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Benzylic Thio and Seleno Newman-Kwart Rearrangements

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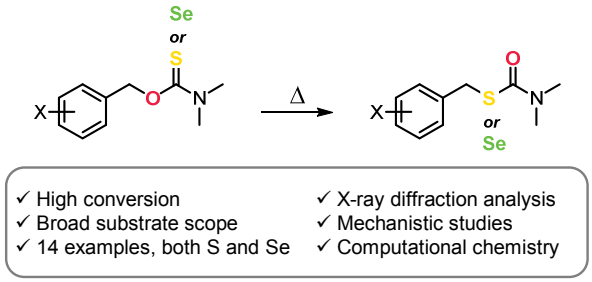


Abstract

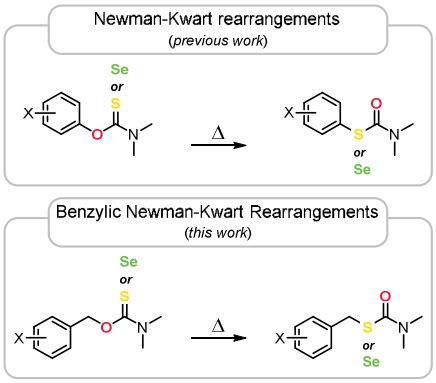
The thermally induced $O_{Bn} \rightarrow S_{Bn}$ and $O_{Bn} \rightarrow Se_{Bn}$ migration reactions facilitate the rearrangement of *O*-benzyl thio- and selenocarbamates [BnOC(=X)NMe$_2$] (X = S *or* Se) into their corresponding *S*-benzyl thio- and *Se*-benzyl selenocarbamates [BnXC(=O)NMe$_2$] (X = S *or* Se). A series of substituted *O*-benzyl thio- and selenocarbamates were synthesised and rearranged in good yield of 33 – 88 %. The reaction rates are higher for substrates with electron donating groups in the 2- or 4-position of the aromatic ring but the rearrangement also proceeds with electron withdrawing substituents. The rearrangement follows first order reaction kinetics and proceeds via a tight ion pair intermediate consisting of the benzylic carbocation and the thio- or selenocarbamate moiety. Computational studies support these findings.

Introduction

Thiols and selenols play important parts in a range of chemistry, biochemistry, and materials applications.[1-6] Their use as ligands in inorganic chemistry and as components in supramolecular assemblies are two central examples.[7-9] The subtle interplay between the thiol/disulfide and the selenol/diselenide through oxidation/reduction reactions are a defining trait of the chemical properties of these functional groups.[10-13] Prominent-

ly, both the thiol and selenol is part of the chiral amino acids as cysteine and selenocysteine, respectively. Selenocysteine is known as the 21st amino acid,[14] and the role of selenocysteine (selenol) and selenocystine (diselenide) in protein function and structure is becoming increasingly recognized, as is the role of the more common cysteine/cysteine system.[12, 14-15] The presence of selenocysteine is known to influence the catalytic properties of enzymes and can provide a mean to alter the structural properties of the protein as compared to the corresponding proteins containing cysteine.[12-13, 16] Native chemical ligation with selenocysteine is also known to be highly effective,[17-19] and selenols/diselenides are also efficient in catalysing the disulfide exchange reaction.[8]

The thiol functionality can efficiently be introduced via the Newman-Kwart rearrangement which facilitates the conversion from phenol to thiophenol via the thermal $O_{Ar} \rightarrow S_{Ar}$ rearrangement of aromatic thiocarbamates (Scheme 1, top).[20-21] However, the wide spread use of selenols is hampered by their limited synthetic availability. We have initiated a research program focused at identifying new reactions that make selenols, and also thiols, readily available. Recently, we described how the conversion of a phenol into the corresponding selenophenol can be performed effectively by expanding the Newman-Kwart rearrangement from using *O*-aryl thiocarbamate substrates to *O*-aryl selenocarbamate substrates.[22] The rearrangement yields *Se*-aryl selenocarbamates that can then conveniently be hydrolysed to the arylselenols using aqueous base (Scheme 1, top). Attempts to introduce aliphatic versions of the Newman-Kwart rearrangement have been hampered by competitive reaction pathways, especially elimination pathways yielding alkenes instead.[23-24] One example describing a derived benzylic version of the original Newman-Kwart rearrangement has been published. Here, the conversion of *O*-(*o*-azidobenzyl) thiocarbamates into *S*-(*o*-azidobenzyl) thiocarbamate was found to proceed as a [1,3]-shift via an uncoupled concerted mechanism.[25] Computational studies suggested that the benzylic rearrangement is activated by electron donating groups substituted on the aromatic ring and thereby exhibits the opposite pattern, compared to the $O_{Ar} \rightarrow S_{Ar}$ and $O_{Ar} \rightarrow Se_{Ar}$ rearrangements.



Scheme 1 The original Newman-Kwart rearrangements (top) and the two new benzylic Newman-Kwart rearrangements presented here (bottom).

In this contribution, we describe the use of benzylic substrates for the Newman-Kwart rearrangement using both *O*-benzyl thiocarbamates and *O*-benzyl selenocarbamates to yield the corresponding *S*-benzyl thiocarbamates and *Se*-benzyl selenocarbamates (Scheme 1, bottom). A fundamental change in mechanism is inevitable when changing the phenyl group in the original Newman-Kwart rearrangement to a benzyl group. Instead of a nucleophilic attack on an sp^2 hybridised carbon atom, the rearrangement is now initiated via an sp^3 hybridised carbon atom. We present general reaction conditions for both types of conversions and discuss the reaction mechanism based on reaction scope, kinetics- and computational studies. The reaction mechanism involves a solvated ion-pair, and the reaction rate is favoured by substituents on the aromatic ring of the benzyl group that aid in the stabilization of the benzylic carbocation, and is thus favoured by electron donating substituents on the aromatic ring.

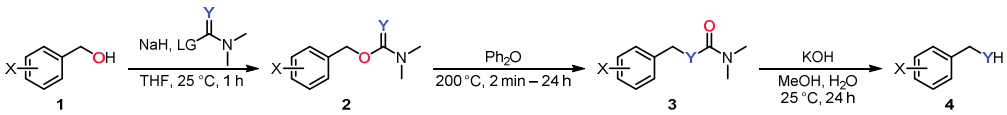
Results and Discussion

Synthesis of the carbamates

The starting material for the thiol version of the benzylic Newman-Kwart rearrangement, the *O*-benzyl thiocarbamates, was prepared by reaction of *N,N*-dimethylthiocarbamoyl chloride with the desired benzyl alcohol in the presence of sodium hydride in THF giving the products in good yields of 82 to 99 % (Table 1, step 1). The *O*-benzyl selenocarbamate equivalents were more arduous to synthesise since the seleno analogue of *N,N*-

dimethylthiocarbamoyl chloride, *N*,*N*-dimethylselenocarbamoyl chloride, is both air- and moisture sensitive.[26] This makes it unpractical to handle, and we therefore explored *S*-phenyl *N,N*-dimethylthioselenocarbamate as a shelf stable alternative.[26-27] This reacts readily with the benzyl alcohols upon addition of sodium hydride in THF to form the *O*-benzyl selenocarbamates in excellent yields ranging from 89 to 93 % (Table 1, step 1). All compounds were characterised by ^{1}H, ^{13}C, and ^{77}Se NMR spectroscopy (when appropriate) together with a high-resolution mass spectrometry analysis and the details hereof are presented in the Experimental Section.

Table 1 Overview of synthesised *O*-benzyl thio- and selenocarbamates **2** and their conversion to the corresponding *S*-benzyl thio- and *Se*-benzyl selenocarbamates **3**.[a]



Compound	X	Y	Isolated yield of **2**	Isolated yield of **3**	Conversion of **2** after 10 h[f]
a	2-OMe	S	97 %	48 %	100 %[h]
b	3-OMe	S	94 %	59 %	35 %
c	4-OMe	S	96 %	70 %	100 %[h]
d	4-OMe[b]	S	98 %	60 %	100 %[h]
e	4-OEt	S	82 %	54 %	100 %[h]
f	4-OEt[b]	S	91 %	62 %	100 %[h]
g	4-Me	S	87 %	41 %	75 %
h	4-H	S	92 %	33 %	66 %
i	(*rac*)-4-H[c]	S	96 %	–[d]	–[d]
j	(*R*)-4-H[c]	S	98 %	–[d]	–[d]
k	4-Cl	S	99 %	51 %	45 %
l	4-Br	S	90 %	59 %	55 %

m	4-CO_2CH_3	S	83 %	67 %	40 %
n	4-NO_2	S	52%	-	Trace
o	4-OMe	Se	93 %	88 %[e]	100 %[h]
p	4-H	Se	93 %	54 %	100 %[h]
q	(*rac*)-4-H[c]	Se	97 %	–[d]	–[d]
r	4-Br	Se	89 %	61 %	100 %[h]
s[g]	4-Cl	Se	-	-	-
t[g]	4-NO_2	Se	-	-	-

[a] The notation "LGC(=Y)NMe_2" corresponds to the reagents *N,N*-dimethylthiocarbamoyl chloride (used for **2a** – **2n**) or *S*-phenyl *N,N*-dimethylthioselenocarbamate (used for **2o** – **2t**).

[b] The carmabate group is the ethyl derivative, *N*,*N*-diethylthiocarbamate.

[c] The benzylic position is methylated, i.e. the phenol used is 1-phenylethan-1-ol.

[d] No rearrangement occurs, instead an elimination reaction take place.

[e] The rearrangement was performed at 150 °C.

[f] Monitored by ^{1}H NMR spectroscopy, see supporting information for further information.

[g] The compound is not synthesised and only used for computational studies.

[h] The reaction is complete before 10 hours.

With the *O*-benzyl thiocarbamates in hand we were ready to investigate whether the various substrates were prone to rearrange to the corresponding *S*-benzyl thiocarbamates (Table 1, step 2). The migration reaction was initially tested in 1-methylpyrrolidin-2-one (NMP), a solvent often used for Newman-Kwart rearrangements,[28-29] as well as *N*,*N*-dimethylformamide (DMF) and diphenyl ether, where diphenyl ether was found superior. With the optimal solvent found the reaction temperature was investigated next. When heating *O*-(4-methylbenzyl) *N*,*N*-dimethylthiocarbamate (**2g**) to 150 °C in diphenyl ether for two days no reaction happened and no notable de-composition was observed. Increasing the temperature to 175 °C some conversion was seen after two days but

unfortunately together with a non-negligible amount of unwanted by-products. Finally, adjusting the temperature to 200 °C complete conversion was observed within one day thus showing the importance of a high reaction temperature to overcome the reaction barrier. The desired product **3g** was however only isolated in 41 % yield showing how rearrangement and degradation are competing reactions. Most other substrates gave better yields.

