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One-Pot Indium Iodide Mediated Synthesis of Chiral β-Seleno Amides and Selenocysteine Derivatives by Ring-Opening Reaction of 2-Oxazolines

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A set of chiral β-seleno amides were efficiently synthesized by a simple and efficient procedure involving a ring-opening reaction of 2-oxazoline with diorganyl dichalcogenides mediated by indium(I) iodide. As an application, the synthesis of selenocysteine derivatives was accomplished.

Introduction

Organoselenium compounds have emerged as an exceptional class of structures in recent years due to their pivotal role in the synthesis of a large number of biological compounds (e.g., selenocarbohydrates, selenoamino acids, and selenopeptides) and as important therapeutic compounds ranging from antiviral and anticancer agents to naturally occurring food supplements.[1] In addition, selenoamino acids are important as building blocks for the synthesis of selenoproteins[2] and because of their potential biological activity in, for example, the protection against neurodegenerative diseases, such as Parkinson's and Alzheimer's diseases.[3] Additionally, there is continuing interest in the development of new methods for the synthesis of enantiomerically pure amino acids with substituents strategically placed at side-chain positions with the ability to install unsaturation. In this context, selenocysteine derivatives (mainly phenylselenocysteines) can serve as convenient precursors to dehydroamino acids,[4] which are useful electrophilic handles for the chemoselective preparation of peptide conjugates.[5] Moreover, chiral selenides and diselenides-containing ligands have been employed as useful catalysts in various asymmetric transformations.[6] Therefore, the development of new methods for the introduction of selenium-containing groups into organic molecules,[7] particularly in a stereocontrolled manner, remains a significant challenge.

Reduction of Se–Se bonds, especially cleavage of diphenyl or diaryl diselenides, has recently received much effort for the preparation of unsymmetrical diorganyl selenides. Chemical cleavage of Se–Se bonds in diaryl diselenides was realized with reducing agents such as $NaBH_4$, Na/NH_3, Bu_3SnH, and $LiAlH_4$.[8]

In recent years, some protocols with indium(I) iodide mediated cleavage of diorganyl diselenides were developed to prepare vinylic selenides,[9] selenoesters,[10] and β-hydroxy selenides[11] with special attention given to unsymmetrical diorganyl selenides.[12]

We recently developed an indium(I) protocol for the preparation of selenocysteine and selenothreonine derivatives by an aziridine-2-carboxylate ring-opening reaction promoted by in situ generated bis(organoseleno)iodoindium(III).[13] By this method, a series of selenoamino acids could be synthesized in excellent yields, and these compounds displayed some interesting structural diversity.

We also reported Lewis acid (LA) mediated nucleophilic ring opening of chiral 2-oxazolines to provide nonracemic β-seleno amides, and a mechanism was proposed that consisted of an S_N2-type pathway to rationalize the formation of the chiral products. In this work, the selenium nucleophile required to open the oxazoline ring was generated by reduction of the diselenide with sodium borohydride in ethanol.[14] Additionally, by this method, it was possible to synthesize a selenocysteine derivative in moderated yield.

Attempting to disclose further extension of these works, we examined the reaction between indium(III) chalcogenolates **3**, obtained from indium(I) iodide and diorganyl diselenides, and several types of chiral 2-oxazolines **1** (Scheme 1). The work resulted in an efficient synthesis of β-seleno amides **2** and selenocysteine derivatives **5** under mild and neutral conditions.

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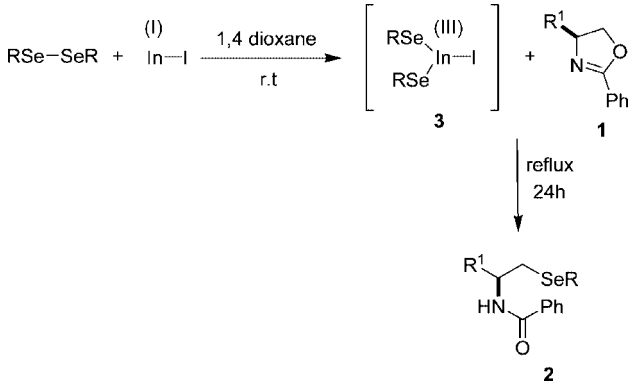


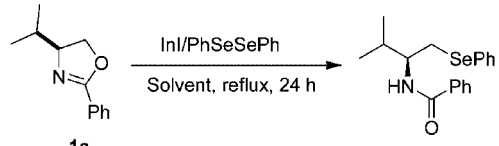
Scheme 1. Indium(I) iodide mediated oxazoline ring opening with diorganoyl diselenides.

