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Visible Light-Mediated Organocatalyzed Thiol-Ene Reaction Initiated by Proton-Coupled Electron Transfer

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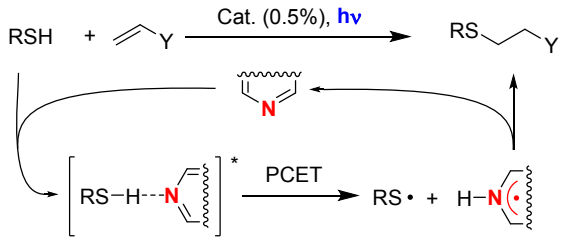


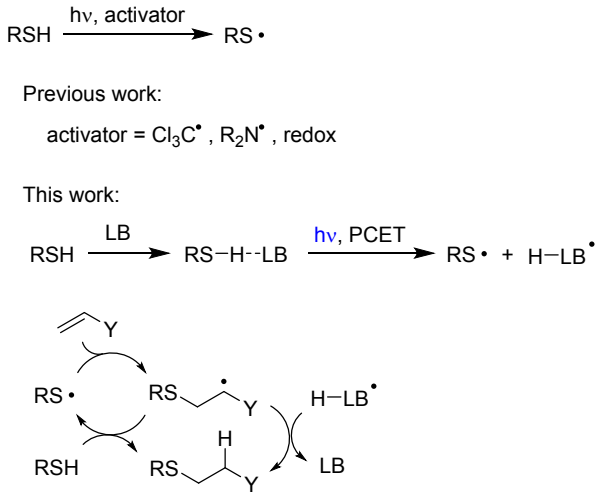
ABSTRACT: A convenient method for performing thiol-ene reaction is described. The reaction is performed under blue light irradiation and catalyzed by photoactive Lewis basic molecules such as acridine orange or naphthalene-fused N-acylbenzimidazole. It is believed that the process is initiated by a proton-coupled electron transfer within the complex between the thiol and the Lewis basic catalyst.

Thiol-ene reaction has emerged as a powerful tool for stitching together two molecules.[1] This process has been exploited in many fields such as polymer and materials sciences,[2] biological applications,[3] and others.[4] While thiols and alkenes are typically unreactive towards each other, their interaction can be triggered by various initiators leading to a radical addition reaction. This atom-economic process is tolerant to a variety of functional groups, and, owing to its potential efficiency it can also be considered as a click-reaction.[5] Herein we report a convenient protocol for performing thiol-ene reaction featuring mild conditions, use of small amounts (less than 1%) of readily accessible non-metal catalyst, a close to stoichiometric ratio of coupling components, and visible light as initiator.[6,7]

Photocatalytic versions of thiol-ene reaction have previously been reported based on application of precious metal photocatalysts,[8] metal oxides as light absorbing systems,[9] as well as acridinium salts[10] and benzophenone or 2,2-dimethoxyphenyl acetophenone.[11,12] A key initiating step in these reactions is the hydrogen atom abstraction from the thiol to generate S-centered radical, which subsequently enters

into a chain process.[13] For this purpose, an additive such as bromotrichloromethane to generate an activator species, is used (Scheme 1).

Scheme 1. Generation of thiyl radicals.

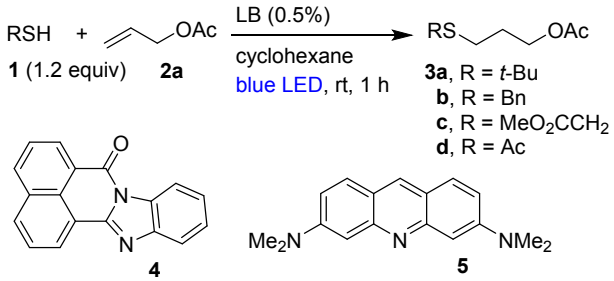


In this work, the thiyl radical is generated via proton-coupled electron transfer (PCET). Indeed, a simultaneous exchange of a proton and an electron is frequently encountered in biological processes, and is increasingly used in synthetic transformations.[14,15] As a catalyst we propose to use a photoactive Lewis basic species capable of binding to acidic thiol (Scheme 1). Under irradiation, the PCET step can take place, which can be realized via different pathways (*vide infra*), resulting in generation of thiyl radical. The latter can be involved in a typical chain mechanism involving H-atom transfer between the C-centered radical and thiol (left part). Alternatively, the alkyl radical can abstract hydrogen atom from a highly reactive radical originating from PCET (right part). In this step, the radical chain is terminated along with the regeneration of Lewis basic photocatalyst.

tert-Butylthiol (**1a**) and allylacetate (**2a**) were selected as model substrates and their coupling was evaluated (Table 1). A small excess of thiol (1.2 equiv) was used throughout this work, which facilitates product isolation. Reactions were performed in cyclohexane under argon atmosphere for one hour by irradiation with blue light, and conversion of the alkene was determined by GC analysis. There was no reaction without catalyst, but addition of 0.5 mol% of readily accessible benzimidazole-based compound **4**[16] caused noticeable conversion of the alkene (entries 1 and 2). With more basic catalyst,

acridine orange (**5**), the reaction was faster, leading to virtually complete conversion after 5 hours (entry 4). Experiments with more acidic thiols such as benzylthiol, methyl thioglycolate and thioacetic acid showed that these reactions proceed faster, and even catalyst **4** can be applied (entries 5-9). When the reaction was performed in the air atmosphere, there was no deleterious effect to the product yield, while sufloxide by-products were not detected by GC-MS analysis.[17] At the same time, household lamp as a light source in combination with catalyst **4** was notably less efficient compared to 400 LED (see entry 7).

Table 1. Optimization studies.