The unambiguously proof of the successful benzylic Newman-Kwart rearrangement came by single-crystal X-ray crystallography where it transpires how the oxygen and sulfur atoms are exchanged during the rearrangement of **2k** into **3k** (Figure 1a and b).[30]

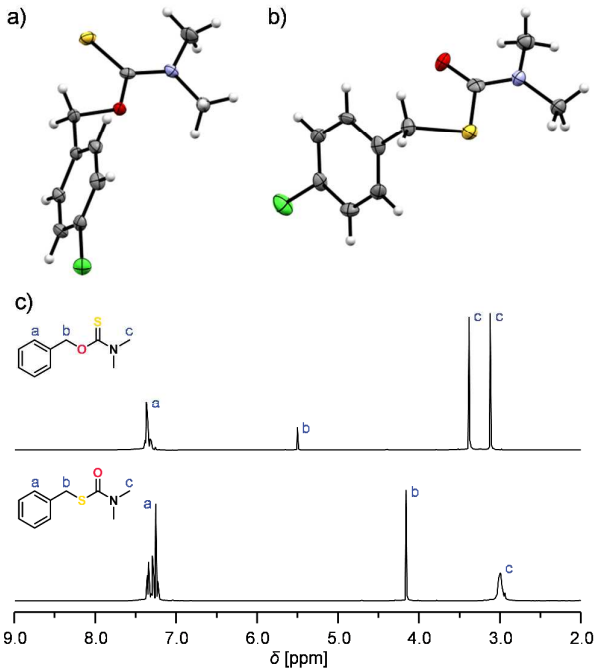


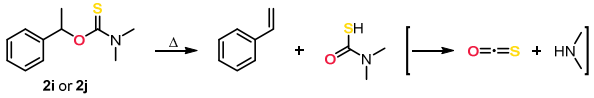
Figure 1 Analytical data supporting the $O_{Bn} \rightarrow S_{Bn}$ rearrangement by showing *a*) single-crystal X-ray structure of **2k**, *b*) single-crystal X-ray structure of **3k** (colour code, S: yellow, O: red, N: blue, Cl: green, C: grey, H: white), *c*) ^{1}H NMR spectra (500 MHz, $CDCl_3$, 25 °C) of **2h** and **3h**. Assignment of the signals is based on the labelling shown on the structures.

The progress of the rearrangement can easily be monitored by ^{1}H NMR spectroscopy as shown in Figure 1c where the ^{1}H NMR spectra of *O*-benzyl *N*,*N*-dimethylthiocarbamate (**2h**) and the corresponding rearranged **3h** are shown. Focusing on the signals corresponding to the *N*,*N*-dimethylamino group (H_c) it transpires how the two well-resolved singlets in the reactant merges into one broad singlet in the product. This is a result of a changed

energy barrier for the internal rotation about the C–N thiocarbamate bond going from reactant to product. In **2h** the rotational energy barrier is sufficiently high to allow slow exchange on the NMR timescale thus showing two distinctive peaks for the *N*,*N*-dimethylamino group whereas the barrier in **3h** is lower giving rise to a merger of the two peaks as the domain of fast exchange is entered. The peak corresponding to the benzylic protons (H_b) moves 1.34 ppm upfield during the rearrangement showing how the electron density decreases on the benzylic centre as oxygen is exchanged for sulfur. Similar trends are observed in the corresponding ^{13}C NMR spectra (see Supporting Information).

The benzylic Newman-Kwart rearrangement shows great tolerance towards a wide range of functional groups ranging from methoxy, through alkyl and halogens, to ester substituted *O*-benzyl thiocarbamates (Table 1, step 2). Performing the rearrangement with electron donating groups increases the reaction time. For example, the conversions of the ethers **2c**, **2d**, **2e**, and **2f** were complete within two hours at 200 °C while the halogens **2k** and **2l** required 24 hours for complete conversion. The rearrangement also allows substituents in both the 2-, 3-, and 4-position of the aromatic unit (**2a**, **2b**, **2c**) and extending the *N*,*N*-dimethylamino group to an *N*,*N*-diethylamino group is also feasible (**2d** and **2f**). The rearrangement is also possible when the electron withdrawing nitro group is placed in the *para* position (**2s**). However, the reaction time is, not surprisingly, very long and the rearrangement was only 50 % complete after heating to 200 °C for 3 days.

In addition, the racemic and enantiomerically pure *O*-(1-phenylethyl) *N*,*N*-dimethylthiocarbamate (**2i** and **2j**, respectively) were tested if feasible for the $O_{Bn} \rightarrow S_{Bn}$ rearrangement. It was envisaged that the products of these could give insight to the stereochemical aspect of the reaction mechanism as whether we would obtain an inversion of the configuration or a racemic mixture of the rearranged product. Analysis of the reaction mixture did not show the desired rearranged product but instead complete and clean conversion to styrene (Figure 2 and Supporting Information). The presence of a β-proton in similar *O*-benzyl thiocarbamates are known to facilitate elimination over rearrangement through a Chugaev-like elimination.[23]



2i or **2j**

Figure 2 Heating *O*-(1-phenylethyl) *N*,*N*-dimethylthiocarbamate does not give the rearranged product but instead styrene and *N*,*N*-dimethylthiocarbamic acid where the latter react further to form carbonyl sulfide and *N*,*N*-dimethylamine.

After the successful rearrangement of the *O*-benzyl thiocarbamates we were intrigued to investigate whether the selenium analogues would be just as efficient. The first substrate examined was the *O*-(4-methoxybenzyl) *N*,*N*-dimethylselenocarbamate (**2o**) which was found to rearrange just within five minutes when heated to 200 °C. Comparing this with the sulfur analogue **2c** heating for two hours was necessary to obtain same conversion. This observation, showing how the $O_{Bn} \rightarrow Se_{Bn}$ rearrangement proceeds significantly faster than the $O_{Bn} \rightarrow S_{Bn}$ rearrangement, is also known for the aryl versions of the Newman-Kwart rearrangement.[22] The *O*-benzyl *N*,*N*-dimethylselenocarbamate (**2p**) and the bromo derivative **2r** also smoothly underwent rearrangement and again with reaction times substantially shorter than their sulfur analogues (Table 1, step 2).

A single-crystal suitable for X-ray crystallography of the rearranged product **3p** was obtained proving the connectivity in the product (Figure 3a).[31] Consulting the ^{1}H NMR spectra of the $O_{Bn} \rightarrow Se_{Bn}$ rearrangement of substrate **2p** into **3p** similar trends are observed as in the $O_{Bn} \rightarrow S_{Bn}$ rearrangement (Figure 1c *vs* Figure 3b). As the rearrangement proceeds the signals corresponding to the *N*,*N*-dimethylamino group (H_c) alters from being two well separated singlets in **2p** to approach each other forming two closely connected broad singlets in **3p**. In comparison, the H_c protons in the sulfur analogue merged completely. This agrees with the reported observation that the rotational barrier increases from amides through thioamides to selenoamides.[32-33] Again, the benzylic protons H_b shifts substantially upfield during the rearrangement but besides increasing the shielding of the H_b protons the selenium atom also causes the signal to split into a triplet (Figure 3b). Selenium has six naturally occurring isotopes from which only ^{77}Se (7.58%) is NMR active having a nuclear spin quantum number of I = 1/2. Therefore, it is possible in the ^{1}H NMR spectrum of rearranged product **3p** to observe a $^2J_{Se-H}$ spin-spin coupling between the H_b protons and the selenium atom with a strength of 11 Hz, which are in agreement with the literature.[34] In comparison, no coupling is observed in **2p** as the $^4J_{Se-H}$ coupling is too small to observe. Similar observations can be done in the corresponding ^{13}C NMR spectra (see Supporting Information).

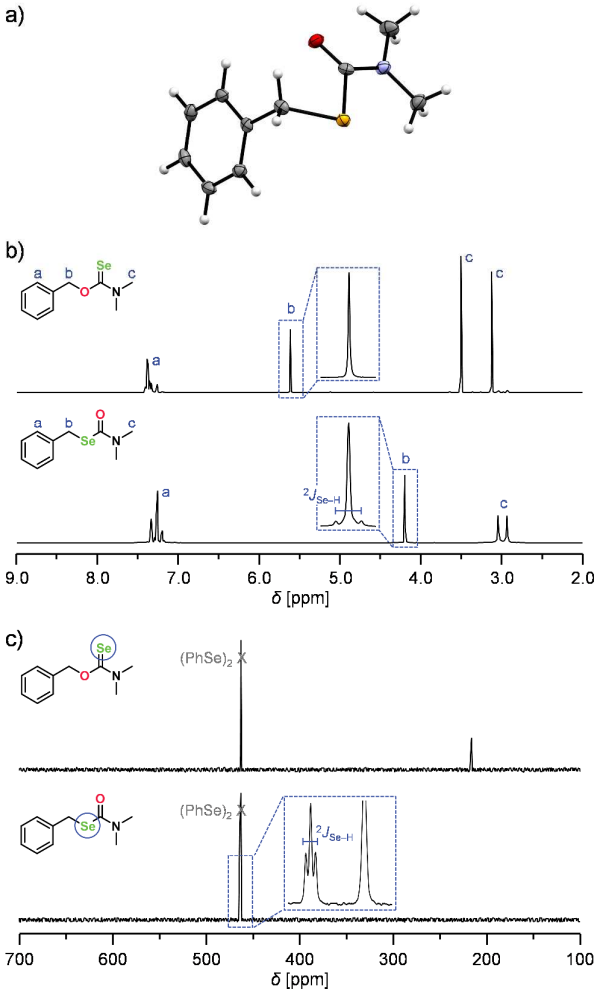


Figure 3 Analytical data supporting the $O_{Bn} \rightarrow Se_{Bn}$ rearrangement by showing *a*) single-crystal X-ray structure of **3p** (colour code, Se: orange, O: red, N: blue, C: grey, H: white), *b*) ^{1}H NMR spectra (500 MHz, $CDCl_3$, 25 °C) of **2p** and **3p**, and *c*) ^{77}Se NMR spectra (57 MHz, $CDCl_3$ with a saturated solution of $(PhSe)_2$ in $CDCl_3$ as external standard, 25 °C) of **2p** and **3p**. The spectra shows an enlargement of selected ^{77}Se,^{1}H-coupled signals, assignment of the signals is based on the labelling shown on the structures.