Results and Discussion

It is well know that indium(I) compounds, through their oxidative insertion into a suitable substrate, generate the corresponding indium(III) derivatives. Thus, complex bis-(organoylseleno)iodoindium(III) **3** is readily prepared by the reaction of equimolar amounts of InI and RSeSeR in 1,4 dioxane.[9,12a,15]

Our studies started by the determination of the best solvent in which to perform this reaction by using oxazoline **1a** and the bis(organoseleno)iodoindium(III) prepared through the reaction between PhSeSePh and InI as shown in Table 1.

Table 1. Ring-opening reactions of oxazoline **1a** with the use of various solvents.



1a **2a**

Entry	Solvent	Yield [%][a]
1	DCM	30
2	THF	94
3	1,4-dioxane	99
4	MeCN	61
5	toluene	81
6[b]	EtOH/H_2O	15
7[c]	1,4-dioxane	99
8[c]	THF	89
9[c]	toluene	75

[a] Yields refer to those of pure isolated products characterized by spectroscopic methods. [b] EtOH/H_2O, 2:1. [c] InBr was used.

When dichloromethane was employed as the solvent, the product was obtained in a very unsatisfactory yield (Table 1, Entry 1). By increasing the polarity and boiling point of the solvent system (Table 1, Entries 2–4), better results were obtained, and the most efficient ring-opening process was achieved when 1,4 dioxane was used (99%; Table 1, Entry 3 vs. 2 and 4). By changing the solvent to toluene, a small decrease in the reaction yield was observed (Table 1, Entry 5). Concerning the high stability of organic indium compounds in water relative to other metals, we evaluated the reaction in EtOH/H_2O (2:1), but unfortunately the product was obtained in low yield (Table 1, Entry 6). Presumably under these conditions, the indium(III) selenolates are readily hydrolyzed to produce the corresponding selenol and indium(III) hydroxide.[9b]

We also varied the indium salt which promotes the cleavage of the Se–Se bond. Thus, the bis(organoseleno)bromoindium(III) was generated by reduction of PhSeSePh with InBr and applied in the ring-opening reaction of **1a** to furnish **2a** in same yield for dioxane (Table 1, compare Entries 7 and 3) and with a small decrease in the yield for THF and toluene (Table 1, Entries 8 and 9).

Notably, indium selenolate **3** promoted the oxazoline ring-opening reaction in the absence of a Lewis acid. We envisage that this fact is probably due to coordination of the indium(III) complex with the nitrogen atom of the oxazoline moiety (Figure 1), which itself acts as a Lewis acid.[13] The preparation of β-seleno amides proceeds through regio- and chemoselective nucleophilic attack of the organoyl selenide anion at the C5 position of the ring, which leads to cleavage of the C5–O1 bond and furnishes the desired product without any loss of enantiomeric purity, as determined by chiral HPLC.

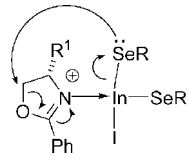
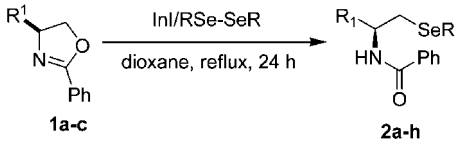


Figure 1. Proposed mechanism for the oxazoline ring-opening reaction.

With the optimal conditions in hand, the present reaction was extended to a broader range of oxazolines and diselenides in order to evaluate the scope and limitations of the mild reaction procedure.

