Regioselective C-H Thioarylation of Electron-Rich Arenes by Iron(III) Triflimide Catalysis

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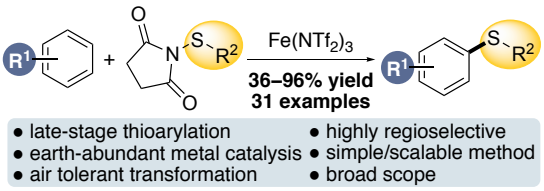


Abstract: A mild and regioselective method for the preparation of unsymmetrical biaryl sulfides using iron(III)-catalysis is described. Activation of *N*-(arylthio)succinimides using the powerful Lewis acid, iron(III) triflimide allowed the efficient thiolation of a range of arenes, including anisoles, phenols, acetanilides and *N*-heterocycles. The method was applicable for the late-stage thiolation of tyrosine and tryptophan derivatives and was used as the key step for the synthesis of pharmaceutically relevant biaryl sulfur-containing compounds such as the antibiotic, dapsone and the antidepressant, vortioxetine. Kinetic studies revealed that while *N*-(arylthio)succinimides bearing electron-deficient arenes underwent thioarylation catalyzed entirely by iron(III) triflimide, *N*-(arylthio)succinimides with electron-rich arenes displayed an autocatalytic mechanism promoted by the Lewis basic product.

INTRODUCTION

Aryl thioethers are important structural components of various natural products and pharmaceutically active agents,[1] such as the antiallergenic compound, AZD4407,[2] the immunosuppressive agent, azathioprine[3] and axitinib, a tyrosine kinase inhibitor (Figure 1).[4] As well as applications in material science,[5] aryl thioethers are also useful synthetic precursors of sulfoxides and sulfones.[6] For these reasons, a wide range of methods for the preparation of aryl thioethers have been reported. The most common approaches involve the reaction of organometallic reagents[7] or arylboronic acid derivatives[8] with electrophilic arylsulfur reagents, or the cross-coupling of aryl halides or pseudohalides with thiols or disulfides using transition metals, including palladium, copper and nickel.[9]

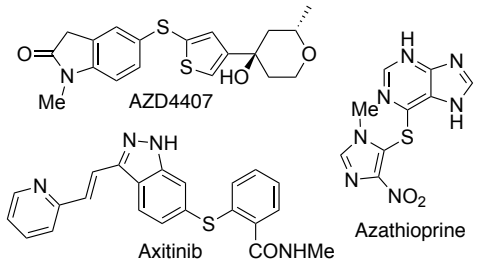
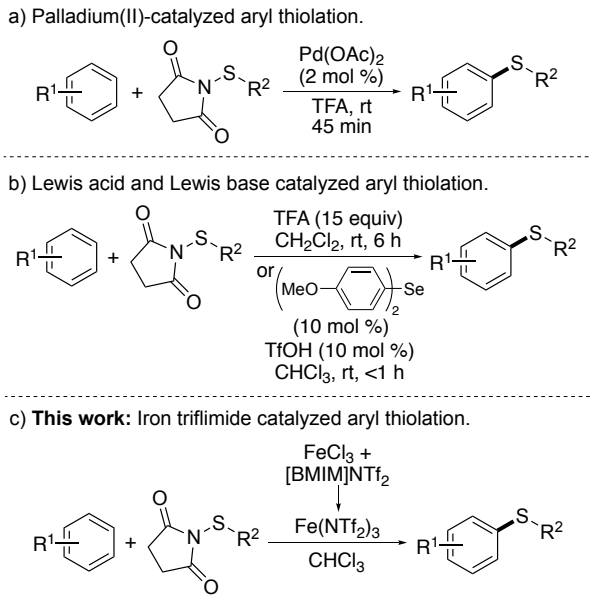


Figure 1. Examples of medicinally relevant biaryl sulfides.

To avoid the use of prefunctionalized arenes, methods have been developed allowing direct thiolation of aryl C–H bonds.[10] Although many examples have been reported that utilize directing group assisted, transition metal-catalyzed aryl C–H activation, followed by C–S bond formation,[11] there has been much recent interest in exploring aromatic thiolation via electrophilic aromatic substitution. In particular, several approaches have described arene thiolation using *N*-thiosuccinimides (Scheme 1).[12–15] For example, rapid thiolation of electron-rich arenes was achieved using palladium catalysis in trifluoroacetic acid (TFA) (Scheme 1a),[12] while others have demonstrated thioarylation of highly activated arenes such as phenols[13a] or anilines[13b] using Lewis acid catalysis or elevated temperatures. The Cossy research group showed that superstoichiometric quantities of TFA could be used for the room temperature activation of *N*-thiosuccinimides and the subsequent thiolation of (hetero)arenes (Scheme 1b).[14] More recently,

Gustafson and co-workers used a Lewis base/Bronsted acid catalyzed combination, involving a diarylselenide and triflic acid for the rapid thiolation of a wide range of (hetero)arenes (Scheme 1b).[15]

Scheme 1. Electrophilic Aromatic Thiolation of Arenes Using *N*-Thiosuccinimides



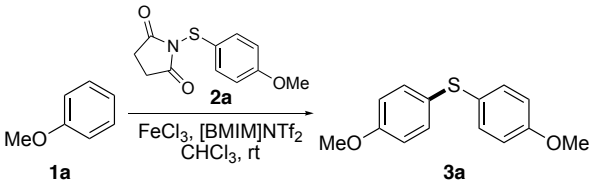
Although some of these methods allow the fast and efficient thiolation of aromatic compounds, they require the use of either precious metal catalysis and/or acidic conditions. We were interested in developing a highly regioselective, mild thioarylation reaction using *N*-thiosuccinimides that involved neither precious transition metals nor strongly acidic conditions. In recent years, we have reported the use of the super Lewis acid, iron(III) triflimide, generated from iron(III) chloride and the readily available and inexpensive ionic liquid, [BMIM]NTf_2, for the activation of *N*-halosuccinimides and the regioselective halogenation of arenes.[16] More recently, this transformation was combined with intramolecular copper-catalyzed C–N and C–O bond forming processes, for the one-pot synthesis of benzannulated heterocycles.[17] Based on these results, we proposed that iron(III) triflimide could also be an effective Lewis acid catalyst for the thioarylation of arenes (Scheme 1c). We now report a regioselective synthesis of unsymmetrical biaryl thioethers via iron(III) triflimide activation of *N*-(arylthio)succinimides. As well as describing the different reaction pathways through kinetic analysis, we

also demonstrate the use of this reaction for the late-stage thioarylation of amino acids and drug compounds and, as the key step for the preparation of medicinally important sulfides and sulfones.

RESULTS AND DISCUSSION

The reaction was optimized by investigation of the reaction of anisole (**1a**) with *N*-(4-methoxyphenylthio)succinimide (**2a**) (Table 1).[18] Initially, the role of iron(III) chloride and [BMIM]NTf_2, that generate iron(III) triflimide in situ, was explored. In the absence of both species, or using only the ionic liquid, no reaction was observed (entries 1 and 2). The reaction did proceed in the presence of iron(III) chloride (2.5 mol %), and after 5 hours, gave bis(4-methoxyphenyl)sulfane (**3a**) as a single regioisomer in 67% yield (entry 3). This result was significantly improved using iron(III) triflimide, which gave **3a** in 90% yield after a 2 hour reaction (entry 4). Although higher catalyst loadings resulted in a faster reaction (entry 5), the overall benefit did not warrant the increased amounts of reagents. A solvent screen was also performed and while dichloromethane (entry 6) and acetonitrile (entry 7) did produce **3a**, the reaction times were considerably longer. Hence, chloroform was deemed the optimal solvent.[19]

Table 1. Optimization Studies for Iron(III) Triflimide Catalyzed Synthesis of Bis(4-methoxyphenyl)sulfane (3a)

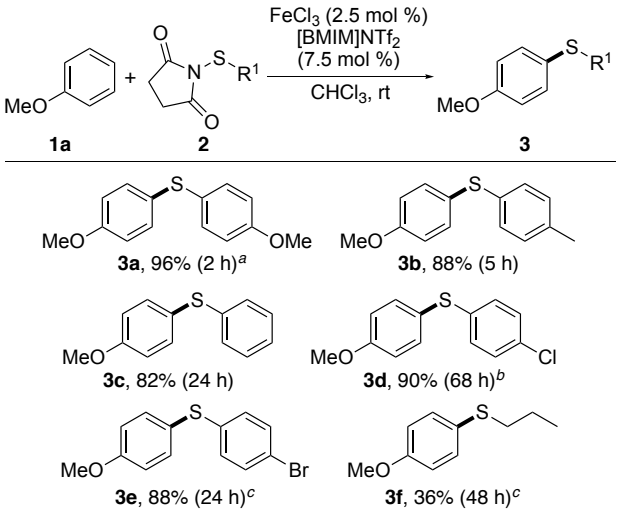


entry	$FeCl_3$ (mol %)	[BMIM]NTf_2 (mol %)	time (h)	yield (%)[a]
1	0	0	---	0
2	0	7.5	---	0
3	2.5	0	5	67
4	2.5	7.5	2	90
5	5	15	1.5	90
6[b]	2.5	7.5	16	55
7[c]	2.5	7.5	16	75

[a]Isolated yields. [b]Reaction conducted in CH_2Cl_2. [c]Reaction conducted in MeCN.

With optimized conditions, the scope of the transformation with a range of *N*-thiosuccinimides was investigated (Scheme 2). The use of these reagents containing electron-rich thioaryl moieties allowed room temperature reactions, yielding the corresponding biaryl sulfides **3a**–**3c** in high yields (82–96%). Similar yields (88–90%) were also obtained for electron-deficient analogues (**3d** and **3e**), although higher reaction temperatures (60–75 ºC) and longer reaction times (24–68 h) were required. In all cases, only the *para*-regioisomer was observed from these reactions. The main limitation of this approach was found when using *N*-(alkylthio)succinimides. For example, reaction of anisole (**1a**) with *N*-(propanethio)succinimide (**2f**) required a reaction temperature of 75 ºC and after 48 hours gave the corresponding sulfide **3f** in only 36% yield. In this part of the study, a larger scale reaction was also developed. A 96% yield was achieved for the synthesis of **3a** when performed on a one-gram scale reaction under the optimized conditions (rt, 2 h). At this scale, lower catalyst loadings were also effective (e.g. $FeCl_3$: 1 mol %; [BMIM]NTf_2: 3 mol %) for the synthesis of **3a** (94% yield), although a longer reaction time was required (8 h).

