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Lipase-catalyzed resolution of β-hydroxy selenides

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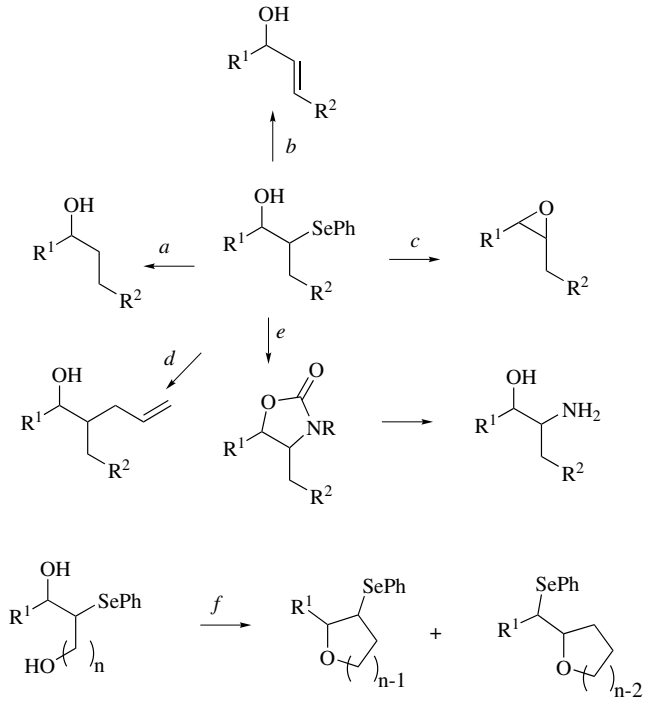
Abstract—Eleven β-hydroxy selenides were kinetically resolved using an immobilized lipase (Amano PS-C II) in toluene in the presence of vinyl acetate at 30 °C. This approach provided, in several cases, both enantiomers in high enantiomeric excess. The role of the size of substituents and the behaviour of cyclic β-hydroxy selenides is also discussed. Enantiopure β-hydroxy selenides are useful building blocks. As an application of this chemistry, enantiopure (1*S*,2*R*)-indene oxide was obtained in one step from the proper enantiopure β-hydroxy selenide.

1. Introduction

One of the most important strategies for the preparation of non-racemic materials is the synthesis using the 'natural chiral pool' as the main source of chirality.[1] However, both bioconversion,[2] and asymmetric catalysis[3] have emerged as powerful methodologies to access new chiral synthons out of the 'chiral pool'. In the last few years, we have been interested in the stereoselective synthesis using organoselenium compounds,[4–7] biocatalysis[8] or organocatalysis.[9] Organoselenium chemistry is a powerful tool in organic synthesis.[10,11] In this context, β-hydroxy-selenides are useful starting materials for several syntheses (Scheme 1). They can be reduced to alcohols (route a),[12] transformed to allylic alcohols by oxidative elimination (route b),[11] to epoxides (route c),[4,11] to allyl substituted alcohols (route d),[13] or substituted 1,3-oxazolidin-2-ones (route e).[14] The latter compounds are important molecules, which display good antibacterial properties[15,16] and are used in the pharmaceutical chemistry.[17,18] 1,3-Oxazolidin-2-ones, known as Evans' chiral auxiliaries,[19] have been used in a wide range of asymmetric reactions, such as aldol condensations, alkylations and Diels–Alder reactions. Moreover, such compounds, can also be employed for the synthesis of substituted 1,2-amino alcohols.[14] Hydroxy selenides containing an hydroxyl group in a suitable position were successfully used in the synthesis of substituted tetrahydrofurans and tetrahydropyrans both in the *exo* and *endo* modes (route f).[20–22]



Scheme 1. Transformations of β-hydroxy selenides.

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Chiral, non-racemic β-hydroxy selenides are usually obtained using the following approaches. The natural chiral pool as source of chirality is employed in the reactions carried out using camphor diselenide as a source of electrophilic selenium reagents. Good yields and moderate to good facial selectivities were obtained in the asymmetric selenohydroxylation of alkenes with camphorselenenyl sulfate.[23]

Enantiomerically enriched β-hydroxy selenides can be obtained by regiospecific ring opening of the corresponding chiral, non-racemic epoxides using sodium phenyl selenolate in ethanol.[14] High selectivities were observed in selenohydroxylation with a chiral, non-racemic sulfur-containing diselenide[24] or with nitrogen containing chiral diselenides, especially for styrene substrates.[25] Enantiomerically enriched β-hydroxy selenides were also obtained after the kinetic resolution of allylic alcohols promoted by a chiral electrophilic selenium reagent.[26,27] Finally, the enantioselective ring-opening reaction of *meso*-epoxides with aryl selenols to give β-hydroxy selenides, using a chiral Ti–Ga–Salen heterometallic catalyst, has been performed.[28]