As delineated in Table 2, all the β-seleno amides were obtained in good-to-excellent yields for all the oxazolines studied. Concerning the R group, the presence of an electron-donating group, such as the methoxy group, or an electron-withdrawing group, such as a chloro atom, in the aromatic rings of the diselenides had no significant influence on the reactivity of the process, as the products were obtained with only a slight decrease in the reaction yield (Table 2, Entries 2 and 3). The reaction was also performed with dialkyl diselenides as a nucleophilic source of selenium and products **2d**–**f** were furnished in good yields (Table 2, Entries 4–6). The nature of the side chain on the oxazoline did not play a significant role in terms of conversion to the desired product, as the results obtained with different lipophilic groups were quite similar (Table 2, Entries 7 and 8).

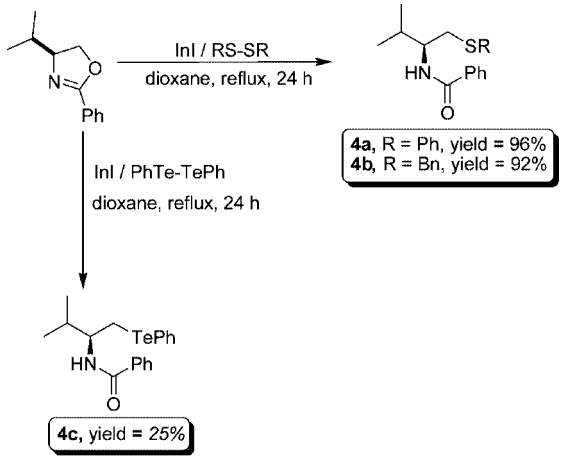
Table 2. Ring-opening Reaction of oxazolines **1a**–**c**.



Entry	Oxazoline	R^1	R	Product, yield [%][a]
1	**1a**	*i*Pr	Ph	**2a**, 99
2	**1a**	*i*Pr	*p*-$MeOC_6H_4$	**2b**, 89
3	**1a**	*i*Pr	*p*-ClC_6H_4	**2c**, 90
4	**1a**	*i*Pr	Bn	**2d**, 40
5	**1a**	*i*Pr	Bu	**2e**, 62
6	**1a**	*i*Pr	Et	**2f**, 53
7	**1b**	Bn	Ph	**2g**, 98
8	**1c**	*i*Bu	Ph	**2h**, 95

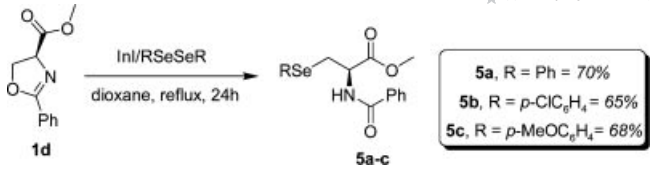
[a] Yields refer to those of pure isolated products characterized by spectroscopic methods.

As a further extension of the present approach, we attempted to synthesize several chiral β-chalcogeno amides, and the results are summarized in Scheme 2. Chiral β-thio amides **4a** (R = Ph) and **4b** (R = Bn) were obtained in excellent yields, but corresponding tellurium derivative **4c** (R = Ph) was obtained in low yield.



Scheme 2. Synthesis of chiral β-chalcogeno amides.

Because of their potential biological activity, in the last years some recent and classical successful approaches aimed at the synthesis of selenocysteines and their derivatives were documented.[16] In this context, a formidable challenge still remains to develop novel synthetic methods that can permit the introduction of selenium into optically active amino acids, which could be widely explored as building blocks for the synthesis of seleno peptides and derivatives.[16c,16d] Thus, we also focused our attention on the synthetic usefulness of this method by evaluating its viability in the synthesis of selenocysteine derivatives, and 2-oxazoline-4-carboxylate was employed as the starting material (Scheme 3).



Scheme 3. Synthesis of selenocysteine derivatives.

