Hydroxynaphthalen-1-ylthio)-1*H*-indol-5-ol (3ba): Column chromatography on silica gel (eluent: cyclohexane/ethyl acetate = 70:30) gave product **3ba** in 76% isolated yield as a yellow oil. ^{1}H NMR (CD_3OD): δ = 6.61–6.64 (m, 1 H), 7.07–7.17 (m, 3 H), 7.25 (t, *J* = 8.1 Hz, 1 H), 7.43 (s, 1 H), 7.48 (t, *J* = 7.3 Hz, 1 H), 7.68–7.71 (m, 2 H), 8.71 (d, *J* = 8.5 Hz, 1 H) ppm. ^{13}C NMR (CD_3OD): δ = 106.0, 112.7, 119.5, 120.1, 120.7, 123.0, 124.3, 126.2, 128.0, 129.5, 130.1, 130.9, 132.1, 135.3, 136.9, 137.9, 157.7 ppm. IR (neat): $\tilde{\nu}$ = 3457, 1303, 1508 cm^{-1}. ESI-MS: positive ion mode: *m*/*z* = 308 $[M + H]^+$, 330 $[M + Na]^+$; negative ion mode: *m*/*z* = 307 $[M - H]^-$, 342 $[M + Cl]^-$. HRMS: calcd. for $C_{18}H_{14}NO_2S$ $[M + H]^+$ 308.0745; found 308.0744.

Ethyl 2-(1*H*-Indol-3-ylthio)-3-oxobutanoate (3ac): Column chromatography on silica gel (eluent: cyclohexane/ethyl acetate = 70:30) gave product **3ac** in 79% isolated yield as a brown oil. ^{1}H NMR ($CDCl_3$): δ = 1.23 (t, *J* = 6.4 Hz, 3 H), 1.35 (t, *J* = 6.4 Hz, 3 H), 2.35 (s, 3 H), 2.57 (s, 3 H), 4.16–4.22 (dd, *J* = 6.8, *J′* = 14.1 Hz, 2 H), 4.24–4.29 (dd, *J* = 6.8, *J′* = 14.1 Hz, 2 H), 7.20–7.23 (m, 2 H), 7.34–7.37 (m, 2 H), 7.41 (s, 1 H), 7.75–7.76 (m, 4 H), 7.86–7.87 (m, 3 H), 8.26 (br. s, 1 H), 8.51 (br. s, 1 H) ppm. ^{13}C NMR ([D_6]DMSO): δ = 13.6, 26.8, 61.7, 62.9, 118.2, 120.4, 122.5, 123.2, 132.4, 133.3, 134.3, 134.4, 168.7, 205.5 ppm. IR (neat): $\tilde{\nu}$ = 3406, 2496, 1772, 1413 cm^{-1}. ESI-MS: positive ion mode: *m*/*z* = 300 $[M + Na]^+$. HRMS: calcd. for $C_{14}H_{16}NO_3S$ $[M + H]^+$ 278.0851; found 278.0849.

3,5-Dimethoxy-2-(5-nitro-1*H*-indol-3-ylthio)phenol (3cd): Column chromatography on silica gel (eluent: cyclohexane/ethyl acetate = 70:30) gave product **3cd** in 75% isolated yield as a green solid, m.p. 129–132 °C (ethanol). ^{1}H NMR (CD_3OD): δ = 3.30 (s, 3 H), 4.86 (s, 3 H), 6.69 (d, *J* = 3.40 Hz, 1 H), 7.44–7.49 (m, 1 H), 7.77–7.83 (m, 2 H), 8.01–8.04 (dd, *J* = 2.14, *J′* = 8.97 Hz, 1 H), 8.55 (d, *J* = 2.11 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 105.2, 105.2, 111.3, 111.3, 112.0, 117.8, 118.2, 119.2, 123.8, 127.6, 127.7, 134.6, 138.2, 142.6, 168.3 ppm. IR (neat): $\tilde{\nu}$ = 3104, 2479, 1558, 1413, 1321 cm^{-1}. ESI-MS: positive ion mode: *m*/*z* = 347 $[M + H]^+$. HRMS: calcd. for $C_{16}H_{15}N_2O_5S$ $[M + H]^+$ 347.0702; found 347.0700.