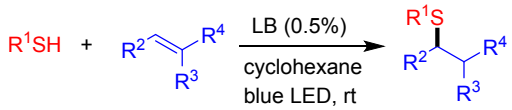
#	Thiol	LB	Product	Conv. of **2a**, %[a]
1	*t*-BuSH (**1a**)	-	**3a**	< 1
2	*t*-BuSH (**1a**)	**4**	**3a**	17
3	*t*-BuSH (**1a**)	**5**	**3a**	67
4[b]	*t*-BuSH (**1a**)	**5**	**3a**	98 (86[c])
5	BnSH (**1b**)	**5**	**3b**	99 (91[c])
6	BnSH (**1b**)	**4**	**3b**	46
7[d]	BnSH (**1b**)	**4**	**3b**	39
8	MeO_2CCH_2SH (**1c**)	**4**	**3c**	100 (97[c])
9	AcSH (**1d**)	**4**	**3d**	100 (95[c])

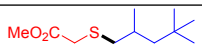
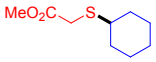
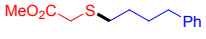
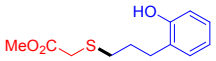
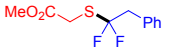
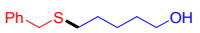
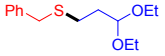
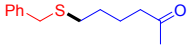
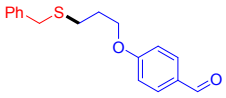
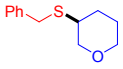
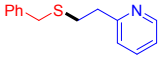
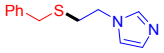
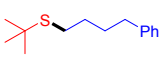
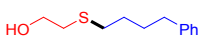
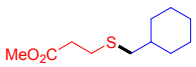
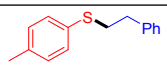
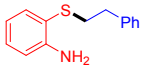
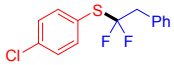
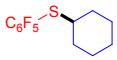
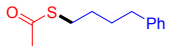
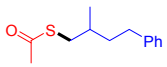
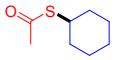
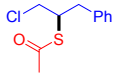
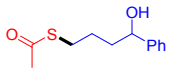
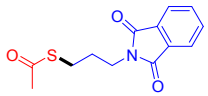
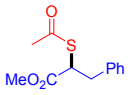
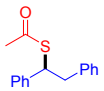
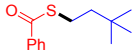
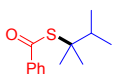
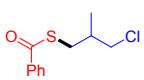
[a] Determined by GC. [b] Reaction time 5 h. [c] Yield of **3**. [d] Irradiation with household lamp, 15W CFL.

Using photocatalysts **4** and **5**, a series of thiols were combined with alkenes (Table 2). The reaction has wide scope with respect to both components affording, typically, high yields of products. Indeed,

aliphatic and aromatic thiols, as well as those bearing unprotected hydroxy or amino groups, worked well in this process. At the same time, terminal and internal alkenes can be used leading to the product with regioselectivity characteristic for radical addition. The alkene component may contain hydroxyl, ester, aldehyde, keto, and acetal groups. Difluorinated alkenes, which are readily available from aldehydes via Wittig olefination,[18] also afforded corresponding products in good yields (entries 5, 19, 20). Electron-rich alkenes such as dihydropyrane and *N*-vinylimidazole also were successfully employed (entries 11 and 13). Notably, cinnamyl chloride, bearing a reactive C-Cl bond, gave the desired addition product (entry 25). Concerning thio-component, thioacids were most reactive, affording addition product even with tetrasubstituted double bond (entry 31). Though most reactions were complete within few hours, for some examples longer time was required. For substrates having more acidic S-H fragment such as thioacids, catalyst **4** was successfully used, whereas acridine orange **5** worked well for less acidic aliphatic thiols. The disadvantage of acridine orange is that at longer reaction times (> 6 h), it can lose its activity as reflected by noticeable rate retardation.

Table 2. Photocatalyzed thiol-ene reaction.

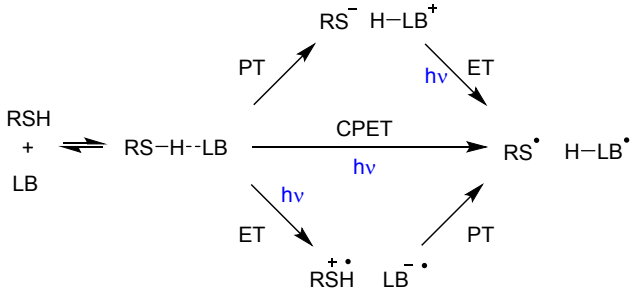


#	Product		LB	Time, h	Yield, %
1		**3e**	**5**	3	85
2		**3f**	**5**	2	96
3[a]		**3g**	**4**	0.25	92
4		**3h**	**5**	1.5	98
5		**3i**	**4**	48	92
6		**3j**	**5**	5	90
7		**3k**	**5**	1	99
8		**3l**	**5**	2	92
9		**3m**	**5**	1	98
10		**3n**	**4**	18	90
11		**3o**	**5**	18	74
12		**3p**	**5**	2	58
13		**3q**	**5**	1	88
14		**3r**	**5**	3	99
15		**3s**	**4**	4	97
16		**3t**	**5**	1	98
17		**3u**	**4**	1	99
18		**3v**	**5**	24	92
19		**3w**	**5**	1	98
20		**3x**	**4**	18	98
21		**3y**	**4**	18	98
22		**3z**	**4**	0.5	98
23		**3za**	**4**	1	98
24		**3zb**	**4**	1	97
25		**3zc**	**4**	15	92
26		**3zd**	**4**	18	90
27[b]		**3ze**	**4**	2	91
28		**3zf**	**4**	18	77
29[a]		**3zg**	**4**	15	90
30		**3zh**	**4**	2	99
31		**3zi**	**4**	12	77
32		**3zj**	**4**	2	82

[a] CH_2Cl_2 was used as solvent. [b] EtOAc was used as solvent.

Mode of action of the Lewis basic photocatalysts deserves additional comments. PCET process for the generation of thiyl radicals can be realized via different pathways[18] (Scheme 2). Consecutive proton transfer (PT) and electron transfer (ET) steps (top and bottom paths), as well as concerted proton-electron transfer (CPET) should be considered. In general, given that the reaction proceeds efficiently in non-polar solvent (cyclohexane), the formation of charged species seems unfavorable. In the literature, for an analogous system involving light mediated PCET process between acridine orange and a phenol, the CPET mechanism was suggested based on transient absorption spectroscopy measurements.[19] Correspondingly, the concerted pathway is likely in case of thiols. On the other hand, the mechanism may depend on particular thiol/catalyst combination. Indeed, it was noted that reactions proceed faster with more acidic thiols. This observation suggests some thiol/catalyst interaction, which would precede the electron transfer step.[20,21]

Scheme 2. PCET process.