As outlined in Scheme 3, this route may constitute an attractive option for the preparation of various structurally diverse selenocysteine derivatives, as the strategy presented herein does not require the use of protecting groups such as Boc, Cbz, or Fmoc. It is worth mentioning that phenylselenocysteine derivatives, such as compound **5a**, have been used as precursors for the solid-phase peptide synthesis (SPPS) of selenocysteine-containing peptides, which are used for the mild oxidative introduction of dehydroalanines.[4a–4c]

Conclusions

The present procedure with indium(I) iodide provides a practical and concise synthesis of a wide range of useful chiral β-seleno amides **2a**–**h** and their derivatives in an easy, straightforward, and flexible synthetic route that starts from chiral 2-oxazolines. This method offers significant improvements with regard to operational simplicity, reaction conditions (neutral medium), and high isolated yields of products. Most importantly, with the bis(organoylseleno)-iodoindium(III) complexes **3** we could also achieve the efficient synthesis of selenocysteine derivatives **5a**–**c**.

Experimental Section

General Procedure for the Synthesis of Chiral β-Seleno Amides 2 or 5: In a 25-mL round-bottomed flask equipped with a reflux condenser, under an argon atmosphere, InI (powder, 121 mg, 0.5 mmol) was added to a solution of the appropriate diorganyl diselenide (0.5 mmol) in dry 1,4 dioxane (5 mL). The mixture was allowed to stir until all InI (15–45 min) was dissolved and then the appropriate oxazoline (0.5 mmol) was added, and the resulting solution was stirred and heated at reflux for 24 h. The mixture was quenched with a saturated NH_4Cl solution and extracted with CH_2Cl_2, and the combined organic fractions were collected, dried with $MgSO_4$, and filtered; the solvent was then removed in vacuo to yield crude products **2a**–**h** or **5a**–**c**, which were purified by flash chromatography.

(*S*)-*N*-[3-Methyl-1-(phenylselanyl)butan-2-yl]benzamide (2a): The enantiomeric purity was determined by HPLC analysis (Chiralcel-OD column; hexane/2-propanol, 90:10; flow rate 1.0 mL min^{-1}; *R* isomer t_R = 9.33 min; *S* isomer t_R = 13.47 min) and found to be >99.9%. Yield: 0.171 g (99%). White solid. M.p. 101–103 °C. $[\alpha]_D^{20}$ = +210 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60–7.35 (m, 7 H), 7.25–7.19 (m, 3 H), 6.29 (d, *J* = 8.4 Hz, 1 H), 4.22 (m, 1 H), 3.25–3.23 (m, 2 H), 2.05–2.00 (m, 1 H), 0.98–0.96 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0, 134.5, 132.7, 131.1, 129.9, 129.1, 128.3, 126.9, 126.7, 54.7, 31.7, 31.6, 19.3, 18.5 ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 251.5 ppm. IR (KBr): $\tilde{\nu}$ = 3313, 2965, 1633, 1533, 1470, 1178, 733, 693 cm^{-1}. HRMS

(ESI): calcd. for $C_{18}H_{21}NNaOSe$ $[M + Na]^+$ 370.0680; found 370.0677.

(*S*)-*N*-[1-(4-Methoxyphenylselanyl)-3-methylbutan-2-yl]benzamide (2b): Yield: 0.167g (89%). White solid. M.p. 100–102 °C. $[\alpha]_D^{20}$ = +99 (c = 1.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.61–7.59 (m, 2 H), 7.48–7.36 (m, 5 H), 6.75–6.73 (m, 2 H), 6.10 (d, J = 8.8 Hz, 1 H), 4.21–4.15 (m, 1 H), 3.74 (s, 3 H), 3.14 (m, 2 H), 2.06–1.99 (m, 1 H), 0.97–0.93 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0, 159.4, 135.6, 134.7, 131.2, 128.4, 126.8, 119.7, 114.9, 55.1, 54.9, 32.8, 31.7, 19.3, 18.5 ppm. IR (KBr): $\tilde{\nu}$ = 3308, 2965, 1633, 1551, 1249, 1183, 696 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{23}NNaO_2Se$ $[M + Na]^+$ 400.0786; found 400.0777.