Scheme 2. Reaction Scope of *N*-Thiosuccinimides

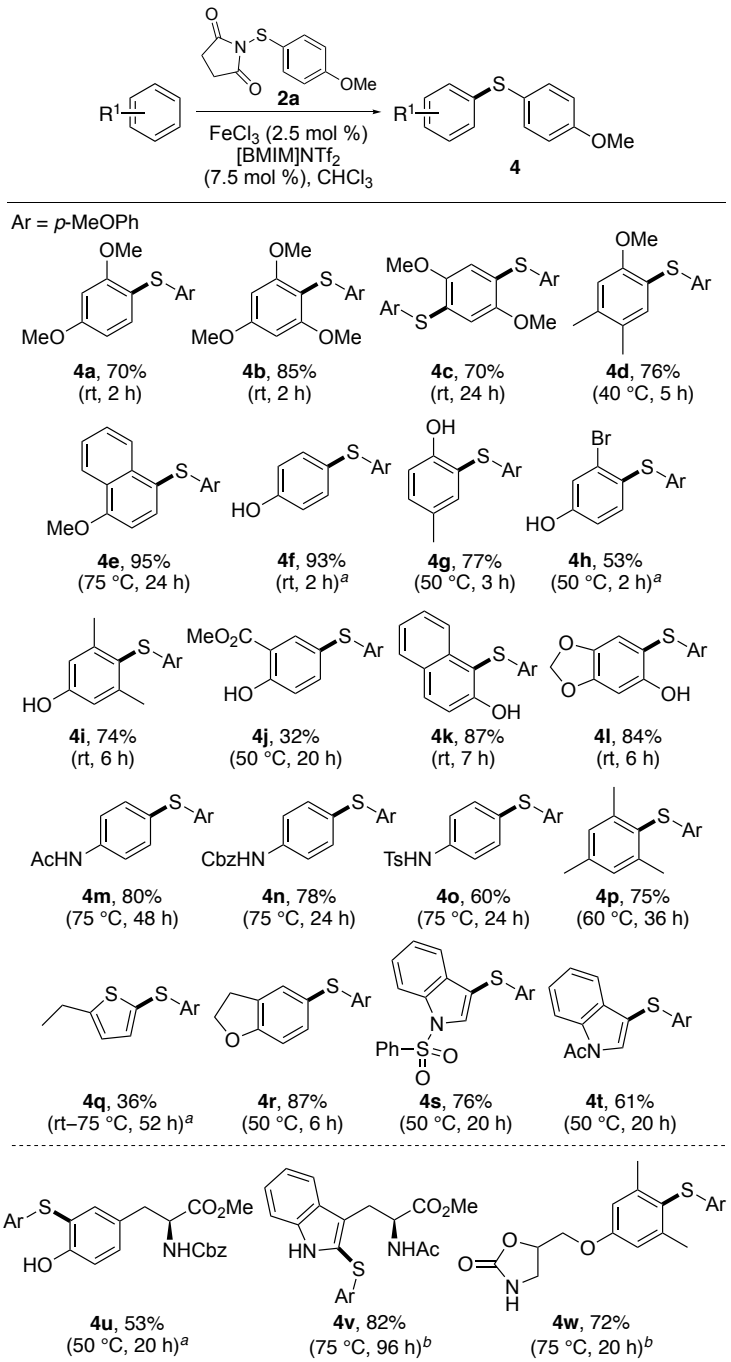


[a]Gram scale reaction. [b]Reaction performed at 60 ºC. [b]Reaction performed at 75 ºC.

The study then focused on exploring the scope of the arene component (Scheme 3). The reaction was found to be compatible and efficient for a wide range of electron-rich arenes, including anisoles, phenols, protected anilines and heterocycles, with various substitution patterns. As well as the generation of mono-thioarylated products as single regioisomers, di-substituted compounds (e.g. **4c**) from arenes with several activated positions were also isolated cleanly. The reaction also tolerated deactivating groups, however, these substrates required higher catalyst loadings and elevated temperatures, giving the products in moderate yields (**4h** and **4j**). Less activated compounds such as mesitylene also required a higher reaction temperature (60 ºC) but gave the thioarylated product, **4p** in 75% yield. Issues were only found for highly activated heterocycles. Although mono-substituted products such as thiophene **4q** were isolated cleanly, the yields were compromised by the formation of poly-thioarylated side-products. In the case of indole, the use of deactivating protecting groups overcame solubility issues and allowed selective mono-thioarylation. For example, sulfonamide or acetyl protected derivatives gave products, **4s** and **4t**, in 76% and 61% yields, respectively.

A major goal of this study was the development of a thioarylation reaction that could be used for the late-stage functionalization of amino acids for chemical biology applications and biologically active compounds for use in drug discovery. Therefore, methods were developed for the thioarylation of tyrosine and tryptophan derivatives, as well as metaxalone,[20] a drug used for pain relief and as a muscle relaxant (Scheme 3). Optimization studies revealed that higher catalyst loadings (5–10 mol % of $FeCl_3$) were required for the amino acid derivatives, however, highly regioselective mono-thioarylation was observed and gave the products **4u** and **4v** in 53% and 82% yields, respectively. Similarly, a 10 mol % catalyst loading of $FeCl_3$ was found to be optimal for thioarylation of metaxalone and in combination with a 75 ºC reaction temperature, gave **4w** as the sole product in 72% yield.

Scheme 3. Reaction Scope of Arenes

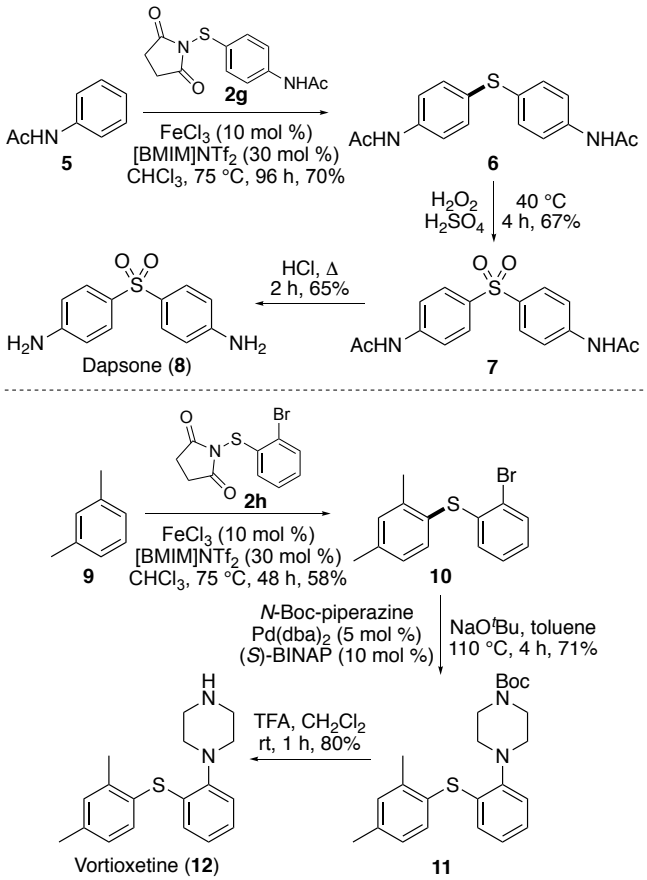


[a]$FeCl_3$ (5 mol %) and [BMIM]NTf_2 (15 mol %) was used. [b]$FeCl_3$ (10 mol %) and [BMIM]NTf_2 (30 mol %) was used.

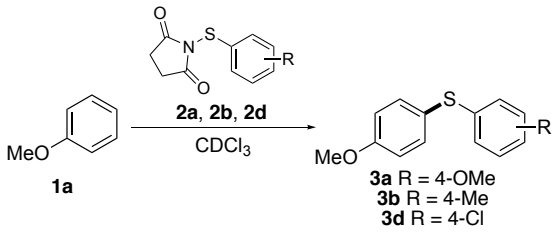
Iron(III) triflimide-catalyzed thioarylation was also used as the key step for the syntheses of dapsone (**8**),[21] an antibiotic used to treat leprosy and the antidepressant, vortioxetine (**12**) (Scheme 4).[22] Thioarylation of acetanilide (**5**) with *N*-(arylthio)succinimide **2g** was most effective using a 10 mol %

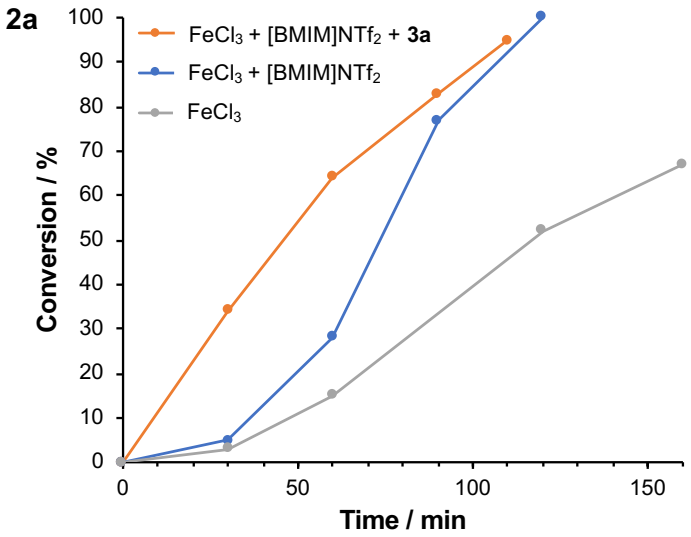
catalyst loading of $FeCl_3$ ($FeCl_3$: 10 mol %; [BMIM]NTf_2: 30 mol %) and gave biaryl sulfide **6** in 70% yield. Oxidation to sulfone **7** with hydrogen peroxide, followed by deprotection under acidic conditions, completed the three-step synthesis of dapsone (**8**). The more challenging synthesis of vortioxetine (**12**) required the thioarylation of *meta*-xylene with electron-deficient *N*-(arylthio)succinimide **2h**. Again, this required a 10 mol % catalyst loading of $FeCl_3$ and elevated temperatures (75 ºC) but gave the corresponding sulfide **10** in 58% yield. This result demonstrates that iron(III) triflimide-catalyzed thioarylation can be used for the functionalization of arenes with minimal activation. The three-step synthesis of vortioxetine (**12**) was completed by palladium-catalyzed Buchwald-Hartwig cross-coupling of **10** with *N*-Boc-piperazine,[22,23] followed by TFA-mediated removal of the Boc-protecting group.[24]