We proposed that the presence of additional Lewis basic species capable of binding to the thiol in competition with the photocatalyst may influence on the reaction efficiency. Indeed, when pyridine (2 equiv) was present in the mixture of benzylthiol **1b** with allylacetate **2a** in the presence of catalyst **4**, only 23% conversion of **2a** was noted compared to 46% without pyridine under otherwise identical conditions (30 min reaction time).

To obtain some insights on the interaction of catalysts **4** and **5** with thiols, their combinations were evaluated spectroscopically. Thus, chemical shifts of **4** in ^{1}H NMR spectrum (in $CDCl_3$) and its UV-vis absorption spectrum (in CH_2Cl_2) were unaffected by addition of excess of strongly acidic thioacetic acid. However, AcSH caused quenching of fluorescence of **4** (Stern-Volmer analysis) thereby supporting the interaction of the catalyst's excited state with the thiol. A combination of more basic

catalyst **5** with less acidic benzylthiol **1b** in cyclohexane behaved similarly (no change in NMR, and UV-vis, observation of Stern-Volmer fluorescence quenching). However, in more polar acetonitrile, gradual addition of large excess of the thiol to **5** led to notable change in its absorption spectrum (see Supporting Information for details). The difference in spectra in cyclohexane and acetonitrile may be associated with the propensity of formation of protonated form of **5** (**5**·H^+) in more polar solvent, and, therefore, another mechanism involving oxidation of the thiol by **5**·H^+ may be operative in this case. However, when a typical reaction of benzylthiol **1b** with allylacetate **2a** mediated by **5** was performed in acetonitrile, the reaction proceeded notably slower compared to that in cyclohexane. This means that the oxidation of the thiol by **5**·H^+ cannot be the dominating reaction pathway.

The chain character of the process was supported by the measurement of the quantum yield for the reaction of benzylthiol **1b** with allylacetate **2a**, which gave the value of 6.[22] However, the light is necessary to maintain this reaction, since in a light/dark sequence, there was a significant retardation in the dark periods (see Supporting Information). This points to the chain interruption via H-atom transfer from highly reactive H-LB radical species to the alkyl radical[23] (see Scheme 1).

In summary, a convenient protocol for the visible light-promoted thiol-ene click reaction is described. The method has wide substrate scope, and prescribes the use of close to stoichiometric ratio of thiol and alkene. The Lewis basic nature of the photocatalyst is believed to be the key issue responsible for the reaction efficiency.

EXPERIMENTAL SECTION

General Methods: Column chromatography was carried out employing silica gel (230-400 mesh). Precoated silica gel plates F-254 were used for thin-layer analytical chromatography visualizing with UV and/or acidic aq. $KMnO_4$ solution. High resolution mass spectra (HRMS) were measured using electrospray ionization (ESI) and time-of-flight (TOF) mass analyzer (Bruker MicrOTOF II). The measurements were done in a positive ion mode (interface capillary voltage –4500 V) or in a negative ion mode (3200 V); mass range from m/z 50 to m/z 3000. For NMR measurements, Bruker AM300

spectrometer was used. Fluorescence and absorption spectra were recorded on a Fluorat-02-Panorama spectrofluorometer (Lumex Instruments). For irradiation, a strip of light emitting diodes (SMD2835-120LED 1M-Blue, 12V, 24W/m, 465 nm) was used. Reactions were performed in DURAN culture tubes (Roth cat. # K248.1, outside diameter 12 mm). Chemicals were purchased from Acros. (2,2-Difluoroethenyl)benzene,[24] 4-phenyl-2-methylbut-1-ene,[25] 1-phenylbut-3-en-1-ol,[26] and N-allylphthalimide[27] were prepared according to literature procedures.

1,8-Naphthoylene-1',2'-benzimidazole (**4**).[28] Naphthalic anhydride (4.0 g, 20 mmol) and *o*-phenylenediamine (2.38 g, 22 mmol) were mixed in 15 mL of propionic acid. The mixture was heated by a hot plate to 135 °C (the temperature was measured by a thermometer immersed in the reaction mixture) and was stirred at this temperature for 30 min. The heating bath was removed, the stirring was discontinued, and the mixture was allowed to cool to room temperature, and was kept overnight to effect crystallization. The crystals were filtered, washed twice with acetic acid and twice with methyl *tert*-butyl ether, and dried. The obtained crystals were successively recrystallized from toluene and 2-ethoxyethanol. Yield 4.38 g (80%). Mp 192–193°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.43–7.54 (m, 2H), 7.70–7.80 (m, 2H), 7.83–7.91 (m, 1H), 8.07 (d, 1H, J = 8.2 Hz), 8.21 (d, 1H, J = 8.1 Hz), 8.49–8.57 (m, 1H), 8.72 (d, 1H, J = 7.2 Hz), 8.77 (d, 1H, J = 7.2 Hz). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 160.6 149.3, 143.9, 135.3, 132.2, 132.0, 131.8, 131.6, 127.4, 127.1, 127.0, 126.9, 125.8, 125.5, 123.2, 120.6, 120.1, 116.0.

Thiol-ene reaction (General procedure). In a screw-cap tube, alkene (1.5 mmol) and thiol (1.8 mmol) were mixed under argon in 2 mL of degassed solvent (for all compounds **3** except **3g,ze,zg**, solvent - cyclohexane; for **3g,zg**, solvent - CH_2Cl_2; for **3ze**, solvent - EtOAc). Photocatalyst **4** or **5** (0.0075 mmol, 0.5%) was added. The tube was sealed and then stirred with irradiation by a strip of blue LED for the time indicated in Table 2. During irradiation the mixture was cooled with room temperature water (for the reaction set-up, see Supporting information). For all compounds **3** except **3g,ze,zg**, the reaction mixture was transferred to a silica gel column, which was eluted with hexanes/EtOAc. For compounds **3g,zg**, the reaction mixture was evaporated under vacuum, and the residue was purified by

chromatography on silica gel with hexanes/EtOAc. For compound **3ze**, the reaction mixture was eluted with EtOAc through a silica gel pad, evaporated, and the residue was recrystallized from *n*-heptane/EtOAc (2/1).

