Modular Synthesis of Chiral N-Protected β-Seleno Amines and Amides via Cleavage of 2-Oxazolidinones and Application in Palladium-Catalyzed Asymmetric Allylic Alkylation

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Abstract: A set of chiral β-seleno amines have been efficiently synthesized via the ring-opening reaction of chiral N-acyl oxazolidinones by selenium nucleophiles. These compounds could be transformed into β-seleno amides by reaction with acid chlorides. The present method is applicable to the synthesis of β-chalcogeno amides containing selenium, sulfur and tellurium atoms in good yields. Additionally, these new compounds were evaluated as ligands in the palladium-catalyzed asymmetric allylic alkylation, giving the corresponding alkylated products in up to 98% ee.

Key words: β-seleno amines, allylic alkylation, oxazolidinone ring-opening, asymmetric catalysis

Organoselenium chemistry has led to the emergence of an exceptional class of structures in recent years due to its pivotal role in the synthesis of a large number of biological compounds (e.g., selenocarbohydrates, selenoamino acids and selenopeptides) and its importance in therapeutic compounds ranging from antiviral and anticancer agents to naturally occurring food supplements.[1] Indeed, recent advances in the synthesis of compounds containing selenium have been driven by the interesting reactivities[2] and their potential pharmaceutical significance.[3] In particular, chiral selenium-based methods have received special attention from organic chemists over the last decade, and are now a very important tool for stereoselective transformations.[4]

On the other hand, 2-oxazolidinones are a very important class of heterocyclic compounds.[5] Chiral 2-oxazolidinones are widely used as chiral auxiliaries in many important asymmetric syntheses[6] and their derivatives have shown important pharmacological properties, in particular as antibacterial agents.[7] Among the many applications to organic synthesis, these compounds can also undergo ring-opening reactions with nucleophiles, resulting in interesting β-substituted compounds.[8]

At the same time, some of the more exciting areas of research using chiral organoselenium compounds have been the catalytic asymmetric reactions used to provide enantiomerically enriched compounds; these represent a new trend in this field of organometallic chemistry.[9] In this context, chiral selenides and diselenide-containing ligands have been employed as useful catalysts in various asymmetric transformations such as enantioselective addition of diethylzinc to aldehydes,[10] conjugate addition to enones[11] and palladium-catalyzed asymmetric allylic substitution.[12] The latter asymmetric transformation is currently one of the most important transition-metal-catalyzed reactions known through which to form carbon–carbon and carbon–heteroatom bonds,[13] and it is a widely applied process in the synthesis of optically active small molecules and in the total synthesis of natural products.[14]

Recently, we have described the synthesis of a wide range of chiral β-seleno amides and their derivatives by ring-opening reaction of 2-oxazolines. The organoselenium compounds were successfully applied in the palladium-catalyzed asymmetric allylic alkylation, furnishing the corresponding alkylated products in excellent yields and enantiomeric excesses.[15]

In the course of our growing interest in the preparation of a wide range of chiral organoselenium compounds and their application in asymmetric synthesis, we describe herein the behavior of *N*-acyl 2-oxazolidinones in the presence of various selenium nucleophiles. In particular, we wish to report an inexpensive, modular and straightforward route to chiral β-seleno amines and their analogues containing sulfur and tellurium. These compounds could be easily converted into their amides by reaction with appropriate acyl chlorides in excellent yields. Furthermore, additional studies on these seleno amides containing a range of acyl groups were also performed with regard to the palladium-catalyzed asymmetric allylic alkylation.

Initially, the N-protected 2-oxazolines were synthesized starting from the commercially available chiral 2-oxazolidinone **1** as described below (Scheme 1).

Treatment of compound **1** with di-*tert*-butyl dicarbonate (Boc_2O) in acetonitrile furnished the *N*-Boc-2-oxazolidinone **2a** in quantitative yield. Additionally, the reaction of oxazolidinone **1** with *n*-butyllithium in tetrahydrofuran at 0 °C and subsequent addition of an appropriate electrophile furnished a variety of N-protected oxazolidinones **2b–e** in good yields.[16] With the N-protected 2-oxazolidinones **2a–e** in hand, we turned our attention to investigating the behavior of these compounds in the presence of chalcogen nucleophiles as summarized in Table 1.

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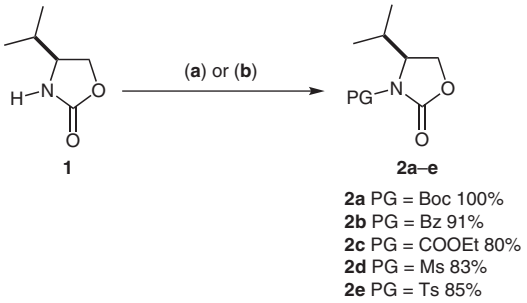


Scheme 1 *Reagents and conditions*: (a) Boc_2O, MeCN, 24 h; (b) *n*-BuLi, THF, 0 °C, electrophile, 24 h.

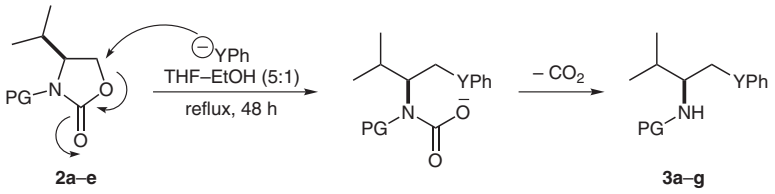
As outlined in the sequence shown in Table 1, the mechanism for the ring-opening of five-membered heterocycles leading to β-chalcogeno amines is known to proceed through a regio- and chemoselective nucleophilic attack of the chalcogenide at the C-5 position of the ring,[8,15a] leading to C(5)–O(1) bond cleavage and decarboxylation of the corresponding intermediate to furnish the desired products **3a–g**, without any racemization (determined by chiral HPLC).