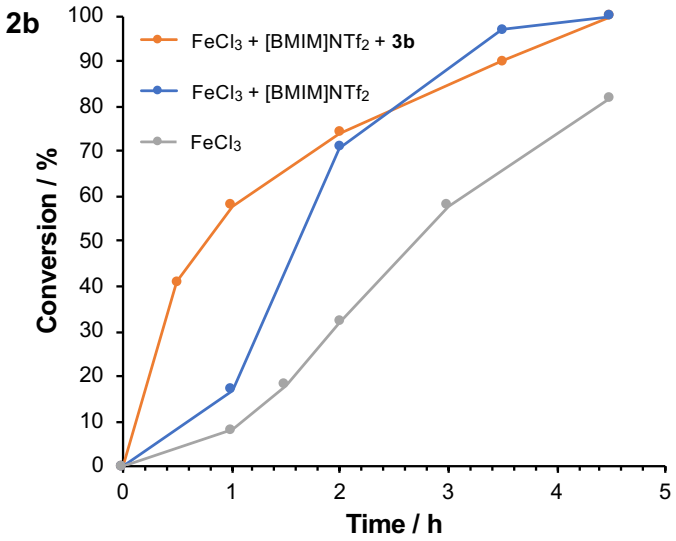
Scheme 4. Synthesis of Dapsone (8) and Vortioxetine (12)



During optimization studies for the synthesis of **3a**, NMR experiments revealed that while the reaction was complete after 2 hours (Table 1, entry 4), <10% conversion was observed after 0.5 hours. Based on this, a kinetic study was performed to further investigate the transformation (Figure 2a). Conversion studies undertaken on the reactions employing iron(III) chloride, or the iron catalyst combined with the ionic liquid, revealed the difference in relative rates between these two catalytic systems. For example, while the reaction with iron(III) triflimide was complete (100% conversion) after 2 hours, only 52% conversion was observed with iron(III) chloride at the same time point. More importantly, these reactions displayed sigmoidal curves, characteristic of autocatalytic processes in which there is an initial reaction lag before an increase in reaction rate. Gustafson and co-workers observed similar autocatalysis in a TFA-promoted thioarylation reaction.[15] We proposed that the autocatalytic nature of these transformations is due to the Lewis basic character of **3a**. As expected, the addition of **3a** (10 mol %) to the iron(III) triflimide catalyzed reaction showed no induction period, confirming the role of **3a** in promoting the reaction. To determine the extent of autocatalysis, conversion studies were also performed during the synthesis of other biaryl sulfides with different electronic character. Similar results were observed during the synthesis of (4-methoxyphenyl)(*p*-tolyl)sulfane (**3b**) (Figure 2b). Despite being a weaker Lewis base than **3a**, autocatalysis using $FeCl_3$ or $Fe(NTf_2)_3$ was observed. The induction period during these experiments was avoided by the addition of **3b** (10 mol %), again confirming the autocatalytic role of the product in the reaction. In contrast, the same conversion graphs for the synthesis of (4'-chlorophenyl)(4-methoxyphenyl)sulfane (**3d**) using $FeCl_3$ or $Fe(NTf_2)_3$ displayed no lag period (Figure 2c). In this case, the presence of an electron-withdrawing substituent and the significantly lower Lewis base character of **3d**, resulted in a transformation that is catalyzed predominantly by the iron catalyst.


2a, 2b, 2d
CDCl3
MeO
1a
MeO
3a R = 4-OMe
3b R = 4-Me
3d R = 4-Cl


2a
FeCl3 + [BMIM]NTf2 + 3a
FeCl3 + [BMIM]NTf2
FeCl3
Conversion / %
Time / min


2b
FeCl3 + [BMIM]NTf2 + 3b
FeCl3 + [BMIM]NTf2
FeCl3
Conversion / %
Time / h

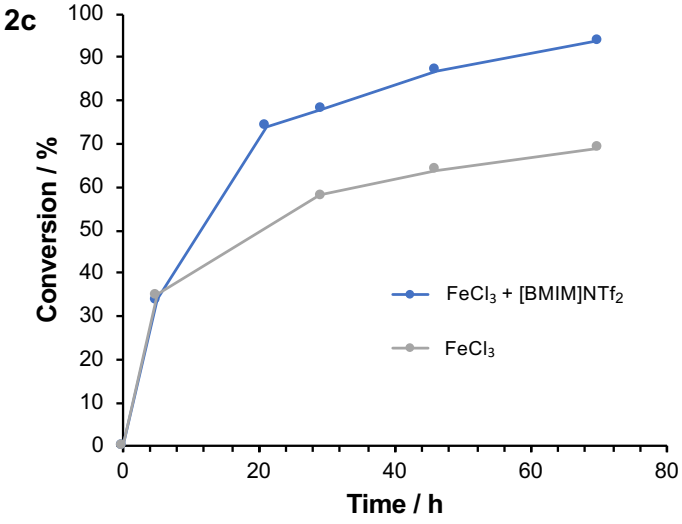
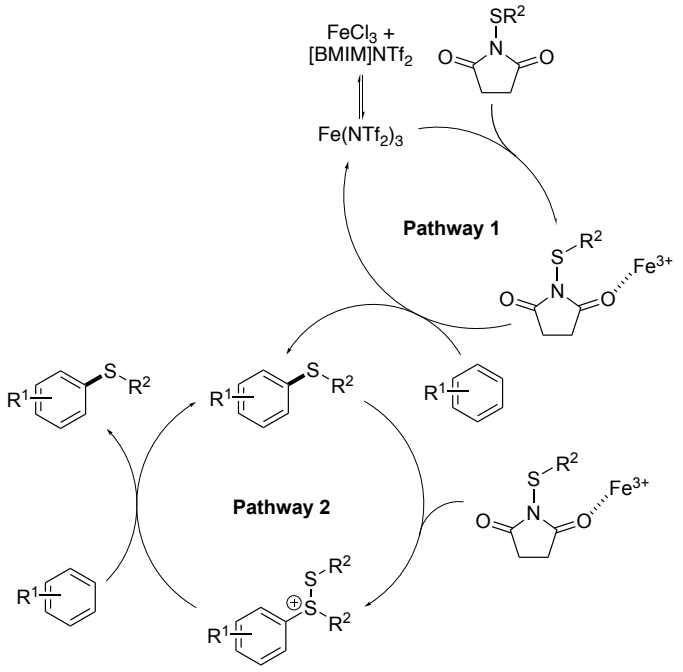

2c
FeCl3 + [BMIM]NTf2
FeCl3
Conversion / %
Time / h

Figure 2. Conversion graphs for synthesis of **3a**, **3b** and **3d** (measured using ^{1}H NMR spectroscopy in $CDCl_3$ and hexamethylcyclotrisiloxane as an internal standard). Reactions with **2a** and **2b** were performed at room temperature, while the reaction with **2d** was done at 60 ºC.

Based on the kinetic study and previous experimental observations,[16,17] catalytic cycles have been proposed for iron(III) triflimide-catalyzed thioarylation with *N*-(arylthio)succinimides of differing electronic character (Scheme 5). Reactions that use *N*-(arylthio)succinimides with electron-deficient aryl groups, resulting in biaryl sulfides with weak Lewis base character proceed via pathway 1. For these cases, iron(III) triflimide activates the *N*-(arylthio)succinimide and is followed by an electrophilic aromatic substitution reaction to give the product. In reactions using *N*-(arylthio)succinimides with electron-rich aryl groups, the same pathway initially forms the biaryl sulfide product. However, when enough of the biaryl sulfide has accumulated, a second pathway involving the use of the product as a Lewis base permits autocatalysis and acceleration of the thioarylation reaction. In this case, the product can react with the iron(III)-activated *N*-(arylthio)succinimide, forming a cationic disulfide intermediate. As a charged species, this reacts rapidly with a second arene, resulting in the generation of the biaryl sulfide and regenerating the same compound for further autocatalysis.

Scheme 5. Proposed Catalytic Pathways for Iron(III)- and Biaryl sulfide-promoted Thioarylation.



CONCLUSIONS

In summary, a method for the regioselective synthesis of biaryl sulfides has been developed using an iron(III) triflimide-catalyzed reaction of *N*-(arylthio)succinimides with electron-rich arenes. In general, the process required low catalyst loadings of an earth–abundant, nonprecious transition metal and a readily available, inexpensive ionic liquid. Kinetic analysis demonstrated that *N*-thiosuccinimides bearing electron-deficient arenes underwent thioarylation catalyzed by iron(III) triflimide, while electron-rich systems displayed an autocatalytic mechanism partially promoted by the Lewis basic product. Overall, this allowed the thioarylation of a wide range of electron-rich arenes, as well as the late-stage functionalization of biologically important compounds such as amino acids and pharmaceutically relevant substances. Work is currently underway to discover new applications of metal triflimide catalyzed arene functionalization.

EXPERIMENTAL SECTION

All reagents and starting materials were obtained from commercial sources and used as received. Reactions were performed open to air unless otherwise mentioned. Brine refers to a saturated aqueous solution of sodium chloride. Flash column chromatography was performed using silica gel 60 (35–70 μm). Aluminium-backed plates pre-coated with silica gel $60F_{254}$ were used for thin layer chromatography and were visualized with a UV lamp or by staining with potassium permanganate. ^{1}H NMR spectra were recorded on a NMR spectrometer at either 400 or 500 MHz and data are reported as follows: chemical shift in ppm relative to tetramethylsilane as the internal standard, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or overlap of non-equivalent resonances, integration). ^{13}C NMR spectra were recorded on a NMR spectrometer at either 101 or 126 MHz and data are reported as follows: chemical shift in ppm relative to tetramethylsilane or the solvent as internal standard ($CDCl_3$, δ 77.0 ppm; DMSO-d_6, δ 39.5 ppm), multiplicity with respect to hydrogen (deduced from DEPT experiments, C, CH, CH_2 or CH_3). Infrared spectra were recorded on a FTIR spectrometer; wavenumbers are indicated in cm^{-1}. Mass spectra were recorded using electron impact or electrospray techniques. HRMS spectra were recorded using a dual-focusing magnetic analyzer mass spectrometer. Melting points are uncorrected.

General Procedure A: Preparation of *N*-thiosuccinimides. *N*-Chlorosuccinimide (1.0 equiv.) was added to a stirred solution of thiol (1.0 equiv.) in toluene (4 mL toluene/1.0 mmol thiol) at room temperature under argon. After 1 h, the solution had changed color from colorless to yellow-orange. A solution of triethylamine (1.0 equiv.) in toluene (1.6 mL toluene/1.0 mmol triethylamine) was then added dropwise over a period of 0.5 h. The resulting reaction mixture was stirred at 40 °C for 16 h before being diluted with diethyl ether (12 mL ether/1.0 mmol thiol). The resulting white precipitate was filtered and the filtrate concentrated *in vacuo* to yield the crude product, which was purified by flash column chromatography.