Very few examples have been reported for the synthesis of chiral, non-racemic β-hydroxy selenides by enzymatic kinetic resolution. Synthetically useful chiral synthons (*R*)- and (*S*)-2-cyclohexen-1-ols and (*R*)- and (*S*)-2-cyclohepten-1-ols were prepared via enantioselective transesterification of racemic *trans*-2-(phenylseleno)cyclohexanol[29] and *trans*-2-(phenylseleno)cycloheptanol[30] with vinyl acetate or butyrate using lipase, followed by selenoxide elimination and hydrolysis. More recently, investigations on the enzymatic resolution of several racemic β-hydroxy selenides using immobilized *Candida antarctica* lipase type B (Novozym 435) have been reported.[31]

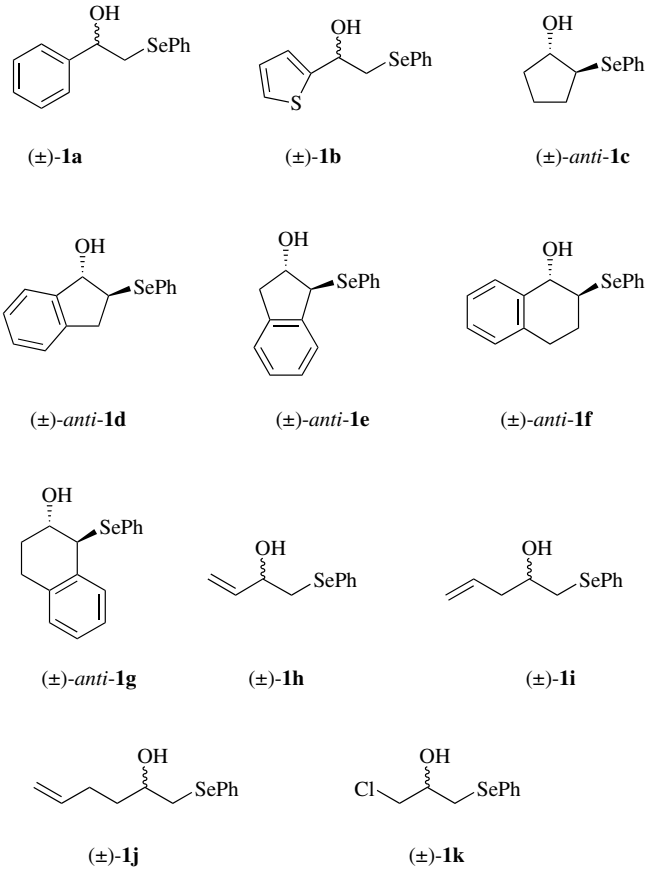
Considering the synthetic usefulness of β-hydroxy selenides and in connection with our synthetic investigations with organoselenium compounds, we have started a study on enzymatic resolution of such compounds.

2. Results and discussion

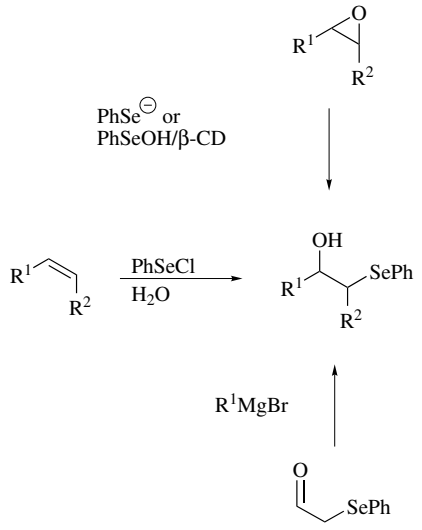
In order to study how the different nature of substituents may affect the enzymatic resolution, we prepared several model β-hydroxy selenides, both open-chain and annelated (see Schemes 2 and 3).

2.1. Synthesis of compounds 1a–k

Compounds **1a**, **1c**, **1d** and **1f** were prepared by a hydroxyselenenylation reaction of the corresponding alkenes with PhSeCl in acetonitrile/water.[32] Compounds **1b**, **1h** and **1i** were prepared by the reaction of phenylselenenylacetaldehyde with the appropriate Grignard reagent.[33] Compounds **1g** and **1j** were prepared by epoxide ring opening with PhSeSePh and $NaBH_4$.[34] Compound **1k** was prepared by epoxide ring opening with PhSeOH in the presence of β-cyclodextrin.[35] Compound **1e** was prepared in situ from *trans*-2-bromo-1-indanol.[36] Racemic 1,2-epoxy-1,2,3,4-tetrahydronaphthalene used for the synthesis of compound **1g** was prepared by epoxidation of the corresponding alkene.[37] The racemic 1,2-epoxy-5-hexene used for the synthesis of compound **1j** was commercially available.



