ω-Transaminases as efficient biocatalysts to obtain novel chiral selenium-amine ligands for Pd-catalysis†‡

Leandro H. Andrade,*[a] Alexandre V. Silva,[a] Priscila Milani,[a] Dominik Koszelewski[b] and Wolfgang Kroutil[b]

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ω-Transaminases have been evaluated as biocatalysts in the reductive amination of organoselenium acetophenones to the corresponding amines, and in the kinetic resolution of racemic organoselenium amines. Kinetic resolution proved to be more efficient than the asymmetric reductive amination. By using these methodologies we were able to obtain both amine enantiomers in high enantiomeric excess (up to 99%). Derivatives of the obtained optically pure *o*-selenium 1-phenylethyl amine were evaluated as ligands in the palladium-catalyzed asymmetric alkylation, giving the alkylated product in up to 99% *ee*.

Introduction

Since the discovery of organoselenium compounds by Löwig in 1836,[1] these compounds have been largely used as synthetic intermediates for the formation of several chemical species. Among of them, we can mention the preparation of ketones through a seleno-Pummerer reaction,[2a] carbon–carbon double bonds from *syn* selenoxide elimination[2b] and the formation of heterocycles through the seleniranium ion.[2c] Besides these applications, it is worth remarking that these compounds possess biological activities, such as anti-inflammatory and antioxidant.[3a,b] More recently, chiral organoselenium compounds have been widely used in asymmetric synthesis.[4] Several chiral selenides and diselenides have been applied as chiral ligands in asymmetric hydrosilylation of ketones and imines,[5a–c] enantioselective addition of diorganozinc reagents to aldehydes,[5d,e] enantioselective conjugate addition of organometallic reagents to enones,[5c] and palladium-catalyzed asymmetric allylic alkylation.[4c,5f–i] Regarding these applications, some synthetic tools have been developed to synthesize organoselenium compounds in enantiomerically pure form. Among them, we can mention the use of chiral precursors,[6] selenocyclization,[4a] and more recently, enantioselective synthesis mediated by enzymes.[7] Organoselenium amine is one of the subclasses of selenium compounds that we have directed our efforts to obtain in their optically active form using enzymes. By using enzymatic kinetic resolution and chemoenzymatic dynamic kinetic resolution of organoselenium amines with lipases, we have prepared organoselenium amides in excellent enantiomeric excess (up to 99%).[8] However, at this moment, as we required the free amino group for further synthetic transformation, these protocols were not suitable, because they afforded the amide group, which was not easily removed by standard hydrolysis conditions. A literature survey revealed that chiral unprotected amines can be obtained through transamination reactions catalyzed by transaminases.[9] Inspired by these reactions, we describe in this paper the stereoselective amination of organoselenium acetophenones and kinetic resolution of the racemic organoselenium amines catalyzed by transaminases to yield the corresponding chiral organoselenium amines in enantiomerically pure form. In addition, we applied both methodologies to prepare novel chiral organoselenium ligands, which were evaluated in the palladium-catalysed asymmetric substitution of 1,3-diphenyl-2-propenyl acetate with dialkyl malonates.

Results and discussion

The synthesis of organoselenium acetophenones **2a–d** and the racemic organoselenium-1-phenylethanamines **3a–d** were carried out according to Scheme 1.

The *in situ* preparation of the diazonium salt from 1-(4-aminophenyl)ethanone followed by addition of KSeCN afforded the selenocyanate acetophenone **1** (64% yield). Then, the alkylation of the selenium atom was carried out with $NaBH_4$ and an appropriate alkyl halide to give the organoselenium acetophenones **2a–d** (up to 75% yield). The reductive amination of ketones **2a–d** gave racemic amines **3a–d** in up to 73% yield. In order to facilitate the enantiomeric separation by chiral HPLC analysis, the amines **3a–d** were transformed to the corresponding amides **4a–d** by reaction with acetic anhydride.

The stereoselective amination of organoselenium acetophenones **2a–d** with ω-transaminases (ATA-117, ATA-113, ATA-114 and ATA-103) and alanine as amino donor was carried out under different reaction conditions. In order to shift the equilibrium to the product side, the co-product pyruvate was reduced by lactate dehydrogenase (LDH) in the presence of NADH-recycling using the glucose dehydrogenase/glucose system (Table 1).

As we can see in Table 1, we evaluated different ω-transaminases, different amounts of biocatalyst (6, 10 or 15 mg) and the influence of DMSO as a co-solvent (Table 1). Excellent enantioselectivities were observed when biocatalysts ATA-117 and ATA-113 were used

[a]*Institute of Chemistry, University of São Paulo, Av. Prof. Lineu Prestes, 748, CEP 05508-900, São Paulo, SP, Brazil. E-mail: leandroh@iq.usp.br; Fax: +55-11-3815-5579; Tel: +55-11-3091-2287*
[b]*Research Centre Applied Biocatalysis, Department of Chemistry, Organic and Bioorganic Chemistry, University of Graz, Graz, Austria*

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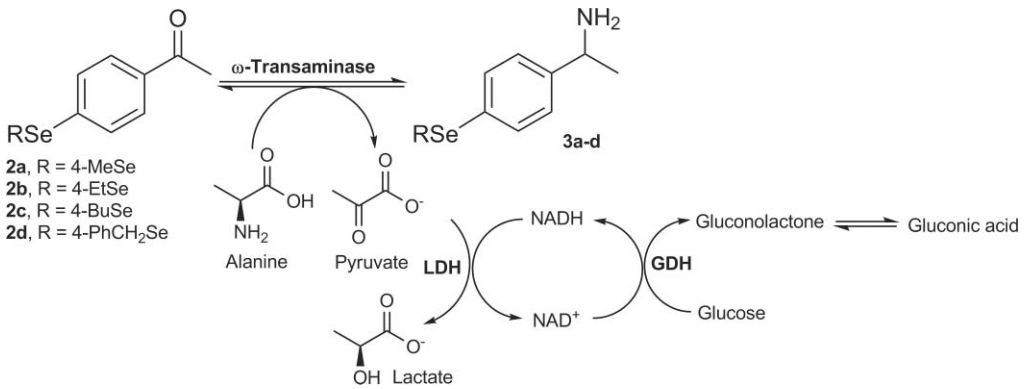
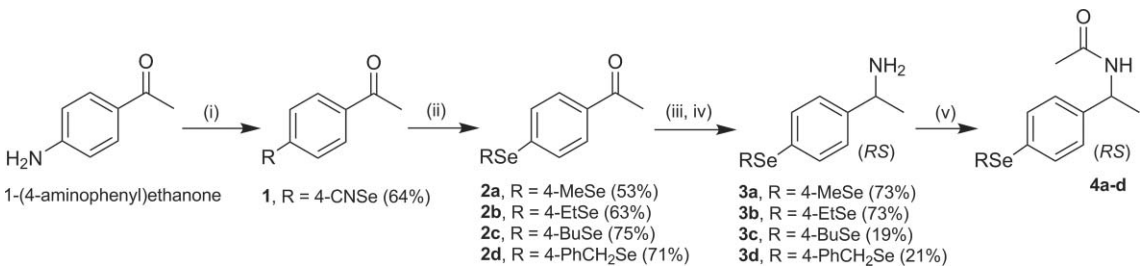
‡ Electronic supplementary information (ESI) available: Characterization data (^1H and ^{13}C NMR, IR and mass spectrometry) for all compounds and enantiomeric separation for chiral amides by chiral HPLC. See DOI: 10.1039/b920946h

Table 1 Stereoselective amination of organoselenium acetophenones **2a–d**[a]