General Procedure B: Preparation of sulfenylated products. Iron(III) trichloride (2.5 mol%) was dissolved in [BMIM]NTf_2 (7.5 mol%) and left to stir for 0.5 h at room temperature before being added to

a solution of *N*-thiosuccinimide (1.2 equiv.) in chloroform (1.0 M in arene). The arene (1.0 equiv.) was then added and the reaction mixture was left to stir at the required temperature for 2 – 68 h. The reaction mixture was concentrated *in vacuo* and purified using flash column chromatography.

General Procedure C: Preparation of sulfenylated products. Iron(III) trichloride (5 mol%) was dissolved in [BMIM]NTf_2 (15 mol%) and left to stir for 0.5 h at room temperature before being added to a solution of *N*-thiosuccinimide (1.2 equiv.) in chloroform (1.0 M in arene). The arene (1.0 equiv.) was then added and the reaction mixture was left to stir at the required temperature for 2 – 20 h. The reaction mixture was concentrated *in vacuo* and purified using flash column chromatography.

General Procedure D: Preparation of sulfenylated products. Iron(III) trichloride (10 mol%) was dissolved in [BMIM]NTf_2 (30 mol%) and left to stir for 0.5 h at room temperature before being added to a solution of *N*-thiosuccinimide (1.2 equiv.) in chloroform (1.0 M in arene). The arene (1.0 equiv.) was then added and the reaction mixture was left to stir at the required temperature for 20 – 96 h. The reaction mixture was concentrated *in vacuo* and purified using flash column chromatography.

Time Dependent NMR Studies. To a solution of $CDCl_3$ (0.5 mL), was added anisole (**1a**) (50 μL, 0.46 mmol), 1.2 equivalents of *N*-thiosuccinimide and hexamethylcyclotrisiloxane (2 mg, as an internal standard). An NMR spectrum was recorded prior to the addition of catalyst for internal standard calibration. The catalysts ($FeCl_3$, 2.5 mol %; [BMIM]NTf_2, 7.5 mol %) were added and the reaction mixture divided into 5 vials corresponding to each time point. Spectra were recorded at the relevant time points and conversion was determined by internal standard with integration of the *N*-thiosuccinimide peak.

***N*-(4-Methoxyphenylthio)succinimide (2a).**[14a] The reaction was performed as described in general procedure A using 4-methoxythiophenol (614 μL, 4.99 mmol). Purification by flash column chromatography (hexane/ethyl acetate, 3:2) gave *N*-(4-methoxyphenylthio)succinimide (**2a**) (878 mg, 74%) as a pale pink solid. Mp 102−103 °C (lit.[14a] 106−110 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.75 (s, 4H), 3.80 (s, 3H), 6.82–6.87 (m, 2H), 7.72–7.76 (m 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 28.7 (2 ×

CH_2), 55.6 (CH_3), 114.8 (2 × CH), 124.7 (C), 137.5 (2 × CH), 161.9 (C), 176.6 (2 × C); MS (ESI) *m/z* 260 ($M + Na^+$, 100).

***N*-(4-Methylphenylthio)succinimide (2b).**[14a] The reaction was performed as described in general procedure A using 4-methylthiophenol (500 mg, 4.03 mmol). Purification by flash column chromatography (hexane/ethyl acetate, 3:2) gave *N*-(4-methylphenylthio)succinimide (**2b**) (798 mg, 90%) as a white solid. Mp 113−114 °C (lit.[14a] 113−115 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 2.77 (s, 4H), 7.13 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 8.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 21.4 (CH_3), 28.7 (2 × CH_2), 130.2 (2 × CH), 130.5 (C), 133.8 (2 × CH), 141.0 (C), 176.6 (2 × C); MS (ESI) *m/z* 244 ($M + Na^+$, 100).

***N*-(Phenylthio)succinimide (2c).**[14a] The reaction was performed as described in general procedure A using thiophenol (466 μL, 4.54 mmol). Purification by flash column chromatography (hexane/ethyl acetate, 3:2) gave *N*-(phenylthio)succinimide (**2c**) (447 mg, 47%) as a white solid. Mp 112–113 °C (lit.[14a] 115–116 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 2.81 (s, 4H), 7.30–7.37 (m, 3H), 7.59–7.64 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 28.7 (2 × CH_2), 129.5 (2 × CH), 130.1 (CH), 132.5 (2 × CH), 134.1 (C), 176.5 (2 × C); MS (ESI) *m/z* 230 ($M + Na^+$, 100).

***N*-(4-Chlorophenylthio)succinimide (2d).**[25] The reaction was performed as described in general procedure A using 4-chlorothiophenol (500 mg, 3.46 mmol). Purification by flash column chromatography (hexane/ethyl acetate, 3:2) gave *N*-(4-chlorophenylthio)succinimide (**2d**) (453 mg, 54%) as a white solid. Mp 141−143 °C (lit.[25] 142−144 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 2.82 (s, 4H), 7.29–7.34 (m, 2H), 7.57–7.63 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 28.7 (2 × CH_2), 129.7 (2 × CH), 132.3 (C), 134.5 (2 × CH), 136.8 (C), 176.3 (2 × C); MS (ESI) *m/z* 264 ($M + Na^+$, 100).

***N*-(4-Bromophenylthio)succinimide (2e).**[14a] The reaction was performed as described in general procedure A using 4-bromothiophenol (500 mg, 2.64 mmol). Purification by flash column chromatography (hexane/ethyl acetate, 3:2) gave *N*-(4-bromophenylthio)succinimide (**2e**) (321 mg, 43%)

as a white solid. Mp 141−143 °C (lit.[14a] 140−144 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.81 (s, 4H), 7.45–7.52 (m, 4H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 28.7 (2 × CH_2), 124.9 (C), 132.7 (2 × CH), 133.0 (C), 134.4 (2 × CH), 176.3 (2 × C); MS (ESI) *m/z* 310 (M + Na^+, 100).

***N*-(Propanethio)succinimide (2f).[26]** *N*-Chlorosuccinimide (877 mg, 6.57 mmol) was dissolved in toluene (25 mL) under an atmosphere of argon. 1-Propanethiol (610 µL, 6.57 mmol) in toluene (7 mL) was added dropwise and the resulting suspension was left to stir at 40 °C for 1 h. A solution of triethylamine (916 µL, 6.57 mmol) in toluene (5 mL) was added dropwise and the reaction mixture was left to stir at 40 °C for 16 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was dissolved in water (30 mL). The aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the crude product. Purification by flash column chromatography (hexane/ethyl acetate, 3:2) gave *N*-(propanethio)succinimide (**2f**) (927 mg, 82%) as a colorless oil. Spectroscopic data were consistent with the literature.[26] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, J = 7.3 Hz, 3H), 1.55 (sext., J = 7.3 Hz, 2H), 2.81 (t, J = 7.3 Hz, 2H), 2.83 (s, 4H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 13.1 (CH_3), 21.6 (CH_2), 28.7 (2 × CH_2), 39.7 (CH_2), 177.3 (2 × C); MS (ESI) *m/z* 196 (M + Na^+, 100).

***N*-(4-Acetamidophenylthio)succinimide (2g).** A round bottomed flask was charged with a solution of *N*-chlorosuccinimide (399 mg, 2.99 mmol) in chloroform (5 mL) under an atmosphere of argon. To the flask was added a suspension of 4-acetamidothiophenol (500 mg, 2.99 mmol) in chloroform (10 mL) dropwise and the resulting suspension was left to stir at 50 °C for 1 h. A solution of triethylamine (417 µL, 2.99 mmol) in chloroform (5 mL) was added dropwise and the resulting reaction mixture was left to stir at 50 °C for 20 h. The reaction mixture was allowed to cool to room temperature prior to the addition of saturated aqueous ammonium chloride (30 mL). The organic layer was separated and the aqueous layer was further extracted with dichloromethane (2 × 30 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the crude product. Purification

by flash column chromatography (hexane/ethyl acetate, 1:9) gave *N*-(4-acetamidophenylthio)succinimide (**2g**) (320 mg, 41%) as a yellow solid. Mp 145–147 °C; IR (neat) 3348, 2984, 1713, 1684, 1591, 1520, 1288, 1142, 1007, 816 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16 (s, 3H), 2.79 (s, 4H), 7.47 (d, J = 8.5 Hz, 2H), 7.58–7.70 (m, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 24.8 (CH_3), 28.7 (2 × CH_2), 120.3 (2 × CH), 128.5 (C), 135.3 (2 × CH), 140.2 (C), 168.7 (C), 176.6 (2 × C); MS (ESI) *m/z* 287 (M + Na^+, 100); HRMS (ESI) calcd for $C_{12}H_{12}N_2NaO_3S$ (M + Na^+) 287.0461, found 287.0466.

***N*-(2-Bromophenylthio)succinimide (2h).[25]** The reaction was performed as described in general procedure A using 2-bromothiophenol (1.00 g, 5.28 mmol). Purification by flash column chromatography (hexane/ethyl acetate, 3:2) gave *N*-(2-bromophenylthio)succinimide (**2h**) (0.842 g, 56%) as a white solid. Mp 126−129 °C (lit.[25] 128−130 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.97 (s, 4H), 6.80 (dd, J = 8.0, 1.5 Hz, 1H), 7.06−7.11 (m, 1H), 7.22−7.27 (m, 1H), 7.52 (dd, J = 8.0, 1.3 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 29.0 (2 × CH_2), 119.2 (C), 125.2 (CH), 128.2 (CH), 128.4 (CH), 133.3 (CH), 135.5 (C), 175.9 (2 × C); MS (ESI) *m/z* 310 (M + Na^+, 100).

Bis(4-methoxyphenyl)sulfane (3a).[27] The reaction was performed as described in general procedure B using anisole (**1a**) (1.00 mL, 9.25 mmol). The reaction mixture was stirred at room temperature for 2 h. Purification by flash column chromatography (hexane/dichloromethane, 3:2) gave bis(4-methoxyphenyl)sulfane (**3a**) (2.19 g, 96%) as a white solid. Mp 43−44 °C (lit.[27] 44−45 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 6H), 6.80–6.88 (m, 4H), 7.24–7.34 (m, 4H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 55.5 (2 × CH_3), 114.9 (4 × CH), 127.6 (2 × C), 132.9 (4 × CH), 159.1 (2 × C); MS (ESI) *m/z* 269 (M + Na^+, 100).