The reaction was initially studied with compound **2a** and phenyl selenolate, which was easily generated by reduction of diphenyl diselenide (PhSeSePh) with *n*-butyllithium in tetrahydrofuran. Under these conditions, the desired oraganoselenium compound **3a** was obtained in moderate yield (56%). This result prompted us to further investigate the reaction by varying the counterion of the selenium nucleophile. Thus, the phenyl selenolate was also generated by reduction of PhSeSePh with metallic sodium and $NaBH_4$. However, improvement could only be observed when $NaBH_4$ was employed (Table 1, entry 3). Having found the best way to generate the selenium nucleophile, the nature of the protecting group was also evaluated. We noted that the electron-withdrawing group attached to the oxazolidinone had a strong influence on the ring-opening reaction. The best results were obtained with *tert*-butoxycarbonyl (Boc) and benzoyl (Bz) as protecting groups, which led to the corresponding products **3a** and **3b** in 81% and 65% yields, respectively (Table 1, entries 3 and 4). The presence of electron-withdrawing groups attached to the nitrogen atom, such as ethylcarbamate (CO_2Et), mesyl (Ms), and tosyl (Ts), led to the respective organoselenium compounds **3c–e** in lower yields and complicated product purification (Table 1, entries 5–7).

The chiral *N*-Boc-2-oxazolidinone **2a** was also submitted to ring-opening reactions using ditellurides and thiols. The tellurium nucleophile was generated in the presence of $NaBH_4$ in a mixture of solvents (THF–EtOH, 5:1). Under these conditions, the desired organotellurium compound **3f** was obtained in 67% yield (Table 1, entry 8). On the other hand, the sulfur anion was generated starting from the commercially available thiophenol, using potassium *tert*-butoxide as base, to give the respective product **3g** in good yield (Table 1, entry 9). Thiophenol was used as the nucleophilic source since it is commercially available, stable toward air oxidation and inexpensive, thus avoiding the preparation of the corresponding disulfide.

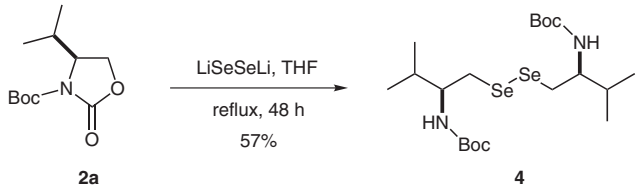
The ring-opening reaction of chiral 2-oxazolidinone **2a** was also extended to the synthesis of diselenide **4**, employing LiSeSeLi as the nucleophile,[17] to give the desired

Table 1 2-Oxazolidinone Ring-Opening Reaction with a Variety of Chalcogen Nucleophiles



Entry	Oxazolidinone	PG	Nucleophile	Base[a]	Y	Product	Yield (%)
1	**2a**	Boc	PhSeSePh	*n*-BuLi[b]	Se	**3a**	56
2	**2a**	Boc	PhSeSePh	Na[b]	Se	**3a**	27
3	**2a**	Boc	PhSeSePh	$NaBH_4$	Se	**3a**	81
4	**2b**	Bz	PhSeSePh	$NaBH_4$	Se	**3b**	65
5	**2c**	CO_2Et	PhSeSePh	$NaBH_4$	Se	**3c**	51
6	**2d**	Ms	PhSeSePh	$NaBH_4$	Se	**3d**	57
7	**2e**	Ts	PhSeSePh	$NaBH_4$	Se	**3e**	35
8	**2a**	Boc	PhTeTePh	$NaBH_4$	Te	**3f**	67
9	**2a**	Boc	HSPh	*t*-BuOK[b]	S	**3g**	77

[a] THF–EtOH (5:1) used as solvent.
[b] THF used as solvent.



2a 4

Scheme 2

diselenide in satisfactory yield (Scheme 2). It is important to mention that this compound acted as a catalyst in the enantioselective addition of diethylzinc to aldehydes.[10d]

In order to closer examine the effects of substitution in the aromatic ring of the *N*-acyl-β-seleno amides on the asymmetric allylic alkylation reaction, the compounds **6a–g** were also synthesized, as depicted in Scheme 3. The preparation of these compounds was initiated with the ring-opening reaction of 2-oxazolidinone **2a** to furnish the *N*-Boc-β-seleno amine **3a** in 81% yield. This was submitted to a deprotection reaction to give the amino selenide **5** in quantitative yield without further purification. The intermediate **5**, containing a free amine group, was then treated with the appropriate acyl chloride to afford the corresponding compounds **6a–g** in yields ranging from 77% to 93% (Scheme 3). In this reaction, the nature of the acid chloride did not significantly influence the outcome of reaction, since all desired compounds were obtained in high yields and purity.

All the compounds were evaluated as chiral ligands in the palladium-catalyzed allylic alkylation reaction in order to examine the influence of the group attached to the nitrogen atom of the β-seleno amides. These results are summarized in Table 2.