(*S*)-*N*-[1-(4-Chlorophenylselanyl)-3-methylbutan-2-yl]benzamide (2c): Yield: 0.171g (90%). White solid. M.p. 122–124 °C. $[\alpha]_D^{20}$ = +189 (c = 1.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.61–7.59 (m, 2 H), 7.48–7.39 (m, 5 H), 7.16–7.14 (m, 2 H), 6.07 (d, J = 8.0 Hz, 1 H), 4.23–4.17 (m, 1 H), 3.21–3.18 (m, 2 H), 2.05–1.96 (m, 1 H), 0.98 (d, J = 3.2 Hz, 3 H), 0.96 (d, J = 3.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0, 134.4, 134.2, 133.3, 131.3, 129.2, 128.4, 128.1, 126.7, 54.7, 32.0, 31.6, 19.4, 18.4 ppm. IR (KBr): $\tilde{\nu}$ = 3298, 2955, 1628, 1546, 1470, 1091, 691 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{21}ClNOSe$ $[M + H]^+$ 382.0476; found 382.0479.

(*S*)-*N*-[1-(Benzylselanyl)-3-methylbutan-2-yl]benzamide (2d): Yield: 0.072g (40%). White solid. M.p. 108–110 °C. $[\alpha]_D^{20}$ = +215 (c = 1.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.73–7.71 (m, 2 H), 7.50–7.43 (m, 3 H), 7.27–7.14 (m, 5 H), 6.11 (d, J = 8.0 Hz, 1 H), 4.15–4.12 (m, 1 H), 3.81 (d, J = 12 Hz, 1 H), 3.76 (d, J = 12 Hz, 1 H), 2.84 (dd, J = 12.4 Hz, J = 6.4 Hz, 1 H), 2.74 (dd, J = 12.4 Hz, J = 4.8 Hz, 1 H), 1.92–1.87 (m, 1 H), 0.95 (d, J = 4.4 Hz, 3 H), 0.93 (d, J = 4.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.1, 139.0, 134.8, 131.3, 129.0, 128.8, 128.5, 126.9, 126.8, 53.8, 32.0, 27.7, 27.6, 19.4, 18.4 ppm. IR (KBr): $\tilde{\nu}$ = 3298, 2965, 1639, 1526, 1178, 731, 691 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{23}NNaOSe$ $[M + Na]^+$ 384.0842; found 384.0824.

(*S*)-*N*-[1-(Butylselanyl)-3-methylbutan-2-yl]benzamide (2e): Yield: 0.101g (62%). Pale yellow oil. $[\alpha]_D^{20}$ = +118 (c = 1.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.79–7.77 (m, 2 H), 7.51–7.41 (m, 3 H), 6.30 (d, J = 8.4 Hz, 1 H), 4.17–4.10 (m, 1 H), 2.95 (dd, J = 12.6 Hz, J = 5.8 Hz, 1 H), 2.78 (dd, J = 12.6 Hz, J = 5.0 Hz, 1 H), 2.58 (t, J = 7.6 Hz, 2 H), 2.01–1.92 (m, 1 H), 1.65 (q, J = 7.4 Hz, 2 H), 1.36 (sex, J = 7.4 Hz, 2 H), 1.01–0.98 (m, 6 H), 0.86 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0, 134.8, 131.3, 128.5, 126.8, 54.2, 32.7, 31.6, 27.7, 24.8, 22.9, 19.5, 18.5, 13.4 ppm. IR (film): $\tilde{\nu}$ = 3298, 2960, 1634, 1541, 1178, 701 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{26}NOSe$ $[M + H]^+$ 328.1179; found 328.1178.

(*S*)-*N*-[1-(Ethylselanyl)-3-methylbutan-2-yl]benzamide (2f): Yield: 0.079g (53%). Pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.81–7.31 (m, 5 H), 6.33 (d, J = 7.8 Hz, 1 H), 4.21–4.11 (m, 1 H), 2.88 (dd, J = 16 Hz, J = 5.8 Hz, 2 H), 2.60 (dd, J = 7.4 Hz, J = 15 Hz, 2 H), 2.05–1.88 (m, 1 H), 1.38 (t, J = 7.6 Hz, 3 H), 1.12–1.05 (m 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.78, 134.48, 131.08, 128.31, 128.26, 128.00, 127.90, 126.52, 53.82, 31.3, 26.9, 19.2, 18.1, 18.0, 15.5 ppm. HRMS (ESI): calcd. for $C_{14}H_{21}NNaOSe$ $[M + Na]^+$ 322.0688; found 322.0681.