Entry	ketone	ATA	Amount/mg	DMSO (% v/v)	Conv. (%)[b]	ee_{amine} (%)[c]
1	**2a**	117	6	—	5	nd
2	**2b**	117	6	—	4	nd
3	**2c**	117	6	—	<1	nd
4	**2d**	117	6	—	<1	nd
6	**2a**	117	10	10	17	>99 (*R*)
7	**2b**	117	10	10	27	48 (*R*)
8	**2a**	113	6	—	30	81 (*S*)
9	**2b**	113	6	—	14	nd
10	**2c**	113	6	—	2	nd
11	**2d**	113	6	—	<1	nd
13	**2a**	113	10	10	13	nd
14	**2b**	113	10	10	13	nd
15	**2a**	113	15	10	13	nd
16	**2b**	113	15	10	23	>99 (*S*)
17	**2a**	114	6	—	8	nd
18	**2b**	114	6	—	8	nd
19	**2c**	114	6	—	<1	nd
20	**2d**	114	6	—	<1	nd
22	**2a**	114	10	10	1	nd
23	**2b**	114	10	10	1	nd
24	**2a**	103	6	—	14	nd
25	**2b**	103	6	—	12	nd
26	**2c**	103	6	—	2	nd
27	**2d**	103	6	—	<1	nd
29	**2a**	103	10	10	3	nd
30	**2b**	103	10	10	9	nd

[a] Reaction conditions: Pi-buffer pH 7, pyridoxal-5′-phosphate (1 mM), ω-transaminase, L- or D-alanine (250 mM) (D-ala in the case of ATA-117, otherwise L-ala), pyruvate reductase mix, ketone **2a–d** (50 mM), 30 °C, 24 h. [b] Determined by GC. [c] Determined by chiral HPLC analysis after derivatization with acetic anhydride. nd = not determined due to low conversion.

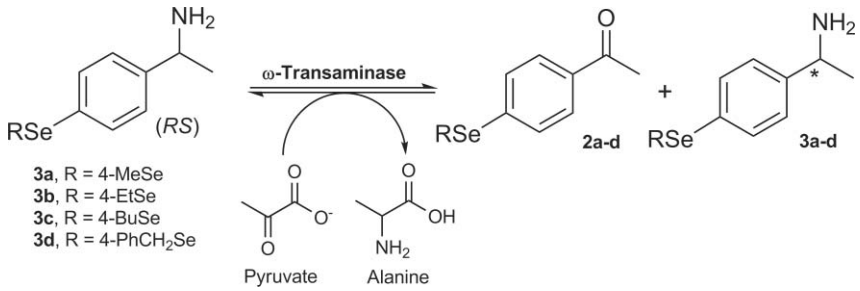


Scheme 1 Reagents and conditions: (i) $NaNO_2$, HCl 2 M, pH 4.3, 0 °C, then KSeCN, 1 h; (ii) RBr, $NaBH_4$, MeOH, 0 °C, 2 h; (iii) $Ti(OCH(CH_3)_2)_4$, NH_3/EtOH (2 M), 12 h; (iv) $NaBH_4$, 12 h, r.t.; (v) acetic anhydride, Et_3N, CH_2Cl_2.

with substrates **2a** and **2b**. For example, by using ATA-117 (10 mg) and 10% of DMSO as co-solvent, the amine (*R*)-**3b** was obtained with >99% *ee* and 17% conversion. Employing the same reaction conditions, the reductive amination of ketone **2a** afforded amine (*R*)-**3a** with 48% *ee* and 27% conversion.

On the other hand, by using ATA-113 as biocatalyst, we observed the formation of the opposite enantiomer. The reductive amination of ketone **2b** by ATA-113 (6 mg) with no co-solvent gave the amine (*S*)-**3b** with 30% conversion (81% *ee*). Using the same enzyme (15 mg) and 10% of DMSO as co-solvent,

Table 2 Kinetic resolution of racemic amines (**3**)[a]



Entry	Substrate	ATA	Conv. (%)[b]	ee_{amine} (%)[c]	E[d]
1	**3a**	117	49	98 (*S*)	>200
2	**3b**	117	47	98 (*S*)	>200
3	**3c**	117	47	91 (*S*)	>200
4	**3d**	117	35	nd	—
6	**3a**	113	53	>99 (*R*)	>200
7	**3b**	113	54	93 (*R*)	30
8	**3c**	113	48	77 (*R*)	26
9	**3d**	113	56	76 (*R*)	9

[a] Reaction conditions: Pi buffer pH 7, pyridoxal-5′-phosphate (1 mM), ω-transaminase, sodium pyruvate (50 mM), amines **3a–d** (50 mM), 30 °C, 24 h. [b] Determined by GC. [c] Determined by chiral HPLC analysis after derivatization with acetic anhydride. [d] $E = \ln[1 - c(1 + ee\ \mathbf{P})]/\ln[1 - c(1 - ee\ \mathbf{P})]$, c = conversion, **P** = product. nd = not determined due to low conversion.

the amine (*S*)-**3a** (>99% *ee*) was obtained with 23% conversion. Organoselenium acetophenones **2c–d** did not react satisfactorily under these conditions. From these results, we deduced that the size of the carbon chain attached to the selenium atom plays an important role in the reaction. As the size of the carbon chain increased, no reaction was observed.

DMSO as a co-solvent improved, in some cases, the rate of the reaction (Table 1, *e.g.* entry 6 and 8). We also observed that the amount of the biocatalyst influenced the conversion of the reaction (Table 1, *e.g.* entry 14 and 16); thus, the more catalyst, the higher the conversion.

Alternatively to the reductive amination of organoselenium acetophenones, we studied the kinetic resolution of the racemic 1-(organoseleno-phenyl)ethanamines **3a–d**, catalyzed by ω-transaminases and sodium pyruvate, to achieve the optically pure amines **3** (Table 2). In this reaction, the amines **3a–d** act as the amino donor, and pyruvate as the amine acceptor is transformed to alanine. Thus, ω-transaminases can convert one enantiomer from amine to the corresponding ketone, leaving the other enantiomer intact. The substrates **3a–d** were treated with ω-transaminases ATA-113 and 117 and pyruvate in aqueous solution (Table 2).

As expected, the ω-transaminases ATA-117 and ATA-113 showed opposite enantiopreference (Table 2). Thus, by changing the biocatalyst we can obtain both enantiomers (*R*)- or (*S*)-**3a–c** with high conversion and *ee* values (Table 2, entries 1–3 and 6–8). In several cases the enantioselectivity (*E*-value) was higher than 200. For example, the kinetic resolution (KR) of the substrate **3d** by ATA-113 afforded (*R*)-**3d** with 76% *ee* and 56% conversion (Table 2, entry 9). ATA-117 showed, for all cases, that the substrate was transformed with perfect enantioselectivity, while ATA-113 showed varied enantioselectivity depending on the substrate.

Recently, it was reported by Braga *et al.* that organoselenium amides can complex to palladium ligands, affording chiral chelates that exhibited efficient potential as catalysts for asymmetric allylic alkylation.[10] Besides, it has been described that selenium-containing imines[11] and tertiary amines[11a,12] can also be used as ligands in palladium-catalyzed reactions.

Inspired by the selenium and nitrogen ability to form palladium chelates, we envisioned novel Se–N derivatives, such as amines, imines and amides, which can be prepared from 1-(2-organoseleno-phenyl)ethanamines **I** (Fig. 1). Each compound can chelate to palladium, affording six-membered ring chelates, which can exhibit interesting catalytic potential. Of special interest are the organoselenium amines **I** since they are modulable at the N and Se atoms.

