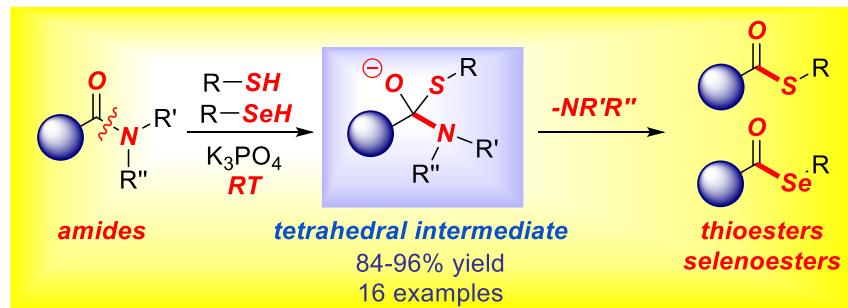


Thioesterification and Selenoesterification of Amides via Selective N–C(=O) to S/Se–C(=O) Interconversion

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Abstract The direct nucleophilic addition to amides represents an attractive methodology in organic synthesis that tackles amidic resonance by ground-state-destabilization. This approach has been recently accomplished with carbon, nitrogen and oxygen nucleophiles. Herein, we report an exceedingly mild method for the direct thioesterification and selenoesterification of amides by selective N–C(=O) bond cleavage in the absence of transition-metals. Acyclic amides undergo N–C(=O) to S/Se–C(=O) interconversion to give the corresponding thioesters and selenoesters in excellent yields at room temperature via a tetrahedral intermediate pathway (cf. acyl metal).

Key words amides, N–C activation, metal-free, thioesters, selenoesters, thioesterification, selenoesterification, tetrahedral intermediates

1. Introduction

Amides represent an extremely important class of functional groups in chemistry.¹ As a result, the development of new methods for the direct interconversion of amides has been a field of intense study since the early days of organic synthesis.^{2,3} The recent 5 years have witnessed the establishment of powerful amide bond cross-coupling reactions by selective N–C(=O) cleavage enabled by amide bond twist and ground-state-destabilization concept introduced by our group in 2015 (Figure 1A).^{4–7} These reactions enable the use of amides in generic cross-coupling reactions of high synthetic value via acyl- and aryl-intermediates (after CO loss)^{4b} using Pd, Ni, Rh, Co and Cr catalysis.⁸ Of particular interest is the fact that acyl-type reactivity of amides is feasible in the absence of transition-metals via direct nucleophilic addition pathway via tetrahedral intermediates (Figure 1B).⁹ This mode of reactivity has been accomplished with carbon, nitrogen and oxygen nucleophiles,¹⁰ and relies on the capacity of the amide bond to undergo ground-state-destabilization to overcome amidic resonance (15–20 kcal/mol, $n_N \rightarrow \pi^*_{CO}$ conjugation).

In this *Special Issue*, we report an exceedingly mild method for direct thioesterification¹¹ and selenoesterification¹² of amides