3-(*tert*-Butylthio)propyl acetate (3a). Yield 245 mg (86%). Colorless oil. Chromatography: hexanes/EtOAc, 15/1. R_f 0.22 (hexanes/EtOAc, 15/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.29 (s, 9H), 1.83 (quint, 2H, *J* = 6.7 Hz), 1.99 (s, 3H), 2.52 (t, 2H, *J* = 6.3 Hz), 4.09 (t, 2H, *J* = 7.4 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 20.9, 24.7, 29.0, 30.9, 42.0, 63.3, 170.8. HRMS (ESI): Calcd for $C_9H_{18}NaO_2S$ (M+Na) 213.0920; found 213.0929.

3-(Benzylthio)propyl acetate (3b).[29] Yield 306 mg (91%). Colorless oil. Chromatography: gradient elution hexanes/EtOAc, 15 /1→10/1. R_f 0.24 (hexanes/EtOAc, 10/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.88 (quint, 2H, *J* = 7.0 Hz), 2.04 (s, 3H), 2.49 (t, 2H, *J* = 7.3 Hz), 3.73 (s, 2H), 4.13 (t, 2H, *J* = 6.4 Hz), 7.22–7.36 (m, 5H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 20.9, 27.6, 28.3, 36.2, 63.1, 127.0, 128.5, 128.9, 138.3, 171.0.

Methyl 2-[(3-acetoxypropyl)thio]acetate (3c). Yield 300 mg (97%). Colorless oil. Chromatography: hexanes/EtOAc, 4/1. R_f 0.23 (hexanes/EtOAc, 4/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.85 (quint, 2H, *J* = 6.5 Hz), 1.97 (s, 3H), 2.62 (t, 2H, *J* = 7.3 Hz), 3.15 (s, 2H), 3.65 (s, 3H), 4.07 (t, 2H, *J* = 6.3 Hz). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 20.8, 28.0, 28.9, 33.2, 52.2, 62.7, 170.6, 170.7. HRMS (ESI): Calcd for $C_8H_{14}NaO_4S$ (M+Na) 229.0505; found 229.0500.

3-(Acetylthio)propyl acetate (3d). Yield 251 mg (95%). Colorless oil. Chromatography: hexanes/EtOAc, 5/1. R_f 0. 31 (hexanes/EtOAc, 5/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.84 (quint, 2H, *J* = 7.0 Hz), 1.99 (s, 3H), 2.26 (s, 3H), 2.87 (t, 2H, *J* = 7.2 Hz), 4.04 (t, 2H, *J* = 6.2 Hz). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 20.8, 25.6, 28.6, 30.5, 62.7, 170.8, 195.3. HRMS (ESI): Calcd for $C_7H_{12}NaO_3S$ (M+Na) 199.0399; found 199.0405.

Methyl 2-[(2,4,4-trimethylpentyl)thio]acetate (3e). Yield 337 mg (85%). Colorless oil. Chromatography: hexanes/EtOAc, 15/1. R_f 0.28 (hexanes/EtOAc, 15/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.89 (s, 9H), 1.01 (d, 3H, *J* = 6.6 Hz). 1.09 (dd, 1H, *J* = 13.9; 6.6 Hz), 1.35 (dd, 1H, *J* = 13,9; 3.7 Hz),

1.65–1.80 (m, 1H), 2.44 (dd, 1H, *J* = 12.3; 8.1 Hz), 2.61 (dd, 1H, *J* = 12.3; 5.9 Hz), 3.19 (s, 2H), 3.71 (s, 3H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ: 22.1, 29.3, 29.9, 31.0, 33.8, 42.4, 50.2, 52.2, 171.0. HRMS (ESI): Calcd for $C_{11}H_{22}NaO_2S$ (M+Na) 241.1233; found 241.1235

Methyl 2-(cyclohexylthio)acetate (3f).[30] Yield 721 mg (96%). Colorless oil. Chromatography: hexanes/EtOAc, 12/1. R_f 0.33 (hexanes/EtOAc, 10/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.20–1.40 (m, 5H), 1.56–1.66 (m, 1H), 1.70–1.84 (m, 2H), 1.91–2.05 (m, 2H), 2.73–2.86 (m, 1H), 3.26 (s, 2H), 3.73 (s, 3H). $^{13}C\{^{1}H\}$ NMR (75MHz, $CDCl_3$) δ: 25.8, 26.0, 31.8, 33.1, 44.0, 52.4, 171.3.

Methyl 2-[(4-phenylbutyl)thio]acetate (3g). Yield 392 mg (92%). Colorless oil. Chromatography: hexanes/EtOAc, 10/1. R_f 0.26 (hexanes/EtOAc, 10/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.61–1.82 (m, 4H), 2.66 (t, 2H, *J* = 7.3 Hz), 2.69 (t, 2H, *J* = 7.2 Hz), 3.23 (s, 2H), 3.75 (s, 3H). 7.17–7.24 (m, 3H), 7.27–7.35 (m, 2H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ: 28.5, 30.4, 32.6, 33.5, 35.4, 52.3, 125.8, 128.3, 128.4, 142.1, 171.0. HRMS (ESI): Calcd for $C_{13}H_{18}NaO_2S$ (M+Na) 261.0920; found 261.0919.