(*S*)-*N*-[3-Phenyl-1-(phenylselanyl)propan-2-yl]benzamide (2g): Yield: 0.193g (98%). White solid. M.p. 148,5–150.5 °C. $[\alpha]_D^{20}$ = +52 (c = 1.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.19 (m, 15 H), 6.20 (d, J = 7.2 Hz, 1 H), 4.64–4.59 (m, 1 H), 3.24–2.97 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.8, 137.3, 134.3, 132.7, 131,4, 129.7, 129.4, 129.1, 128.6, 128.4, 127.2, 126.7, 126.7, 50.8, 39.1, 32.1 ppm. IR (KBr): $\tilde{\nu}$ = 3313, 2919, 1641, 1536, 1475, 1203, 737, 691 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{21}NNaOSe$ $[M + Na]^+$ 418.0680; found 418.0677.

(*S*)-*N*-[4-Methyl-1-(phenylselanyl)pentan-2-yl]benzamide (2h): Yield: 0.171g (95%). White solid. M.p. 99–101 °C. $[\alpha]_D^{20}$ = +65 (c = 1.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.17 (m, 10 H), 6.16 (d, J = 8.4 Hz, 1 H), 4.53–4.48 (m, 1 H), 3.27 (dd, J = 12.6 Hz, J = 5.2 Hz, 1 H), 3.20 (dd, J = 12.6 Hz, J = 4.6 Hz, 1 H), 1.65–1.46 (m, 3 H), 0.92–0.89 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7, 134.5, 132.6, 131.2, 130.0, 129.2, 128.3, 127.0, 126.7, 47.6, 43.6, 34.3, 25.0, 22.8, 22.3 ppm. IR (KBr): $\tilde{\nu}$ = 3293, 2960, 1628, 1552, 1470, 1178, 732, 696 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{23}NNaOSe$ $[M + Na]^+$ 384.0837; found 384.0837.

(*S*)-*N*-[3-Methyl-1-(phenylthio)butan-2-yl]benzamide (4a): Yield: 0.144g (96%). White solid. M.p. 114–116 °C. $[\alpha]_D^{20}$ = +45 (c = 1.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, J = 7.2 Hz, 2 H), 7.45–7.34 (m, 5 H), 7.23 (t, J = 7.6 Hz, 2 H), 7.15–7.14 (m, 1 H), 6.22 (d, J = 8.4 Hz, 1 H), 4.23–4.19 (m, 1 H), 3.23–3.21 (m, 2 H), 2.10–2.05 (m, 2 H), 0.98 (d, J = 3.6 Hz, 3 H), 0.97 (d, J = 3.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2, 136.1, 134.6, 131.28, 129.7, 129.0, 128.4, 126.8, 126.3, 54.5, 37.0, 30.8, 19.4, 18.4 ppm. HRMS (ESI): calcd. for $C_{18}H_{21}NNaOS$ $[M + Na]^+$ 322.1247; found 322.124.

(*S*)-*N*-[1-(Benzylthio)-3-methylbutan-2-yl]benzamide (4b): Yield: 0.147g (94%). White solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.76–7.22 (m, 10 H), 6.13 (d, J = 8.4 Hz, 1 H), 4.20–4.12 (m, 1 H), 3.75 (d, J = 1.2 Hz, 2 H), 2.70–2.63 (m, 2 H), 2.03–1.86 (m, 1 H), 0.96–0.91 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.3, 138.1, 134.8, 131.4, 129.6, 128.9, 128.6, 128.6, 128.5, 128.4, 127.1, 126.9, 53.4, 36.5, 34.1, 31.2, 19.4, 18.4 ppm.