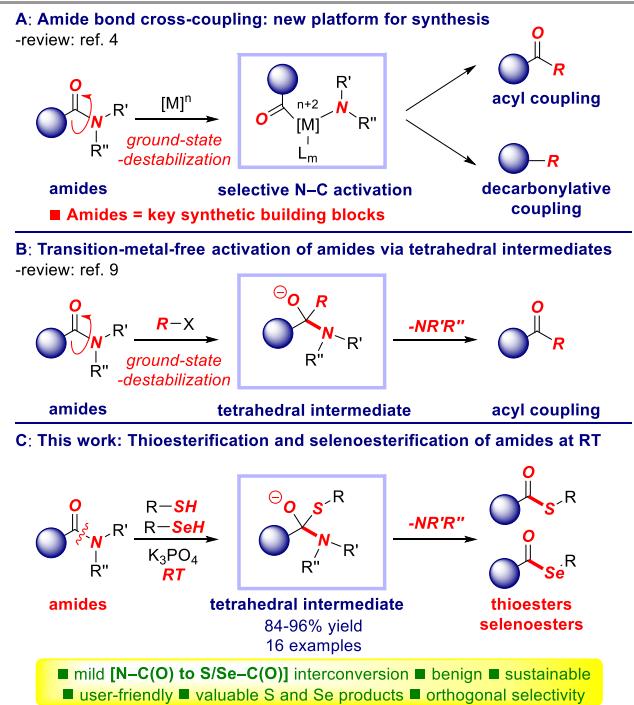


Figure 1 (A) Cross-coupling of amides. (B) Transition-metal-free activation of amides. (C) Thioesterification and selenoesterification of amides, N–C(=O) to S/Se–C(=O) interconversion at room temperature (this work).

by selective N–C(=O) bond cleavage in the absence of transition-metals (Figure 1C). Acyclic amides undergo N–C(=O) to S/Se–C(=O) interconversion to give the corresponding thioesters and selenoesters in excellent yields at room temperature via a tetrahedral intermediate pathway (cf. acyl metal). More broadly, this methodology enables rapid access to thioester and selenoester architectures from amides^{13,14} and further highlights the advantages of mild transition-metal-free tactic of amide bond functional group interconversion.

2. Results and Discussion

Transition-metal-free reactions of amides create new opportunity for organic synthesis by exploiting the tetrahedral intermediate avenue of ground-state-destabilized amides. In this context, N-acyl-tosylamides ($\text{Ar} = \text{Ph}$, $\text{R} = \text{Ph}$, $\text{RE} = 9.7$ kcal/mol; Winkler-Dunitz parameters, $\tau = 18.8^\circ$; $\chi_N = 18.9^\circ$ ^{5a}) have been established as broadly useful amides to achieve both (1) amide bond interconversion via direct metal insertion into the N-C(O) bond, and (2) amide bond interconversion via tetrahedral intermediates in the absence of transition-metals.⁴⁻⁹

Encouraged by our results in transition-metal-free esterification and transamidation reactions of N-acyl-tosylamides,^{9,10} we focused our efforts on identifying optimum conditions for mild, transition-metal-free thioesterification (Table 1). We were delighted to find that the reaction proceeds in excellent yield at room temperature using excess of K_3PO_4 as a base and close to a stoichiometric amount of thiophenol (Table 1, entry 1). Under these conditions, cleavage of the alternative amide bond was not observed, consistent with the high capacity of N-tosylamide to activate the acyclic amide bond. Furthermore, the amount of base could be decreased to 2.0 equiv without deleterious effect (Table 2, entry 2); however, further decrease resulted in lower reaction efficiency (Table 2, entry 3). A brief solvent screen indicated THF to be the optimal solvent; however, reasonable efficiency was also observed in dioxane, CH_2Cl_2 , toluene and CH_3CN (Table 2, entries 4-7). Finally, solvent concentration is an important parameter (Table 2, entries 8-9), as expected in transition-metal-free interconversion of amides to favor the acyl addition over amide N-deprotection pathway.

With optimized conditions in hand, we next evaluated the scope of amides and thiols that can participate in this mild N-C(O) to S-C(O) interconversion (Table 2). As shown in Table 2, we were delighted to find that a broad range of amides is compatible with these mild conditions, including neutral- (**3a-3b**), electron-rich (**3c**), electron-deficient (**3d**), and sterically-hindered amides (**3e**). Pleasingly, the reaction is compatible with sensitive halide substituents such as bromo (**3f**), which would be problematic in transition-metal-catalyzed protocols. Furthermore, full chemoselectivity in the nucleophilic addition to the amide bond occurred in the presence of an alkyl ester (**3g**), indicating that N-Ts amides ($\text{RE} = 9.7$ kcal/mol) are the preferred addition site over methyl esters (C-O isomerization barrier, 12.8 kcal/mol). The reaction is also compatible with heterocycles (**3h**) and aliphatic amides (**3i**). Furthermore, we were pleased to find that electron-rich (**3j**) as well as more challenging electron-poor benzenethiols (**3k-3l**) undergo the desired addition in excellent yields. Moreover, this protocol can be applied to sterically-hindered benzenethiols (**3m**), while less challenging aliphatic thiols (**3n**, *vide infra*) are also well tolerated. Finally, we were pleased to find that this protocol could be extended to N-Ms amides that bear atom-economic N-mesyl activating group without any decrease in the reaction efficiency (Table 2, entry 15). Note that N-alkyl amides, such as N-Me, are also amenable substrates. 2-Pyridylthiols have not been tested at this stage of reaction development. Future studies will address the use of disulfides under reductive conditions. Overall, this mild N-C(O) to S-C(O) interconversion method enables to prepare a variety of valuable thioesters from amides. Given the plethora of metal-catalyzed and metal-free reactions of thioesters as well as the