Methyl 2-{[3-(2-hydroxyphenyl)propyl]thio}acetate (3h). Yield 353 mg (98%). Colorless oil. Chromatography: hexanes/EtOAc, 3/1. R_f 0.28 (hexanes/EtOAc, 3/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.95 (quint, 2H, *J* = 7.5 Hz), 2.69 (t, 2H, *J* = 7.3 Hz), 2.75 (t, 2H, *J* = 7.5 Hz), 3.27 (s, 2H), 3.74 (s, 3H), 6.22 (s, 1H), 6.82 (dd, 1H, *J* = 8.1; 1.1 Hz), 6.86 (td, 1H, *J* = 7.5; 1.3 Hz), 7.08 (td, 1H, *J* = 7.7; 1.8 Hz), 7.12 (dd, 1H, *J* = 7.5; 1.5 Hz). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ: 28.8, 28.9, 32.4, 33.5, 52.6, 115.5, 120.6, 127.4, 127.5, 130.4, 154.0, 171.7. HRMS (ESI): Calcd for $C_{12}H_{16}NaO_3S$ (M+Na) 263.0712; found 263.0707 .

Methyl 2-[(1,1-difluoro-2-phenylethyl)thio]acetate (3i). Yield 339 mg (92%). Colorless oil. Chromatography: hexanes/EtOAc, 10/1. R_f 0.28 (hexanes/EtOAc, 10/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.47 (t, 2H, *J* = 14.8 Hz), 3.61 (s, 2H), 3.76 (s, 3H), 7.30 – 7.41 (m, 5H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ: 29.9 (t, *J* = 4.4 Hz), 45.2 (t, *J* = 23.7 Hz), 52.7, 128.0, 128.6, 129.3 (t, *J* = 279.7 Hz), 130.5, 131.5 (t, *J* = 3.6 Hz), 169.5. ^{19}F NMR (282 MHz, $CDCl_3$) δ: -73.9 (t, *J* = 14.8 Hz). HRMS (ESI): Calcd for $C_{11}H_{12}F_2NaO_2S$ (M+Na) 269.0418; found 269.0427.

3-(Benzylthio)propan-1-ol (**3j**).[8a] Yield 246 mg (90%). Colorless oil. Chromatography: hexanes/EtOAc, 3/1. R_f 0.15 (hexanes/EtOAc, 3/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.81 (quint, 2H, *J* = 6.6 Hz), 2.10 (br s, 1H), 2.55 (t, 2H, *J* = 7.1 Hz), 3.70 (t, 2H, *J* = 6.1 Hz), 3.74 (s, 2H), 7.22–7.36 (m, 5H). ^{13}C{^{1}H} NMR (75MHz, $CDCl_3$) δ: 28.0, 31.6, 36.3, 61.6, 127.0, 128.5, 128.9, 138.4.

4-(Benzylthio)pentan-1-ol (3k). Yield 312 mg (99%). Colorless oil. Chromatography: gradient elution hexanes/EtOAc, 3 /1→2/1. R_f 0.24 (hexanes/EtOAc, 2/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.36–1.66 (m, 4H), 2.20 (s, 1H), 2.44 (t, 2H, *J* = 6.9 Hz), 3.60 (t, 2H, *J* = 6.6 Hz), 3.72 (s, 2H), 7.21–7.35 (m, 5H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 25.0, 29.0, 31.3, 32.2, 36.4, 62.5, 126.9, 128.5, 128.9, 138.6. HRMS (ESI): Calcd for $C_{12}H_{18}NaOS$ (M+Na) 233.0971; found 233.0961

Benzyl(3,3-diethoxypropyl)sulfane (3l). Yield 350 mg (92%). Colorless oil. Chromatography: hexanes/EtOAc, 15/1. R_f 0.23 (hexanes/EtOAc, 15/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.20 (t, 6H, *J* = 7.3 Hz), 1.84–1.92 (m, 2H), 2.49 (t, 2H, *J* = 7.3 Hz), 3.48 (dq, 2H, *J* = 9.5; 7.3 Hz), 3.64 (dq, 2H, *J* = 9.5; 7.3 Hz), 3.72 (s, 2H), 4.58 (t, 1H, *J* = 5.4 Hz), 7.21–7.30 (m, 1H), 7.30–7.34 (m, 4H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 15.3, 26.5, 33.4, 36.3, 61.5, 101.7, 126.9, 128.4, 128.9, 138.4. HRMS (ESI): Calcd for $C_{14}H_{22}NaO_2S$ (M+Na) 277.1233; found 277.1232.

6-(Benzylthio)hexan-2-one (3m). Yield 326 mg (98%). Color less oil. Chromatography: hexanes/EtOAc, 5/1. R_f 0.26 (hexanes/EtOAc, 5/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.48–1.68 (m, 4H), 2.10 (s, 3H), 2.38 (t, 2H, *J* = 6.6 Hz), 2.40 (t, 2H, *J* = 6.6 Hz), 7.20–7.27 (m, 1H), 7.28–7.32 (m, 4H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 22.9, 28.6, 29.9, 31.0, 36.2, 43.1, 126.9, 128.4, 128.9, 138.5, 208.5. HRMS (ESI): Calcd for $C_{13}H_{18}NaOS$ (M+Na) 245.0971; found 245.0980.

4-[3-(Benzylthio)propoxy]benzaldehyde (3n). Yield 387 mg (90%). Colorless oil. Chromatography: hexanes/EtOAc, 5/1. R_f 0.29 (hexanes/EtOAc, 4/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.05 (quint, 2H, *J* = 6.6 Hz), 2.63 (t, 2H, *J* = 7.1 Hz), 3.74 (s, 2H), 4.10 (t, 2H, *J* = 6.1 Hz), 6.97 (d, 2H, *J* = 8.8 Hz), 7.21 – 7.36 (m, 5H), 7.83 (d, 2H, *J* = 8.8 Hz), 9.89 (s, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 27.6, 28.6, 36.3, 66.5, 114.7, 127.0, 128.5, 128.8, 130.0, 131.9, 138.2, 163.8, 190.6. HRMS (ESI): Calcd for $C_{17}H_{18}NaO_2S$ (M+Na) 309.0920; found 309.0922.