(4-Methoxyphenyl)(*p*-tolyl)sulfane (3b).[27] The reaction was performed as described in general procedure B using anisole (**1a**) (50 μL, 0.46 mmol). The reaction mixture was stirred at room temperature for 5 h. Purification by flash column chromatography (hexane/dichloromethane, 4:1) gave (4-methoxyphenyl)(*p*-tolyl)sulfane (**3b**) (93 mg, 88%) as a white solid. Mp 42−43 °C (lit.[27] 43−44 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H), 3.81 (s, 3H), 6.85–6.89 (m, 2H), 7.04–7.09 (m, 2H), 7.11–7.16

(m, 2H), 7.34–7.39 (m, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 21.1 (CH_3), 55.5 (CH_3), 115.0 (2 × CH), 125.8 (C), 129.6 (2 × CH), 129.9 (2 × CH), 134.5 (2 × CH), 134.5 (C), 136.3 (C), 159.6 (C); MS (EI) *m/z* 230 (M^+, 100), 215 (35).

(4-Methoxyphenyl)(phenyl)sulfane (3c).[28] The reaction was performed as described in general procedure B using anisole (**1a**) (50 µL, 0.46 mmol). The reaction mixture was stirred at room temperature for 24 h. Purification by flash column chromatography (hexane/dichloromethane, 4:1) gave (4-methoxyphenyl)(phenyl)sulfane (**3c**) (82 mg, 82%) as a colorless oil. Spectroscopic data was consistent with the literature.[28] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 6.88–6.93 (m, 2H), 7.12–7.27 (m, 5H), 7.40–7.45 (m, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 55.5 (CH_3), 115.1 (2 × CH), 124.5 (C), 125.9 (CH), 128.4 (2 × CH), 129.0 (2 × CH), 135.5 (2 × CH), 138.7 (C), 160.0 (C); MS (EI) *m/z* 216 (M^+, 100), 201 (84), 129 (30), 83 (28).

(4'-Chlorophenyl)(4-methoxyphenyl)sulfane (3d).[28] The reaction was performed as described in general procedure B using anisole (**1a**) (50.0 µL, 0.460 mmol). The reaction mixture was stirred at 60 °C for 68 h. Purification by flash column chromatography (hexane/dichloromethane, 4:1) gave (4'-chlorophenyl)(4-methoxyphenyl)sulfane (**3d**) (103 mg, 90%) as a white solid. Mp 59−61 °C (lit.[28] 59.2−60.5 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H), 6.88–6.93 (m, 2H), 7.05–7.10 (m, 2H), 7.16–7.21 (m, 2H), 7.38–7.43 (m, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 55.5 (CH_3), 115.3 (2 × CH), 124.0 (C), 129.2 (2 × CH), 129.5 (2 × CH), 131.8 (C) 135.6 (2 × CH), 137.5 (C), 160.2 (C); MS (EI) *m/z* 250 (M^+, 100), 235 (39), 172 (24), 83 (22).

(4'-Bromophenyl)(4-methoxyphenyl)sulfane (3e).[29] The reaction was performed as described in general procedure B using anisole (**1a**) (50.0 µL, 0.460 mmol). The reaction mixture was stirred at 75 °C for 24 h. Purification by flash column chromatography (hexane/dichloromethane, 7:1) gave (4'-bromophenyl)(4-methoxyphenyl)sulfane (**3e**) (119 mg, 88%) as a white solid. Mp 59−61 °C (lit.[29] 60 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H), 6.89–6.93 (m, 2H), 6.99–7.02 (m, 2H), 7.32–7.35 (m, 2H), 7.39–7.43 (m, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 55.5 (CH_3), 115.3 (2 × CH), 119.5 (C), 123.7

(C), 129.6 (2 × CH), 132.1 (2 × CH), 135.8 (2 × CH), 138.3 (C), 160.3 (C); MS (EI) *m/z* 296 (M^+, 100), 294 (98), 281 (30), 172 (33).

4-Methoxyphenyl propylsulfane (3f).[30] The reaction was performed as described in general procedure D using anisole (**1a**) (50 µL, 0.46 mmol). The reaction mixture was stirred at 75 °C for 48 h. Purification by flash column chromatography (hexane/dichloromethane, 9:1) gave 4-methoxyphenyl propylsulfane (**3f**) (30 mg, 36%) as a colorless oil. Spectroscopic data was consistent with the literature.[30] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, J = 7.3 Hz, 3H), 1.60 (sext., J = 7.3 Hz, 2H), 2.79 (t, J = 7.3 Hz, 2H), 3.79 (s, 3H), 6.81−6.87 (m, 2H), 7.32−7.37 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 13.5 (CH_3), 22.8 (CH_2), 38.0 (CH_2), 55.5 (CH_3), 114.6 (2 × CH), 127.0 (C), 133.2 (2 × CH), 158.9 (C); MS (EI) *m/z* 182 (M^+, 100), 153 (52), 140 (98), 125 (55), 84 (42).

(2,4-Dimethoxyphenyl)(4'-methoxyphenyl)sulfane (4a).[31] The reaction was performed as described in general procedure B using 1,3-dimethoxybenzene (47 µL, 0.36 mmol). The reaction mixture was stirred at room temperature for 2 h. Purification by flash column chromatography (hexane/diethyl ether, 3:1) gave (2,4-dimethoxyphenyl)(4'-methoxyphenyl)sulfane (**4a**) (70 mg, 70%) as a colorless oil. Spectroscopic data was consistent with the literature.[31] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 3.79 (s, 3H), 3.83 (s, 3H), 6.43 (dd, J = 8.5, 2.5 Hz, 1H), 6.49 (d, J = 2.5, Hz, 1H), 6.81–6.86 (m, 2H), 7.08 (d, J = 8.5 Hz, 1H), 7.24–7.29 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 55.4 (CH_3), 55.6 (CH_3), 56.0, (CH_3), 99.2 (CH), 105.3 (CH), 114.8 (2 × CH), 115.9 (C), 126.4 (C), 132.8 (2 × CH), 133.5 (CH), 158.9 (C), 159.0 (C), 160.8 (C); MS (ESI) *m/z* 299 (M + Na^+, 100).

(4'-Methoxyphenyl)(2,4,6-trimethoxyphenyl)sulfane (4b).[14a] The reaction was performed as described in general procedure B using 1,3,5-trimethoxybenzene (50 mg, 0.30 mmol). The reaction mixture was stirred at room temperature for 2 h. Purification by flash column chromatography (hexane/diethyl ether, 1:1) gave (4'-methoxyphenyl)(2,4,6-trimethoxyphenyl)sulfane (**4b**) (77 mg, 85%) as a white solid. Mp 83–85 °C (lit.[14a] 86–89 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 3H), 3.81 (s, 6H), 3.85 (s, 3H), 6.19 (s, 2H), 6.70–6.77 (m, 2H), 7.01–7.12 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ

55.4 (CH_3), 55.5 (CH_3), 56.4 (2 × CH_3), 91.4 (2 × CH), 100.9 (C), 114.4 (2 × CH), 128.8 (2 × CH), 129.4 (C), 157.7 (C), 162.5 (2 × C), 162.7 (C); MS (ESI) *m/z* 329 (M + Na^+, 100).

1,2-Bis-[(4'-methoxyphenyl)sulfane]-2,5-dimethoxybenzene (4c). The reaction was performed as described in general procedure B using 1,4-dimethoxybenzene (50.0 mg, 0.360 mmol) and *N*-(4-methoxyphenylthio)succinimide (**2a**) (189 mg, 0.800 mmol). The reaction mixture was stirred at room temperature for 24 h. Purification by flash column chromatography (hexane/dichloromethane, 2:3) gave 1,2-bis-[(4'-methoxyphenyl)sulfane]-2,5-dimethoxybenzene (**4c**) (105 mg, 70%) as an orange solid. Mp 156–158 °C; IR (neat) 2941, 1589, 1489, 1447, 1246, 1024, 829 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.63 (s, 6H), 3.82 (s, 6H), 6.43 (s, 2H), 6.87–6.93 (m, 4H), 7.35–7.42 (m, 4H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 55.5 (2 × CH_3), 56.6 (2 × CH_3), 112.6 (2 × CH), 115.1 (4 × CH), 123.6 (2 × C), 125.2 (2 × C), 135.3 (4 × CH), 151.0 (2 × C), 159.9 (2 × C); MS (ESI) *m/z* 437 (M + Na^+, 100); HRMS (ESI) calcd for $C_{22}H_{22}NaO_4S_2$ (M + Na^+) 437.0852, found 437.0847.

(2-Methoxy-4,5-dimethylphenyl)(4'-methoxyphenyl)sulfane (4d). The reaction was performed as described in general procedure B using 3,4-dimethylanisole (51 μL, 0.37 mmol). The reaction mixture was stirred at 40 °C for 5 h. Purification by flash column chromatography (hexane/dichloromethane, 3:2) gave (2-methoxy-4,5-dimethylphenyl)(4'-methoxyphenyl)sulfane (**4d**) (76 mg, 76%) as a white solid. Mp 61–62 °C; IR (neat) 2963, 1591, 1491, 1244, 1057, 1030, 825 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.09 (s, 3H), 2.23 (s, 3H), 3.81 (s, 3H), 3.85 (s, 3H), 6.68 (s, 1H), 6.75 (s, 1H), 6.84–6.90 (m, 2H), 7.32–7.38 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 18.9 (CH_3), 20.0 (CH_3), 55.5 (CH_3), 56.2 (CH_3), 112.8 (CH), 114.9 (2 × CH), 122.3 (C), 125.0 (C), 129.3 (C), 131.7 (CH), 134.3 (2 × CH), 136.3 (C), 155.1 (C) 159.4 (C); MS (ESI) *m/z* 297 (M + Na^+, 100); HRMS (ESI) calcd for $C_{16}H_{18}NaO_2S$ (M + Na^+) 297.0920, found 297.0915.

(4-Methoxynaphthalen-1-yl)(4'-methoxyphenyl)sulfane (4e).[32] The reaction was performed as described in general procedure B using 1-methoxynaphthalene (46 μL, 0.32 mmol). The reaction mixture was stirred at 75 °C for 24 h. Purification by flash column chromatography (hexane/dichloromethane,

2:1) gave (4-methoxynaphthalen-1-yl)(4'-methoxyphenyl)sulfane (**4e**) (89 mg, 95%) as a white solid. Mp 87–88 °C (lit.[32] 83–85 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74 (s, 3H), 4.02 (s, 3H), 6.74–6.78 (m, 2H), 6.79 (d, J = 8.0 Hz, 1H), 7.10–7.16 (m, 2H), 7.48–7.56 (m, 2H), 7.66 (d, J = 8.0 Hz, 1H), 8.30 (dd, J = 7.9, 1.4 Hz, 1H), 8.37 (dd, J = 7.9, 1.0 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 55.5 (CH_3), 55.8 (CH_3), 104.1 (CH), 114.8 (2 × CH), 122.6 (CH), 122.7 (C), 125.8 (CH), 125.9 (CH), 126.6 (C), 127.5 (CH), 128.7 (C), 130.4 (2 × CH), 133.9 (CH), 134.7 (C), 156.6 (C), 158.4 (C); MS (ESI) *m/z* 319 (M + Na^+, 100).