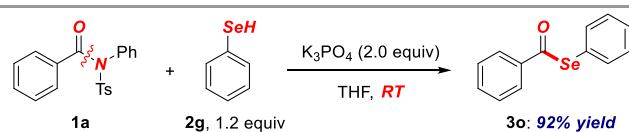
importance of thioesters in biochemical tagging, this mild process provides useful alternative inter-connecting amides with thioesters.^{11,15}

Table 1 Optimization of Room Temperature Thioesterification of Amides by Selective N-C(O) Bond Cleavage^a

1a	2a	K_3PO_4	solvent, RT	3a
Entry	Thiol (equiv)	K_3PO_4 (equiv)	Solvent	Yield ^b (%)
1	1.2	3.0	THF	>98
2	1.2	2.0	THF	>98
3	1.2	1.5	THF	81
4	1.2	2.0	Dioxane	86
5	1.2	2.0	CH_2Cl_2	91
6	1.2	2.0	Toluene	95
7	1.2	2.0	CH_3CN	87
8 ^c	1.2	2.0	THF	93
9 ^d	1.2	2.0	THF	91

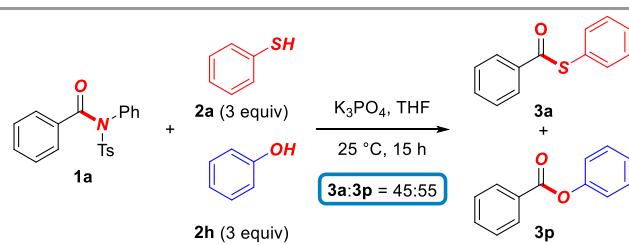
^aConditions: amide (1.0 equiv), thiol (1.2 equiv), K_3PO_4 (1.5-3.0 equiv), solvent (0.25 M), 25 °C, 15 h. ^bGC/¹H NMR yields. ^c0.50 M. ^d1.0 M.

To further demonstrate the synthetic potential of this approach, we applied this method to the synthesis of a selenoester using PhSeH via N-C(O) to Se-C(O) interconversion (Scheme 1). Since selenoesters represent an important class of acyl transfer reagents and radical precursors in organic synthesis, while recent studies show their utility in chemical ligation, our mild method permits to exploit amides as selenoester precursors.^{12,15}

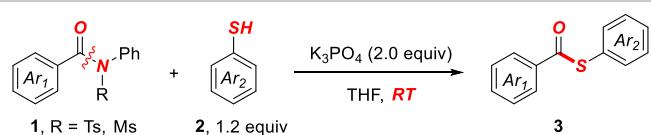


Scheme 1 Room Temperature Selenoesterification of Amides by N-C Cleavage

To gain preliminary insight in the reaction mechanism, we performed intermolecular competition experiments (Schemes 2-5). Most interestingly, intermolecular competition between thiophenol and phenol indicated similar reactivity ($3\text{a}:3\text{p} = 45:55$, Scheme 2), which bodes well for future application of this [N-C(O) \rightarrow S-C(O)] protocol in organic synthesis. Note that the ester is unreactive under the reaction conditions. Excess of reagents was used to stop the reaction at <30% conversion. Furthermore, electron-deficient amides are inherently more reactive ($3\text{c}:3\text{d} = 30:70$, Scheme 3), which is consistent with the electrophilicity of the amide bond.