1-(1-Methyl-1*H*-indol-3-ylthio)naphthalen-2-ol (3da): Column chromatography on silica gel (eluent: cyclohexane/ethyl acetate = 89:20) gave product **3da** in 90% isolated yield as a brown solid. ^{1}H NMR (CD_3OD): δ = 3.71 (s, 3 H), 6.99 (t, *J* = 7.3 Hz, 1 H), 7.09–7.17 (m, 2 H), 7.26–7.29 (m, 2 H), 7.41 (s, 1 H), 7.49 (t, *J* = 7.7 Hz, 1 H), 7.66–7.73 (m, 3 H), 8.71 (d, *J* = 8.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 33.2, 103.3, 109.8, 112.5, 116.9, 119.3, 120.4, 122.5, 123.6, 125.1, 127.5, 128.7, 128.7, 129.6, 131.7, 132.7, 135.2, 137.1, 155.8 ppm. IR (neat): $\tilde{\nu}$ = 3362, 1241, 1508 cm^{-1}. ESI-MS: positive ion mode: *m*/*z* = 306 $[M + H]^+$, 308 $[M + Na]^+$; negative ion mode: *m*/*z* = 304 $[M - H]^-$. HRMS: calcd. for $C_{19}H_{16}NOS$ $[M + H]^+$ 306.0953; found 306.0949.

3-(2-Hydroxynaphthalen-1-ylthio)-1*H*-indole-5-carbonitrile (3ea): Column chromatography on silica gel (eluent: cyclohexane/ethyl acetate = 70:30) gave product **3ea** in 70% isolated yield as a yellow oil. ^{1}H NMR (CD_3OD): δ = 7.18 (d, *J* = 8.97 Hz, 1 H), 7.26–7.32 (m, 2 H), 7.40 (d, *J* = 8.55 Hz, 1 H), 7.49–7.53 (m, 1 H), 7.66 (s, 1 H), 7.70–7.75 (m, 2 H), 8.11 (s, 1 H), 8.70 (d, *J* = 8.55 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.5, 29.9, 112.7, 117.1, 123.9, 124.5, 124.6, 124.9, 126.0, 127.9, 128.9, 128.9, 132.4, 132.4, 135.2 ppm. IR (neat): $\tilde{\nu}$ = 3447, 2225, 1462 cm^{-1}. ESI-MS: negative ion mode: *m*/*z* = 315 $[M - H]^-$. HRMS: calcd. for $C_{19}H_{13}N_2OS$ $[M + H]^+$ 317.0749; found 317.0745.

1-(5-Nitro-1*H*-indol-3-ylthio)naphthalen-2-ol (3ca): Column chromatography on silica gel (eluent: cyclohexane/ethyl acetate = 70:30) gave product **3ca** in 73% isolated yield as an orange oil. ^{1}H NMR (CD_3OD): δ = 6.68 (d, *J* = 3.42 Hz, 1 H), 7.44–7.49 (m, 2 H), 7.78–7.84 (m, 5 H), 8.01–8.04 (dd, *J* = 2.60, *J′* = 9.00 Hz, 1 H), 8.55 (d, *J* = 2.14 Hz, 1 H) ppm. ^{13}C NMR (CD_3OD): δ = 105.1, 112.4, 117.8, 118.5, 124.2, 125.9, 127.9, 128.8, 129.5, 130.9, 131.0, 132.0, 133.1, 134.4, 135.5, 171.1 ppm. IR (neat): $\tilde{\nu}$ = 3627, 3095, 1602, 1561, 1330 cm^{-1}. ESI-MS: negative ion mode: *m*/*z* = 335 $[M - H]^-$. HRMS: calcd. for $C_{18}H_{13}N_2O_3S$ $[M + H]^+$ 337.0647; found 337.0644.