(*S*)-*N*-[3-Methyl-1-(phenyltellanyl)butan-2-yl]benzamide (4c): Yield: 0.050g (25%). Yellow solid. M.p. 79–81 °C. $[\alpha]_D^{20}$ = +55 (c = 1.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.72–7.70 (m, 2 H), 7.61–7.58 (m, 2 H), 7.45–7.11 (m, 6 H), 6.18 (d, J = 8.4 Hz, 1 H), 4.17–4.13 (m, 1 H), 3.26 (dd, J = 12.4 Hz, J = 6.5 Hz, 1 H), 3.21 (dd, J = 12.4 Hz, J = 4.7 Hz, 1 H), 1.95–1.89 (m, 1 H), 0.96 (d, J = 6.7 Hz, 3 H), 0.92 (d, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0, 138.5, 134.6, 131.3, 129.3, 128.4, 127.8, 126.8, 111.2, 55.1, 33.3, 19.4, 18.5, 14.6 ppm. IR (KBr): $\tilde{\nu}$ = 3329, 2955, 1643, 1547, 1178, 732, 691 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{21}NNaOTe$ $[M + Na]^+$ 420.0577; found 420.0565.

(*R*)-Methyl 2-Benzamido-3-(phenylselanyl)propanoate (5a): Yield: 0.127g (70%). White solid. M.p. 74–76 °C. $[\alpha]_D^{20}$ = +35 (c = 1.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.61–7.19 (m, 10 H), 6.95 (d, J = 7.2 Hz, 1 H), 5.19–5.14 (m, 1 H), 3.55–3.51 (m, 4 H), 3.42 (dd, J = 13.6 Hz, J = 4.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 166.7, 133.3, 133.2, 131.2, 129.1, 128.5, 128.3, 127.4, 126.9, 52.6, 52.3, 29.8 ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 268.5 ppm. IR (KBr): $\tilde{\nu}$ = 3359, 3073, 2960, 1741, 1649, 1516, 1208, 1162, 742, 681 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{17}NNaO_3Se$ $[M + Na]^+$ 386.0265; found 386.0261.

(*R*)-Methyl-2-benzamido-3-(4-chlorophenylselanyl) Propanoate (5b): Yield: 0.129g (65%). White solid. M.p. 85–87 °C. $[\alpha]_D^{20}$ = +30 (c = 1.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, J = 7.6 Hz, 2 H), 7.50–7.41 (m, 5 H), 7.17–7.15 (m, 2 H), 6.84 (d, J = 7.2 Hz, 1 H), 5.20–5.16 (m, 1 H) 3.62 (s, 3 H), 3.57 (dd, J = 13.4 Hz, J = 4.5 Hz, 1 H), 3.39 (dd, J = 13.4 Hz, J = 4.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 166.7, 135.0, 133.9, 133.3, 131.9, 129.3, 128.5, 126.9, 126.8, 52.9, 52.6, 30.1 ppm. IR (KBr): $\tilde{\nu}$ = 3344, 3067, 2944, 1736, 1644, 1516, 1224, 1091, 809 cm^{-1}. HRMS

(ESI): calcd. for $C_{17}H_{16}ClNNaO_3Se$ $[M + Na]^+$ 419.9876; found 419.9867.

(*R*)-Methyl-2-benzamido-3-(4-methoxyphenylselanyl) Propanoate (5c): Yield: 0.133g (68%). White solid. M.p. 79–81 °C. $[\alpha]_D^{20}$ = +38 (c = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64–7.62 (m, 2 H), 7.53–7.49 (m, 3 H), 7.45–7.40 (m, 2 H), 6.94 (d, J = 7.0 Hz, 1 H), 6.78–6.76 (m, 2 H), 5.19–5.16 (m, 1 H), 3.75 (s, 3 H), 3.62 (s, 3 H), 3.48 (dd, J = 13.3 Hz, J = 4.4 Hz, 1 H), 3.34 (dd, J = 13.3 Hz, J = 5.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 166.6, 159.5, 136.1, 131.6, 128.3, 128.2, 126.9, 118.3, 114.8, 55.1, 52.8, 52.4, 30.5 ppm. IR (KBr): $\tilde{\nu}$ = 3327, 2951, 1736, 1641, 1521 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{19}NNaO_4Se$ $[M + Na]^+$ 416.0379; found 416.0374.

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