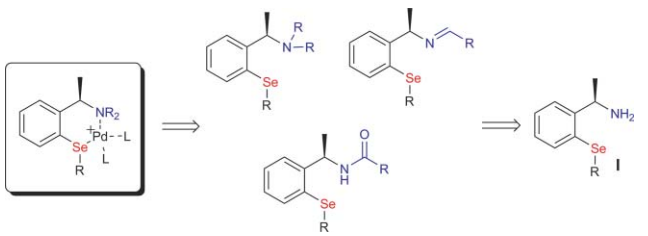
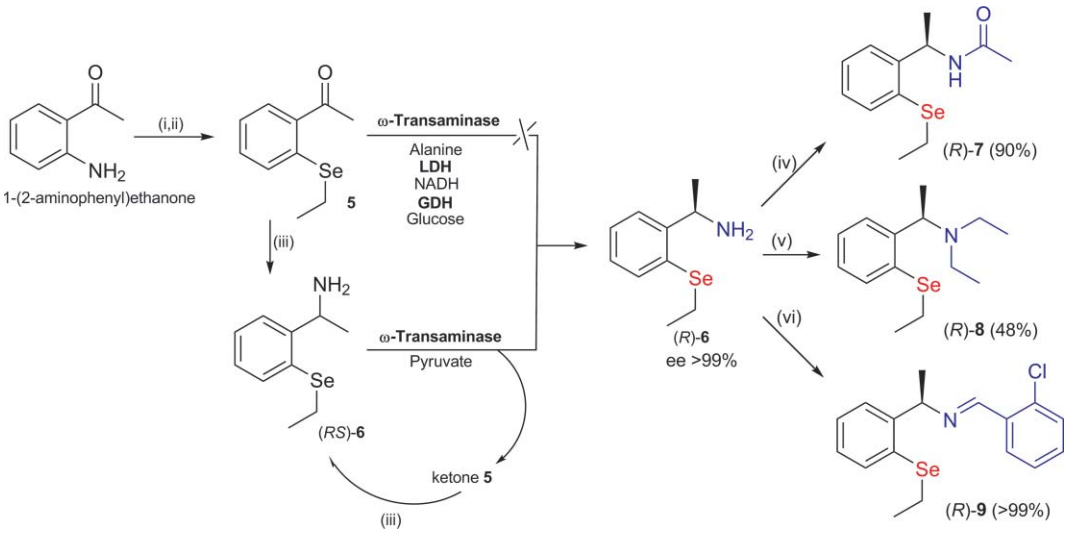


Fig. 1 Design of new chiral selenium ligands from a single chiral precursor.

In order to evaluate our catalytic system, we decided to synthesize the organoselenium amine **6** using the same chemoenzymatic protocol employed for compounds **2a–d** and **3a–d** (Scheme 2).

Initially, we tried to prepare the chiral organoselenium amine **6** by reductive amination of the ketone **5** using ω-transaminases 117, 113, 114 and 103 and alanine as amino donor. However, this methodology was not efficient to produce the desired selenium amine **6** (conversion lower than 5%).

Alternatively, ω-transaminases 117, 113, 114 and 103 were used in the KR of amine (*RS*)-**3e** (Scheme 2). Fortunately, the



Scheme 2 Reagents and conditions: (i) $NaNO_2$, HCl 2 M, pH 4.3, 0 °C, then KSeCN, 1 h; (ii) RBr, $NaBH_4$, MeOH, 0 °C, 2 h; (iii) a. $Ti(OCH(CH_3)_2)_4$, NH_3/EtOH (2 M), 12 h; b. $NaBH_4$, 12 h, r.t.; (iv) DMAP, Et_3N, acetyl chloride, CH_2Cl_2; (v) K_2CO_3, C_2H_5Br, CH_2Cl_2; (vi) 2-Cl-benzaldehyde, $MgSO_4$, CH_2Cl_2.

KR with ω-transaminase 113 furnished excellent results and the organoselenium amide **3e** was obtained in enantiomerically pure form (>99% *ee* and 50% conversion). The ω-transaminases 117, 114 and 103 were not efficient (conversion lower than 5%, data not shown).

After finding the appropriate ω-transaminase, the KR was repeated at 120 mg scale to obtain the optically active amine in a larger quantity. The organoselenium amine (*R*)-**6** was transformed into amide (*R*)-**7**, substituted amine (*R*)-**8** and imine (*R*)-**9** in good yields as shown in Scheme 2.

After the synthesis of the organoselenium compounds (*R*)-**7**–**9**, we turned our attention to the investigation of their potential as chiral ligands in the palladium-catalyzed asymmetric allylic alkylation. The substitution reaction of 1,3-diphenyl-2-propenyl acetate **10** with different nucleophiles derived from malonate was the model reaction employed to evaluate the chiral selenium compounds as new ligands, Table 3.

As we can see in Table 3, we initiated our investigation by using all of the organoselenium ligands **7**–**9**, *N*,*O*-bis(trimethylsilyl)acetamide (BisSi)/KOAc as base and CH_2Cl_2 as solvent at 0 °C (Table 3, entries 1–3). The best result with respect to yield was obtained with organoselenium amide **7** as ligand, in which the nucleophile was transferred to the allyl system with high yield and stereoselectivity (Table 3, entry 1). When organoselenium amine **8** was used as ligand, no product was observed. However, the organoselenium imine **9** furnished the substitution product **12** with 87% yield and high enantioselectivity, 82% *ee* (Table 3, entry 3).

After the evaluation of the ligands, we investigated different reaction conditions and nucleophiles (Table 3, entries 4–9). For example, if the reaction was performed at room temperature using ligand **7** and base BisSi/KOAc, the substitution product was obtained in good yield (89%) but with low enantioselectivity (79%). On the other hand, performing the reaction at –20 °C, no product was observed (Table 3, entry 5). By using the ligand organoselenium amide **7** (10 mol %), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (5 mol %), NaH as base and THF as solvent, the substitution product **12** was obtained in a reasonable yield (66%), but in racemic form (Table 3, entry 6).

In addition, we turned our attention to investigating different nucleophiles derived from malonate **11** and the ligand **7**. The substitution products **12** were obtained with different levels of enantioselectivity but in low yield. The best result was obtained with diethyl phenyl malonate, which furnished >99% of enantiomeric excess (Table 3, entry 9).

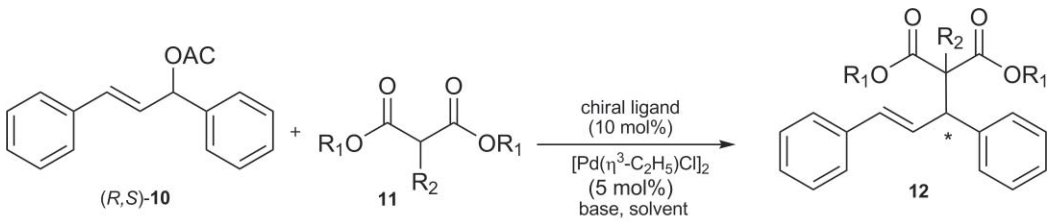
It is worth mentioning that the absolute configuration of all alkylated products was enantiocomplementary to those products reported by Braga *et al.*, including the results related to diethyl ethyl malonate and diethyl phenyl malonate (Table 3, entries 8 and 9).[10]

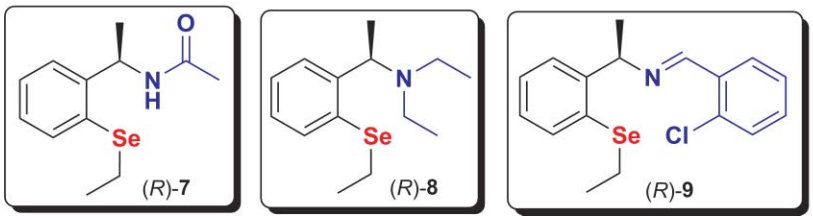
In summary, we have demonstrated that optically pure organoselenium-1-phenylethanamines can be obtained by reductive amination of organoselenium ketones and kinetic resolution of organoselenium amines using ω-transaminases as biocatalysts. Kinetic resolution showed to be more efficient than the asymmetric reductive amination. We have applied both methodologies to prepare novel chiral organoselenium ligands which were evaluated in the palladium-catalysed asymmetric substitution of 1,3-diphenyl-2-propenyl acetate with dialkyl malonates. The substitution products were obtained in high yield (up to 94%) and enantiomeric excess (up to >99%), which revealed that the organoselenium amide and organoselenium imine prepared from chiral 1-(2-(ethylselanyl)phenyl)ethanamine have promising potential as chiral ligands.

Experimental section

Unless otherwise noted, commercially available materials were used without further purification. ω-Transaminases were commercially available from Codexis, Redwood, USA. All solvents were HPLC or ACS grade. Solvents used for moisture sensitive operations were distilled from drying reagents under a nitrogen atmosphere: THF was distilled from Na/benzophenone, CH_2Cl_2 was distilled from $MgSO_4$.