2-(1*H*-Indol-3-ylthio)-4-methoxyphenol (3ae): Column chromatography on silica gel (eluent: cyclohexane/ethyl acetate = 80:20) gave product **3af** in 82% isolated yield as a yellow oil. ^{1}H NMR (CD_3OD): δ = 3.63 (s, 3 H), 6.18 (d, *J* = 3.00 Hz, 1 H), 6.43–6.46 (m, 1 H), 6.67 (d, *J* = 8.55 Hz, 1 H), 7.04–7.9 (m, 1 H), 7.44–7.47 (t, *J* = 7.26 Hz, 1 H), 7.51 (s, 1 H) 7.75–7.82 (m, 2 H) ppm. ^{13}C

NMR (CD_3OD): δ = 55.9, 101.6, 111.6, 113.1, 113.7, 115.3, 115.6, 115.2, 117.1, 121.1, 130.6, 132.8, 138.7, 148.4, 154.9 ppm. IR (neat): $\tilde{\nu}$ = 3660, 3457, 1604 cm^{-1}. ESI-MS: negative ion mode: *m/z* = 270 $[M - H]^-$. HRMS: calcd. for $C_{15}H_{14}NO_2S$ $[M + H]^+$ 272.0745; found 272.0743.

1-[1-(Phenylsulfonyl)-1*H*-indol-3-ylthio]naphthalen-2-ol (3fa): Column chromatography on silica gel (eluent: toluene/cyclohexane/ethyl acetate = 60:35:5) gave product **3fa** in 85% isolated yield as a yellow oil. ^1H NMR (CD_3OD): δ = 6.25 (d, *J* = 10.26 Hz, 1 H), 6.91 (s, 1 H), 7.30–7.32 (m, 1 H), 7.36–7.39 (m, 3 H), 7.44–7.46 (m, 1 H), 7.46–7.54 (m, 5 H), 7.57 (d, *J* = 10.26 Hz, 1 H), 7.76 (d, *J* = 9.00 Hz, 1 H), 7.88 (d, *J* = 8.12 Hz, 1 H), 7.98 (d, *J* = 6.83 Hz, 1 H) ppm. ^{13}C NMR (200 MHz, $CDCl_3$, Me_4Si): δ = 111.2, 121.3, 123.1, 124.0, 124.8, 127.1, 127.9, 128.5, 128.5, 129.2, 130.1, 130.2, 130.4, 120.5, 131.8, 134.6, 141.4, 152.4, 187.2 ppm. IR (neat): $\tilde{\nu}$ = 3062, 2906, 1668, 1214 cm^{-1}. HRMS: calcd. for $C_{24}H_{18}NO_3S_2$ $[M + H]^+$ 432.0728; found 432.0724.

5-Bromo-3-(2,4-dimethoxyphenylthio)-1*H*-indole (3gb): Column chromatography on silica gel (eluent: cyclohexane/ethyl acetate = 80:20) gave product **3gb** in 88% isolated yield as a white solid, m.p. 138–140 °C (ethanol). ^1H NMR ($CDCl_3$): δ = 3.73 (s, 3 H), 3.92 (s, 3 H), 6.25–6.28 (dd, *J* = 1.7, *J′* = 8.55 Hz, 1 H), 6.46 (d, *J* = 2.14 Hz, 1 H), 6.65 (d, *J* = 8.55 Hz, 1 H), 7.29 (d, *J* = 1.28 Hz, 1 H), 7.45 (d, *J* = 2.12 Hz, 1 H), 7.73–7.78 (m, 1 H), 7.84–7.86 (m, 1 H), 8.81 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 55.7, 56.1, 99.1, 102.9, 105.3, 113.2, 114.5, 118.1, 122.6, 123.8, 126.1, 128.4, 131.4, 132.1, 132.8, 134.6 ppm. IR (neat): $\tilde{\nu}$ = 3677, 1508, 1303 cm^{-1}. ESI-MS: positive ion mode: *m/z* = 265 $[M + H]^+$; negative ion mode: *m/z* = 263 $[M - H]^-$, 399 $[M + Cl]^-$. HRMS: calcd. for $C_{16}H_{15}BrNO_2S$ $[M + H]^+$ 364.0007; found 364.0005.