We studied the palladium-catalyzed asymmetric allylic alkylation (AAA) of 1,3-diphenyl-2-propenylacetate with dimethyl malonate in the presence of 2.5 mol% of $[Pd(\eta^3C_3H_5)Cl]_2$ and dichloromethane as solvent. As previously reported by our research group,[15a] the β-seleno amide **3b** (10 mol%) catalyzes the AAA reaction in a mixture of *N*,*O*-bis(trimethylsilylacetamide) (BSA), a catalytic amount of potassium acetate and dichloromethane as solvent, furnishing the desired alkylated product (*R*)-**9** in excellent yield and enantiomeric excess (Table 2, entry 1).

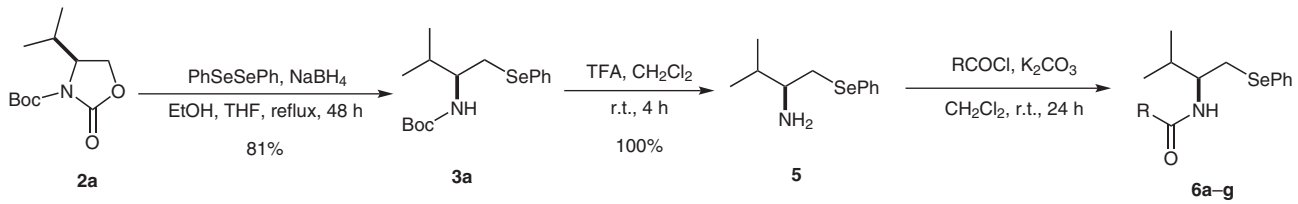
This result prompted us to further investigate the effects of the substituents located at the nitrogen atom of the N-protected β-seleno amides on the catalytic reaction. The reaction using compound **3a** was not evaluated in this study because of disappointing results obtained previously in our research; this compound furnished the alkylated product **9** as a racemic mixture.

The respective alkylated products were obtained in only moderate yields and essentially in racemic form when compounds **3c–e** were used as ligands (Table 2, entries 2, 4 and 6), and the catalytic performance of these ligands in the presence of tetrahydrofuran and sodium hydride as a solvent/base system only afforded a small improvement in the yield and enantioselectivity (Table 2, entries 3, 5 and 7). These disappointing results show that the nature of the group attached to the nitrogen atom in the β-seleno amides moiety play an important role in the catalytic activity of these compounds, indicating that the nitrogen atom is directly involved in the transition state.

Based on our previous report concerning the preparation and application of the chiral β-seleno amides,[15a] we turned our attention to the effects of the acyl substitution in this class of ligands for the palladium-catalyzed asymmetric allylic alkylation, as summarized in Table 2.

When the reaction was performed with compound **6a**, the alkylated product (*R*)-**9** was obtained in high yields and 75% ee (Table 2, entry 8). The ligand **6b** furnished the desired product with a slight increase in the enantioselectivity (Table 2, entry 9). These results may indicate that the enantioselectivity induced by this class of ligands is dependent of the bulkiness of the acyl group attached to the nitrogen atom in the β-seleno amides. However, to our surprise, when the reaction was carried out with sterically hindered pivaloyl group attached to the β-seleno amide **6c**, compound **9** was obtained in only moderate yield and in lower ee (Table 2, entry 10). This result shows that a high steric demand around the nitrogen atom hinders the complexation of the ligand with the palladium atom.

The AAA reaction was also performed in the presence of β-seleno amide **6d**, bearing a trifluoromethyl group (Table 2, entries 11 and 12), under standard conditions and also using sodium hydride as base. This ligand fur-

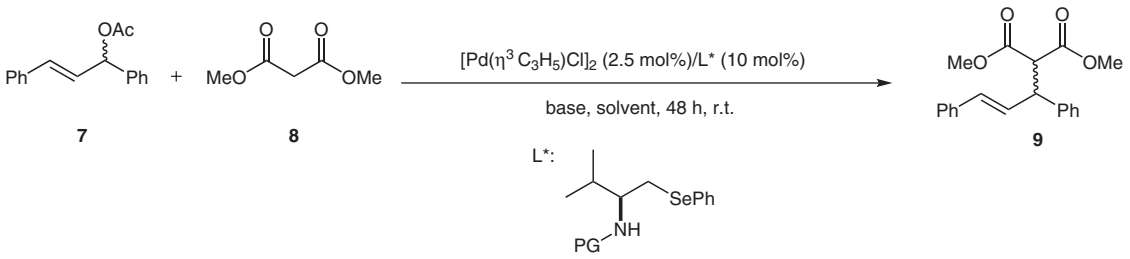


2a 3a 5 6a–g

6a R = Me 93%
6b R = Et 81%
6c R = *t*-Bu 89%
6d R = CF_3 87%
6e R = 4-$O_2NC_6H_4$ 77%
6f R = 2-ClC_6H_4 83%
6g R = 4-MeC_6H_4 91%

Scheme 3

Table 2 N-Protected β-Seleno Amides as Chiral Ligands in the Palladium-Catalyzed Asymmetric Allylic Alkylation (AAA)



Entry	L*	PG	Base[a]	Yield (%)[c]	ee (%)[d,e]
1[f]	**3b**	Bz	AcOK/BSA	98	98
2	**3c**	EtO_2C	AcOK/BSA	45	13
3	**3c**	EtO_2C	NaH[b]	69	21
4	**3d**	Ms	AcOK/BSA	37	*rac*
5	**3d**	Ms	NaH[b]	55	17
6	**3e**	Ts	AcOK/BSA	45	*rac*
7	**3e**	Ts	NaH[b]	67	21
8	**6a**	MeCO	AcOK/BSA	87	75
9	**6b**	EtCO	AcOK/BSA	91	89
10	**6c**	*t*-BuCO	AcOK/BSA	56	61
11	**6d**	CF_3CO	AcOK/BSA	73	43
12	**6d**	CF_3CO	NaH[b]	97	78
13	**6e**	*p*-NO_2PhCO	AcOK/BSA	95	56
14	**6f**	*o*-ClPhCO	AcOK/BSA	94	49
15	**6g**	*p*-MePhCO	AcOK/BSA	98	85