Table 3 Evaluation of novel chiral organoselenium compounds **7–9** as ligands in the palladium-catalyzed asymmetric allylic alkylation[a]





Entry	Ligand	Base	Solvent	R_1	R_2	Temp./°C	Yield (%)[b]	*ee* (%)[c]
1	**7**	BisSi/KOAc	CH_2Cl_2	Me	H	0	94	89 (*S*)
2	**8**	BisSi/KOAc	CH_2Cl_2	Me	H	0	—	—
3	**9**	BisSi/KOAc	CH_2Cl_2	Me	H	0	87	82 (*S*)
4	**7**	BisSi/KOAc	CH_2Cl_2	Me	H	r.t.	89	79 (*S*)
5	**7**	BisSi/KOAc	CH_2Cl_2	Me	H	–20	—	—
6	**7**	NaH	THF	Me	H	r.t.	66	rac.
7	**7**	BisSi/KOAc	CH_2Cl_2	Me	Me	0	6	rac.
8	**7**	BisSi/KOAc	CH_2Cl_2	Et	Et	0	11	88 (nd)
9	**7**	BisSi/KOAc	CH_2Cl_2	Et	Ph	0	18	>99 (nd)

[a] Reaction conditions: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (5 mol%), chiral ligand **7–9** (10 mol%), (*E*)-1,3-diphenylallyl acetate (0.25 mmol), appropriate malonate (dimethyl malonate, diethyl ethyl malonate or diethyl phenyl malonate, 0.5 mmol), BisSi (*N*,*O*-bis(trimethylsilylacetamide, 0.75 mmol), potassium acetate (1 mol%). [b] Isolated yield. [c] Determined by chiral HPLC analysis. nd = not determined.

Analytical thin-layer chromatography (TLC) was performed by using aluminium-backed silica plates coated with a 0.25 mm thickness of silica gel 60 F_{254} (Merck), visualized with an ultraviolet light (λ = 254 nm), followed by exposure to *p*-anisaldehyde solution, potassium permanganate solution, or vanillin solution and heating.

Standard chromatographic purification procedures were followed using 35–70 mm (240–400 mesh) silica gel purchased from Acros Organics®.

Nuclear magnetic resonance (NMR) spectra were recorded on a *Bruker DPX* spectrometer at operating frequencies of 200, 300 or 500 MHz (^{1}H NMR) and 50, 75 or 125 MHz (^{13}C NMR). The ^{1}H NMR chemical shifts are reported in *ppm* relative to TMS peak. Data are reported as follows: chemical shift (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sext = sextuplet, m = multiplet, br = broadened signal), and coupling constant (*J*) in Hertz and integrated intensity. The ^{13}C NMR chemical shifts are reported in *ppm* relative to $CDCl_3$.

Infrared spectra were recorded from KBr discs or from a thin film between NaCl plates on a Bomem Michelson model 101 FTIR spectrometer with internal referencing. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}).

Low-resolution mass spectra were obtained on a GC-MS Shimadzu spectrometer, operating at 70 eV. High-resolution mass spectra (HRMS) were acquired using a Bruker Daltonics MicroTOF instrument, operating electrospray ionization (ESI) mode.

Optical rotations were measured on a Perkin Elmer-343 digital polarimeter in a 1 mL cuvette with a 1 dm pathlength. All values are reported in the following format: $[\alpha]_D$(temperature of measurement) = specific rotation (concentration of the solution reported in units of 10 mg sample per 1 mL solvent used).

Gas chromatography (GC) analyses for measurement of enantiomeric excesses were obtained using a Shimadzu 17-A Gas Chromatograph, equipped with autosampler, flame ionization detector (FID), and a chiral column Varian CP-Chirasil-DEX CB b-ciclodextrin (25 m × 0.32 mm × 0.25 μm). The temperature of the detector and injector was 220 °C; flow = 100 kPa, H_2.

High performance liquid chromatograph (HPLC) analyses for measurement of enantiomeric excesses were performed on a Shimadzu, LC-10AD liquid chromatograph equipped with autosampler and a variable wavelength UV detector (deuterium lamp 190–600 nm). Chiral columns: Chiralcel® OJ-H (0.46 cm*f* × 25 cm), Chiralcel® OD-H (0.46 cm*f* × 25 cm), Chiralcel® AD-H (0.46 cm*f* × 25 cm) or Chiralcel® OD (0.46 cm*f* × 25 cm) from Daicel Chemical Ind. *i*-PrOH and hexane (60% *n*-hexane) HPLC grade purchased from J. T. Baker were used as the eluting solvents.

General procedure for synthesis of 1-((selenocyanate)phenyl)ethanones

To an Erlenmeyer flask, *para* or *ortho*-aminoacetophenone (3.51 g, 26 mmol) and an aqueous HCl solution (50 mL, 2 M) were added. The solution was cooled to 0 °C and a water solution of $NaNO_2$

(24 mmol, 12 mL, 2 M) was added dropwise. At 0 °C, sodium acetate (8 g, 60 mmol) was added, followed by the addition of acetate buffer solution until pH 4.3. The KSeCN (5 g, 35 mmol) was then added under vigorous agitation and the solution was kept at 0 °C for 1 h. Sodium acetate was added until pH 5.5. The resulting solution was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried over $MgSO_4$. The solvent was removed in vacuum and the residue purified by silica gel column chromatography, using a mixture of hexane and ethyl acetate (4 : 1) as solvent. The solvent was removed to give the selenocyanate acetophenone **1**.

1-((4-Selenocyanate)phenyl)ethanone (1). Yield: 65%. IR (KBr) cm^{-1}: 3434, 3342, 2964, 2920, 2151, 1685, 1586, 1394, 1360, 1266, 1185, 960, 816, 587, 520, 464. ^1H NMR (200 MHz, $CDCl_3$) δ: 7.99-7.95 (m, 2H), 7.73-7.68 (m, 2H), 2.62 (s, 3H). ^{13}C NMR (50 MHz) δ: 196.99, 137.73, 132.88, 129.40, 128.55, 100.62, 26.84. LRMS [EI], *m/z* (relative abundance): 225 (M^+, 50), 210 (100), 208 (71), 182 (47), 180 (23), 76 (31), 63 (19), 43 (82). HRMS [ESI(+)], calcd for $[C_9H_7NOSe + Na]^+$: 247.9591, found 247.9586.

1-((2-Selenocyanate)phenyl)ethanone. Yield: 60%. IR (KBr) cm^{-1}: 3439, 3072, 2994, 2144, 1645, 1582, 1555, 1430, 1363, 1300, 1280, 1265, 1026, 962, 703, 603, 481. ^1H NMR (500 MHz, $CDCl_3$) δ: 8.11-8.08 (m, 2H), 7.65-7.61 (m 1H), 7.53-7.50 (m, 1H), 2,70 (s 3H). ^{13}C NMR (125 MHz) δ: 199.90, 134.75, 132.74, 132.13, 131.56, 130.68, 127.71, 106.77, 25.75. LRMS [EI], *m/z* (relative abundance): 225 (M^+, 37), 210 (53), 208 (26), 182 (18), 180 (8), 43 (100). HRMS [ESI(+)], calcd for $[C_9H_7NOSe + Na]^+$: 247.9591, found 247.9584.

General procedure for synthesis of 1-((alkylselanyl)phenyl)ethanones (2a–d and 5)

To a two necked round-bottomed flask under N_2, selenocyanate acetophenones **1** (225 mg, 1 mmol) and methanol (5 mL) were added. The solution was cooled to 0 °C and alkyl halide (MeI, EtBr, BuBr or BnBr, 4 mmol) was added, followed by the slow addition of $NaBH_4$ (42 mg, 1.1 mmol). The solution was stirred for 2 h at 0 °C. The solvent was removed in vacuum and the residue was diluted in ethyl acetate (3 mL) followed by addition of saturated aqueous solution of NH_4Cl (3 mL). After phase separation, the aqueous phase was extracted with ethyl acetate (2 × 3 mL). The combined organic phases were dried over $MgSO_4$. The solvent was removed in vacuum and the residue purified by silica gel column chromatography, using a mixture of hexane and ethyl acetate (4 : 1) as solvent. The solvent was removed to give the organoselenium acetophenones **2a–d** and **5**.