4-(*tert*-Butyldimethylsilyloxy)-6-(1*H*-indol-3-ylthio)-2,3-dimethylphenol (3af): Column chromatography on silica gel (eluent: cyclohexane/ethyl acetate = 80:20) gave product **3af** in 77% isolated yield as a yellow oil. ^1H NMR ($CDCl_3$): δ = 0.05 (s, 6 H), 0.96 (s, 9 H), 2.08 (s, 3 H), 2.18 (s, 3 H), 7.17–7.24 (m, 2 H), 6.80 (s, 1 H), 7.30–7.32 (m, 2 H) 7.73 (d, *J* = 7.7 Hz, 1 H), 8.26 (br. s, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.2, 18.4, 26.1, 105.4, 111.8, 117.2, 119.5, 120.4, 121.0, 123.2, 124.3, 128.6, 128.7, 130.0, 136.5, 146.9, 148.1 ppm. IR (neat): $\tilde{\nu}$ = 3600, 3500, 1453 cm^{-1}. ESI-MS: positive ion mode: *m/z* = 400 $[M + H]^+$; negative ion mode: *m/z* = 398 $[M - H]^-$. HRMS: calcd. for $C_{22}H_{30}NO_2SSi$ $[M + H]^+$ 400.1767; found 400.1767.

Naphtho[2′,1′:2,3][1,4]oxathiepino[6,5-*b*]indol-8(9*H*)-one (3ha): Column chromatography on silica gel (eluent: cyclohexane/ethyl acetate = 80:20) gave product **3ha** in 80% isolated yield as an orange oil. ^1H NMR (C_6D_6): δ = 5.95 (d, *J* = 9.8 Hz, 1 H), 6.45 (d, *J* = 10.9 Hz, 1 H), 6.68 (d, *J* = 7.3 Hz, 1 H), 6.86–6.97 (m, 2 H), 7.18–7.26 (m, 1 H), 7.29–7.31 (m, 1 H), 7.45 (d, *J* = 8.1 Hz, 1 H), 7.57 (d, *J* = 7.7 Hz, 1 H), 8.08 (d, *J* = 8.1 Hz, 1 H) ppm. ^{13}C NMR (C_6D_6): δ = 121.8, 123.6, 124.4, 125.0, 127.4, 128.1, 128.2, 128.4, 128.6, 128.8, 128.9, 130.1, 130.2, 130.4, 132.5, 136.3, 140.9, 153.2, 186.6 ppm. IR (neat): $\tilde{\nu}$ = 3046, 1675, 1507, 1456 cm^{-1}. ESI-MS: negative ion mode: *m/z* = 317 $[M - H]^-$. HRMS: calcd. for $C_{19}H_{12}NO_2S$ $[M + H]^+$ 318.0589; found 318.0586.

4-Methoxy-2-(1*H*-pyrrol-2-ylthio)phenol (8ae): Column chromatography on silica gel (eluent: cyclohexane/ethyl acetate = 80:20) gave product **8ae** in 86% isolated yield as a grey solid, m.p. 73–75 °C (petroleum ether). ^1H NMR ($CDCl_3$): δ = 3.70 (s, 3 H), 6.01 (br. s, 1 H), 6.20–6.22 (m, 1 H), 6.51 (s, 1 H), 6.72–6.78 (s, 1 H), 6.82–6.85 (m, 2 H), 7.76–7.80 (m, 1 H), 8.39 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 55.9, 110.4, 115.9, 116.4, 116.8, 117.4, 121.8, 123.8, 134.5, 149.1, 153.7 ppm. IR (neat): $\tilde{\nu}$ = 3422, 3603, 1542 cm^{-1}. EI-MS: *m/z* (%) = 221 (100) $[M]^+$, 188, 126. HRMS: calcd. for $C_{11}H_{12}NO_2S$ $[M + H]^+$ 222.0589; found 222.0588.