(4-Hydroxyphenyl)(4'-methoxyphenyl)sulfane (4f).[33] The reaction was performed as described in general procedure C using phenol (50.0 mg, 0.530 mmol). The reaction mixture was stirred at room temperature for 2 h. Purification by flash column chromatography (dichloromethane) gave (4-hydroxyphenyl)(4'-methoxyphenyl)sulfane (**4f**) (114 mg, 93%) as a pale orange solid. Mp 61–62 °C (lit.[33] 60 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 4.98 (s, 1H), 6.73–6.79 (m, 2H), 6.81–6.87 (m, 2H), 7.19–7.25 (m, 2H), 7.26–7.31 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 55.5 (CH_3), 114.9 (2 × CH), 116.4 (2 × CH), 127.4 (C), 127.9 (C), 133.0 (4 × CH), 155.0 (C), 159.1 (C); MS (EI) *m/z* 232 (M^+, 100), 217 (33), 84 (53).

(2-Hydroxy-5-methylphenyl)(4'-methoxyphenyl)sulfane (4g).[34] The reaction was performed as described in general procedure B using *p*-cresol (50 mg, 0.46 mmol). The reaction mixture was stirred at 50 °C for 3 h. Purification by flash column chromatography (hexane/dichloromethane, 1:1) gave (2-hydroxy-5-methylphenyl)(4'-methoxyphenyl)sulfane (**4g**) (88 mg, 77%) as a colorless oil. Spectroscopic data was consistent with the literature.[34] ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 3H), 3.76 (s, 3H), 6.40 (s, 1H), 6.78−6.83 (m, 2H), 6.93 (d, J = 8.3 Hz, 1H), 7.10−7.17 (m, 3H), 7.31 (d, J = 1.9 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 20.5 (CH_3), 55.5 (CH_3), 115.1 (2 × CH), 115.2 (CH), 118.0 (C), 126.5 (C), 130.1 (2 × CH), 130.6 (C), 132.5 (CH), 136.3 (CH), 154.7 (C), 158.9 (C); MS (ESI) *m/z* 269 (M + Na^+, 100).

(2-Bromo-4-hydroxyphenyl)(4'-methoxyphenyl)sulfane (4h). The reaction was performed as described in general procedure C using 3-bromophenol (50 mg, 0.39 mmol). The reaction mixture was stirred at 50 °C for 2 h. Purification by flash column chromatography (dichloromethane) gave (2-bromo-4-hydroxyphenyl)(4'-methoxyphenyl)sulfane (**4h**) (47 mg, 53%) as a brown solid. Mp 74–77 °C; IR (neat) 3387, 2938, 1589, 1491, 1464, 1244, 1018, 826 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 5.07 (s, 1H), 6.67 (dd, J = 8.6, 2.7 Hz, 1H), 6.87–6.92 (m, 3H), 7.10 (d, J = 2.7 Hz, 1H), 7.33–7.38 (m, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 55.6 (CH_3), 115.3 (2 × CH), 115.7 (CH), 120.3 (CH), 124.5 (C), 124.8 (C), 130.2 (C), 131.9 (CH), 134.8 (2 × CH), 154.8 (C), 159.8 (C); MS (ESI) *m/z* 333 ($M + Na^+$, 100); HRMS (ESI) calcd for $C_{13}H_{11}{}^{79}BrNaO_2S$ ($M + Na^+$) 332.9555, found 332.9559.

(2,6-Dimethyl-4-hydroxyphenyl)(4'-methoxyphenyl)sulfane (4i). The reaction was performed as described in general procedure B using 3,5-dimethylphenol (50 mg, 0.41 mmol). The reaction mixture was stirred at room temperature for 6 h. Purification by flash column chromatography (dichloromethane) gave (2,6-dimethyl-4-hydroxyphenyl)(4'-methoxyphenyl)sulfane (**4i**) (78 mg, 74%) as a white solid. Mp 150–152 °C; IR (neat) 3345, 2947, 1587, 1489, 1227, 1163, 1013, 812 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 6H), 3.75 (s, 3H), 4.75 (s, 1H), 6.66 (s, 2H), 6.73–6.78 (m, 2H), 6.86–6.91 (m, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 22.1 (2 × CH_3), 55.5 (CH_3), 114.8 (2 × CH), 115.4 (2 × CH), 123.1 (C), 127.5 (2 × CH), 129.5 (C), 145.8 (2 × C), 156.0 (C), 157.5 (C); MS (ESI) *m/z* 283 ($M + Na^+$, 100); HRMS (ESI) calcd for $C_{15}H_{16}NaO_2S$ ($M + Na^+$) 283.0763, found 283.0760.

Methyl 2-hydroxy-5-(4'-methoxyphenylsulfanyl)benzoate (4j). The reaction was performed as described in general procedure B using methyl salicylate (43 μL, 0.33 mmol). The reaction mixture was stirred at 50 °C for 20 h. Purification by flash column chromatography (hexane/dichloromethane, 1:1) gave methyl 2-hydroxy-5-(4'-methoxyphenylsulfanyl)benzoate (**4j**) (30 mg, 32%) as a colorless oil. IR (neat) 3175, 2951, 1674, 1589, 1491, 1439, 1285, 1030, 827 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 3.93 (s, 3H), 6.84 (d, J = 8.6 Hz, 2H), 6.92 (d, J = 8.6 Hz, 1H), 7.28 (d, J = 8.6 Hz, 2H), 7.41 (dd, J = 8.6, 1.8 Hz, 1H), 7.89 (d, J = 1.8 Hz, 1H), 10.76 (s, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 52.6

(CH_3), 55.5 (CH_3), 113.1 (C), 115.0 (2 × CH), 118.9 (CH), 126.5 (C), 126.9 (C), 133.0 (CH), 133.0 (2 × CH), 139.2 (CH), 159.3 (C), 161.1 (C), 170.2 (C); MS (ESI) *m/z* 313 ($M + Na^+$, 100); HRMS (ESI) calcd for $C_{15}H_{14}NaO_4S$ ($M + Na^+$) 313.0505, found 313.0497.

(2-Hydroxynaphthalen-1-yl)(4'-methoxyphenyl)sulfane (4k).[35] The reaction was performed as described in general procedure B using 2-naphthol (50 mg, 0.35 mmol). The reaction mixture was stirred at room temperature for 7 h. Purification by flash column chromatography (hexane/dichloromethane, 1:1) gave (2-hydroxynaphthalen-1-yl)(4'-methoxyphenyl)sulfane (**4k**) (85 mg, 87%) as a white solid. Mp 73–75 °C (lit.[35] 71–73 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 3.70 (s, 3H), 6.71–6.77 (m, 2H), 7.01–7.09 (m, 2H), 7.30 (s, 1H), 7.33 (d, J = 8.9 Hz, 1H), 7.35–7.39 (m, 1H), 7.47–7.53 (m, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.86 (d, J = 8.9 Hz, 1H), 8.26 (d, J = 8.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 55.5 (CH_3), 109.9 (C), 115.1 (2 × CH), 117.0 (CH), 123.9 (CH), 124.9 (CH), 126.1 (C), 128.0 (CH), 128.7 (CH), 128.9 (2 × CH), 129.6 (C), 132.7 (CH), 135.5 (C), 156.8 (C), 158.6 (C); MS (ESI) *m/z* 305 ($M + Na^+$, 100).

[2-Hydroxy-4,5-(methylenedioxy)phenyl](4'-methoxyphenyl)sulfane (4l). The reaction was performed as described in general procedure B using 2*H*-1,3-benzodioxol-5-ol (50 mg, 0.45 mmol). The reaction mixture was stirred at room temperature for 6 h. Purification by flash column chromatography (hexane/dichloromethane, 2:3) gave [2-hydroxy-4,5-(methylenedioxy)phenyl](4'-methoxyphenyl)sulfane (**4l**) (84 mg, 84%) as a white solid. Mp 113–115 °C; IR (neat) 3385, 2899, 1472, 1242, 1173, 1032, 820 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 5.94 (s, 2H), 6.51 (s, 1H), 6.59 (s, 1H), 6.78–6.82 (m, 2H), 6.93 (s, 1H), 7.08–7.13 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 55.5 (CH_3), 97.4 (CH), 101.7 (CH_2), 107.9 (C), 114.3 (CH), 115.1 (2 × CH), 127.0 (C), 129.6 (2 × CH), 141.7 (C), 150.7 (C), 153.3 (C), 158.9 (C); MS (ESI) *m/z* 299 ($M + Na^+$, 100); HRMS (ESI) calcd for $C_{14}H_{12}NaO_4S$ ($M + Na^+$) 299.0349, found 299.0345.

***N*-{4-[(4'-Methoxyphenyl)thio]phenyl}acetamide (4m).** The reaction was performed as described in general procedure B using acetanilide (50 mg, 0.37 mmol). The reaction mixture was stirred at 75 °C for 48 h. Purification by flash column chromatography (30–60% ethyl acetate in hexane) gave *N*-{4-[(4'-methoxyphenyl)thio]phenyl}acetamide (**4m**) (80 mg, 80%) as an off-white solid. Mp 94–96 °C; IR (neat) 3296, 2837, 1661, 1587, 1244, 1171, 1028, 814 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.15 (s, 3H), 3.81 (s, 3H), 6.84–6.89 (m, 2H), 7.14–7.20 (m, 2H), 7.28 (br s, 1H), 7.32–7.42 (m, 4H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 24.7 (CH_3), 55.5 (CH_3), 115.1 (2 × CH), 120.7 (2 × CH), 125.5 (C), 130.2 (2 × CH), 133.3 (C), 134.5 (2 × CH), 136.4 (C), 159.7 (C), 168.4 (C); MS (ESI) *m/z* 296 ($M + Na^+$, 100); HRMS (ESI) calcd for $C_{15}H_{15}NNaO_2S$ ($M + Na^+$) 296.0716, found 296.0713.