The $^{2}J_{Se-H}$ spin-spin coupling can also be observed in the corresponding ^{77}Se NMR spectrum (Figure 3c). The non-rearranged **2p** shows a singlet, as expected, at 216 ppm while the signal for the rearranged **3p** appears as a triplet at 464 ppm with the equivalent $^{2}J_{Se-H}$ spin-spin coupling of 11 Hz between the H_b protons and the selenium atom (Figure 3c). Besides the spin-spin coupling the ^{77}Se NMR spectrum also gives information on the chemical envi-

ronment of the selenium atom within the molecule.[34] As the rearrangement occurs the signal for the selenium atom shifts remarkably 248 ppm downfield in the spectrum demonstrating a changed environment for the selenium atom which corresponds well with the change in connectivity within the molecule due to the rearrangement.

The $O_{Bn} \rightarrow Se_{Bn}$ rearrangement was also investigated for the (*rac*)-*O*-(1-phenylethyl) *N*,*N*-dimethylselenocarbamate (**2q**), but again, the presence of β-protons favoured a very efficient Chugaev-like elimination[23] thus affording styrene (Figure 2 and Supporting Information).

Hydrolysis of the rearranged products gives access to the corresponding benzyl thiols or selenols (Table 1, step 3). As representative examples, both the 4-methoxy substituted *S*-benzyl thio- and *Se*-benzyl selenocarbamates **3c** and **3o** were treated with potassium hydroxide in a methanol/water mixture thus giving the hydrolysed products **4c** and **4o**, respectively, in quantitative yield. The benzyl selenol **4o** was isolated as the diselenide, 1,2-bis(4-methoxyphenyl)diselane, due to the rapid oxidation of the selenol functionality.

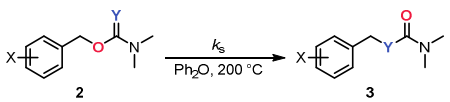
Mechanistic studies

To gain insight to the course of the reaction the kinetics for the $O_{Bn} \rightarrow S_{Bn}$ rearrangement of *O*-(4-methoxybenzyl) *N*,*N*-dimethylthiocarbamate (**2c**) was studied in detail and compared with previously reported results from the $O_{Ar} \rightarrow S_{Ar}$ and $O_{Ar} \rightarrow Se_{Ar}$ rearrangements. The conversion from **2c** into **3c** follows clearly first order reaction kinetics which is similar to the aryl version of the rearrangement. Measuring the conversion at different temperatures the activation parameters were derived. The enthalpy of activation ($\Delta H^{\ddagger}$) was calculated to 35.7 kcal/mol while the entropy of activation ($\Delta S^{\ddagger}$) was 1.45 cal/mol·K (see Supporting Information). The $O_{Ar} \rightarrow S_{Ar}$ and $O_{Ar} \rightarrow Se_{Ar}$ rearrangements have both been reported to proceed in a unimolecular concerted manner via a four-membered cyclic transition state why it would be reasonable to believe that the benzylic version would follow the same route.[22, 35] However, the activation parameters obtained from those studies differ substantially from the ones obtained in this study thus contradicting the mechanistic proposal ($\Delta H^{\ddagger}(O_{Ar} \rightarrow S_{Ar})$ = 28.8 kcal/mol, $\Delta S^{\ddagger}(O_{Ar} \rightarrow S_{Ar})$ = – 10.0 cal/mol·K and $\Delta H^{\ddagger}(O_{Ar} \rightarrow Se_{Ar})$= 26.7 kcal/mol, $\Delta S^{\ddagger}(O_{Ar} \rightarrow Se_{Ar})$= – 11.9 cal/mol·K, all values obtained for the 4-nitro substituted derivative).[22, 35] The $\Delta H^{\ddagger}$ value of the $O_{Bn} \rightarrow S_{Bn}$ rearrangement is increased greatly compared to

both aryl rearrangements indicating that the C–O bond breaking in the reactant is more important for the benzylic rearrangement than the aryl rearrangements. Also, the $\Delta S^{\ddagger}$ value changes significantly. The large negative values obtained in the aryl rearrangements correspond well to the strained four-membered cyclic transition state. In comparison, the $\Delta S^{\ddagger}(O_{Bn} \rightarrow S_{Bn})$ value is small and positive indicating that the transition state is not very constrained structurally. The positive $\Delta S^{\ddagger}$ value point towards a dissociative mechanism, where the bond breaking has occurred to a higher extend than bond formation in the transition state, with the extreme case being the S_N1 reaction mechanism. Comparing the $\Delta S^{\ddagger}$ values the $O_{Bn} \rightarrow S_{Bn}$ rearrangement possess less S_N2 character compared to the aryl version, but has not quite reached the limiting domain of the S_N1 mechanism.

In order to clarify the influence of the substituents on the aromatic ring upon the reaction rate of the benzylic rearrangement, the kinetics was studied on the different substrates (Table 2 and Supporting Information). The $O_{Bn} \rightarrow S_{Bn}$ reaction rate shows strong dependency on the nature of the substituent. Substrates with an electron donating group attached, i.e. the ether group in **2c** and **2f**, accelerates the reaction rate by more than one order of magnitude compared to the unsubstituted compound **2h**. Conversely, the rate constant gets even smaller when electron withdrawing substituents are attached to the aromatic unit, like the ester **2m**, however the reaction still proceeds. The reaction rate is also influenced by the position of the substituent on the aromatic ring where the 2- and 4-positions are favoured over the 3-position (**2a** and **2c** *vs* **2b**).

Table 2 Overview of the obtained rate constants (k_s) for the rearrangement of substituted *O*-benzyl thio- and selenocarbamates into their corresponding *S*-benzyl thio- and *Se*-benzyl selenocarbamates in diphenyl ether (0.4 M) at 200 °C. The values are obtained with ^{1}H NMR spectroscopy analysis unless otherwise stated.



Compound	X	Y	k_s [s^{-1}]
a	2-OMe	S	$8.38 \cdot 10^{-5}$
b	3-OMe	S	$1.53 \cdot 10^{-5}$

c	4-OMe	S	$5.03 \cdot 10^{-4}$
f	4-OEt[a]	S	$2.97 \cdot 10^{-4}$
g	4-Me	S	$3.65 \cdot 10^{-5}$
h	4-H	S	$3.59 \cdot 10^{-5}$
k	4-Cl	S	$2.89 \cdot 10^{-5}$
l	4-Br	S	$2.49 \cdot 10^{-5}$
m	4-CO_2CH_3	S	$1.42 \cdot 10^{-5}$
o	4-OMe	Se	$9.25 \cdot 10^{-3}$ [b]
p	4-H	Se	$8.51 \cdot 10^{-4}$ [b,c]

[a] The carmabate group is the ethyl derivative, *N*,*N*-diethylthiocarbamate.

[b] Determined by LC-MS analysis.

[c] Performed in with a substrate concentration of 20 mM.

The substrates for the $O_{Bn} \rightarrow Se_{Bn}$ rearrangement have already shown to proceed at lower reaction temperatures and have faster reaction rates than the corresponding $O_{Bn} \rightarrow S_{Bn}$ rearrangements. This is also proven quantitatively, and the reaction rates of the seleno analogues are found to be about two orders of magnitude larger than the equivalent sulfur analogues, both following first order reaction kinetics (Table 2). Again, electron donating groups accelerate the rearrangement compared to the unsubstituted analogue (**2o** *vs* **2p**). The electronic demand in the $O_{Bn} \rightarrow S_{Bn}$ and $O_{Bn} \rightarrow Se_{Bn}$ rearrangements is thus found to be completely opposite compared to the $O_{Ar} \rightarrow S_{Ar}$ and $O_{Ar} \rightarrow Se_{Ar}$ rearrangements. Here, electron withdrawing substituents increases the rate significantly while electron donating substituents deter the rearrangement from proceeding.[22, 28]

In order to elucidate the reaction mechanism a linear free energy relationship study was made on the $O_{Bn} \rightarrow S_{Bn}$ rearrangement. Ordinary Hammett plots were constructed from the obtained rate constants of the substrates in Table 2 and the tabulated substituent constants σ, σ^+, and σ^- (see Supporting Information).[36] Unfortunately, none of these gave linear correlations. The plot against the σ^+ substituent constant presented the best, but still

not optimal, correlation in agreement with the observation that electron donating substituents increases the reaction rate. The $O_{Ar} \rightarrow S_{Ar}$ rearrangement has previously been analysed successfully with the Yukawa-Tsuno equation, why we also applied this analytical method on the $O_{Bn} \rightarrow S_{Bn}$ rearrangement (see Supporting Information).[37-40] For a particular substituent the σ value is generally considered constant, however for compounds in which the transition state bears a nearly full charge, this no longer apply and the Hammett equation becomes invalid. The Yukawa-Tsuno equation manages to account for the enhanced resonance effects that are present in such reactions with high electron demand. A good linear relationship was obtained with this modified version of the Hammett equation and a value of – 0.44 was obtained for the Hammett reaction constant (ρ) while the Yukawa-Tsuno constant, the enhanced resonance parameter (*r*) equals 5.40 (Figure 4).

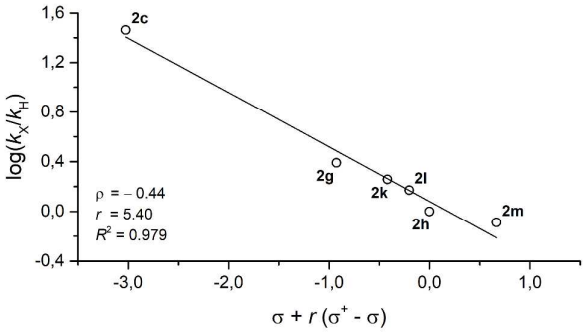


Figure 4 Yukawa-Tsuno plot used to descibe the $O_{Bn} \rightarrow S_{Bn}$ rearrangement in diphenyl ether at 200 °C. The parameters obtained are ρ = – 0.44 and *r* = 5.40.