1-(4-(Methylselanyl)phenyl)ethanone (2a). Yield: 53%. IR (KBr) cm^{-1}: 2999, 1669, 1587, 1396, 1353, 1279, 1268, 1189, 1084, 814, 591, 494, 456, 426. NMR ^1H (200 MHz, $CDCl_3$) δ: 7.83-7.79 (m, 2H), 7.43-7.38 (m, 2H), 2.56 (s, 3H), 2.40 (s, 3H). NMR ^{13}C (50 MHz) δ: 197.32, 140.10, 134.44, 128.64, 128.59, 26.36, 6.36. LRMS [EI], *m/z* (relative abundance): 214 (M^+, 70), 199 (100), 184 (25), 171 (16), 104 (5), 91 (74), 76 (17), 43 (67). HRMS [ESI(+)], calcd for $[C_9H_{10}OSe + H]^+$: 214.1431, found 214.9978.

1-(4-(Ethylselanyl)phenyl)ethanone (2b). Yield: 63%. IR (KBr) cm^{-1}: 3438, 2966, 2929, 2870, 1677, 1586, 1393, 1357, 1269, 1234, 1182, 1083, 858, 812, 605, 588, 458. ^1H NMR (200 MHz, $CDCl_3$) δ: 7.84-7.79 (m, 2H), 7.49-7.45 (m, 2H), 3.01 (quart., $J = 7.5$ Hz, 2H), 2.57 (s, 3H), 1.48 (t, $J = 7.5$ Hz, 3H). ^{13}C NMR (50 MHz) δ: 196.72, 138.19, 134.15, 129.57, 128.03, 25.77, 19.79, 14.45. LRMS [EI], *m/z* (relative abundance): 228 (M^+, 84), 213 (100), 209 (18), 185 (44), 181 (26), 156 (17), 105 (18), 91 (11), 77 (22), 63 (12), 43 (86). HRMS [ESI(+)], calcd for $[C_{10}H_{12}OSe + H]^+$: 229.0131, found 229.0131; $(M + Na)^+$; for $[C_{10}H_{12}OSe + Na]$: 250.9951, found 250.9946.

1-(4-(Butylselanyl)phenyl)ethanone (2c). Yield: 75%. IR (KBr) cm^{-1}: 2959, 2930, 1680, 1588, 1395, 1358, 1268, 1183, 1083, 956, 817, 606, 590, 458. NMR ^1H (200 MHz, $CDCl_3$) δ: 7.83-7.79 (m, 2H), 7.49-7.27 (m, 2H), 2.99 (t, $J = 6.2$ Hz, 2H), 2.57 (s, 3H), 1.80-1.66 (m, 2H), 1.54-1.36 (m, 2H), 0.93 (t, $J = 7.02$ Hz, 3H). NMR ^{13}C (50 MHz) δ: 197.37, 139.21, 134.72, 130.13, 128.65, 31.85, 26.62, 26.41, 22.94, 13.49. LRMS [EI], *m/z* (relative abundance): 256 (M^+, 58), 241 (13), 200 (37), 185 (70), 154 (8), 77 (17), 57 (54), 43 (100). HRMS [ESI(+)], calcd for $[C_{12}H_{16}OSe + H]^+$: 257.0445, found 257.0444.

1-(4-(Benzylselanyl)phenyl)ethanone (2d). Yield: 71%. IR (KBr) cm^{-1}: 3335, 3064, 2998, 1968, 1891, 1809, 1676, 1585, 1359, 1278, 1181, 1060, 955, 811, 766, 696, 585, 459. NMR ^1H (200 MHz, $CDCl_3$) δ: 7.81-7.77 (m, 2H), 7.49-7.45 (m, 2H), 7.26 (s, 5H), 4.20 (s, 2H), 2.56 (s, 3H). NMR ^{13}C (50 Hz) δ: 197.42, 138.60, 137.51, 135.28, 131.28, 128.83, 128.65, 128.57, 127.18, 31.31, 26.45. LRMS [EI], *m/z* (relative abundance): 290 (M^+, 4), 199 (1), 154 (1), 91 (100), 75 (1), 65 (11), 41 (1). HRMS [ESI(+)], calcd for $[C_{15}H_{14}OSe + H]^+$: 291.0289, found 291.0288; $(M + Na)^+$; calcd for $[C_{15}H_{14}OSe + Na]^+$: 313.0108, found 313.0112.

1-(2-(Ethylselanyl)phenyl)ethanone (5). Yield: 65%. IR (KBr) cm^{-1}: 2960, 2923, 2850, 1665, 1585, 1455, 1431, 1359, 1251, 1038, 956, 753, 599, 468. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.91 (dd, $J =$ 7.5 Hz, $J = 1.5$ Hz, 1H), 7.51-7.48 (m, 1H), 7.44-7.38 (m, 1H), 7.27-7.22 (m, 1H), 2.86 (quart., $J = 7.5$ Hz, 2H), 2.63 (s, 3H), 1.47 (t, $J = 7.5$ Hz, 3H). ^{13}C NMR (75 MHz) δ: 198.80, 138.24, 135.36, 132.30, 131.78, 128.26, 124.23, 27.52, 18.49, 13.65. LRMS [EI], *m/z* (relative abundance): 228 (M^+, 19), 199 (100), 182 (5),157 (9), 91 (40), 77 (17), 51 (10),43 (62). HRMS [ESI(+)], calcd for $[C_{10}H_{12}OSe + H]^+$: 229.0131, found 229.0124; $(M + Na)^+$; calcd for $[C_{10}H_{12}OSe + Na]$: 250.9951, found 250.9952.

General procedure for synthesis of (*RS*)-1-((ethylselanyl)phenyl)ethanamines (3a–d and 6)

To a two necked round-bottomed flask under N_2, alkylselenium acetophenones **2a–d** and **5** (1 mmol), titanium(IV) isopropoxide (0.6 mL, 2 mmol) and a solution of NH_3 in ethanol (5 mmol, 2.5 mL, 2 M) were added. The solution was stirred at room temperature for 12 h. After this period, $NaBH_4$ (57 mg, 1.5 mmol) was added and the resulting solution was stirred for an additional 12 h. Finally, the reaction was quenched with aqueous ammonia solution (2.5 mL, 2 M) and the resulting mixture was filtered off under vacuum. The remaining solid was washed with ethyl acetate (2 × 3 mL). The phases were separated and the aqueous phase was extracted with ethyl acetate (3 × 3 mL). The organic phases were combined and then extracted with an aqueous HCl solution (3 × 3 mL, 1 M). Saturated aqueous NaOH solution was added to the resulting acidic aqueous phase until pH 10 and it was then extracted with ethyl acetate (4 × 5 mL). The

combined organic phases were washed once with brine (3 mL) and dried over $MgSO_4$. The solvent was removed in vacuum to give the (*RS*)-organoselenium amines **3a–d** and **6** in a pure form. These compounds were employed directly in the enzymatic kinetic resolution.

(*RS*)-1-(4-(Methylselanyl)phenyl)ethanamine (3a). Yield: 73%. IR (KBr) cm^{-1}: 3357, 2966, 1615, 1582, 1454, 1370, 1272, 1098, 1072, 1012, 904, 817, 722, 539. NMR ^1H (200 MHz, $CDCl_3$) δ: 7.39-7.35 (m, 2H), 7.24-7.20 (m, 2H), 4.06 (quart., $J = 6.6$ Hz, 1H), 2.32 (s, 3H), 1.71 (s, 2H), 1.35 (d, $J = 6.6$ Hz, 3H). NMR ^{13}C (50 MHz) δ: 145.67, 130.51, 129.54, 126.31, 50.69, 25.41, 7.20. LRMS [EI], *m/z* (relative abundance): 215 (M^+, 22), 200 (100), 185 (39), 154 (3), 120 (13), 104 (22), 91 (17), 78 (22), 42 (32). HRMS [ESI(+)], calcd for $[C_9H_{13}NSe–NH_2]^+$: 199.0025, found 199.0021.