[a] CH_2Cl_2 as solvent.
[b] THF as solvent.
[c] Isolated yield.
[d] Determined by HPLC with a Chiralcel OD column.
[e] Configuration of the product was assigned as *R*.[15]
[f] Data from Braga et al.[15a]

nished good results for both conditions, delivering the corresponding alkylated product in excellent yield (97%) and in up to 78% ee. The effect of different substituents located at aromatic ring in the *N*-benzoyl-β-seleno amides was also evaluated and the results are shown in Table 2. The AAA reaction was initially conducted with ligands bearing electron-withdrawing groups such as **6e** (nitro) and **6f** (chloro). The respective ligands furnished the corresponding alkylated product (*R*)-**9** in high yields (up to 95%) but in lower enantiomeric excess when compared to non-substituted *N*-benzoyl-β-seleno amide **3b** (Table 2, compare entries 13–14 and 1). However, the β-seleno amide **6g**, bearing an electron-donating methyl group, furnished good results for the respective alkylated product when compared to the results obtained with ligands bearing electron-withdrawing groups. These data indicate that the nature of the substituents at the aromatic ring of the *N*-benzoyl-β-seleno amides play an important role in the enantioselection event in the palladium-catalyzed asymmetric allylic alkylation. The configuration of the product **9** was assigned as *R* for all ligands employed.[15]

In summary, we have presented herein a practical, concise and modular synthesis of a wide range of chiral N-protected β-seleno amines through an easy and flexible synthetic route, starting from chiral 2-oxazolidinones. These compounds were easily transformed into the corresponding β-seleno amides by reaction with acyl chlorides. All the new seleno amides with acyl substituents were evaluated as chiral ligands in the palladium-catalyzed asymmetric allylic alkylation and delivered the corresponding alkylated products in good yields and enantiomeric excess. More importantly, with this methodology we could obtain β-se-

leno amines or amides in a modular and flexible way, including the variation of the substituents on the nitrogen atom, nicely complementing the previously published method of preparing of β-seleno amides recently developed by us,[15a] where this flexibility was not present.

Malonate and other reagents were purchased from commercial suppliers. THF was dried and purified by distillation from sodium with benzophenone ketyl indicator. All other solvents were ACS or HPLC grade unless otherwise noted. Air- and moisture-sensitive reactions were conducted in flame-dried or oven-dried glassware equipped with tightly fitting rubber septa and under a positive atmosphere of dry nitrogen or argon. Reagents and solvents were handled using standard syringe techniques. Temperatures higher than room temperature were maintained by use of a mineral oil bath with an electrically heated coil connected to a controller.

^{1}H NMR spectra were obtained at 400 MHz, with peaks referenced to the solvent peak for $CDCl_3$. ^{13}C NMR spectra were obtained at 100 MHz. High-resolution mass spectra were recorded on a double focusing magnetic sector mass spectrometer using EI at 70 eV. HPLC analyses were carried out on Chiralcel OD and OD-H columns. Column chromatography was performed using silica gel (230–400 mesh). Thin-layer chromatography (TLC) was performed using silica gel GF_{254} plates, 0.25 mm thickness. Most reactions were monitored by TLC for disappearance of starting material. For visualization, TLC plates were either placed under UV light, or stained with iodine vapor or acidic vanillin.

Synthesis of *N*-Acyl Oxazolidinone 2; General Procedure

To a cooled solution (–78 °C) of oxazolidinone **1** (3 mmol) in THF (15 mL) was added dropwise *n*-BuLi (1.6 M in hexanes, 0.68 mL, 1.1 mmol). After stirring the lithiated oxazolidinone for 15–20 min, the appropriate acyl chloride (1.1 mmol) was added. The reaction was allowed to stir at –78 °C for 15 min then warmed to r.t. and stirring was continued for 24 min. The mixture was quenched with sat. NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL) and the volatiles were removed. The organic layer was concentrated and the residue was purified by column chromatography to furnish the desired products.

Synthesis of Chiral β-Chalcogeno Amines 3; General Procedure

Under an argon atmosphere, the diphenyldiselenide anion was generated by reaction of the corresponding diselenide (0.6 mmol) with $NaBH_4$ (1.5 mmol) in a mixture of THF (1.5 mL) and EtOH (0.5 mL) and stirred for 30 min. The *N*-acyl oxazolidinone **2** (1 mmol) was added to the mixture and the resulting solution was stirred for 48 h under reflux. The mixture was quenched with sat. NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic fractions were collected, dried over $MgSO_4$, and filtered. The solvent was removed in vacuum, yielding the crude products **3a–g**, which were purified by flash chromatography.

(*S*)-*tert*-Butyl 3-Methyl-1-(phenylselanyl)butan-2-ylcarbamate (3a)

Yield: 81%; $[\alpha]_D^{20}$ +35 (*c* 1, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.53–7.51 (m, 2 H), 7.26–7.22 (m, 3 H), 4.43 (d, *J* = 8.0 Hz, 1 H), 3.68–3.62 (m, 1 H), 3.06 (d, *J* = 3.2 Hz, 2 H), 1.84 (oct, *J* = 6.8 Hz, 1 H), 1.42 (s, 9 H), 0.89 (d, *J* = 6.8 Hz, 3 H), 0.88 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 155.4, 132.8, 130.2, 128.9, 126.9, 79.3, 55.5, 32.3, 31.6, 28.2, 19.3, 17.9.