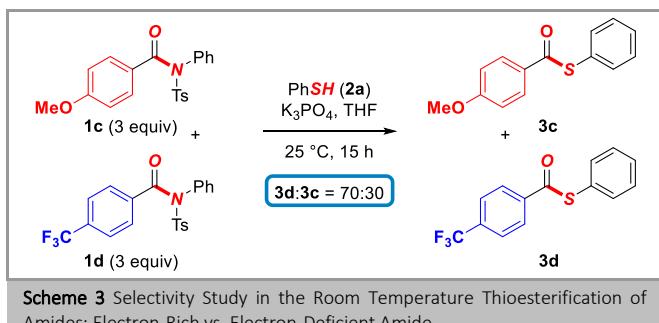
Scheme 2 Selectivity Study in the Room Temperature Thioesterification of Amides: Thiophenol vs. Phenol

Table 2 Substrate Scope of Room Temperature Thioesterification of Amides by N–C Cleavage^a

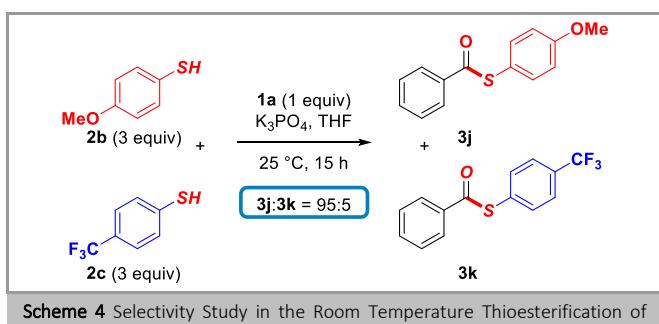
Entry	Amide (1)	Thiol (2)	Product (3)	3	Yield (%)
1				3a	92
2				3b	93
3				3c	91
4				3d	94
5				3e	86
6				3f	90
7				3g	89
8				3h	88
9				3i	85
10				3j	94
11				3k	84
12				3l	86
13				3m	92
14				3n	96
15				3a	92

^aConditions: amide (1.0 equiv), thiol (1.2 equiv), K₃PO₄ (2.0 equiv), THF (0.25 M), 25 °C, 15 h. Isolated yields.

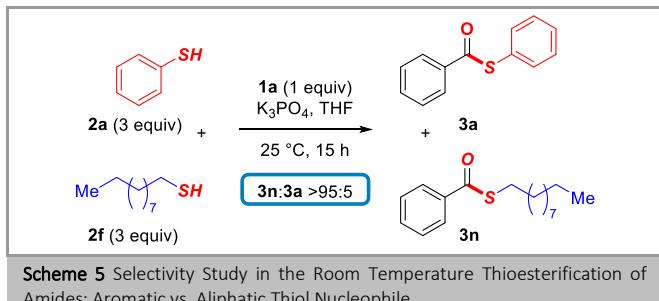
Moreover, electron-rich thiophenols react preferentially (Scheme 4, **3j:3k** = 95:5), while aliphatic thiols are significantly more reactive than aromatic thiols (Scheme 5, **3n:3a** > 95:5). Overall, these experiments are consistent with thiol nucleophilicity via a tetrahedral addition pathway.



Scheme 3 Selectivity Study in the Room Temperature Thioesterification of Amides: Electron-Rich vs. Electron-Deficient Amide



Scheme 4 Selectivity Study in the Room Temperature Thioesterification of Amides: Electron-Rich vs. Electron-Deficient Thiol



Scheme 5 Selectivity Study in the Room Temperature Thioesterification of Amides: Aromatic vs. Aliphatic Thiol Nucleophile

3. Conclusions

In conclusion, we have reported a mild method for the direct thioesterification and selenoesterification of amides by selective N-C(O) bond cleavage. This protocol is highlighted by the absence of transition-metals, operational simplicity and excellent reaction efficiency. It is worthwhile to point out that all amides used could be conveniently prepared from common secondary or primary amides.^{4a-g} Future studies will implement the transition-metal-free manifold in medicinal chemistry targets. More generally, this tactic accomplishes [N-C(O) \rightarrow S/Se-C(O)] interconversion to connect amides with thioesters and selenoesters. The tetrahedral intermediate pathway of ground-state-destabilized amides is a serious alternative to acyl-metals that should be considered as the first choice in all occasions when available.⁴⁻⁹