(*RS*)-1-(4-(Ethylselanyl)phenyl)ethanamine (3b). Yield: 73%. IR (KBr) cm^{-1}: 3359, 3286, 3070, 2961, 2923, 2866, 1591, 1492, 1447, 1372, 1230, 1014, 822, 770, 541. ^1H NMR (200 MHz, $CDCl_3$) δ: 7.47-7.42 (m, 2H), 7.26-7.22 (m, 2H), 4.08 (quart., $J = 6.5$ Hz, 1H), 2.89 (quart., $J = 7.5$ Hz, 2H), 1.81 (s, 2H), 1.42 (t, $J = 7.0$ Hz, 3H), 1.37 (d, $J = 6.6$ Hz, 3H). ^{13}C NMR (50 MHz) δ: 146.52, 133.22, 128.42, 126.67, 51.15, 25.74, 21.66, 15.72. LRMS [EI], *m/z* (relative abundance): 229 (M^+, 27), 214 (100), 185 (39), 120 (20), 104 (21), 78 (33), 42 (42). HRMS [ESI(+)], calcd for $[C_{10}H_{15}NSe–NH_2]^+$: 213.0182, found 213.0174.

(*RS*)-1-(4-(Butylselanyl)phenyl)ethanamine (3c). Yield: 19%. IR (KBr) cm^{-1}: 3357, 3287, 2959, 2929, 2871, 1592, 1492, 1463, 1371, 1202, 1014, 821, 721, 541. NMR ^1H (200 MHz, $CDCl_3$) δ: 7.35-7.31 (m, 2H), 7.13-7.09 (m, 2H), 3.95 (quart., $J = 6.6$ Hz, 1H), 2.78 (t, $J = 7.5$ Hz, 2H), 1.83 (s, 2H), 1.65-1.50 (m, 2H), 1.40-1.23 (m, 5H), 0.79 (t, $J = 7.5$ Hz, 3H). NMR ^{13}C (50 MHz) δ: 145.70, 133.88, 132.28, 128.29, 126.11, 50.52, 31.87, 27.33, 25.15, 22.56, 13.23. LRMS [EI], *m/z* (relative abundance): 257 (M^+, 21), 242 (100), 200 (6), 185 (24), 120 (22), 106 (21), 91 (10), 78 (29), 42 (40). HRMS [ESI(+)], calcd for $[C_{12}H_{19}NSe–NH_2]^+$: 241.0496, found 241.0493.

(*RS*)-1-(4-(Benzylselanyl)phenyl)ethanamine (3d). Yield: 21%. IR (KBr) cm^{-1}: 3376, 3027, 2970, 1597, 1579, 1561, 1494, 1470, 1453, 1361, 1324, 1268, 1011, 814, 759, 696, 535, 465. NMR ^1H (200 MHz, $CDCl_3$) δ: 7.26-7.22 (m, 2H), 7.04-7.02 (m, 7H), 3.90-3.82 (m, 3H), 1.34 (s, 2H), 1.17 (d, $J = 8.0$ Hz, 3H). NMR ^{13}C (50 MHz) δ: 146.62, 138.21, 133.20, 128.38, 127.93, 126.34, 126.00, 50.39, 31.79, 25.31. LRMS [EI], *m/z* (relative abundance): 291 (M^+, 6), 276 (16), 200 (2), 120 (6), 104 (4), 91 (100), 78 (8), 65 (17), 42 (13). HRMS [ESI(+)], calcd for $[C_{15}H_{17}NSe–NH_2]^+$: 275.0339, found 275.0324.

(*RS*)-1-(2-(Ethylselanyl)phenyl)ethanamine (6). Yield: 63%. IR (KBr) cm^{-1}: 3357, 3287, 3055, 2962, 2923, 2866, 1660, 1585, 1447, 1371, 1230, 1032, 755, 663, 598, 549, 462. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.51-7.44 (m, 2H), 7.29-7.23 (m, 1H), 7.18-7.12 (m, 1H), 4.59 (quart., $J = 6.6$ Hz,1H), 2.91 (quart., $J = 5.7$ Hz, 2H), 2.21 (s, 2H), 1.43 (t, $J = 7.5$ Hz, 3H), 1.39 (d, $J = 7.2$ Hz, 3H). ^{13}C NMR (75 MHz) δ: 148.02, 132.38, 129.84, 127.42, 127.29, 125.28, 48.86, 24.34, 21.46, 15.20. LRMS [EI], *m/z* (relative abundance): 229 (M^+, 22), 214 (12), 200 (52), 183 (55), 157 (6), 119 (46), 104 (85), 91 (29), 77 (42), 51 (24), 44 (100). HRMS [ESI(+)], calcd for $[C_{10}H_{15}NSe–NH_2]^+$: 213.0182, found 213.0170; calcd for $[C_{10}H_{15}NSe + H]^+$: 230.0448, found 230.0441.

General procedure for synthesis of *N*-(1-((alkylselanyl)phenyl)ethyl)acetamides (4a–d and 7)

To a Schlenck flask, organoselenium amines **3a–d** and **6** (50 mg, 0.22 mmol), CH_2Cl_2 (1 mL), acetic anhydride (62 μL, 0.66 mmol) and triethylamine (62 μL, 0.44 mmol) were added. The resulting solution was stirred for 1 h at 50 °C. After this period, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and the resulting solution was then washed with an aqueous HCl solution (2 × 2 mL, 1 M). The organic phase was washed with brine (2 mL), dried over $MgSO_4$ and the solvent was removed in vacuum to give organoselenium amides **4a–d** and **7**.

(*RS*)-*N*-(1-(4-(Methylselanyl)phenyl)ethyl)acetamide (4a). Yield: 93%. IR (KBr) cm^{-1}: 3282, 1640, 1546, 1367, 1120, 1010, 817, 740, 612, 586, 530. NMR ^1H (300 MHz, $CDCl_3$) δ: 7.39-7.36 (m, 2H), 7.27-7.18 (m, 2H), 6.05 (s, 1H), 5.09-5.04 (m, 1H), 2.34 (s, 3H), 1.96 (s, 3H), 1.45 (d, $J = 6.0$ Hz, 3H). NMR ^{13}C (75 MHz) δ: 169.21, 141.38, 130.70, 130.62, 126.93, 48.39, 23.36, 21.66, 7.34. LRMS [EI], *m/z* (relative abundance): 257 (M^+, 40), 242 (21), 200 (82), 181(8), 120 (25), 104 (30), 91 (17), 77 (20), 43 (100). HRMS [ESI(+)], calcd for $[C_{11}H_{15}NOSe + Na]^+$: 280.0217, found 280.0216; $(M + K)^+$; calcd for $[C_{11}H_{15}NOSe + K]^+$: 295.9956, found 295.9967.

(*RS*)-*N*-(1-(4-(Ethylselanyl)phenyl)ethyl)acetamide (4b). Yield: 97%. IR (KBr) cm^{-1}: 3314, 3075, 2971, 2927, 2867, 2822, 1646, 1545, 1374, 1137, 816, 724, 535. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.46-7.43 (m, 2H), 7.26-7.19 (m, 2H), 5.98 (s, 1H), 5.08 (quart., $J = 7.2$ Hz, 1H), 2.90 (quart., $J = 7.0$ Hz, 2H), 2.01 (s, 3H), 1.47 (d, $J = 7.0$ Hz, 3H), 1.42 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (75 MHz) δ: 169.38, 141.70, 132.84, 129.25, 126.91, 48.60, 23.31, 21.62, 21.43, 15.51. LRMS [EI], *m/z* (relative abundance): 271 (M^+, 61), 253 (39), 214 (99), 181 (18), 156 (14), 120 (45), 104 (33), 78 (26), 43 (100). HRMS [ESI(+)], calcd for $[C_{12}H_{17}NOSe + H]^+$: 272.0554, found 272.0556.