HRMS: *m*/*z* calcd for $C_{16}H_{25}NO_2SeNa$: 366.0942; found: 366.0947.

(*S*)-*N*-[3-Methyl-1-(phenylselanyl)butan-2-yl]benzamide (3b)

Yield: 65%; $[\alpha]_D^{20}$ +210 (*c* 1.0, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): 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).

^{13}C NMR ($CDCl_3$, 100 MHz): 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.

HRMS: *m*/*z* calcd for $C_{18}H_{21}NOSeNa$: 370.0680; found: 370.0677.

(*S*)-Ethyl 3-Methyl-1-(phenylselanyl)butan-2-ylcarbamate (3c)

Yield: 51%; $[\alpha]_D^{20}$ +27 (*c* 3.5, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.52–7.50 (m, 2 H), 7.25–7.21 (m, 3 H), 4.90 (d, *J* = 8.0 Hz, 1 H), 4.06 (q, *J* = 7.2 Hz, 2 H), 3.75–3.63 (m, 1 H), 3.06 (d, *J* = 4.8 Hz, 2 H), 1.87 (oct, *J* = 6.8 Hz, 1 H), 1.19 (t, *J* = 6.8 Hz, 3 H), 0.91–0.87 (m, 6 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 156.1, 132.6, 130.0, 128.8, 126.7, 60.4, 56.0, 31.8, 31.4, 19.2, 17.6, 14.3.

HRMS: *m*/*z* calcd for $C_{14}H_{21}NO_2SeNa$: 338.0635; found: 338.0629.

(*S*)-*N*-[3-Methyl-1-(phenylselanyl)butan-2-yl]methanesulfonamide (3d)

Yield: 57%; $[\alpha]_D^{20}$ +26 (*c* 3, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.52–7.50 (m, 2 H), 7.63–7.25 (m, 3 H), 5.07 (d, *J* = 8.8 Hz, 1 H), 3.43–3.36 (m, 1 H), 3.08 (d, *J* = 6.4 Hz, 2 H), 2.92 (s, 3 H), 2.00 (oct, *J* = 6.0 Hz, 1 H), 0.93 (d, *J* = 6.8 Hz, 3 H), 0.89 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 132.5, 129.4, 129.1, 127.1, 59.2, 41.5, 31.6, 31.4, 18.7, 17.4.

HRMS: *m*/*z* calcd for $C_{12}H_{19}NO_2SSeNa$: 344.0199; found: 344.0193.

(*S*)-4-Methyl-*N*-[3-methyl-1-(phenylselanyl)butan-2-yl]benzenesulfonamide (3e)

Yield: 37%; $[\alpha]_D^{20}$ –17 (*c* 3, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.65 (d, *J* = 8.0 Hz, 2 H), 7.35–7.33 (m, 2 H), 7.21–7.15 (m, 5 H), 5.24 (d, *J* = 8.8 Hz, 1 H), 3.24–3.18 (m, 1 H), 3.00 (dd, ^1J = 12.6 Hz, ^2J = 4.8 Hz, 1 H), 2.77 (dd, ^1J = 12.6 Hz, ^2J = 7.2 Hz, 1 H), 2.35 (s, 3 H), 1.99 (oct, *J* = 6.8 Hz, 1 H), 0.78 (d, *J* = 6.8 Hz, 3 H), 0.76 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 142.9, 137.6, 132.7, 129.3, 128.9, 127.0, 126.9, 58.4, 31.1, 30.2, 21.3, 18.9, 16.9.

HRMS: *m*/*z* calcd for $C_{18}H_{23}NO_2SSeNa$: 420.0512; found: 420.0506.

(*S*)-*tert*-Butyl 3-Methyl-1-(phenyltellanyl)butan-2-ylcarbamate (3f)

Yield: 67%; $[\alpha]_D^{20}$ +25 (*c* 0.8, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.78–7.74 (m, 2 H), 7.34–7.23 (m, 1 H), 7.22–7.18 (m, 2 H), 4.44 (d, *J* = 8.0 Hz, 1 H), 3.97–3.91 (m, 1 H), 3.15–3.71 (m, 2 H), 1.84 (oct, *J* = 6.8 Hz, 1 H), 1.42 (s, 9 H), 0.89 (d, *J* = 6.8 Hz, 3 H), 0.88 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 155.4, 132.8, 130.2, 128.9, 126.9, 55.5, 32.3, 31.6, 28.2, 19.3, 17.9.

(*S*)-*tert*-Butyl 3-Methyl-1-(phenylthio)butan-2-ylcarbamate (3g)

Yield: 77%; $[\alpha]_D^{20}$ +26 (*c* 3, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.34 (d, *J* = 7.6 Hz, 2 H), 7.26 (t, *J* = 7.8 Hz, 2 H), 7.17 (t, *J* = 7.2 Hz, 1 H), 4.56 (d, *J* = 6.8 Hz, 1 H), 3.70–3.59 (m, 1 H), 3.06 (d, *J* = 4 Hz, 2 H), 1.91 (oct, *J* = 6.4 Hz, 1 H), 1.42 (s, 9 H), 0.92 (d, *J* = 6.8 Hz, 3 H), 0.89 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 155.6, 136.4, 129.7, 128.9, 126.1, 79.1, 55.2, 37.5, 30.8, 28.3, 19.4, 17.8.