4. Experimental Section

General Methods. All starting materials reported in the manuscript have been previously described in the literature or prepared by a method reported previously. All solvents were purchased at the highest commercial grade and used as received or after purification by passing through activated alumina columns or distillation from Na/benzophenone. All solvents were deoxygenated prior to use. All other chemicals were purchased at the highest commercial grade and used as received. Reaction glassware was oven-dried at 140 °C for at least 24 h or flame-dried prior to use, allowed to cool under vacuum and purged with argon (three cycles). ¹H NMR and ¹³C NMR spectra were recorded in CDCl₃ on Bruker and Varian spectrometers at 500 and 600 MHz (¹H NMR) and 125 and 150 MHz (¹³C NMR). All shifts are reported in parts per million (ppm) relative to residual CHCl₃ peak (7.27 and 77.2 ppm, ¹H NMR and ¹³C NMR, respectively). All coupling constants (J) are reported in hertz (Hz). Abbreviations are: s, singlet; d, doublet; t, triplet; q, quartet; br s, broad singlet. GC-MS chromatography was performed using Agilent HP6890 GC System and Agilent 5973A inert XL EI/CI MSD using helium as the carrier gas at a flow rate of 1 mL/min and an initial oven temperature of 50 °C. High-resolution mass spectra (HRMS) were measured on a 7T Bruker Daltonics FT-MS instrument. All flash chromatography was performed using silica gel, 60 Å, 300 mesh. TLC analysis was carried out on glass plates coated with silica gel 60 F254, 0.2 mm thickness. The plates were visualized using a 254 nm ultraviolet lamp or aqueous potassium permanganate solutions. ¹H NMR and ¹³C NMR data are given for all compounds in the Supporting Experimental for characterization purposes. ¹H NMR, ¹³C NMR, HRMS and Mp are reported for all new compounds.

General Procedure for Thioesterification of Amides. An oven-dried reaction flask equipped with a stir bar was charged with an amide substrate (0.10 mmol, 1.0 equiv), thiol (0.12 mmol, 1.2 equiv) and K₃PO₄ (0.20 mmol, 2.0 equiv). THF (0.40 mL, 0.25 M) was added with vigorous stirring at room temperature, and the reaction mixture was stirred at room temperature for 15 h. After the indicated time, the reaction mixture was diluted with CH₂Cl₂ (3 mL) filtered and washed with water (1 x 3 mL). The aqueous layer was extracted with CH₂Cl₂ (2 x 3 mL), the combined organic layers were dried, filtered, and concentrated. The sample was analysed by ¹H NMR (CDCl₃, 500 MHz) and GC-MS to obtain conversion, yield and selectivity using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (EtOAc/hexanes) afforded analytically pure product.

General Procedure for Selenoesterification of Amides. An oven-dried reaction flask equipped with a stir bar was charged with an amide substrate (0.10 mmol, 1.0 equiv), selenol (0.12 mmol, 1.2 equiv) and K₃PO₄ (0.20 mmol, 2.0 equiv). THF (0.40 mL, 0.25 M) was added with vigorous stirring at room temperature, and the reaction mixture was stirred at room temperature for 15 h. After the indicated time, the reaction mixture was diluted with CH₂Cl₂ (3 mL) filtered and washed with water (1 x 3 mL). The aqueous layer was extracted with CH₂Cl₂ (2 x 3 mL), the combined organic layers were dried, filtered, and concentrated. The sample was analysed by ¹H NMR

(CDCl₃, 500 MHz) and GC-MS to obtain conversion, yield and selectivity using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (EtOAc/hexanes) afforded analytically pure product.

All products have been previously reported. See SI (Supporting Information) for details.

S-Phenyl benzothioate (Table 2, 3a)

White solid. Yield 92% (19.7 mg).

¹H NMR (500 MHz, CDCl₃) δ 8.04 (d, *J* = 8.1 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.55 – 7.45 (m, 7H).