The obtained negative ρ value indicates that the reaction rate is favoured by electron donating substituents on the aromatic ring, due to an accumulation of positive charge in the transition state structure, which is in accordance with the observed reaction rates (Table 2). The greater the magnitude of ρ, the more sensitive the rearrangement is to the nature of the substituents. However, the comparison should always be relative to other related systems. A ρ value of +1.92 was obtained for the $O_{Ar} \rightarrow S_{Ar}$ rearrangement (using σ^- values).[40] According to this, the reaction mechanism of the $O_{Ar} \rightarrow S_{Ar}$ and $O_{Bn} \rightarrow S_{Bn}$ rearrangements are not equivalent as the electronic demand in the transition state in the benzylic version is completely opposite to the aryl version.

The enhanced resonance parameter *r* is a measure of the influence of resonance on the reaction. Positive values show that the reaction is more sensitive to resonance effects than the standard, unsubstituted reaction, while negative values are less sensitive.[41] As stated the *r* value for the $O_{Bn} \rightarrow S_{Bn}$ rearrangement is 5.40 and in comparison the $O_{Ar} \rightarrow S_{Ar}$ rearrangement has an *r* value of 1.6 (using σ^- values).[40] This is in agreement with the proposal that the mechanism of the $O_{Bn} \rightarrow S_{Bn}$ rearrangement possess more S_N1 character, i.e. retain more ionic character, than the $O_{Ar} \rightarrow S_{Ar}$ rearrangement and is thereby more stabilised by resonance than the aryl version in which only partial charges in the transition state structure are present.

The benzylic Newman-Kwart rearrangement was further investigated by a crossover experiment to examine whether the rearrangement is inter- or intramolecular. The two similar, but distinguishable, reactants *O*-(4-methoxybenzyl) *N*,*N*-dimethylthiocarbamate (**2c**) and its ethyl analogue **2f** possess similar reaction rates (Table 2) and were thus chosen for further investigation. Performing the crossover experiment at high concentrations (1.0 M, diphenyl ether, 200 °C) the two non-crossover rearranged products **3c** and **3f** formed with comparable rates together with a minor fraction of the crossover products **3d** and **3e** as observed by ^{13}C NMR spectroscopy and MS analysis (Figure 5 and Supporting Information). Thus, under the presented conditions, the rearrangement proceeds via an ionic reaction mechanism where the substrates rearrange mainly intramolecularly but also to a less degree intermolecularly. However, a 10-fold decrease in concentration (0.1 M, diphenyl ether, 200 °C) gave only the products **3c** and **3f** and none of the crossover products were observed. This indicates that even though the rearrangement follows an ionic reaction mechanism, the low concentration crossover experiments shows that the rearrangement has not reached the pure domain of an S_N1 mechanism. Instead it proceeds via a tight ion pair intermediate consisting of the benzylic carbocation and the thiocarbamate moiety.

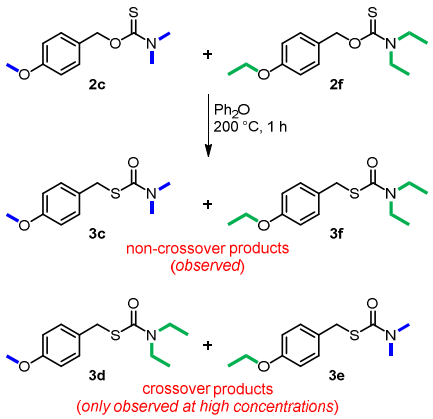


Figure 5 Cross-over experiment between **2c** and **2f** indicating that the benzylic Newman-Kwart rearrangement proceeds via an ionic mechanism.

Computational studies

A theoretical study was sought to get further insight into the reaction mechanism of the rearrangement. The study included both *O*-benzyl thio- and selenocarbamates substituted with electron donating (**2c** and **2o**), neutral (**2h** and **2p**), halogen (**2k** and **2s**), and electron withdrawing groups (**2n** and **2t**) on the aromatic unit. The fourth generation composite method referred to as G4MP2 was used as the level of theory with the GAUSSIAN09 suite of programs.[42-43] The G4MP2 is approximating a large basis set CCSD(T) single point calculations on a B3LYP/6-31G(2df,p) geometry and is incorporating a so-called higher level correction that is derived by a fit to the experimental values in the G3/05 test set with 454 experimental entries. The average absolute derivation from the experimental test set values is 1.04 kcal/mol.[44]

A potential energy diagram has been constructed to visualise the mechanism showing the reactant, transition state, and product for the $O_{Bn} \rightarrow S_{Bn}$ and $O_{Bn} \rightarrow Se_{Bn}$ conversion of **2h** into **3h** and **2p** into **3p**, respectively (Figure 6 and Supporting Information). The local minima on the potential energy surfaces were characterised by real vibrational frequencies while the transition states were characterised by one imaginary frequency corresponding to a molecular displacement along the reaction coordinate. The nature of the transition state structures was investigated by an intrinsic reaction coordinate (IRC) calculation that showed the transition state to the reactions and

products without intermediates.[45-46] An optimisation of the end-points of the IRC was compared to the optimised reactants and products and found similar, indicating that the transition state structures are reliable. According to the IRC, the mechanism contains one transition state and no intermediates.

Based on the optimised structures, the activation energies ($\Delta E^{\ddagger}$) and reaction energies ($\Delta E°$), including zero point vibrational energies, were calculated. The $O_{Bn} \rightarrow S_{Bn}$ rearrangement of substrate **2h** into **3h** gives an $\Delta E^{\ddagger}$ value of 178.1 kJ/mol and $\Delta E°$ of 56.7 kJ/mol while the corresponding $O_{Bn} \rightarrow Se_{Bn}$ rearrangement of **2p** into **3p** gives values of 168.7 kJ/mol and 61.6 kJ/mol for $\Delta E^{\ddagger}$ and $\Delta E°$, respectively (Figure 6). These values show, in agreement with the experimental work, how the $O_{Bn} \rightarrow Se_{Bn}$ rearrangement proceeds with a lower activation barrier, and thus a higher reaction rate, compared to the $O_{Bn} \rightarrow S_{Bn}$ rearrangement. The $\Delta E^{\ddagger}$ values of the benzylic rearrangements are comparable in size to the corresponding aryl versions, which has been calculated to 159 kJ/mol for the $O_{Ar} \rightarrow S_{Ar}$ rearrangement (B3LYP/6-31+G(d,p) level of theory)[47] and 142 kJ/mol for the $O_{Ar} \rightarrow Se_{Ar}$ rearrangement (MP2/6-31G(d) level of theory).[22]

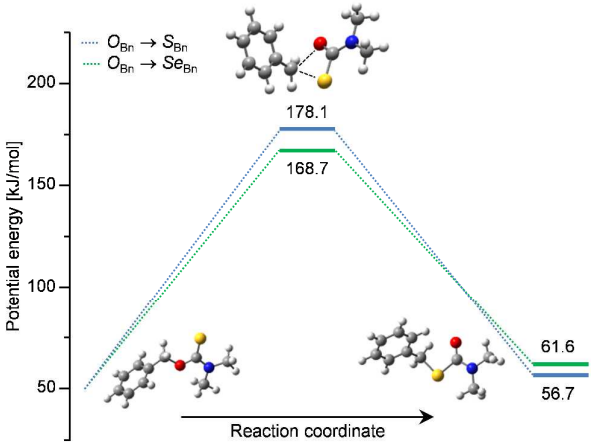


Figure 6 Schematic potential energy profile comparing the $O_{Bn} \rightarrow S_{Bn}$ conversion (**2h** into **3h**, G4MP2 calculated structures are shown) and $O_{Bn} \rightarrow Se_{Bn}$ conversion (**2p** into **3p**). The energies are given in kJ/mol and the reactants for both reactions are set at 0 kJ/mol with an offset at 50 kJ/mol.

Comparing the energies for all examined substrates it transpires how the activation energy for the rearrangement generally decreases with electron donating groups attached on the aromatic unit and *vice versa* for electron

withdrawing groups (Figure 7). This is in accordance with the experimental results. The activation barrier is, however, only lowered 6-7 kJ/mol altering the substituent from an electron withdrawing to an electron donating substituent (**2c** *vs* **2n** or **2o** *vs* **2t**). This makes it possible to rearrange a wider collection of derivatives with different electronic demands, a possibility which are not feasible for the aryl rearrangements. These results are also confirmed experimentally.

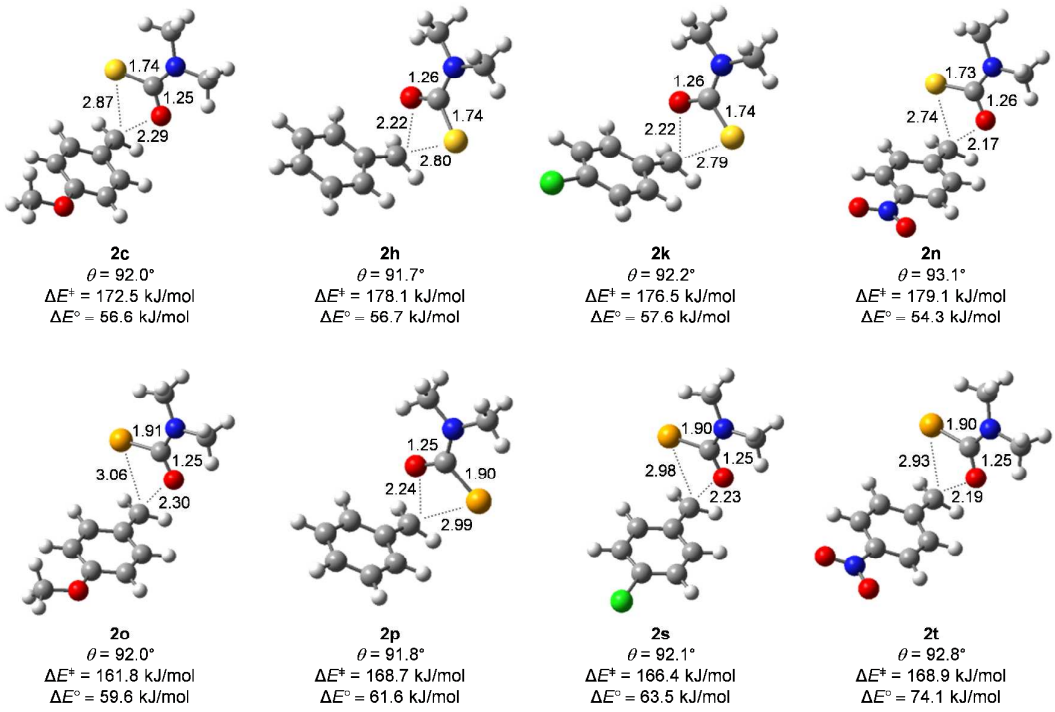


Figure 7 G4MP2 optimised transition state structures for the $O_{Bn} \rightarrow S_{Bn}$ conversion (top) and $O_{Bn} \rightarrow Se_{Bn}$ conversion (bottom). Selected bond lengths are shown in angstrom on the structure while the dihedral angle (θ), the activation energy ($\Delta E^{\ddagger}$), and the reaction energy (ΔE°) are given below for each structure. Colour code, S: yellow, Se: orange, O: red, N: blue, Cl: green, C: grey, and H: white.