HRMS: *m*/*z* calcd for $C_{16}H_{25}NO_2SNa$: 318.1504; found: 318.1498.

Synthesis of Chiral β-Seleno Amine 4

Under an argon atmosphere, the lithium diselenide was generated by reaction of elemental selenium (1.1 mmol) in a mixture of THF (8 mL) and Super-hydride (1.1 mmol). After stirring for 30 min, the *N*-acyl oxazolidinone (**2a**; 1 mmol) was added to the mixture and the resulting solution was stirred for 48 h under reflux. The mixture was quenched with sat. NH_4Cl (10 mL), extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic fractions were collected, dried over $MgSO_4$, and filtered. Purification of the crude product by column chromatography (hexane–EtOAc, 90:10) furnished the desired β-seleno amide **4**.

Yield: 57%.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.80 (d, *J* = 9.2 Hz, 1 H), 3.67–3.60 (m, 1 H), 3.17–3.12 (m, 2 H), 1.97–1.78 (m, 1 H), 1.44 (s, 9 H), 0.92 (t, *J* = 7.6 Hz, 6 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 156.7, 79.1, 56.3, 34.5, 31.2, 28.4, 19.4, 17.7.

HRMS: *m*/*z* calcd for $C_{20}H_{40}N_2O_4Se_2Na$: 555.1216; found: 555.1210.

Synthesis of Chiral β-Seleno Amides 6; General Procedure

Compound **3a** (10 mmol) was treated with TFA (5 mL) in CH_2Cl_2 (30 mL) and stirred for 4 h to remove the Boc group. The organic solvent was evaporated, CH_2Cl_2 (10 mL) was added and evaporated. The residue was used in the next step without any further purification.

The seleno amine **5** (1 mmol) obtained above, was stirred with CH_2Cl_2 (8 mL) and K_2CO_3 (2.4 mmol) under argon atmosphere. The corresponding acyl chloride (1.1 mmol) was added and the solution was stirred at r.t. for 24 h. The mixture was quenched with sat. NH_4Cl (15 mL) and extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic fractions were collected, dried over $MgSO_4$, and evaporated. The crude material was purified by column chromatography to give the desired products **6a**–**g**.

(*S*)-*N*-[3-Methyl-1-(phenylthio)butan-2-yl]acetamide (6a)

Yield: 93%; $[\alpha]_D^{20}$ +8 (*c* 3, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.52–7.50 (m, 2 H), 7.24–7.22 (m, 3 H), 5.65 (d, *J* = 8.4 Hz, 1 H), 4.04–3.97 (m, 1 H), 3.13–3.09 (m, 2 H), 2.21 (s, 3 H), 1.88 (oct, *J* = 6.8 Hz, 1 H), 0.89 (d, *J* = 6.4 Hz, 6 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 173.2, 132.5, 130.1, 129.0, 126.9, 54.0, 31.6, 31.3, 29.5, 19.2, 18.2.

HRMS: *m*/*z* calcd for $C_{13}H_{19}NOSeNa$: 308.0530; found: 308.0524.

(*S*)-*N*-[3-Methyl-1-(phenylthio)butan-2-yl]propionamide (6b)

Yield: 81%; $[\alpha]_D^{20}$ +5 (*c* 3, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.52–7.50 (m, 2 H), 7.24–7.22 (m, 3 H), 5.65 (d, *J* = 8.4 Hz, 1 H), 4.04–3.97 (m, 1 H), 3.13–3.09 (m, 2 H), 2.13–2.02 (m, 2 H), 1.88 (oct, *J* = 6.8 Hz, 1 H), 1.07 (t, *J* = 7.6 Hz, 3 H), 0.89 (d, *J* = 6.4 Hz, 6 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 173.2, 132.5, 130.1, 129.0, 126.9, 54.0, 31.6, 31.3, 29.5, 19.2, 18.2, 9.2.

HRMS: *m*/*z* calcd for $C_{14}H_{21}NOSeNa$: 322.0686; found: 322.0680.

(*S*)-*N*-[3-Methyl-1-(phenylthio)butan-2-yl]pivalamide (6c)

Yield: 89%; $[\alpha]_D^{20}$ +21 (*c* 3, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.51–7.49 (m, 2 H), 7.26–7.20 (m, 3 H), 5.73 (d, *J* = 8.4 Hz, 1 H), 4.03–3.96 (m, 1 H), 3.18 (dd, ^1J = 12.4 Hz, ^2J = 6.0 Hz, 1 H), 3.09 (dd, ^1J = 12.4 Hz, ^2J = 4.8 Hz, 1 H), 1.89 (oct, *J* = 7.2 Hz, 1 H), 1.12 (s, 9 H), 0.90 (d, *J* = 6.8 Hz, 3 H), 0.89 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 177.6, 132.4, 130.1, 129.0, 126.8, 53.5, 38.6, 31.8, 31.4, 27.3, 19.3, 18.2.

HRMS: *m*/*z* calcd for $C_{16}H_{25}NOSeNa$: 350.0999; found: 350.0993.

(*S*)-2,2,2-Trifluoro-*N*-[3-methyl-1-(phenylthio)butan-2-yl]acetamide (6d)

Yield: 87%; $[\alpha]_D^{20}$ +4 (*c* 3, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.53–7.51 (m, 2 H), 7.27–7.25 (m, 3 H), 6.49 (d, *J* = 7.6 Hz, 1 H), 4.01–3.94 (m, 1 H), 3.11–3.05 (m, 2 H), 1.94 (oct, *J* = 6.4 Hz, 1 H), 0.90 (d, *J* = 6.8 Hz, 3 H), 0.90 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 156.9 (q, *J* = 146.8 Hz), 133.2, 132.8, 129.2, 127.6, 115.7 (q, *J* = 1146.0 Hz), 55.4, 31.5, 30.7, 19.0, 18.0.