3-(Benzylthio)tetrahydro-2*H*-pyran (3o). Yield 282 mg (74%). Colorless oil. Chromatography: hexanes/EtOAc, 10/1. R_f 0.24 (hexanes/EtOAc, 10/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.40–1.55 (m, 1H), 1.60–1.72 (m, 2H), 1.99–2.09 (m, 1H), 2.74 (ddt, 1H, *J* = 15.0; 14.3; 4.0 Hz), 3.27 (dd, 1H, *J* = 11.2; 10.1 Hz), 3.34–3.44 (m, 1H), 3.76 (s, 2H), 3.85 (dm, 1H, *J* = 11.4 Hz), 3.95 (ddd, 1H, *J* = 11.4; 4.2; 2.0 Hz), 7.23–7.36 (m, 5H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 26.3, 30.3, 35.2, 40.7, 68.0, 72.5, 127.1, 128.6, 128.8, 138.6. HRMS (ESI): Calcd for $C_{12}H_{16}NaOS$ (M+Na) 231.0814; found 231.0820.

2-[2-(Benzylthio)ethyl]pyridine (3p). Yield 179 mg (52%). Yellowish oil. Chromatography: hexanes/EtOAc, 2/1. R_f 0.2 (hexanes/EtOAc, 2/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.87 (t, 2H, *J* = 7.3 Hz), 3.05 (t, 2H, *J* = 7.3 Hz), 3.73 (s, 2H), 7.10–7.16 (m, 2H), 7.21–7.36 (m, 5H), 7.60 (td, 1H, *J* = 7.7; 1.8 Hz), 8.55 (dd, 1H, *J* =5.2; 1.9 Hz). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 31.0, 36.4, 38.0, 121.3, 123.0, 126.8, 128.4, 128.7, 136.2, 138.3, 149.3, 159.9. HRMS (ESI): Calcd for $C_{14}H_{16}NS$ (M+H) 230.0998; found 230.0993.

1-[2-(Benzylthio)ethyl]-1*H*-imidazole (3q). Yield 288 mg (88%). Colorless oil. Chromatography: hexanes/*i*-PrOH, 3/1. R_f 0.17 (hexanes/*i*-PrOH, 3/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.63 (t, 2H, *J* = 6.9 Hz), 3.51 (s, 2H), 3.87 (t, 2H, *J* = 6.9 Hz), 6.91 (s, 1H), 6.99 (s, 1H), 7.16–7.31 (m, 5H), 7.36 (s, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 31.9, 36.2, 46.6, 118.6, 127.1, 128.4, 128.6, 129.2, 136.9, 137.5. HRMS (ESI): Calcd for $C_{12}H_{15}N_2S$ (M+H) 219.0950; found 219.0959.

***tert*-Butyl(4-phenylbutyl)sulfane (3r).**[31] Yield 330 mg (99%). Colorless oil. Chromatography: hexanes/EtOAc, 15/1. R_f 0.50 (hexanes/EtOAc, 15/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.37 (s, 9H), 1.62–1.73 (m, 2H), 1.73–1.86 (m, 2H), 2.60 (t, 2H, *J* = 7.2 Hz), 2.69 (t, 2H, *J* = 7.4 Hz), 7.19–7.26 (m, 3H) 7.28–7.36 (m, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 28.3, 29.6, 31.1, 35.7, 41.9, 125.8, 128.8, 142.4.

2-[(4-Phenylbutyl)thio]ethan-1-ol (3s). Yield 306 mg (97%). Colorless oil. Chromatography: hexanes/EtOAc, 3/1. R_f 0.20 (hexanes/EtOAc, 3/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.59–1.84 (m, 4H), 2.57 (t, 2H, *J* = 7.1 Hz), 2.61–2.70 (m, 2H), 2.72 (t, 2H, *J* = 6.1 Hz), 3.72 (t, 2H, *J* = 6.3 Hz), 7.17–7.26

(m, 3H), 7.27–7.36 (m, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 29.3, 30.5, 31.6, 35.2, 35.5, 60.5, 125.8, 128.4, 128.4, 142.1. HRMS (ESI): Calcd for $C_{12}H_{18}NaOS$ (M+Na) 233.0971; found 233.0978.

Methyl 3-[(cyclohexylmethyl)thio]propanoate (3t). Yield 318 mg (98%). Colorless oil. Chromatography: hexanes/EtOAc, 15/1. R_f 0.20 (hexanes/EtOAc, 15/1). ^1H NMR (300 MHz, $CDCl_3$) δ: 0.83–0.99 (m, 2H), 1.05–1.29 (m, 3H), 1.36–1.51 (m, 1H), 1.51–1.75 (m, 3H), 1.76–1.87 (m, 2H), 2.40 (d, 2H, J = 6.9 Hz), 2.58 (t, 2H, J = 7.2 Hz), 2.74 (t, 2H, J = 7.2 Hz), 3.68 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 26.1, 26.4, 27.6, 32.8, 34.8, 37.8, 39.9, 51.7, 172.5. HRMS (ESI): Calcd for $C_{11}H_{20}NaO_2S$ (M+Na) 239.1076; found 239.1070.

Phenethyl(*p*-tolyl)sulfane (3u).[32] Yield 339 mg (99%). Colorless oil. Chromatography: hexanes/EtOAc, 20/1. R_f 0.44 (hexanes/EtOAc, 20/1). ^1H NMR (300 MHz, $CDCl_3$) δ: 2.42 (s, 3H). 2.99 (dd, 2H, J = 9.4, 6.3 Hz), 3.21 (dd, 2H, J = 9.0, 6.3 Hz), 7.16–7.42 (m, 9H). $^{13}C\{^1H\}$ NMR (75MHz, $CDCl_3$) δ: 21.1, 35.9, 36.0, 126.5, 128.6, 128.7, 129.9, 130.2, 132.7, 136.2, 140.4.

2-(Phenethylthio)aniline (3v).[33] Yield 316 mg (92%). Colorless oil. Chromatography: gradient elution hexanes/EtOAc, 12 /1→10/1. R_f 0.2 (hexanes/EtOAc, 10/1). ^1H NMR (300 MHz, $CDCl_3$) δ: 2.89–2.96 (m, 2H), 3.04–3.11 (m, 2H), 4.33 (br s, 2H), 6.74–6.82 (m, 2H), 7.16–7.39 (m, 6H), 7.48 (dd, 1H, J = 8.1; 1.6 Hz). $^{13}C\{^1H\}$ NMR (75MHz, $CDCl_3$) δ: 35.8, 115.0, 117.8, 118.7, 126.4, 128.5, 128.6, 129.7, 135.9, 140.4, 148.3.