Examination of the geometry of the various substituted transition states gives access to more knowledge of the reaction mechanism for the rearrangement. All eight transition state structures possess two planar units; one consisting of the benzylic carbocation and one comprising the thio- or selenocarbamate moiety. The two elements are placed perpendicular to each other in all cases, as seen by the measured dihedral angle (θ) given for

each structure (Figure 7). Analysis of the bond length distances between the two units gives an indication whether the structures are connected covalently or through ionic interactions. The average distance between the C–O, C–S, and C–Se atoms was found to be 2.2 Å, 2.8 Å, and 3.0 Å, respectively. These values are all larger than the values for a corresponding covalent bond (C–O: 1.4 Å, C–S: 1.8 Å, and C–Se: 2.0 Å)[13] thus indicating an ionic interaction. The measured distances are, however, still relatively close to the covalent bond lengths, supporting the proposal of a tight ion pair intermediate consisting of the benzylic carbocation and the thio- or selenocarbamate moiety. Also, the changes in geometry of the transition states as a function of the different substituents have been examined (Figure 7). Here it transpire, how both the C–O and the C–S/Se distance between the two ionic species increases when an electron donating group (**2c** and **2o**) is introduced and similarly decreases upon substitution of an electron withdrawing substituent (**2n** and **2t**). The chlorine atom in **2k** and **2s** can both donate a lone pair into the aromatic ring but is also electronegative and can thus withdraw electron density inductively. These two opposing effects are why a difference in the bond lengths between the chlorine (**2k** and **2s**) and unsubstituted (**2h** and **2p**) substrates are not observed.

These computational studies of the benzylic Newman-Kwart rearrangement further support a tight ion pair intermediate consisting of the benzylic carbocation and the thio- or selenocarbamate moiety. The electron donating substituents are able to stabilise the benzylic carbocation to a higher degree than the electron withdrawing derivatives, thus giving rise to a more ionic intermediate, envisaged through longer bond lengths, and thus lower activation energies.

Conclusion

In this paper we have presented a systematic and in-depth study of the $O_{Bn} \rightarrow S_{Bn}$ and $O_{Bn} \rightarrow Se_{Bn}$ Newman-Kwart rearrangements. Synthetic procedures have been shown together with thorough mechanistic studies as well as a theoretical elucidation of the reaction mechanism. The values obtained from computational chemistry support the experimental results that the rearrangement proceeds via an ionic reaction mechanism. The rate determining step is the bond breaking of the $C_{benzylic}$–O bond in the reactant thus forming a tight ion pair intermediate consist-

ing of a benzylic carbocation and a thio- or selenocarbamate moiety. The ion pair formation is feasible due to the benzylic stabilisation of charge. This mechanism supports the trend that electron donating groups increases the rate of the rearrangement and the electronic demand is thereby opposite that of the original aryl version of the Newman-Kwart rearrangement.

Experimental Section

General methods

All chemicals, unless otherwise stated, were purchased from commercial suppliers and used as received. Solvents were HPLC grade and used as received except THF, which was tapped from a Solvent Purification System, Innovative Technology, Inc., and diphenyl ether, which was distilled prior to use. All reactions involving selenium were carried out under an anhydrous nitrogen atmosphere.

Analytical thin layer chromatography (TLC) was performed on Merck DC-Alufolien SiO_2 60 F_{254} 0.2 mm thick precoated TLC plates and visualised under UV light (254 nm). Column chromatography and dry column vacuum chromatography was performed using SiO_2 from ROCC (SI 1721, 60 Å, 40 – 63 µm and SI 1722, 60 Å, 15 – 40 µm respectively). Melting points (mp.) were determined on a Büchi melting point apparatus and are uncorrected.

^{1}H NMR and ^{13}C NMR spectra were recorded at 500 MHz and 126 MHz, respectively, on a Bruker Ultrashield Plus 500 spectrometer using residual non-deuterated solvent as the internal standard. ^{77}Se NMR spectra were recorded on a Bruker spectrometer operating at 57 MHz using a saturated solution of diphenyl diselenide (δ = 463 ppm) in $CDCl_3$ at 20 °C in a sealed tube as external standard. All chemical shifts (δ) are quoted in ppm and coupling constants (*J*) are expressed in Hertz (Hz). The following abbreviations are used for convenience in reporting the multiplicity for NMR resonances: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. The NMR data were processed using MestReNova v. 10.0.2. Assignment of all ^{1}H and ^{13}C resonances was achieved using standard 2D NMR techniques as ^{1}H-^{1}H COSY, ^{1}H-^{13}C HSQC, and ^{1}H-^{13}C HMBC.

Standard HPLC analyses were performed on a Dionex UltiMate 3000 system coupled to an UltiMate 3000 diode array UV/Vis detector. Separations were achieved using a Dionex Acclaim RSLC 120 C18 2.2 µm 120 Å 2.1 × 50 mm

column maintained at 40 °C. The mobile phase solution was prepared with 0.1 % HCOOH in the solvents. The water used as eluent was purified by a Millipore system. LC/MS was carried out on a Bruker MicrOTOF-QII-system with ESI-source with nebuliser 1.2 bar, dry gas 8.0 L min^{-1}, dry temperature 200 °C, capillary – 4500 V, end plate offset – 500 V, funnel 1 RF 200.0 Vpp, ISCID energy 0.0 eV, funnel 2 RF 200.0 Vpp, hexapole RF 100.0 Vpp, quadrupole ion energy 5.0 eV, low mass 100.00 *m*/*z*, collision energy 8.0 eV, collision RF 100.0 Vpp, transfer time 80.0 µs, and pre puls storage 1.0 µs. LC-HRMS samples were calibrated by an automated pre-run internal mass scale calibration of the individual samples by injecting a sodium formate solution, consisting of 10 mM $NaOH_{(aq)}$ in *i*-PrOH:H_2O 1:1 v/v (+ 1 % HCOOH). Subsequent calibration was performed based on the calibrator ions. The LC/MS data were processed using DataAnalysis v. 4.0 SP5. For *Se*-containing ions in the mass spectrum, only the main selenium isotope (^{80}Se) is quoted.

Elemental analyses were performed by the microanalytical service of the Department of Chemistry, University of Copenhagen, Denmark on a CE Instrument, Flash 1112 series EA.

Experimental procedures for the *O*-benzyl thio- and selenocarbamates

General procedure. The desired alcohol (1.0 equiv.) and sodium hydride (60 % in mineral oil, 1.2 equiv. for *S* substrates and 2.2 equiv. for *Se* substrates) were added to anhydrous, degassed THF under a nitrogen atmosphere. The reaction mixture was cooled by a water bath and stirred for 10 minutes. *N,N*-Dimethylthiocarbamoyl chloride (1.0 equiv., used for *S* substrates) *or S*-phenyl *N,N*-dimethylthioselenocarbamate[27] (1.0 equiv., used for *Se* substrates) was added *in situ* and the reaction mixture was further stirred for 1 hour at 25 °C. The mixture was concentrated *in vacuo* before CH_2Cl_2 was added and the solution was filtered through a plug of Celite and concentrated *in vacuo*. If needed, the product was purified by column chromatography.

***O*-(2-Methoxybenzyl) *N,N*-dimethylthiocarbamate (2a).** 2-Methoxybenzyl alcohol (559 mg, 4.05 mmol) and NaH (60 % in mineral oil, 194 mg, 4.86 mmol) in anhydrous THF (25 mL) were reacted with *N,N*-dimethylthiocarbamoyl chloride (500 mg, 4.05 mmol) following the general procedure. The product was isolated as a white powder (884 mg, 3.92 mmol, 97 %), mp. 37–38 °C. ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C): δ = 7.34 – 7.31 (m, 2H), 7.04 – 7.02 (m, 1H), 6.97 – 6.94 (m, 1H), 5.41 (s, 2H), 3.81 (s, 3H), 3.29 (s, 3H), 3.09 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6,

25 °C): δ = 187.0, 156.9, 129.4, 128.8, 123.9, 120.2, 110.8, 67.8, 55.4, 42.3, 37.4. HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ calculated for $C_{11}H_{16}NO_2S$ 226.0896; Found 226.0898.

***O*-(3-Methoxybenzyl) *N*,*N*-dimethylthiocarbamate (2b).** 3-Methoxybenzyl alcohol (559 mg, 4.05 mmol) and NaH (60 % in mineral oil, 194 mg, 4.86 mmol) in anhydrous THF (25 mL) were reacted with *N,N*-dimethylthiocarbamoyl chloride (500 mg, 4.05 mmol) following the general procedure. The product was isolated as a light yellow oil (857 mg, 3.80 mmol, 94 %). ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C): δ = 7.29 (t, *J* = 8.2 Hz, 1H), 6.99 – 6.94 (m, 2H), 6.90 (ddd, *J* = 8.2, 2.5, 0.9 Hz, 1H), 5.42 (s, 2H), 3.75 (s, 3H), 3.29 (s, 3H), 3.12 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6, 25 °C): δ = 186.9, 159.3, 137.8, 129.5, 119.7, 113.3, 113.2, 71.7, 55.0, 42.4, 37.5. HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ calculated for $C_{11}H_{16}NO_2S$ 226.0896; Found 226.0900.