HRMS: *m*/*z* calcd for $C_{13}H_{16}F_3NOSeNa$: 362.0247; found: 362.0241.

(*S*)-*N*-[3-Methyl-1-(phenylthio)butan-2-yl]-4-nitrobenzamide (6e)

Yield: 77%; $[\alpha]_D^{20}$ +69 (*c* 3, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.16 (d, *J* = 8.8 Hz, 2 H), 7.67 (d, *J* = 8.8 Hz, 2 H), 7.52–7.50 (m, 2 H), 7.21–7.20 (m, 3 H), 6.34 (d, *J* = 8.8 Hz, 1 H), 4.25–4.18 (m, 1 H), 3.27 (dd, ^1J = 13.0 Hz, ^2J = 4.4 Hz, 1 H), 3.22 (dd, ^1J = 13.0 Hz, ^2J = 6.4 Hz, 1 H), 2.03 (oct, *J* = 6.4 Hz, 1 H), 0.98 (d, *J* = 6.8 Hz, 3 H), 0.97 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.1, 149.2, 140.0, 132.6, 129.2, 127.9, 127.2, 123.5, 55.4, 31.7, 31.3, 19.2, 18.6.

HRMS: *m*/*z* calcd for $C_{18}H_{20}N_2O_3SeNa$: 415.0537; found: 415.0531.

(*S*)-2-Chloro-*N*-[3-methyl-1-(phenylthio)butan-2-yl]benzamide (6f)

Yield: 77%; $[\alpha]_D^{20}$ +58 (*c* 3, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.54–7.49 (m, 3 H), 7.37–7.20 (m, 6 H), 6.26 (d, *J* = 8.8 Hz, 1 H), 4.26–4.20 (m, 1 H), 3.24–3.15 (m, 2 H), 2.01 (oct, *J* = 6.8 Hz, 1 H), 0.98 (d, *J* = 6.8 Hz, 3 H), 0.97 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 166.1, 135.1, 132.9, 131.8, 131.0, 130.0, 130.0, 129.1, 127.0, 126.9, 55.0, 31.7, 31.4, 19.4, 18.2.

HRMS: *m*/*z* calcd for $C_{18}H_{20}ClNOSeNa$: 404.0296; found: 404.0296.

(*S*)-4-Methyl-*N*-[3-methyl-1-(phenylthio)butan-2-yl]benzamide (6g)

Yield: 77%; $[\alpha]_D^{20}$ +73 (*c* 3, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.52–7.50 (m, 4 H), 7.24–7.14 (m, 5 H), 6.22 (d, *J* = 8.8 Hz, 1 H), 4.25–4.18 (m, 1 H), 3.26–3.17 (m, 2 H), 2.36 (s, 3 H), 2.00 (oct, *J* = 6.8 Hz, 1 H), 0.95 (d, *J* = 6.6 Hz, 3 H), 0.94 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 167.0, 141.6, 132.7, 131.6, 130.0, 129.0, 126.9, 126.7, 54.6, 31.8, 31.6, 21.3, 19.3, 18.5.

HRMS: *m*/*z* calcd for $C_{19}H_{23}NOSeNa$: 384.0843; found: 384.0837.

Palladium-Catalyzed Asymmetric Allylic Alkylation; General Procedure

Under an argon atmosphere, a solution of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol%) and chiral ligand (10 mol%) in CH_2Cl_2 (2 mL) was stirred at r.t. for 30 min. Subsequently, a solution of *rac*-1,3-diphenyl-2-propenyl acetate (**7**; 0.5 mmol), dimethyl malonate (**8**; 1.5 mmol), *N*,*O*-bis(trimethylsilylacetamide) (BSA; 1.5 mmol), and AcOK (cat.) were added. The resulting solution was stirred for 24 h then the mixture was quenched with sat. NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3×15 mL) and the combined organic fractions were collected, dried over $MgSO_4$, and filtered. The solvent was removed under vacuum to give the alkylated product **9**, which was purified by flash chromatography (hexane–EtOAc, 98:2).

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References

(1) (a) Nicolaou, K. C.; Petasis, N. A. In *Selenium in Natural Products Synthesis*; CIS, Inc.: Pennsylvania, **1984**, and references therein. (b) Klayman, D. L.; Günter, W. H. H. In *Organoselenium Compounds: Their Chemistry and Biology*; Wiley-Interscience: New York, **1973**. (c) Mugesh, G.; du Mont, W.-W.; Sies, H. *Chem. Rev.* **2001**, *101*, 2125. (d) Nogueira, C. W.; Zeni, G.; Rocha, J. B. T. *Chem. Rev.* **2004**, *104*, 6255.

(2) (a) Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon: Oxford, U.K., **1986**. (b) Krief, A.; Hevesi, L. *Organoselenium Chemistry I*; Springer: Berlin, **1988**. (c) Comasseto, J. V.; Ling, L. W.; Petragnani, N.; Stefani, H. A. *Synthesis* **1997**, 373. (d) Braga, A. L.; Reckziegel, A.; Silveira, C. C.; Comasseto, J. V. *Synth. Commun.* **1994**, *24*, 1165. (e) *Organoselenium Chemistry: A Practical Approach*; Back, T. G., Ed.; Oxford University Press: U.K., **1999**.