Benzyl [4-(4'-methoxyphenylthio)phenyl]carbamate (4n). The reaction was performed as described in general procedure B using *N*-(benzyloxycarbonyl)aniline (100 mg, 0.440 mmol). The reaction mixture was stirred at 75 °C for 24 h. Purification by flash column chromatography (hexane/ethyl acetate, 4:1) gave benzyl [4-(4'-methoxyphenylthio)phenyl]carbamate (**4n**) (125 mg, 78%) as a white solid. Mp 108−109 °C; IR (neat) 3296, 2943, 1697, 1589, 1512, 1491, 1242, 1026, 829 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 5.19 (s, 2H), 6.66 (br s, 1H), 6.84−6.89 (m, 2H), 7.17−7.22 (m, 2H), 7.27−7.41 (m, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 55.5 (CH_3), 67.3 (CH_2), 115.0 (2 × CH), 119.5 (C), 125.9 (C), 128.5 (2 × CH), 128.5 (2 × CH), 128.8 (2 × CH), 130.8 (2 × CH), 132.1 (C), 134.2 (2 × CH), 136.1 (CH), 136.5 (C), 153.3 (C), 159.6 (C); MS (ESI) *m/z* 388 ($M + Na^+$, 100); HRMS (ESI) calcd for $C_{21}H_{19}NNaO_3S$ ($M + Na^+$) 388.0978, found 388.0974.

***N*-[4-(4'-Methoxyphenylthio)phenyl]toluenesulfonamide (4o).** The reaction was performed as described in general procedure B using phenyl toluenesulfonamide (100 mg, 0.400 mmol). The reaction mixture was stirred at 75 °C for 24 h. Purification by flash column chromatography (hexane/ethyl acetate, 7:3) gave *N*-[4-(4'-methoxyphenylthio)phenyl]toluenesulfonamide (**4o**) (94.0 mg, 60%) as a white solid. Mp 127−129 °C; IR (neat) 3242, 2922, 1593, 1489, 1333, 1146, 922, 812 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 3.81 (s, 3H), 6.81−6.89 (m, 3H), 6.91−6.97 (m, 2H), 7.00−7.06 (m, 2H), 7.22 (d,

J = 8.0 Hz, 2H), 7.31−7.37 (m, 2H), 7.62−7.67 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 21.7 (CH_3), 55.5 (CH_3), 115.2 (2 × CH), 122.5 (2 × CH), 124.4 (C), 127.4 (2 × CH), 129.5 (2 × CH), 129.8 (2 × CH), 134.7 (C), 135.2 (2 × CH), 135.4 (C), 136.2 (C), 144.1 (C), 160.0 (C); MS (ESI) *m/z* 408 ($M + Na^+$, 100); HRMS (ESI) calcd for $C_{20}H_{19}NNaO_3S_2$ ($M + Na^+$) 408.0699, found 408.0696.

Mesityl-(4'-methoxyphenyl)sulfane (4p).[14a] The reaction was performed as described in general procedure B using mesitylene (58 µL, 0.42 mmol). The reaction mixture was stirred at 60 °C for 36 h. Purification by flash column chromatography (hexane/dichloromethane, 4:1) gave mesityl-(4'-methoxyphenyl)sulfane (**4p**) (80 mg, 75%) as a white solid. Mp 66−67 °C (lit.[14a] 69−71 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3H), 2.39 (s, 6H), 3.75 (s, 3H), 6.72–6.77 (m, 2H), 6.87–6.93 (m, 2H), 6.98 (s, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 21.2 (CH_3), 21.9 (2 × CH_3), 55.5 (CH_3), 114.8 (2 × CH), 127.8 (2 × CH), 128.5 (C), 129.2 (C), 129.4 (2 × CH), 139.0 (C), 143.5 (2 × C), 157.6 (C); MS (ESI) *m/z* 258 (M^+, 100).

(5-Ethylthiophen-2-yl)(4'-methoxyphenyl)sulfane (4q). The reaction was performed as described in general procedure B using 2-ethylthiophene (50 µL, 0.45 mmol). The reaction mixture was stirred at room temperature for 24 h, 50 °C for 24 h and 75 °C for 4 h. Purification by flash column chromatography (hexane/dichloromethane, 4:1) gave (5-ethylthiophen-2-yl)(4'-methoxyphenyl)sulfane (**4q**) (36 mg, 30%) as a colorless oil. IR (neat) 2965, 1591, 1491, 1244, 1032, 824 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, J = 7.5 Hz, 3H), 2.81 (qd, J = 7.5, 1.0 Hz, 2H), 3.78 (s, 3H), 6.70 (dt, J = 3.5, 1.0 Hz, 1H), 6.81–6.85 (m, 2H), 7.07 (d, J = 3.5 Hz, 1H), 7.25–7.29 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 15.7 (CH_3), 24.0 (CH_2), 55.5 (CH_3), 114.8 (2 × CH), 124.1 (CH), 129.2 (C), 130.5 (C), 130.7 (2 × CH), 134.7 (CH), 153.0 (C), 158.9 (C); MS (ESI) *m/z* 273 ($M + Na^+$, 100); HRMS (ESI) calcd for $C_{13}H_{14}NaOS_2$ ($M + Na^+$) 273.0378, found 273.0385.

(2,3-Dihydro-1-benzofuran-5-yl)(4'-methoxyphenyl)sulfane (4r). The reaction was performed as described in general procedure B using 2,3-dihydrobenzofuran (47 µL, 0.42 mmol). The reaction mixture was stirred at 50 °C for 6 h. Purification by flash column chromatography (hexane/dichloromethane, 4:3)

gave (2,3-dihydro-1-benzofuran-5-yl)(4'-methoxyphenyl)sulfane (**4r**) (93 mg, 87%) as a colorless oil. IR (neat) 2895, 1589, 1481, 1466, 1231, 818 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.22 (t, J = 8.7 Hz, 2H), 3.84 (s, 3H), 4.62 (t, J = 8.7 Hz, 2H), 6.78 (d, J = 8.3 Hz, 1H), 6.86–6.91 (m, 2H), 7.22 (dd, J = 8.3, 1.9 Hz, 1H), 7.26 (d, J = 1.9 Hz, 1H), 7.29–7.35 (m, 2H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 29.7 (CH_2), 55.5 (CH_3), 71.6 (CH_2), 110.0 (CH), 114.8 (2 × CH), 126.7 (C), 128.3 (C), 128.5 (C), 128.9 (CH), 132.3 (CH), 132.4 (2 × CH), 158.9 (C), 160.0 (C); MS (ESI) *m/z* 281 ($M + Na^+$, 100); HRMS (ESI) calcd for $C_{15}H_{14}NaO_2S$ ($M + Na^+$) 281.0607, found 281.0600.

[1-(Phenylsulfonyl)indol-3-yl](4'-methoxyphenyl)sulfane (4s).[36] The reaction was performed as described in general procedure B using 1-(phenylsulfonyl)indole (100 mg, 0.390 mmol). The reaction mixture was stirred at 50 °C for 20 h. Purification by flash column chromatography (hexane/dichloromethane, 3:2) gave [1-(phenylsulfonyl)indol-3-yl](4'-methoxyphenyl)sulfane (**4s**) (117 mg, 76%) as a white solid. Mp 85−88 °C (lit.[36] 86−88 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 6.75–6.79 (m, 2H), 7.18–7.23 (m, 3H), 7.32–7.36 (m, 1H), 7.44–7.48 (m, 3H), 7.53–7.59 (m, 1H), 7.70 (s, 1H), 7.87–7.92 (m, 2H), 8.00 (d, J = 8.3 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 55.5 (CH_3), 113.9 (CH), 114.9 (2 × CH), 120.5 (CH), 123.9 (CH), 125.5 (CH), 125.8 (C), 127.0 (2 × CH), 129.2 (CH), 129.5 (2 × CH and C), 131.0 (2 × CH), 134.2 (CH and C), 135.6 (C), 138.1 (C), 158.9 (C); MS (ESI) *m/z* 418 ($M + Na^+$, 100).

[1-(Acetyl)indol-3-yl](4'-methoxyphenyl)sulfane (4t). The reaction was performed as described in general procedure B using *N*-acetylindole (100 mg, 0.620 mmol). The reaction mixture was stirred at 50 °C for 20 h. Purification by flash column chromatography (hexane/diethyl ether, 4:1) gave [1-(acetyl)indol-3-yl](4'-methoxyphenyl)sulfane (**4t**) (114 mg, 61%) as a white solid. Mp 91−93 °C; IR (neat) 2999, 1709, 1526, 1491, 1308, 1211, 814 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.63 (s, 3H), 3.76 (s, 3H), 6.77−6.83 (m, 2H), 7.23−7.30 (m, 3H), 7.34−7.40 (m, 1H), 7.47−7.52 (m, 1H), 7.58 (s, 1H), 8.44 (d, J = 8.3 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 24.0 (CH_3), 55.4 (CH_3), 114.3 (C), 114.9 (2 × CH), 116.8 (CH), 120.0 (CH), 124.2 (CH), 126.0 (CH), 126.1 (C), 128.6 (CH), 130.7 (C), 130.8 (2 × CH),

136.3 (C), 158.8 (C), 168.2 (C); MS (ESI) *m/z* 320 (M + Na^+, 100); HRMS (ESI) calcd for $C_{17}H_{15}NNaO_2S$ (M + Na^+) 320.0716, found 320.0713.

***N*-(Benzyloxycarbonyl)-[3'-(4''-methoxyphenylthio)]-L-tyrosine methyl ester (4u).** The reaction was performed as described in general procedure C using *N*-(benzyloxycarbonyl)-L-tyrosine methyl ester (100 mg, 0.30 mmol). The reaction mixture was stirred at 50 °C for 20 h. Purification by flash column chromatography (dichloromethane/diethyl ether, 100:2) gave *N*-(benzyloxycarbonyl)-[3'-(4''-methoxyphenylthio)]-L-tyrosine methyl ester (**4u**) (75.0 mg, 53%) as a colorless oil. IR (neat) 3408, 2949, 1713, 1591, 1491, 1244, 1026, 826, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.99 (dd, J = 14.0, 5.8 Hz, 1H), 3.06 (dd, J = 14.0, 5.6 Hz, 1H), 3.64 (s, 3H), 3.73 (s, 3H), 4.58–4.65 (m, 1H), 5.09 (s, 2H), 5.27 (d, J = 7.9 Hz, 1H), 6.53 (s, 1H), 6.78 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.3 Hz, 1H), 7.03 (dd, J = 8.3, 2.0 Hz, 1H), 7.07–7.15 (m, 2H), 7.23 (d, J = 2.0 Hz, 1H), 7.27–7.40 (m, 5H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 37.4 (CH_2), 52.4 (CH_3), 55.0 (CH), 55.5 (CH_3), 67.1 (CH_2), 115.1 (2 × CH), 115.7 (CH), 118.9 (C), 126.0 (C), 128.2 (2 × CH), 128.3 (CH), 128.5 (C), 128.7 (2 × CH), 130.3 (2 × CH), 132.6 (CH), 136.3 (C), 136.7 (CH), 155.7 (C), 155.9 (C), 159.0 (C), 171.9 (C); MS (ESI) *m/z* 490 (M + Na^+, 100); HRMS (ESI) calcd for $C_{25}H_{25}NNaO_6S$ (M + Na^+) 490.1295, found 490.1293.