4-Methoxy-2-(1-methyl-1*H*-pyrrol-2-ylthio)phenol (8be): Column chromatography on silica gel (eluent: cyclohexane/ethyl acetate = 90:10) gave product **8be** in 80% isolated yield as a brown oil. ^1H NMR ($CDCl_3$): δ = 3.58 (s, 3 H), 3.64 (s, 3 H), 6.25–6.17 (m, 1 H), 6.46 (d, *J* = 3 Hz, 1 H), 6.54–6.56 (m, 1 H), 6.61–6.64 (m, 1 H), 6.77 (s, 1 H), 6.79–6.81 (m, 1 H), 8.4 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 34.5, 55.9, 108.7, 114.8, 116.2, 116.5, 118.9, 123.8, 126.5, 134.5, 148.8, 153.8 ppm. IR (neat): $\tilde{\nu}$ = 3452, 1410, 1260 cm^{-1}. EI-MS: *m/z* (%) = 235 $[M]^+$, 202, 126, 81 (100). HRMS: calcd. for $C_{12}H_{14}NO_2S$ $[M + H]^+$ 236.0745; found 236.0745.

3-(5-Nitro-1*H*-pyrrol-2-ylthio)naphthalen-2-ol (8ca): Column chromatography on silica gel (eluent: cyclohexane/ethyl acetate = 95:5) gave product **8ca** in 84% isolated yield as a brown solid, m.p. 96–98 °C (petroleum ether). ^1H NMR ($CDCl_3$): δ = 6.28 (d, *J* = 10.3 Hz, 1 H), 6.60 (br. s, 1 H), 7.34–7.49 (m, 3 H), 7.51–7.58 (m, 2 H), 7.73–7.77 (m, 1 H), 7.81–7.83 (m, 1 H), 8.16–8.2 (d, *J* = 8.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 121.3, 123.1, 124.1, 124.8, 127.1, 128.0, 128.5, 130.4, 130.5, 131.8, 135.6, 111.4, 152.5, 187.2 ppm. IR (neat): $\tilde{\nu}$ = 3436, 2855, 1552 cm^{-1}. HRMS: calcd. for $C_{14}H_{11}N_2O_3S$ $[M + H]^+$ 287.0490; found 287.0488.

4-(*tert*-Butyldimethylsilyloxy)-2,3-dimethyl-6-(1*H*-pyrrol-2-ylthio)-phenol (8af): Column chromatography on silica gel (eluent: cyclohexane/ethyl acetate = 90:10) gave product **8ag** in 90% isolated yield as a brown oil. ^1H NMR ($CDCl_3$): δ = 0.12 (s, 6 H) 0.98 (s, 9 H), 2.1 (s, 3 H), 2.16 (s, 3 H), 6.07 (s, 1 H), 6.17–6.19 (m, 1 H), 6.44–6.46 (br. s, 1 H), 6.66 (s, 1 H), 6.78–6.80 (dd, *J* = 1.2, *J′* = 2.5 Hz, 1 H), 8.07–8.11 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.1, 13.3, 18.4, 26.0, 29.9, 40.1, 40.0, 110.0, 116.1, 117.5, 117.7, 119.9, 121.2, 123.6, 124.8, 130.1, 137.0, 147.9 ppm. IR (neat): $\tilde{\nu}$ = 3410, 2930, 1600, 1549, 1332 cm^{-1}. EI-MS: *m/z* (%) = 349 $[M]^+$, 225, 198 (100), 73. HRMS: calcd. for $C_{18}H_{28}NO_2SSi$ $[M + H]^+$ 350.1610; found 350.1609.

Supporting Information (see footnote on the first page of this article): IR, EI and ESI mass, ^1H and ^{13}C NMR spectra of 3-sulfenylindoles and 2-sulfenylpyrrole products.

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