(*RS*)-*N*-(1-(4-(Butylselanyl)phenyl)ethyl)acetamide (4c). Yield: 90%. IR (KBr) cm^{-1}: 3278, 2960, 2930, 1650, 1549, 1494, 1454, 1372, 1294, 1136, 1014, 822, 540. NMR ^1H (300 MHz, $CDCl_3$) δ: 7.45-7.42 (m, 2H), 7.26-7.18 (m, 2H), 5.83 (s, 1H), 5.11-5.07 (m, 1H), 2.89 (t, $J = 4.5$ Hz, 2H), 1.97 (s, 3H), 1.71-1.65 (m, 2H), 1.47-1.39 (m,5H), 0.90 (t, $J = 4.5$ Hz, 3H). NMR ^{13}C (75 MHz) δ: 169.14, 141.73, 132.63, 129.57, 126.88, 48.41, 32.24, 27.70, 23.43, 22.95, 21.63, 13.56. LRMS [EI], *m/z* (relative abundance): 299 (M^+, 25), 281 (45), 242 (38), 207 (89), 184 (24), 133 (19), 120 (32), 104 (25), 96 (21), 73 (37), 43 (100). HRMS [ESI(+)], calcd for $[C_{14}H_{21}NOSe + Na]^+$: 322.0686, found 322.0688.

(*RS*)-*N*-(1-(4-(Benzylselanyl)phenyl)ethyl)acetamide (4d). Yield: 92%. IR (KBr) cm^{-1}: 3449, 3342, 2971, 2929, 1646, 1538, 1494, 1370, 1138, 819, 697, 539, 463, 425. NMR ^1H (300 MHz, $CDCl_3$) δ: 7.43-7.39 (m, 2H), 7.28-7.19 (m, 7H), 5.68 (s, 1H), 5.12-5.07 (m, 1H), 4.09 (s, 2H), 1.98 (s, 3H), 1.46 (d, $J = 6.0$ Hz, 3H). NMR ^{13}C (75 MHz) δ: 169.07, 142.40, 138.47, 133.65, 129.39, 128.83, 128.44, 126.88, 126.84, 48.38, 32.24, 23.46, 21.65. LRMS [EI], *m/z* (relative abundance): 333 (M^+, 29), 318 (1), 274 (4) 200 (4) 120 (3) 91 (100), 65 (5), 43 (4). HRMS [ESI(+)], calcd

for $[C_{17}H_{19}NOSe + Na]^+$: 356.0530, found 356.0521; $(M + K)^+$; calcd for $[C_{17}H_{19}NOSe + K]^+$: 372.0269, found 372.0266.

(*RS*)-*N*-(1-(2-(Ethylselanyl)phenyl)ethyl)acetamide (7). Yield: 90%. IR (KBr) cm^{-1}: 3432, 3272, 3079, 2965, 2923, 2856, 1646, 1558, 1443, 1373, 1305, 1033, 752, 512, 458. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.52 (dd, $J = 4.5$ Hz, $J = 0.6$ Hz, 1H), 7.32 (dd, $J = 4.5$ Hz, $J = 0.6$ Hz, 1H), 7.27-7.23 (m, 1H), 7.19-7.16 (m, 1H), 6.36 (s, 1H), 5.46 (quart., $J = 4.2$ Hz, 1H), 2.94 (quart., $J = 4.2$ Hz, 2H), 2.02 (s, 3H), 1.49 (d, $J = 4.2$ Hz, 3H), 1.42 (t, $J = 4.2$ Hz, 3H). ^{13}C NMR (75 MHz) δ: 169.38, 144.68, 134.09, 130.22, 127.91, 127.54, 126.05, 49.68, 29.71, 22.13, 21.85, 15.29. LRMS [EI], *m*/*z* (relative abundance): 271 (M^+, 3), 228 (12), 183 (18), 162 (100), 120 (29), 104 (15), 77 (12), 43 (28). HRMS [ESI(+)], calcd for $[C_{12}H_{17}NOSe + H]^+$: 272.0554, found 272.0552.

General procedure for determination of the enantiomeric excess (*ee*) by HPLC analysis

The enantiomeric purities of the organoselenium amides **4** were measured by HPLC analysis. The analysis was carried out on Chiralcel OD-H column and the peaks detected by a UV detector at 254 nm. Eluent: hexane–isopropanol (95 : 5), flow rate: 1.0 mL min^{-1}. Retention times:

(*RS*)-*N*-(1-(4-(methylselanyl)phenyl)ethyl)acetamide (**4a**): (*R*)-**4a** = 25.11 min; (*S*)-**4a** = 31.68 min.

(*RS*)-*N*-(1-(4-(ethylselanyl)phenyl)ethyl)acetamide (**4b**): (*R*)-**4b** = 20.44 min; (*S*)-**4b** = 24.93 min.

(*RS*)-*N*-(1-(4-(butylselanyl)phenyl)ethyl)acetamide (**4c**): (*R*)-**4c** = 17.56 min; (*S*)-**4c** = 20.87 min.

(*RS*)-*N*-(1-(4-(benzylselanyl)phenyl)ethyl)acetamide (**4d**): (*R*)-**4d** = 56.46 min; (*S*)-**4d** = 63.76 min.

(*RS*)-*N*-(1-(2-(ethylselanyl)phenyl)ethyl)acetamide (**7**): (*R*)-**7** = 16.92 min; (*S*)-**7** = 44.46 min.

General procedure for stereoselective amination of organoselenium acetophenone 2 and 5 catalyzed by ω-transaminases

All biocatalytic reactions were performed at 30 °C for 24 h in sodium phosphate buffer (100 mM, pH 7) with pyridoxal-5′-phosphate (1 mM) in 2 mL eppendorf tubes. The reaction buffer (1 mL) containing DMSO (Table 1) was mixed with ω-transaminase (ATA-113, ATA-114, ATA-117 or ATA-103), L- or D-alanine (250 mM), pyruvate reductase mix (LDH is a mixture of lactate dehydrogenase, glucose dehydrogenase, glucose, NAD^+, 40 mg), and DMSO (150 μL). The reaction mixture contained 50 mM of the corresponding organoselenium acetophenones **2** and **5** (Schemes 1 and 2). The conversion to amines **3** and **6** was followed by GC chromatography. The reaction was stopped by adding aqueous NaOH (200 μL, 10 N), followed by extraction with ethyl acetate (600 μL, twice). The combined organic phase was dried (Na_2SO_4) and analysed. Results are summarized in Table 1.

General procedure for kinetic resolution of organoselenium amines 3 and 6 catalyzed by ω-transaminases

All biocatalytic reactions were performed at 30 °C for 24 h in sodium phosphate buffer (100 mM, pH 7) with pyridoxal-5′-phosphate (1 mM) in 2 mL eppendorf tubes. The reaction buffer (1 mL) containing sodium pyruvate 50 mM (1 equiv.) was mixed with ω-transaminase (10 mg, ATA-113 or ATA-117). The reaction mixture contained 50 mM of the corresponding amine **3** and **6** (Schemes 1 and 2). The conversion to ketone **2** and **5** was followed by GC chromatography. The reaction was stopped by adding aqueous NaOH (200 μL, 10 N), followed by extraction with ethyl acetate (600 μL, twice). The combined organic phase was dried (Na_2SO_4) before being analysed. Results are summarized in Table 2.

Determination of the absolute configuration of the organoselenium amines 3–6 and amides 4–7

The absolute configurations of the organoselenium amides **4** were assigned by chromatographic comparison with standard samples of (*R*)- and (*S*)-*N*-(1-phenylethyl)acetamide after removing the organoselenium group from **4** with *n*-butyllithium according to the procedure above.