***O*-(4-Methoxybenzyl) *N*,*N*-dimethylthiocarbamate (2c).** 4-Methoxybenzyl alcohol (559 mg, 4.05 mmol) and NaH (60 % in mineral oil, 194 mg, 4.86 mmol) in anhydrous THF (25 mL) were reacted with *N,N*-dimethylthiocarbamoyl chloride (500 mg, 4.05 mmol) following the general procedure. The product was isolated as a yellow oil (875 mg, 3.88 mmol, 96 %). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.32 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 5.43 (s, 2H), 3.80 (s, 3H), 3.37 (s, 3H), 3.09 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 188.1, 159.7, 130.0, 128.3, 114.0, 72.9, 55.3, 42.8, 37.9. HRMS (ESI-TOF) *m*/*z*: $[M+Na]^+$ calculated for $C_{11}H_{15}NNaO_2S$ 248.0716; Found 248.0723.

***O*-(4-Methoxybenzyl) *N*,*N*-diethylthiocarbamate (2d).** 4-Methoxybenzyl alcohol (455 mg, 3.29 mmol) and NaH (60 % in mineral oil, 158 mg, 3.95 mmol) in anhydrous THF (25 mL) were reacted with *N,N*-diethylthiocarbamoyl chloride (500 mg, 3.29 mmol) following the general procedure. The product was isolated as a yellow oil (818 mg, 3.23 mmol, 98 %). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.32 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 5.44 (s, 2H), 3.84 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 3.45 (q, *J* = 7.1 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.12 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 187.2, 159.7, 130.0, 128.5, 114.0, 72.6, 55.4, 47.9, 43.5, 13.5, 12.1. HRMS (ESI-TOF) *m*/*z*: $[M+Na]^+$ calculated for $C_{13}H_{19}NNaO_2S$ 276.1029; Found 276.1019.

***O*-(4-Ethoxybenzyl) *N*,*N*-dimethylthiocarbamate (2e).** 4-Ethoxybenzyl alcohol (616 mg, 4.05 mmol) and NaH (60 % in mineral oil, 194 mg, 4.86 mmol) in anhydrous THF (25 mL) were reacted with *N,N*-dimethylthiocarbamoyl chloride (500 mg, 4.05 mmol) following the general procedure. The product was isolated as a yellow oil (794 mg,

3.32 mmol, 82 %). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.31 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.43 (s, 2H), 4.04 (q, J = 7.0 Hz, 2H), 3.38 (s, 3H), 3.10 (s, 3H), 1.41 (t, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 188.2, 159.1, 130.1, 128.2, 114.6, 73.1, 63.6, 42.9, 38.0, 15.0. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calculated for $C_{12}H_{17}NNaO_2S$ 262.0872; Found 262.0873.

***O*-(4-Ethoxybenzyl) *N,N*-diethylthiocarbamate (2f).** 4-Ethoxybenzyl alcohol (502 mg, 3.30 mmol) and NaH (60 % in mineral oil, 158 mg, 3.96 mmol) in anhydrous THF (25 mL) were reacted with *N,N*-diethylthiocarbamoyl chloride (408 mg, 3.30 mmol) following the general procedure. The product was isolated as white crystals (802 mg, 3.00 mmol, 91 %), mp. 44–46 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.31 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 5.43 (s, 2H), 4.04 (q, J = 7.0 Hz, 2H), 3.84 (q, J = 7.1 Hz, 2H), 3.45 (q, J = 7.1 Hz, 2H), 1.42 (t, J = 7.0 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H), 1.12 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 187.3, 159.1, 130.0, 128.3, 114.6, 72.7, 63.6, 47.9, 43.5, 15.0, 13.5, 12.1. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calculated for $C_{14}H_{21}NNaO_2S$ 290.1185; Found 290.1189.

***O*-(4-Methylbenzyl) *N,N*-dimethylthiocarbamate (2g).** 4-Methylbenzyl alcohol (494 mg, 4.04 mmol) and NaH (60 % in mineral oil, 194 mg, 4.85 mmol) in anhydrous THF (25 mL) were reacted with *N,N*-dimethylthiocarbamoyl chloride (500 mg, 4.04 mmol) following the general procedure. The product was isolated as light yellow needles (737 mg, 3.52 mmol, 87 %), mp. 33–35 °C. ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C): δ = 7.29 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 5.40 (s, 2H), 3.28 (s, 3H), 3.08 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6, 25 °C): δ = 186.9, 137.3, 133.2, 128.9, 127.9, 71.9, 42.3, 37.4, 20.7. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calculated for $C_{11}H_{15}NNaOS$ 232.0767; Found 232.0762.

***O*-Benzyl *N,N*-dimethylthiocarbamate (2h).** Benzyl alcohol (438 mg, 4.05 mmol) and NaH (60 % in mineral oil, 194 mg, 4.86 mmol) in anhydrous THF (25 mL) were reacted with *N,N*-dimethylthiocarbamoyl chloride (501 mg, 4.05 mmol) following the general procedure. The product was isolated as a yellow oil (727 mg, 3.72 mmol, 92 %). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.42 – 7.28 (m, 5H), 5.50 (s, 2H), 3.38 (s, 3H), 3.12 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 188.0, 136.2, 128.5, 128.1, 128.0, 72.9, 42.8, 37.9. HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{10}H_{14}NOS$ 196.0791; Found 196.0795.

(*rac*)-*O*-(1-Phenylethyl) *N,N*-dimethylthiocarbamate (2i). 1-Phenylethan-1-ol (494 mg, 4.04 mmol) and NaH (60 % in mineral oil, 194 mg, 4.85 mmol) in anhydrous THF (25 mL) were reacted with *N,N*-dimethylthiocarbamoyl chloride (500 mg, 4.04 mmol) following the general procedure. The product was isolated as a light yellow oil (813 mg, 3.88 mmol, 96 %). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.40 – 7.25 (m, 5H), 6.55 (q, J = 6.6 Hz, 1H), 3.35 (s, 3H), 3.15 (s, 3H), 1.63 (d, J = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 187.3, 141.8, 128.4, 127.7, 126.2, 78.9, 42.6, 37.8, 22.5. HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{11}H_{16}NOS$ 210.0947; Found 210.9050.

(*R*)-*O*-(1-Phenylethyl) *N,N*-dimethylthiocarbamate (2j). (*R*)-1-Phenylethan-1-ol (494 mg, 4.04 mmol) and NaH (60 % in mineral oil, 194 mg, 4.85 mmol) in anhydrous THF (25 mL) were reacted with *N,N*-dimethylthiocarbamoyl chloride (500 mg, 4.04 mmol) following the general procedure. The product was isolated as a light yellow oil (830 mg, 3.97 mmol, 98 %). ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C): δ = 7.43 – 7.34 (m, 4H), 7.37 – 7.25 (m, 1H), 6.40 (q, J = 6.6 Hz, 1H), 3.26 (s, 3H), 3.16 (s, 3H), 1.54 (d, J = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6, 25 °C): δ = 186.1, 141.8, 128.4, 127.6, 125.9, 78.1, 42.2, 37.5, 22.5. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calculated for $C_{11}H_{15}NNaOS$ 232.0767; Found 232.0767. Elemental analysis (%) calculated for $C_{11}H_{15}NOS$: C 63.12, H 7.22, N 6.69; Found: C 63.50, H 7.67, N 5.64.

***O*-(4-Chlorobenzyl) *N,N*-dimethylthiocarbamate (2k).** 4-Chlorobenzyl alcohol (1.00 g, 7.01 mmol) and NaH (60 % in mineral oil, 337 mg, 8.42 mmol) in anhydrous THF (50 mL) were reacted with *N,N*-dimethylthiocarbamoyl chloride (867 mg, 7.01 mmol) following the general procedure. The product was isolated as white crystals (1.59 g, 6.92 mmol, 99 %), mp. 36–37 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.37 – 7.29 (m, 4H), 5.48 (s, 2H), 3.39 (s, 3H), 3.13 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 188.0, 134.9, 134.2, 129.6, 128.9, 72.1, 43.1, 38.1. HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{10}H_{13}ClNOS$ 230.0401; Found 230.0400.

***O*-(4-Bromobenzyl) *N,N*-dimethylthiocarbamate (2l).** 4-Bromobenzyl alcohol (1.00 g, 5.35 mmol) and NaH (60 % in mineral oil, 257 mg, 6.42 mmol) in anhydrous THF (50 mL) were reacted with *N,N*-dimethylthiocarbamoyl chloride (661 mg, 5.35 mmol) following the general procedure. The product was isolated as dark yellow crystals (1.31 g, 4.79 mmol, 90 %), mp. 54–55 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.49 (d, J = 8.5 Hz, 2H), 7.26 (d, J = 8.5 Hz, 2H), 5.46 (s, 2H), 3.39 (s, 3H), 3.13 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 188.0, 135.4, 131.8, 129.9, 122.3,

72.1, 43.1, 38.1. HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ calculated for $C_{10}H_{13}BrNOS$ 273.9896; Found 273.9898. Elemental analysis (%) calculated for $C_{10}H_{12}BrNOS$: C 43.81, H 4.41, N 5.11; Found: C 43.98, H 4.40, N 5.11.

***O*-(4-Carbomethoxybenzyl) *N,N*-dimethylthiocarbamate (2m).** 4-Carbomethoxybenzyl alcohol (1.00 g, 6.02 mmol) and NaH (60 % in mineral oil, 289 mg, 7.22 mmol) in anhydrous THF (50 mL) were reacted with *N,N*-dimethylthiocarbamoyl chloride (744 mg, 6.02 mmol) following the general procedure. The product was isolated as a light yellow solid (1.27 g, 5.01 mmol, 83 %), mp. 67–69 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 8.04 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 8.2 Hz, 2H), 5.57 (s, 2H), 3.92 (s, 3H), 3.40 (s, 3H), 3.17 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 188.0, 166.9, 141.5, 130.0, 130.0, 127.6, 72.2, 52.3, 43.2, 38.1. HRMS (ESI-TOF) *m*/*z*: $[M+Na]^+$ calculated for $C_{12}H_{15}NNaO_3S$ 276.0665; Found 276.0673.