(4-Chlorophenyl)(1,1-difluoro-2-phenylethyl)sulfane (3w).[13] Yield 418 mg (98%). Colorless crystals. Mp 70–71°C. Chromatography: hexanes/CH_2Cl_2, 25/1. R_f 0.20 (hexanes/CH_2Cl_2, 25/1). ^1H NMR (300 MHz, $CDCl_3$) δ: 3.49 (t, 2H, J = 14.8 Hz), 7.30–7.45 (m, 7H), 7.55 (d, 2H, J = 8.5 Hz). $^{13}C\{^1H\}$ NMR (75MHz, $CDCl_3$) δ: 45.3 (t, J = 24.1 Hz), 125.5, 128.0, 128.6, 129.4, 130.6, 131.9, 136.4, 137.5. ^{19}F NMR (282 MHz, $CDCl_3$) δ: –72.1 (t, J = 14.8 Hz).

(1,1-Difluoro-2-phenylethyl)(perfluorophenyl)sulfane (3x).[13] Yield 485 mg (95%). Colorless crystals. Mp 51–52°C. Chromatography: hexanes/EtOAc, 20/1. R_f 0.41 (hexanes/EtOAc, 20/1). ^1H NMR (300 MHz, $CDCl_3$) δ: 3.55 (t, 2H, J = 14.7 Hz), 7.35–7.42 (m, 5H). $^{13}C\{^1H\}$ NMR (75MHz, $CDCl_3$) δ: 45.2 (t, J = 23.1 Hz), 101.3 (t, J = 20.9 Hz), 128.3, 128.4 (t, J = 285.2 Hz), 128.8, 130.6, 137.90 (dm, J =

256.4 Hz), 143.6 (dm, J = 258.9 Hz), 148.9 (dm, J = 250.4 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: –161.1 (m, 2F), –148.6 (tt, 1F, J = 4.8, 20.6 Hz), –129.8 (dm, J = 20.6 Hz), –70.0 (tt, 2F, J = 14.7; 5.3 Hz).

Cyclohexyl(perfluorophenyl)sulfane (3y).[34] Yield 415 mg (98%). Colorless crystals. Mp 54–55 °C. Chromatography: hexanes/EtOAc, 40/1 + 0.5%NEt_3. R_f 0.56 (hexanes/EtOAc, 40/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.17–1.48 (m, 5H), 1.56–1.69 (m, 1H), 1.74–1.97 (m, 4H), 3.15 (tt, 1H, J = 10.4, 3.7 Hz). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 25.5, 25.9, 33.4, 47.6 (q, J = 1.7 Hz), 137.7 (dm, J = 254.9 Hz), 141.3 (dm, J = 269.0 Hz), 148.0 (dm, J = 247.5 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: –161.4 (m, 2F), –152.8 (t, 1F, J = 20.1 Hz), –131.5 (d, 2F, J = 23.6 Hz). HRMS (ESI): Calcd for $C_{12}H_{11}F_5AgS$ (M+Ag) 388.9547; found 388.9547.

***S*-(4-Phenylbutyl) ethanethioate (3z).**[35] Yield 306 mg (98%). Colorless oil. Chromatography: hexanes/EtOAc,15 /1. R_f 0.36 (hexanes/EtOAc, 15/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.59–1.81 (m, 4H), 2.36 (s, 3H), 2.67 (t, 2H, J = 7.1 Hz), 2.94 (t, 2H, J = 6.1 Hz), 7.17–7.26 (m, 3H), 7.27–7.36 (m, 3H). ^{13}C{^{1}H} NMR (75MHz, $CDCl_3$) δ: 29.0, 29.2, 30.6, 30.7, 35.5, 125.9, 128.4, 128.5, 142.1, 195.9.

***S*-(2-Methyl-4-phenylbutyl) ethanethioate (3za).** Yield 394 mg (98%). Colorless oil. Chromatography: hexanes/EtOAc, 20/1. R_f 0.27 (hexanes/EtOAc, 20/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.06 (d, 3H, J = 6.6 Hz), 1.48–1.64 (m, 1H), 1.70–1.84 (m, 2H), 2.37 (s, 3H), 2.58–2.78 (m, 2H), 2.86 (dd, 1H, J = 13.6; 7.3 Hz), 3.03 (dd, 1H, J = 13.6; 5.1 Hz), 7.19–7.25 (m, 3H), 7.29–7.36 (m, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 19.2, 30.7, 33.0, 33.3, 35.9, 37.8, 125.8, 128.4, 142.3, 195.8. HRMS (ESI): Calcd for $C_{13}H_{18}NaOS$ (M+Na) 245.0971; found 245.0975.

***S*-Cyclohexyl ethanethioate (3zb).**[36] Yield 230 mg (97%). Colorless oil. Chromatography: hexanes/EtOAc, 30/1. R_f 0.24 (hexanes/EtOAc, 30/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.15–1.50 (m, 5H), 1.51–1.71 (m, 3H), 1.83–1.96 (m, 2H), 2.27 (s, 3H), 3.42–3.55 (m, 1H). ^{13}C{^{1}H} NMR (75MHz, $CDCl_3$) δ: 25.6, 26.0, 30.8, 33.1, 42.5, 195.7.

***S*-(1-Chloro-3-phenylpropan-2-yl) ethanethioate (3zc).** Yield 315 mg (%). Colorless oil. Chromatography: hexanes/EtOAc, 20/1. R_f 0.28 (hexanes/EtOAc, 20/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.35 (s, 3H), 3.01 (dd, 1H, J = 13.9; 6.8 Hz), 3.19 (dd, 1H, J = 13.9; 7.3 Hz), 3.63 (dd, 1H, J = 11.2; 6.2

Hz), 3.71 (dd, 1H, *J* = 11.2; 3.9 Hz), 4.02–4.12 (m, 1H), 7.26–7.40 (m, 5H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ: 30.7, 37.1, 46.6, 127.0, 128.6, 129.3, 137.4, 194.5. HRMS (ESI): Calcd for $C_{11}H_{13}ClNaOS$ (M+Na) 251.0268; found 251.0264.