To a two necked round-bottomed flask, the chiral organoselenium amides **4** (68 mg, 0.25 mmol), THF (10 mL) and *n*-butyllithium (3.3 mmol) at 0 °C were added, under N_2. The solution was stirred at 0 °C for 2 h and, finally, the reaction was quenched with brine (10 mL). The organic layer was separated and the aqueous phase was extracted with ethyl ether (4 × 3 mL). The combined organic phases were washed once with brine (3 mL) and dried over $MgSO_4$. The solvent was removed in vacuum and the product was readily analyzed by chiral GC and compared with authentic samples of (*R*)- and (*S*)-*N*-(1-phenylethyl)acetamide. GC conditions: injector 220 °C; detector: 220 °C; pressure: 100 kPa; column temperature: 70 °C, 3 °C min^{-1} up to 180 °C. Retention times for (*RS*)-*N*-(1-phenylethyl)acetamide: (*R*) = 25.06 min, (*S*) = 24.21 min.

Synthesis of (*R*)-*N*-(1-(2-(ethylselanyl)phenyl)ethyl)acetamide (7). Yield: 90%. To a Schlenck flask under N_2, (*R*)-organoselenium amine **6** (50 mg, 0.22 mmol), CH_2Cl_2 (1 mL), acetyl chloride (0.66 mmol), triethylamine (0.44 mmol) and DMAP (1 mol%) were added. The resulting solution was stirred for 24 h at 40 °C. After this period, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and the resulting solution was then washed with an aqueous HCl solution (2 × 2 mL, 1 M). The organic phase was washed with $NaHCO_3$ aqueous solution (2 mL, saturated), dried over $MgSO_4$, and the solvent was removed in vacuum to give organoselenium amide **7**. The spectroscopy data were equivalent to those reported above for the compound (*RS*)-*N*-(1-(2-(ethylselanyl)phenyl)ethyl)acetamide. $[\alpha]_D^{25}$ +21.7 (*c* 0.50; EtOAc).

Synthesis of (*R*)-*N*,*N*-diethyl-1-(2-(ethylselanyl)phenyl)-ethanamine (8). To a Schlenck flask under N_2, (*R*)-organoselenium amine **6** (0.13 mmol) and ethanol (0.14 mL) were added. Then, the ethyl bromide was added (0.78 mmol) together with K_2CO_3 (0.26 mmol). The resulting solution was stirred for 24 h at 70 °C. After this period, the reaction mixture was diluted with ethanol (1 mL) and the resulting solution was filtered off. After that, the solvent was removed in vacuum and the residue purified by silica gel column chromatography, using a mixture of hexane and ethyl acetate (4 : 1) as solvent. The solvent was removed to give (*R*)-*N*,*N*-diethyl-1-(2-(ethylselanyl)phenyl)ethanamine **8**.

$[\alpha]_D^{20}$ +18.5 (*c* 1.7; CH_2Cl_2). Yield: 48%. IR (KBr) cm^{-1}: 3056, 2967, 2926, 1728, 1462, 1274, 757. NMR ^1H (200 MHz, $CDCl_3$)

δ: 7.42-7.38 (m, 2H), 7.17-7.14 (m, 2H), 4.12 (quart., $J = 6.58$ Hz, 1H), 2.91-2.84 (m, 2H), 2.60-2.56 (m, 4H), 1.46-1.27 (m, 6H), 1.00-0.93 (m, 6H). NMR ^{13}C (50 MHz, $CDCl_3$) δ: 130.44, 127.90, 127.14, 126.88, 125.81, 59.18, 42.80, 20.31, 16.93, 11.98. LRMS [EI], *m/z* (relative abundance): 285 (M, 16), 270 (67), 256 (83), 213 (33), 185 (21), 100 (100), 72 (49). HRMS [ESI(+)], calcd for $[C_{14}H_{23}NSe + H]^+$: 286.1074, found 286.1068.

Synthesis of (*R*)-*N*-(2-chlorobenzylidene)-1-(2-(ethylselanyl)-phenyl)ethanamine (9). To a Schlenck flask under N_2, (*R*)-organoselenium amine **6** (48 mg, 0.2 mmol) and CH_2Cl_2 (0.2 mL) were added. Then, the *ortho*-chlorobenzaldehyde (0.2 mmol) was added together with $MgSO_4$ (0.04 mg). The resulting solution was stirred for 24 h at 40 °C. After this period, the reaction mixture was diluted with CH_2Cl_2 (1 mL) and the resulting solution was filtered off. After that, the solvent was removed in vacuum to give the (*R*)-organoselenium imine **9**.

$[\alpha]_D^{20}$ −76.9 (*c* 0.9; CH_2Cl_2). Yield: 99%. IR (KBr) cm^{-1}: 3057, 2967, 2923, 1635, 1467, 1440, 1051, 1033, 755. NMR ^{1}H (200 MHz, $CDCl_3$) δ: 8.85 (s, 1H), 8.14-8.12 (m, 1H), 7.74-7.70 (m, 1H), 7.51-7.15 (m, 6H) 5.16 (quart., $J = 6.58$ Hz, 1H), 2.91 (quart., $J = 7.46$ Hz, 2H), 1.56 (d, $J = 6.58$ Hz, 3H), 1.47-1.39 (m, 3H). NMR ^{13}C (50 MHz, $CDCl_3$) δ: 156.63, 146.23, 135.13, 133.43, 132.56, 131.38, 129.64, 128.56, 127.85, 127.31, 127.20, 126.89, 68.19, 24.63, 21.66, 15.19. LRMS [EI], *m/z* (relative abundance): 351 (M, 2), 322 (100), 185 (18), 183 (76), 140 (54), 104 (39). HRMS [ESI(+)], calcd for $[C_{17}H_{18}ClNSe + H]^+$: 352.0371, found 352.0365; calcd for $[C_{17}H_{18}ClNSe + Na]^+$: 374.0191, found 374.0183.

General procedure for asymmetric allylic alkylation catalysed by palladium

To a two necked round-bottomed flask under N_2, a solution containing $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.0125 mmol, 5 mol%) and the chiral ligand **7**, **8** or **9** (0.025 mmol or 10 mol%) in CH_2Cl_2 (1 mL) were stirred for 1 h. Then, a solution of (*E*)-1,3-diphenylallyl acetate (0.25 mmol) in CH_2Cl_2 (2 mL) was added. The resulting solution was stirred for 30 min followed by addition of appropriate malonate (dimethyl malonate, diethyl ethyl malonate or diethyl phenyl malonate, 0.5 mmol), BisSi (*N*,*O*-bis(trimethylsilylacetamide) (0.75 mmol) and potassium acetate (1 mol%). The resulting solution was stirred for 48 h at the appropriate time (Table 3). After this period, NH_4Cl aqueous solution (3 mL, saturated) was added, and then the reaction media was extracted with CH_2Cl_2 (3 × 5 mL). The organic layer was dried with $MgSO_4$, the solvent was removed in vacuum and the residue purified by silica gel column chromatography, using a mixture of hexane and ethyl acetate (9 : 1) as solvent. After removing the solvent, the product was readily analyzed by HPLC.

(*E*)-Dimethyl 2-(1,3-diphenylallyl)malonate. Separation of enantiomers by HPLC analysis (Daicel Chiralcel OD-H column; solvent, 99 : 1 hexane–2-propanol; flow rate 1.0 mL min^{-1}; 254 nm detection). Retention times: (*R*) = 9.67 min; (*S*) = 10.45 min.

(*E*)-Diethyl 2-(1,3-diphenylallyl)-2-ethylmalonate. Separation of enantiomers by HPLC analysis (Daicel Chiralcel AD-H column; solvent, 50 : 50 hexane–isopropanol; flow rate 0.5 mL min^{-1}; 254 nm detection). Retention times: (*R* or *S*) = 3.60 min; (*R* or *S*) = 6.02 min.

(*E*)-Diethyl 2-(1,3-diphenylallyl)-2-phenylmalonate. Separation of enantiomers by HPLC analysis (Daicel Chiralcel AD-H column; solvent, 99 : 1 hexane–isopropanol; flow rate 0.5 ml min^{-1}; 254 nm detection). Retention times: (*R* or *S*) = 17.34 min; (*R* or *S*) = 18.41 min.

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