***O*-(4-Nitrobenzyl) *N,N*-dimethylthiocarbamate (2n).** The 4-nitrobenzyl alcohol (501 mg, 3.27 mmol) was dissolved in anhydrous, degassed THF (50 mL) under a nitrogen atmosphere. The reaction mixture was cooled by a water bath and potassium *tert* butoxide (441 mg, 3.93 mmol.) was added slowly *in situ* to and subsequently stirred for 15 minutes. The reaction mixture turned brown/yellow after 15 min stirring and *N,N*-dimethylthiocarbamoyl chloride (404 mg, 3.27 mmol.) was added *in situ* and the reaction mixture was further stirred for 18 hours at 25 °C. The mixture was concentrated *in vacuo* before CH_2Cl_2 was added and the solution was filtered through a plug of Celite and concentrated *in vacuo*. The reaction mixture was purified by column chromatography (ethyl acetate/heptane, 2 % gradient). The product was isolated as yellow needles (409 mg, 1.70 mmol, 52 %), mp. 32–34 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 8.23 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 8.8, 2H), 5.64 (s, 2H), 3.41 (s, 3H), 3.20 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 187.7, 147.8, 143.8, 128.3, 124.0, 71.2, 43.3, 38.2. HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ calculated for $C_{10}H_{12}N_2O_3S$ 241.06569; Found 241.06555.

***O*-(4-Methoxybenzyl) *N,N*-dimethylselenocarbamate (2o).** 4-Methoxybenzyl alcohol (283 mg, 2.05 mmol) and NaH (60 % in mineral oil, 180 mg, 4.51 mmol) in anhydrous THF (25 mL) were reacted with *S*-phenyl *N,N*-dimethylthioselenocarbamate (500 mg, 2.05 mmol) following the general procedure. The product was isolated as a light yellow oil (518 mg, 1.90 mmol, 93 %). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ =7.33 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J*

= 8.7 Hz, 2H), 5.53 (s, 2H), 3.79 (s, 3H), 3.47 (s, 3H), 3.07 (s, 3H).[48] ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 190.5 (d, J_{C-Se} = 235 Hz), 159.8, 130.1, 127.8, 114.0, 76.5, 55.3, 45.3, 38.2. ^{77}Se NMR (57 MHz, $CDCl_3$, 25° C) δ = 216.2. HRMS (ESI-TOF) *m*/*z*: $[M+Na]^+$ calculated for $C_{11}H_{15}NNaO_2Se$ 296.0160; Found 296.0165.

***O*-Benzyl *N*,*N*-dimethylselenocarbamate (2p).** Benzyl alcohol (221 mg, 2.05 mmol) and NaH (60 % in mineral oil, 180 mg, 4.50 mmol) in anhydrous THF (25 mL) were reacted with *S*-phenyl *N,N*-dimethylthioselenocarbamate (500 mg, 2.05 mmol) following the general procedure. The product was isolated as a light yellow oil (461 mg, 1.90 mmol, 93 %). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.42 – 7.31 (m, 5H), 5.61 (s, 2H), 3.50 (s, 3H), 3.12 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 190.7 (d, J_{C-Se} = 236 Hz), 135.8, 128.7, 128.4, 128.2, 76.6, 45.4, 38.3. ^{77}Se NMR (57 MHz, $CDCl_3$, 25° C) δ = 216.1. HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ calculated for $C_{10}H_{14}NOSe$ 244.0235; Found 244.0231.

(*rac*)-*O*-(1-Phenylethyl) *N*,*N*-dimethylselenocarbamate (2q). 1-Phenylethan-1-ol (250 mg, 2.05 mmol) and NaH (60 % in mineral oil, 180 mg, 4.50 mmol) in anhydrous THF (25 mL) were reacted with *S*-phenyl *N,N*-dimethylthioselenocarbamate (500 mg, 2.05 mmol) following the general procedure. The product was isolated as a yellow oil (508 mg, 1.98 mmol, 97 %). ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C): δ = 7.43 – 7.27 (m, 5H), 6.58 (q, *J* = 6.6 Hz, 1H), 3.37 (s, 3H), 3.16 (s, 3H), 1.57 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6, 25 °C): δ = 188.3 (d, J_{C-Se} = 235 Hz), 141.3, 128.4, 127.7, 126.0, 81.7, 44.6, 37.8, 22.4. ^{77}Se NMR (57 MHz, $CDCl_3$, 25° C) δ = 220.5. HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ calculated for $C_{11}H_{16}NOSe$ 258.0392; Found 258.0374.

***O*-(4-Bromobenzyl) *N*,*N*-dimethylselenocarbamate (2r).** 4-Bromobenzyl alcohol (383 mg, 2.05 mmol) and NaH (60 % in mineral oil, 180 mg, 4.50 mmol) in anhydrous THF (25 mL) were reacted with *S*-phenyl *N,N*-dimethylthioselenocarbamate (500 mg, 2.05 mmol) following the general procedure. The product was isolated as a yellow oil (585 mg, 1.82 mmol, 89 %). ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C): δ = 7.58 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 5.55 (s, 2H), 3.40 (s, 3H), 3.12 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6, 25 °C): δ = 189.2 (d, J_{C-Se} = 236 Hz), 135.4, 131.4, 130.0, 121.3, 74.3, 44.9, 37.9. ^{77}Se NMR (57 MHz, $CDCl_3$, 25° C) δ = 219.9. HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ calculated for $C_{10}H_{13}BrNOSe$ 321.9337; Found 321.9341.

Experimental procedures for the *S*-benzyl thio- and *Se*-benzyl selenocarbamates

***S*-(2-Methoxybenzyl) *N*,*N*-dimethylthiocarbamate (3a).** *O*-(2-Methoxybenzyl) *N*,*N*-dimethylthiocarbamate (132 mg, 586 µmol) was dissolved in Ph_2O (0.5 mL) and heated to 200 °C for 4 hours. The reaction mixture was cooled to 25 °C and the title compound was isolated after column chromatography (SiO_2, heptane to CH_2Cl_2) as a yellow oil (63.4 mg, 281 µmol, 48 %). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.40 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.23 (ddd, *J* = 8.1, 7.5, 1.8 Hz, 1H), 6.89 (td, *J* = 7.5, 1.1 Hz, 1H), 6.85 (dd, *J* = 8.1, 1.1 Hz, 1H), 4.19 (s, 2H), 3.86 (s, 3H), 2.98 (bs, 6H). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 168.6, 157.5, 130.8, 128.7, 126.8, 120.7, 110.6, 55.7, 36.8 (2 × C), 29.7. HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ calculated for $C_{11}H_{16}NO_2S$ 226.0896; Found 226.0900.

***S*-(3-Methoxybenzyl) *N*,*N*-dimethylthiocarbamate (3b).** *O*-(3-Methoxybenzyl) *N*,*N*-dimethylthiocarbamate (210 mg, 932 µmol) was dissolved in Ph_2O (1 mL) and heated to 200 °C for 20 hours. The reaction mixture was cooled to 25 °C and the title compound was isolated after column chromatography (SiO_2, heptane to CH_2Cl_2) as a yellow oil (124 mg, 550 µmol, 59 %). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.21 (t, *J* = 7.9 Hz, 1H), 6.94 (dt, *J* = 7.9, 1.1 Hz, 1H), 6.91 (t, *J* = 2.3 Hz, 1H), 6.78 (ddd, *J* = 7.9, 2.3, 1.1 Hz, 1H), 4.14 (s, 2H), 3.80 (s, 3H), 3.00 (bs, 6H). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 167.9, 159.8, 140.0, 129.7, 121.4, 114.5, 112.9, 55.4, 36.9 (2 × C), 35.0. HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ calculated for $C_{11}H_{16}NO_2S$ 226.0896; Found 226.0895.

***S*-(4-Methoxybenzyl) *N*,*N*-dimethylthiocarbamate (3c).** *O*-(4-Methoxybenzyl) *N*,*N*-dimethylthiocarbamate (100 mg, 444 µmol) was dissolved in Ph_2O (5 mL) and heated to 200 °C for 2 hours. The reaction mixture was cooled to 25 °C and the title compound was isolated after column chromatography (SiO_2, heptane to CH_2Cl_2) as a yellow oil (70.0 mg, 311 µmol, 70 %). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.27 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 4.11 (s, 2H), 3.78 (s, 3H), 3.00 (bs, 6H). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 168.1, 158.9, 130.5, 130.2, 114.1, 55.4, 36.8 (2 × C), 34.5. HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ calculated for $C_{11}H_{16}NO_2S$ 226.0896; Found 226.0893.

***S*-(4-Methoxybenzyl) *N*,*N*-diethylthiocarbamate (3d).** *O*-(4-Methoxybenzyl) *N*,*N*-diethylthiocarbamate (107 mg, 422 µmol) was dissolved in Ph_2O (0.5 mL) and heated to 200 °C for 2 hours. The reaction mixture was cooled to 25 °C and the title compound was isolated after column chromatography (SiO_2, heptane to CH_2Cl_2) as a light yellow oil (64.1 mg, 253 µmol, 60 %). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.27 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H),

4.11 (s, 2H), 3.78 (s, 3H), 3.37 (m, 4H), 1.16 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 167.0, 158.8, 130.4, 130.2, 114.1, 55.4, 42.3, 42.1, 34.2, 13.8, 13.4. HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ calculated for $C_{13}H_{20}NO_2S$ 254.1209; Found 254.1211.

***S*-(4-Ethoxybenzyl) *N*,*N*-dimethylthiocarbamate (3e).** *O*-(4-Ethoxybenzyl) *N*,*N*-dimethylthiocarbamate (168 mg, 702 µmol) was dissolved in Ph_2O (1 mL) and heated to 200 °C for 2 hours. The reaction mixture was cooled to 25 °C and the title compound was isolated after column chromatography (SiO_2, heptane to CH_2Cl_2) as a light yellow oil (90.0 mg, 376 µmol, 54 %). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.26 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 4.11 (s, 2H), 4.00 (q, *J* = 7.0 Hz, 2H), 2.98 (bs, 6H), 1.39 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 168.2, 158.2, 130.3, 130.2, 114.7, 63.6, 36.8 (2 × C), 34.5, 15.0. HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ calculated for $C_{12}H_{18}NO_2S$ 240.1053; Found 240.1052.