(3) (a) Kumar, Y.; Green, R.; Borysko, K. Z.; Wise, D. S.; Wotring, L. L.; Townsend, L. B. *J. Med. Chem.* **1993**, *36*, 3843. (b) Soriano-Garcia, M. *Curr. Med. Chem.* **2004**, *11*, 1657. (c) de Silva, V.; Woznichak, M. M.; Burns, K. L.; Grant, K. B.; May, S. W. *J. Am. Chem. Soc.* **2004**, *126*, 2409.

(4) (a) Wirth, T. *Tetrahedron* **1999**, *55*, 1. (b) Wirth, T. *Angew. Chem. Int. Ed.* **2000**, *39*, 3740. (c) *Topics in Current Chemistry: Organoselenium Chemistry, Modern Developments in Organic Synthesis*; Wirth, T., Ed.; Springer: Berlin, **2000**.

(5) (a) Gabriele, B.; Plastina, P.; Salerno, G.; Mancuso, R.; Costa, M. *Org. Lett.* **2007**, *9*, 3319. (b) Ella-Menye, J.-R.; Wang, G. *Tetrahedron* **2007**, *63*, 10034.

(6) (a) Matsunaga, H.; Ishizuka, T.; Kunieda, T. *Tetrahedron* **2005**, *61*, 8073. (b) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835.

(7) (a) Mukhtar, T. A.; Wright, G. D. *Chem. Rev.* **2005**, *105*, 529. (b) Barbachyn, M. R.; Ford, C. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 2010. (c) Hutchinson, D. K. *Curr. Top. Med. Chem.* **2003**, *3*, 1021.

(8) (a) Hishibashi, H.; Uegaki, M.; Sakai, M. *Synlett* **1997**, 915. (b) Hishibashi, H.; Uegaki, M.; Sakai, M.; Takeda, Y. *Tetrahedron* **2001**, *57*, 2115. (c) Kreisberg, J. D.; Magnus, P.; Shinde, S. *Tetrahedron Lett.* **2002**, *43*, 7393. (d) Poindexter, G. S.; Owens, D. A.; Dolan, P. L.; Woo, E. J. *J. Org. Chem.* **1992**, *57*, 6357.

(9) For reviews, see: (a) Braga, A. L.; Lüdtke, D. S.; Vargas, F.; Braga, R. C. *Synlett* **2006**, 145. (b) Braga, A. L.; Lüdtke, D. S.; Vargas, F. *Curr. Org. Chem.* **2006**, *10*, 1921.

(10) (a) Wirth, T. *Tetrahedron Lett.* **1995**, *36*, 7849. (b) Santi, C.; Wirth, T. *Tetrahedron: Asymmetry* **1999**, *10*, 1019. (c) Braga, A. L.; Rodrigues, O. E. D.; Paixão, M. W.; Appelt, H. R.; Silveira, C. C.; Bottega, D. P. *Synthesis* **2002**, 2338. (d) Braga, A. L.; Paixão, M. W.; Lüdtke, D. S.; Silveira, C. C.; Rodrigues, O. E. D. *Org. Lett.* **2003**, *5*, 2635.

(11) (a) Braga, A. L.; Silva, S. J. N.; Lüdtke, D. S.; Drekener, R. L.; Silveira, C. C.; Rocha, J. B. T.; Wessjohann, L. A. *Tetrahedron Lett.* **2002**, *43*, 7329. (b) Shi, M.; Wang, C.-J.; Zhang, W. *Chem. Eur. J.* **2004**, *10*, 5507.

(12) (a) Sprinz, J.; Kiefer, M.; Helmchen, G.; Reggelin, M.; Huttner, G.; Walter, O.; Zsolnai, L. *Tetrahedron Lett.* **1994**, *35*, 1523. (b) Hiroi, K.; Suzuki, Y.; Abe, I. *Tetrahedron: Asymmetry* **1999**, *10*, 1173. (c) You, S.-L.; Hou, X.-L.; Dai, L.-X. *Tetrahedron: Asymmetry* **2000**, *11*, 1495. (d) Hou, X.-L.; Wu, X.-W.; Dai, L.-X.; Cao, B.-X.; Sun, J. *Chem. Commun.* **2000**, 1195. (e) Braga, A. L.; Paixão, M. W.; Marin, G. *Synlett* **2005**, 1675. (f) Braga, A. L.; Lüdtke, D. S.; Sehnem, J. A.; Alberto, E. E. *Tetrahedron* **2005**, *61*, 11664. (g) Braga, A. L.; Lüdtke, D. S.; Alberto, E. E. *J. Braz. Chem. Soc.* **2006**, *17*, 11. (h) Blajet, M. Z.; Siedlecka, R.; Skarzewski, J. *Tetrahedron: Asymmetry* **2007**, *18*, 131.

(13) (a) Tsuji, J. *Palladium Reagents and Catalysis, Innovations in Organic Synthesis*; Wiley: New York, **1995**. (b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (c) Trost, B. M.; Lee, C. *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, **2000**, 2nd ed.; Chap. 8E, 503.

(14) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.

(15) (a) Braga, A. L.; Vargas, F.; Sehnem, J. A.; Braga, R. C. *J. Org. Chem.* **2005**, *70*, 9021. (b) Braga, A. L.; Vargas, F.; Sehnem, J. A.; Wessjohann, L. A. *Eur. J. Org. Chem.* **2006**, 4993.

(16) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaughary, K. *J. Org. Chem.* **2001**, *66*, 894.

(17) Gladysz, J. A.; Hornby, J. L.; Garbe, J. E. *J. Org. Chem.* **1978**, *43*, 1204.