¹³C NMR (126 MHz, CDCl₃) δ 190.45, 137.00, 135.43, 133.98, 129.85, 129.59, 129.09, 127.82, 127.71.

S-Phenyl 4-methylbenzothioate (Table 2, 3b)

White solid. Yield 93% (21.2 mg).

¹H NMR (500 MHz, CDCl₃) δ 7.94 (d, *J* = 8.2 Hz, 2H), 7.56 – 7.50 (m, 2H), 7.48 – 7.43 (m, 3H), 7.29 (d, *J* = 8.1 Hz, 2H), 2.44 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 190.02, 144.91, 135.46, 134.45, 129.75, 129.53, 127.91, 22.06.

S-Phenyl 4-methoxybenzothioate (Table 2, 3c)

White solid. Yield 91% (22.3 mg).

¹H NMR (500 MHz, CDCl₃) δ 8.04 – 7.99 (m, 2H), 7.54 – 7.49 (m, 2H), 7.48 – 7.43 (m, 3H), 6.98 – 6.94 (m, 2H), 3.89 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 188.91, 164.34, 135.53, 130.05, 129.77, 129.70, 129.50, 128.01, 114.26, 55.89.

S-Phenyl 4-(trifluoromethyl)benzothioate (Table 2, 3d)

White solid. Yield 94% (26.6 mg).

¹H NMR (500 MHz, CDCl₃) δ 8.14 (d, *J* = 8.2 Hz, 2H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.54 – 7.51 (m, 2H), 7.50 – 7.47 (m, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 189.72, 139.79, 135.33, 135.27 (q, *J^F* = 32.9 Hz), 130.22, 129.76, 128.17, 126.91, 126.19 (q, *J^F* = 3.7 Hz), 123.84 (q, *J^F* = 273.3 Hz).

¹⁹F NMR (471 MHz, CDCl₃) δ -63.13.

S-Phenyl 2-methylbenzothioate (Table 2, 3e)

Colorless oil. Yield 86% (19.6 mg).

¹H NMR (500 MHz, CDCl₃) δ 7.95 (d, *J* = 7.7 Hz, 1H), 7.54 – 7.51 (m, 2H), 7.50 – 7.40 (m, 4H), 7.34 – 7.26 (m, 2H), 2.50 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 192.50, 137.77, 137.13, 135.25, 132.34, 132.09, 129.80, 129.60, 128.97, 128.59, 126.20, 21.10.

S-Phenyl 4-bromobenzothioate (Table 2, 3f)

White solid. Yield 90% (26.4 mg).

¹H NMR (500 MHz, CDCl₃) δ 7.92 – 7.87 (m, 2H), 7.66 – 7.62 (m, 2H), 7.53 – 7.49 (m, 2H), 7.48 – 7.46 (m, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 189.59, 135.77, 135.39, 132.41, 130.05, 129.68, 129.27, 129.09, 127.23.

Methyl 4-((phenylthio)carbonyl)benzoate (Table 2, 3g)

White solid. Yield 89% (24.3 mg).

¹H NMR (500 MHz, CDCl₃) δ 8.15 (d, *J* = 8.5 Hz, 2H), 8.08 (d, *J* = 8.5 Hz, 2H), 7.54 – 7.50 (m, 2H), 7.50 – 7.45 (m, 3H), 3.97 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 190.07, 166.42, 140.33, 135.35, 134.79, 130.33, 130.12, 129.73, 127.76, 127.19, 52.88.

S-Phenyl furan-2-carbothioate (Table 2, 3h)

Colorless oil. Yield 88% yield (17.9 mg).

¹H NMR (500 MHz, CDCl₃) δ 7.63 (d, *J* = 0.9 Hz, 1H), 7.52 – 7.49 (m, 2H), 7.47 – 7.43 (m, 3H), 7.26 (dd, *J* = 3.6, 0.5 Hz, 1H), 6.58 (dd, *J* = 3.5, 1.7 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 178.95, 150.70, 146.79, 135.47, 129.98, 129.58, 126.53, 116.56, 112.75.