***S*-(4-Ethoxybenzyl) *N*,*N*-diethylthiocarbamate (3f).** *O*-(4-Ethoxybenzyl) *N*,*N*-diethylthiocarbamate (78.8 mg, 295 µmol) was dissolved in Ph_2O (0.5 mL) and heated to 200 °C for 2 hours. The reaction mixture was cooled to 25 °C and the title compound was isolated after column chromatography (SiO_2, heptane to CH_2Cl_2) as a light yellow oil (49.0 mg, 183 µmol, 62 %). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.26 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 4.11 (s, 2H), 4.01 (q, *J* = 7.0 Hz, 2H), 3.37 (m, 4H), 1.39 (t, *J* = 7.0 Hz, 3H), 1.16 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 167.0, 158.2, 130.2, 130.2, 114.7, 63.6, 42.3, 42.0, 34.3, 15.0, 13.8, 13.4. HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ calculated for $C_{14}H_{22}NO_2S$ 268.1366; Found 268.1365.

***S*-(4-Methylbenzyl) *N*,*N*-dimethylthiocarbamate (3g).** *O*-(4-Methylbenzyl) *N*,*N*-dimethylthiocarbamate (144 mg, 688 µmol) was dissolved in Ph_2O (3 mL) and heated to 200 °C for 19 hours. The reaction mixture was cooled to 25 °C and the title compound was isolated after column chromatography (SiO_2, heptane to CH_2Cl_2) as a yellow oil (59.0 mg, 282 µmol, 41 %). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.24 (d, *J* = 7.8 Hz, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 4.12 (s, 2H), 2.99 (bs, 6H), 2.32 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 168.1, 136.9, 135.4, 129.4, 129.0, 36.8 (2 × C), 34.7, 21.3. HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ calculated for $C_{11}H_{16}NOS$ 210.0947; Found 210.0951.

***S*-Benzyl *N*,*N*-dimethylthiocarbamate (3h).** *O*-Benzyl *N*,*N*-dimethylthiocarbamate (133 mg, 681 µmol) was dissolved in Ph_2O (1 mL) and heated to 200 °C for 22 hours. The reaction mixture was cooled to 25 °C and the title

compound was isolated after column chromatography (SiO_2, heptane to CH_2Cl_2) as a yellow oil (44.0 mg, 225 µmol, 33 %). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.38 – 7.27 (m, 4H), 7.25 – 7.21 (m, 1H), 4.16 (s, 2H), 3.00 (bs, 6H). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 168.0, 138.5, 129.1, 128.7, 127.2, 36.9 (2 × C), 35.0. HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ calculated for $C_{10}H_{14}NOS$ 196.0791; Found 196.0788.

***S*-(4-Chlorobenzyl) *N*,*N*-dimethylthiocarbamate (3k).** *O*-(4-Chlorobenzyl) *N*,*N*-dimethylthiocarbamate (232 mg, 1.01 mmol) was dissolved in Ph_2O (0.5 mL) and heated to 200 °C for 22 hours. The reaction mixture was cooled to 25 °C and the title compound was isolated after column chromatography (SiO_2, heptane to CH_2Cl_2) as an orange solid (119 mg, 518 µmol, 51 %), mp. 40–41 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.32 – 7.23 (m, 4H), 4.11 (s, 2H), 2.99 (bs, 6H). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 167.6, 137.3, 133.0, 130.4, 128.8, 36.9 (2 × C), 34.2. HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ calculated for $C_{10}H_{13}ClNOS$ 230.0401; Found 230.0410.

***S*-(4-Bromobenzyl) *N*,*N*-dimethylthiocarbamate (3l).** *O*-(4-Bromobenzyl) *N*,*N*-dimethylthiocarbamate (324 mg, 1.18 mmol) was dissolved in Ph_2O (0.5 mL) and heated to 200 °C for 23 hours. The reaction mixture was cooled to 25 °C and the title compound was isolated after column chromatography (SiO_2, heptane to CH_2Cl_2) as a light yellow solid (190 mg, 693 µmol, 59 %), mp. 37–38 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.41 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 4.09 (s, 2H), 2.99 (bs, 6H). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 167.6, 137.9, 131.7, 130.8, 121.1, 36.9 (2 × C), 34.3. HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ calculated for $C_{10}H_{13}BrNOS$ 273.9896; Found 273.9888.

***S*-(4-Carbomethoxybenzyl) *N*,*N*-dimethylthiocarbamate (3m).** *O*-(4-Carbomethoxybenzyl) *N*,*N*-dimethylthiocarbamate (176 mg, 695 µmol) was dissolved in Ph_2O (0.5 mL) and heated to 200 °C for 23 hours. The reaction mixture was cooled to 25 °C and the title compound was isolated after column chromatography (SiO_2, heptane to CH_2Cl_2) as a yellow oil (118 mg, 466 µmol, 67 %). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.96 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 4.18 (s, 2H), 3.90 (s, 3H), 3.01 (bs, 6H). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 167.4, 167.0, 144.1, 130.0, 129.4, 129.1, 52.2, 36.9 (2 × C), 34.6. HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ calculated for $C_{12}H_{16}NO_3S$ 254.0845; Found 254.0855.

***S*-(4-Methoxybenzyl) *N*,*N*-dimethylselenocarbamate (3o).** *O*-(4-Methoxybenzyl) *N*,*N*-dimethylselenocarbamate (204 mg, 749 µmol) was dissolved in Ph_2O (0.5 mL) and heated to 150 °C for 2.5 hours. The reaction mixture was

cooled to 25 °C and the title compound was isolated after column chromatography (SiO_2, heptane to CH_2Cl_2) as a yellow oil (179 mg, 659 µmol, 88 %). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.27 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 4.16 (s [d, $^2J_{H–Se}$ = 11.5 Hz], 2H), 3.78 (s, 3H), 3.04 (bs, 3H), 2.93 (bs, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 165.3 (d, $J_{C–Se}$ = 127 Hz), 158.5, 131.5, 130.0, 114.0, 55.3, 37.3, 36.7, 30.0 (d, $J_{C–Se}$ = 58.1 Hz). ^{77}Se-NMR (57 MHz, $CDCl_3$, 25° C) δ = 464.4 (t, $^2J_{Se–H}$ = 11.5 Hz). HRMS (ESI-TOF) m/z: $[M+Na]^+$ calculated for $C_{11}H_{15}NNaO_2Se$ 296.0160; Found 296.0157.

***S*-Benzyl *N*,*N*-dimethylselenocarbamate (3p).** *O*-Benzyl *N*,*N*-dimethylselenocarbamate (200 mg, 826 µmol) was dissolved in Ph_2O (10 mL) and heated to 200 °C for 6 hours. The reaction mixture was cooled to 25 °C and the title compound was isolated after dry column vacuum chromatography (SiO_2, heptane to ethyl acetate with 4 % gradient) as a white solid (108 mg, 446 µmol, 54 %), mp. 55–56 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.37 – 7.17 (m, 5H), 4.20 (s [d, $^2J_{H–Se}$ = 11.4 Hz], 2H), 3.04 (bs, 3H), 2.94 (bs, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 165.3 (d, $J_{C–Se}$ = 126 Hz), 139.7, 129.1, 128.7, 127.0, 37.4, 36.9, 30.6 (d, $J_{C–Se}$ = 58.7 Hz). ^{77}Se-NMR (57 MHz, $CDCl_3$, 25° C) δ = 464.3 (t, $^2J_{Se–H}$ = 11.4 Hz). HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{10}H_{14}NOSe$ 244.0235; Found 244.0237.

***S*-(4-Bromobenzyl) *N*,*N*-dimethylselenocarbamate (3r).** *O*-(4-Bromobenzyl) *N*,*N*-dimethylselenocarbamate (200 mg, 623 µmol) was dissolved in Ph_2O (10 mL) and heated to 200 °C for 4 hours. The reaction mixture was cooled to 25 °C and the title compound was isolated after dry column vacuum chromatography (SiO_2, heptane to ethyl acetate with 4 % gradient) as a yellow oil (122 mg, 380 µmol, 61 %). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.38 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 4.11 (s [*d*, $^2J_{H–Se}$ = 12.4 Hz], 2H), 3.03 (bs, 3H), 2.91 (bs, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 164.7 (d, $J_{C–Se}$ = 125 Hz), 139.0, 131.7, 130.8, 120.7, 37.3, 36.9, 29.7 (d, $J_{C–Se}$ = 59.5 Hz). ^{77}Se-NMR (57 MHz, $CDCl_3$, 25° C) δ = 472.8 (t, $^2J_{Se–H}$ = 12.4 Hz). HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{10}H_{13}BrNOSe$ 321.9337; Found 321.9336.

Experimental procedures for the benzyl thiol and benzyl selenol

4-Methoxybenzenethiol (4c). A solution of *S*-(4-methoxybenzyl) *N*,*N*-dimethylthiocarbamate (53.0 mg, 235 µmol) in 1.75 M KOH in degassed (N_2, 30 minutes) MeOH:H_2O (2:1 v/v, 10 mL) was stirred for 21 hours at 25 °C. The mixture was cooled to 0 °C before concentrated $HCl_{(aq)}$ (3 mL) was added. A white precipitate was formed which

was isolated by centrifugation and washed extensively with water to give the product as white crystals (36.0 mg, 233 µmol, 99 %). ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 7.17 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 3.80 (s, 3H), 3.59 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ = 159.2, 130.7, 129.6, 114.0, 55.4, 42.9. [The analytic data is in accordance with the literature].[49]

1,2-bis(4-Methoxyphenyl)diselane (4o). A solution of *Se*-(4-methoxybenzyl) *N*,*N*-dimethylselenocarbamate (70.5 mg, 259 µmol) in 1.75 M KOH in degassed (N_2, 30 minutes) MeOH:H_2O (2:1 v/v, 15 mL) was stirred for 21 hours at 25 °C. The mixture was cooled to 0 °C before concentrated $HCl_{(aq)}$ (5 mL) was added. A light yellow precipitate was formed which was isolated by centrifugation and washed extensively with water to give the oxidised product, the diselenide, as a light yellow solid (51.0 mg, 127 µmol, 98 %). ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 7.16 (d, J = 8.6 Hz, 4H), 6.83 (d, J = 8.6 Hz, 4H), 3.84 (s, [d, $^{2}J_{Se-H}$ = 7.1 Hz] 4H), 3.79 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ = 158.9, 131.3, 130.3 (d, J_{Se-C} = 16.0 Hz), 114.0, 55.4, 32.4. [The analytic data is in accordance with the literature].[50]

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Supporting Information

Spectral characterisation data together with details from the attempted stereochemical analysis, kinetic studies, linear free energy relationship studies, cross-over studies, X-ray crystallography, and computational studies.

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