***N*-Acetyl-[2'-(4''-methoxyphenylthio)]-L-tryptophan methyl ester (4v).** The reaction was performed as described in general procedure D using methyl *N*-acetyl-L-tryptophanate (50 mg, 0.19 mmol). The reaction mixture was stirred at 75 °C for 96 h. Purification by flash column chromatography (dichloromethane/methanol, 99:1) gave *N*-acetyl-[2'-(4''-methoxyphenylthio)]-L-tryptophan methyl ester (**4v**) (125 mg, 82%) as a pale pink solid. Mp 139−142 °C; IR (neat) 3368, 3281, 2949, 1736, 1655, 1491, 1242, 1173, 1028, 824, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.86 (s, 3H), 3.37 (dd, J = 14.5, 5.9 Hz, 1H), 3.44 (dd, J = 14.5, 5.9 Hz, 1H), 3.70 (s, 3H), 3.76 (s, 3H), 4.92 (dt, J = 7.7, 5.9 Hz, 1H), 6.04 (d, J = 7.7 Hz, 1H), 6.78−6.83 (m, 2H), 7.09−7.16 (m, 3H), 7.17−7.22 (m, 1H), 7.26 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 7.9 Hz, 1H), 8.11 (s, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 23.3 (CH_3), 27.5 (CH_2), 52.7 (CH_3), 53.0 (CH), 55.6 (CH_3), 111.1 (CH), 115.2 (2 × CH), 115.8 (C), 119.1 (CH), 120.3 (CH), 123.5

(CH), 125.8 (C), 125.9 (C), 128.2 (C), 130.5 (2 × CH), 136.9 (C), 159.1 (C), 169.9 (C), 172.4 (C); MS (ESI) *m/z* 421 (M + Na^+, 100); HRMS (ESI) calcd for $C_{21}H_{22}N_2NaO_4S$ (M + Na^+) 421.1192, found 421.1194.

5-{[4'-(4-Methoxyphenylthio)-3',5'-dimethylphenoxy]methyl}oxazolidin-2''-one (4w).[10d] The reaction was performed as described in general procedure D using anisole (50 μL, 0.46 mmol). The reaction mixture was stirred at 75 °C for 20 h. Purification by flash chromatography (dichloromethane/methanol, 49:1) gave 5-{[4'-(4-methoxyphenylthio)-3',5'-dimethylphenoxy]methyl}oxazolidin-2''-one (**4w**) (58 mg, 72%) as a white solid. Mp 38−41 °C (lit.[10d] 40.3−42.5 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 6H), 3.54−3.61 (m, 1H), 3.71−3.78 (m, 4H), 4.12 (d, J = 4.9 Hz, 2H), 4.92−5.00 (m, 1H), 6.26 (s, 1H), 6.69−6.78 (m, 4H), 6.83−6.89 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 22.3 (2 × CH_3), 42.8 (CH_2), 55.4 (CH_3), 67.9 (CH_2), 74.6 (CH), 114.5 (2 × CH), 114.8 (2 × CH), 124.1 (C), 127.5 (2 × CH), 129.0 (C), 145.6 (2 × C), 157.5 (C), 158.3 (C), 160.3 (C); MS (ESI) *m/z* 382 (M + Na^+, 100).

Bis(4-acetylaminophenyl)sulfane (6).[37] The reaction was performed as described in general procedure D using acetanilide (**5**) (50 mg, 0.37 mmol). The reaction mixture was stirred at 75 °C for 96 h. Purification by flash column chromatography (dichloromethane/methanol, 19:1) gave bis(4-acetylaminophenyl)sulfane (**6**) (78 mg, 70%) as a white solid. Mp 209−213 °C (lit.[37] 212−214 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.03 (s, 6H), 7.21−7.26 (m, 4H), 7.54−7.59 (m, 4H), 10.02 (br s, 2H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 24.0 (2 × CH_3), 119.9 (4 × CH), 128.6 (2 × C), 131.4 (4 × CH), 138.7 (2 × C), 168.4 (2 × C); MS (ESI) *m/z* 323 (M + Na^+, 100).

Acedapsone (7).[38] A flask was charged with bis(4-acetylaminophenyl)sulfane (**6**) (150 mg, 0.500 mmol) and sulfuric acid (750 μL, 3.75 mmol) was added. The reaction mixture was cooled to 10 °C before 30% aqueous hydrogen peroxide (150 μL) was added dropwise, maintaining the temperature between 25−30 °C. The mixture was then left to stir at 40 °C for 4 h before being poured into a beaker containing crushed ice. The resulting white precipitate was filtered and washed with water. The solid was then dried

to give acedapsone (**7**) (111 mg, 67%) as an off-white solid. Mp 284−287 °C (lit.[38] 287−288 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.06 (s, 6H), 7.73−7.79 (m, 4H), 7.81−7.86 (m, 4H), 10.35 (br s, 2H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 24.1 (2 × CH_3), 118.9 (4 × CH), 128.4 (4 × CH), 135.1 (2 × C), 143.6 (2 × C), 169.1 (2 × C); MS (ESI) *m/z* 335 (M + Na^+, 100).

Dapsone (8).[39] A suspension of acedapsone (**7**) (80 mg, 0.24 mmol) in 10% aqueous hydrochloric acid (1 mL) was heated under reflux for 1 h. To the reaction mixture was added activated carbon before being heated under reflux for a further 1 h. The mixture was filtered hot and then cooled to room temperature. Sodium hydroxide (2 M) was added dropwise to adjust the pH to 14 and the resulting precipitate was isolated by filtration and dried to give dapsone (**8**) (39 mg, 65%) as a white solid. Mp 169−172 °C (lit.[39] 172.2−172.8 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.98 (br s, 4H), 6.57 (d, J = 8.5 Hz, 4H), 7.43 (d, J = 8.5 Hz, 4H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 112.8 (4 × CH), 128.1 (2 × C), 128.6 (4 × CH), 152.8 (2 × C); MS (ESI) *m/z* 271 (M + Na^+, 100).

(2'-Bromophenyl)(2,4-dimethylphenyl)sulfane (10).[40] The reaction was performed as described in general procedure D using *m*-xylene (**9**) (29 µL, 0.24 mmol). The reaction mixture was stirred at 75 °C for 48 h. Purification by flash column chromatography (hexane) gave (2'-bromophenyl)(2,4-dimethylphenyl)sulfane (**10**) (40 mg, 58%) as a colorless oil. Spectroscopic data were consistent with the literature.[40] ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 2.37 (s, 3H), 6.58 (dd, J = 7.9, 1.6 Hz, 1H), 6.93–6.99 (m, 1H), 7.03–7.11 (m, 2H), 7.18 (d, J = 1.1 Hz, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.53 (dd, J = 7.9, 1.3 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 20.7 (CH_3), 21.4 (CH_3), 121.3 (C), 126.2 (CH), 127.3 (CH), 127.5 (C), 127.8 (CH), 128.2 (CH), 132.1 (CH), 132.9 (CH), 136.3 (CH), 139.6 (C), 140.1 (C), 142.5 (C); MS (ESI) *m/z* 317 (M + Na^+, 100).

***N*-(*tert*-Butoxycarbonyl)vortioxetine (11).**[41] (2'-Bromophenyl)(2,4-dimethylphenyl)sulfane (**10**) (50.0 mg, 0.170 mmol), *N*-(*tert*-butoxycarbonyl)piperazine (63 mg, 0.34 mmol), $Pd(dba)_2$ (4.89 mg, 8.50 µmol) and (*S*)-BINAP (10.6 mg, 17.0 µmol) were added in toluene (0.3 mL). The reaction mixture was purged with nitrogen and sodium *tert*-butoxide (32.7 mg, 0.34 mmol) was added. The reaction mixture

was then heated at 110 °C for 4 h. The reaction mixture was allowed to cool to room temperature and water (10 mL) was added before being filtered through celite and washed with dichloromethane (10 mL). The layers were separated and the aqueous layer was further extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford an orange residue. Purification by flash chromatography (hexane/ethyl acetate, 9:1) gave *N*-(*tert*-butoxycarbonyl)vortioxetine (**11**) (48.0 mg, 71%) as a pale yellow oil. Spectroscopic data were consistent with the literature.[41] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 9H), 2.32 (s, 3H), 2.36 (s, 3H), 2.92−3.08 (m, 4H), 3.55−3.68 (m, 4H), 6.49−6.55 (m, 1H), 6.85−6.90 (m, 1H), 7.01−7.10 (m, 3H), 7.15 (s, 1H), 7.37 (d, J = 7.8 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 20.7 (CH_3), 21.3 (CH_3), 28.6 (3 × CH_3), 43.8 (2 × CH_2), 51.8 (2 × CH_2), 79.8 (C), 120.1 (CH), 124.8 (CH), 125.7 (CH), 126.5 (CH), 128.0 (CH and C), 131.9 (CH), 134.8 (C), 136.3 (CH), 139.4 (C), 142.5 (C), 149.1 (C), 155.1 (C); MS (ESI) *m/z* 421 (M + Na^+, 100).

Vortioxetine (12).[41] To a round bottomed flask containing *N*-(*tert*-butoxycarbonyl)vortioxetine (**11**) (40 mg, 0.10 mmol) was added anhydrous dichloromethane (0.3 mL) and trifluoroacetic acid (0.3 mL). The resulting reaction mixture was left to stir at room temperature for 1 h. The solvent was removed *in vacuo* and the resulting residue was dissolved in dichloromethane (10 mL) and extracted with saturated aqueous sodium bicarbonate (10 mL). The aqueous layer was further extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give vortioxetine (**12**) (24 mg, 80%) as a pale yellow solid. Mp 98−100 °C (lit.[41] 99−101 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 2.36 (s, 3H), 2.46 (br s, 1H), 2.98−3.16 (m, 8H), 6.51 (d, J = 7.8 Hz, 1H), 6.81−6.89 (m, 1H), 7.00−7.10 (m, 3H), 7.15 (br s, 1H), 7.38 (d, J = 7.8 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 20.7 (CH_3), 21.3 (CH_3), 46.5 (2 × CH_2), 52.9 (2 × CH_2), 120.0 (CH), 124.5 (CH), 125.6 (CH), 126.3 (CH), 127.9 (CH), 128.1 (C), 131.8 (CH), 134.8 (C), 136.3 (CH), 139.3 (C), 142.6 (C), 149.6 (C); MS (ESI) *m/z* 299 (M + H^+, 100).

SUPPORTING INFORMATION AVAILABLE. ^{1}H and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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