S-Phenyl decanethioate (Table 2, 3i)

Colorless oil. Yield 85% (22.5 mg).

¹H NMR (500 MHz, CDCl₃) δ 7.44 – 7.37 (m, 5H), 2.65 (t, *J* = 7.5 Hz, 2H), 1.74 – 1.68 (m, 2H), 1.35 – 1.25 (m, 12H), 0.89 (t, *J* = 6.9 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 197.91, 134.82, 129.61, 129.48, 128.35, 44.09, 32.19, 29.72, 29.60, 29.59, 29.31, 25.95, 23.01, 14.45.

S-(4-Methoxyphenyl) benzothioate (Table 2, 3j)

White solid. Yield 94% (23.1 mg).

¹H NMR (500 MHz, CDCl₃) δ 8.06 – 7.99 (m, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.42 (d, *J* = 8.8 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 3.85 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 191.37, 161.15, 137.03, 136.97, 133.89, 129.05, 127.80, 118.25, 115.32, 55.73.

S-(4-(Trifluoromethyl)phenyl) benzothioate (Table 2, 3k)

White solid. Yield 84% (23.7 mg).

¹H NMR (500 MHz, CDCl₃) δ 8.03 (d, *J* = 7.4 Hz, 2H), 7.71 (d, *J* = 8.2 Hz, 2H), 7.67 – 7.62 (m, 3H), 7.51 (t, *J* = 7.8 Hz, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 189.24, 136.60, 135.56, 134.39, 132.54, 131.81 (q, *J^F* = 32.9 Hz), 129.24, 127.92, 126.34 (q, *J^F* = 3.7 Hz), 124.17 (q, *J^F* = 274.6 Hz).

¹⁹F NMR (471 MHz, CDCl₃) δ -62.85.

S-(4-Fluorophenyl) benzothioate (Table 2, 3l)

White solid. Yield 86% (20.1 mg).

¹H NMR (500 MHz, CDCl₃) δ 8.05 – 7.99 (m, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.52 – 7.47 (m, 4H), 7.20 – 7.12 (m, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 190.44, 164.00 (d, *J*^F = 250.6 Hz), 137.50 (d, *J*^F = 8.6 Hz), 136.77, 134.14, 129.15, 127.85, 122.98 (d, *J*^F = 3.5 Hz), 116.89 (d, *J*^F = 22.0 Hz).

¹⁹F NMR (471 MHz, CDCl₃) δ -111.09.

S-(*o*-Tolyl) benzothioate (Table 2, 3m)

Colorless oil. Yield 92% (21.0 mg).

¹H NMR (500 MHz, CDCl₃) δ 8.10 – 8.02 (m, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.52 – 7.48 (m, 3H), 7.41 – 7.35 (m, 2H), 7.30 – 7.26 (m, 1H), 2.41 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 189.96, 143.00, 137.16, 136.75, 133.90, 131.17, 130.56, 129.07, 127.89, 127.16, 127.01, 21.15.

S-Decyl benzothioate (Table 2, 3n)

Yellow oil. Yield 96% (26.6 mg).

¹H NMR (500 MHz, CDCl₃) δ 8.01 – 7.93 (m, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 3.07 (t, *J* = 7.4 Hz, 2H), 1.71 – 1.64 (m, 2H), 1.46 – 1.39 (m, 2H), 1.35 – 1.24 (m, 12H), 0.88 (t, *J* = 6.9 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 192.41, 137.63, 133.48, 128.85, 127.50, 32.22, 29.90, 29.88, 29.84, 29.63, 29.50, 29.39, 29.28, 23.01, 14.43.

Se-Phenyl benzoselenoate (Scheme 1, 3o)

Yellow oil. Yield 92% (24.0 mg).

¹H NMR (500 MHz, CDCl₃) δ 7.98 – 7.91 (m, 2H), 7.65 – 7.58 (m, 3H), 7.50 (t, *J* = 7.8 Hz, 2H), 7.46 – 7.41 (m, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 193.72, 138.89, 136.68, 134.23, 129.72, 129.41, 129.29, 127.69, 126.14.

Funding Information

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be updated with links prior to publication)

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