***S*-(4-Hydroxy-4-phenylbutyl) ethanethioate (3zd).** Yield 302 mg (90%). Colorless oil. Chromatography: gradient elution hexanes/EtOAc, 4/1→3/1. R_f 0.34 (hexanes/EtOAc, 2/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.49–1.88 (m, 4H), 2.29 (s, 3H), 2.75 (s, 1H), 2.87 (t, 2H, *J* = 7.0 Hz), 4.63 (t, 1H, *J* = 5.5 Hz), 7.22–7.37 (m, 5H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ: 25.898, 28.923, 30.607, 37.911, 73.810, 125.9, 127.5, 128.5, 144.6, 196.2. HRMS (ESI): Calcd for $C_{12}H_{16}NaO_2S$ (M+Na) 247.0763; found 247.0757.

***S*-[3-(1,3-Dioxoisoindolin-2-yl)propyl]ethanethioate (3ze).**[37] Yield 359 mg (91%). Yellowish crystals. Mp 86–87 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.93 (quint, 2H, *J* = 7.3 Hz), 1.99 (s, 3H), 2.28 (s, 3H), 2.86 (t, 2H, *J* = 7.3 Hz), 3.71 (t, 2H, *J* = 6.9 Hz), 7.68 (dd, 2H, *J* = 5.5; 3.1 Hz), 7.79 (dd, 2H, *J* = 5.5; 3.1 Hz). $^{13}C\{^{1}H\}$ NMR (75MHz, $CDCl_3$) δ: 26.5, 28.7, 30.7, 37.0, 123.3, 132.1, 134.1, 168.4, 195.3.

Methyl 2-(acetylthio)-3-phenylpropanoate (3zf). Yield 275 mg (77%). Colorless oil. Chromatography: hexanes/EtOAc, 10/1. R_f 0.25 (hexanes/EtOAc, 10/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.32 (s, 3H), 3.04 (dd, 1H, *J* = 13.8; 7.3 Hz), 3.27 (dd, 1H, *J* = 13.8; 8.1 Hz), 3.67 (s, 3H), 4.47 (dd, 1H, *J* = 8.1, 7.3 Hz). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ: 30.2, 38.0, 47.1, 52.6, 127.1, 128.5, 129.1, 137.2, 171.4, 193.4. HRMS (ESI): Calcd for $C_{12}H_{14}NaO_3S$ (M+Na) 261.0556; found 261.0561.

***S*-(1,2-Diphenylethyl) ethanethioate (3zg).** Yield 346 mg (90%). Colorless oil. Chromatography: gradient elution hexanes/EtOAc, 20/1→15/1. R_f 0.37 (hexanes/EtOAc, 15/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.33 (s, 3H), 3.30 (dd, 1H, *J* = 13.7; 8.4 Hz), 3.33 (dd, 1H, *J* = 13.7; 7.1 Hz), 4.92 (dd, 1H, *J* = 8.4; 7.1 Hz), 7.14 – 7.39 (m, 10H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ: 30.6, 42.9, 49.7, 126.6, 127.5, 128.0, 128.3, 128.6, 129.4, 138.4, 141.0, 194.5. HRMS (ESI): Calcd for $C_{16}H_{16}NaOS$ (M+Na) 279.0814; found 279.0824.

***S*-(3,3-Dimethylbutyl) benzothioate (3zh).** Yield 330 mg (99%). Colorless oil. Chromatography: hexanes/EtOAc, 25/1. R_f 0.43 (hexanes/EtOAc, 25/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.00 (s, 9H),

1.54–1.62 (m, 2H), 3.01–3.09 (m, 2H), 7.40–7.47 (m, 2H), 7.55 (tt, 1H, J = 7.4; 1.4 Hz), 7.96–8.01 (m, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 25.0, 29.1, 31.1, 43.7, 127.2, 128.6, 133.2, 137.3, 192.0. HRMS (ESI): Calcd for $C_{13}H_{19}OS$ (M+H) 223.1151; found 223.1160.

***S*-(2,3-Dimethylbutan-2-yl) benzothioate (3zi)**. Yield 257 mg (77%). Colorless oil. Chromatography: hexanes/EtOAc, 30/1. R_f 0.37 (hexanes/EtOAc, 30/1). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.05 (d, 6H, J = 6.9 Hz), 1.60 (s, 6H), 2.33 (sept, 1H, J = 6.9 Hz), 7.39–7.46 (m, 2H), 7.54 (tt, 1H, J = 7.3; 2.1 Hz), 7.93–7.98 (m, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 18.1, 24.6, 36.5, 56.5, 127.0, 128.5, 132.8, 138.7, 192.8. HRMS (ESI): Calcd for $C_{13}H_{18}NaOS$ (M+Na) 245.0971; found 245.0979.

***S*-(3-Chloro-2-methylpropyl) benzothioate (3zj)**. Yield 280 mg (82%). Colorless oil. Chromatography: hexanes/EtOAc, 25/1. R_f 0.29 (hexanes/EtOAc, 25/1). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.17 (d, 3H, J = 6.8 Hz), 2.14–2.29 (m, 1H), 3.15 (dd, 1H, J = 13.6, 6.4 Hz), 3.21 (dd, 1H, J = 13.6, 6.7 Hz), 3.58 (dd, 1H, J = 11.0, 5.2 Hz), 3.61 (dd, 1H, J = 11.0, 5.5 Hz), 7.43–7.50 (m, 2H), 7.59 (tt, 1H, J = 7.4; 1.4 Hz), 7.99–8.02 (m, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 17.4, 32.6, 35.9, 49.5, 127.8, 128.7, 133.5, 136.9, 191.3. HRMS (ESI): Calcd for $C_{11}H_{13}ClNaOS$ (M+Na) 251.0268; found 251.0268.

ASSOCIATED CONTENT

Supporting Information

Stern-Volmer plots, UV-vis measurements, quantum yield determination protocol, copies of NMR spectra for all compounds (PDF). The Supporting Information is available free of charge on the ACS Publications website.

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

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