Scheme 2. β-Hydroxy selenides studied in this work.



Scheme 3. Synthetic routes to β-hydroxy selenides.

2.2. Enzymatic resolution

We started our investigations on the enzymatic resolution using compound (±)-**1a**. We used PS-C II Amano lipase and vinyl acetate in toluene. The first reaction was carried out using a 0.44 M solution of substrate, a 0.4 mmol/50 mg substrate/enzyme ratio and 3 equiv of vinyl acetate at 30 °C. After 48 h, the reaction did not take place (Table 1, entry 1). The reaction was repeated using a larger amount of enzyme (100 mg) and 5 equiv of vinyl acetate. After 48 h, we observed a low conversion (17%, entry 2). The conversion was determined from the ^{1}H NMR of the crude reaction mixture. Column chromatography was used to separate the acetate from the alcohol. The acetate showed a poor ee value (62%). Using the same amounts, we carried out the reaction at a higher temperature (60 °C). After 24 h, the conversion was high (47%) but, as expected, poor ee values were observed for both the alcohol and the acetate (entry 3). We also used different enzymes. No enantioselectivity was observed with immobilized *C. antarctica* lipase (Novozym 435), whereas poor ee values were observed with *Candida Rugosa* lipase (CRL). In both cases, low conversions were obtained (entries 4 and 5).

Compound (±)-**1b** was more reactive. Indeed, when carrying out the reaction at 30 °C, compound (±)-**1b** gave a 50% conversion after 48 h. However, in this case the ee value was low (entry 6).

Excellent resolution was found for compound (±)-**1c**. After 1 h the conversion was 50% with ee values >99% (entry 7). Furthermore compound (±)-**1d** gave excellent resolution. After 48 h, the conversion was 50% with ee values >99% (entry 8). Compound (±)-**1e** bearing the OH and PhSe groups on exchanged positions also gave excellent results (entry 9). The reaction was faster compared to compound (±)-**1d**.

Compound (±)-**1f** showed a behaviour similar to compound (±)-**1a**. No reaction was observed (entry 10). The reaction was repeated using a larger amount of lipase and vinyl acetate at 60 °C (entries 11 and 12); a slow conversion was observed. After 73 h, the conversion was 19% with an ee value of 96%. However, a higher conversion gave a lower ee value (conv. 31%, ee 76%). Conversely, compound **1g** gave excellent resolution ($E = 500$).

We then investigated compounds (±)-**1h–j** having a vinyl, allyl and homoallyl substituent (entries 14–20). Compound (±)-**1h** gave ester **2h** in good ee (93%) after a 25% conversion. The reaction was complete after 2.5 h giving the alcohol and ester in an 80% ee value. Resolution of compound (±)-**1i** gave, after 4 h the alcohol and ester in a 49/51 ratio and with high ee values (99% and 94%, respectively). Compound (±)-**1j** gave almost complete conversion after 25 h giving ester **2j** in 89% ee. Finally, a high enantiomeric ratio was obtained in the resolution of compound (±)-**1k**.

The enantiomeric excesses were determined by HPLC using a Chiracel OD-H chiral column and *n*-hexane/*i*-propanol as eluent (see Experimental).

2.3. Configuration determination

Configurations were determined in selected cases (**1a–b,d,f**) by the comparison with known products with or without

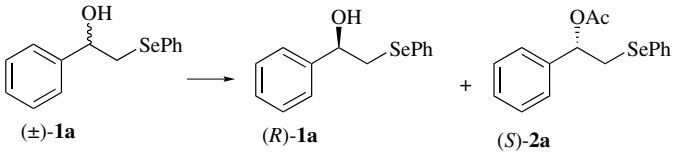
Table 1. Enantioselective lipase-catalyzed kinetic resolutions of compounds (±)-**1a-k**[a]

Entry	Compd	*t* (*h*)	*c* (%)	ee **1** (%)	ee **2** (%)	Conf. **1**	Conf. **2**	*E*[b]
1	(±)-**1a**	48	1	n.d.	n.d.			—
2[c]		48	17	14	62	(*R*)	(*S*)	5
3[c,d]		24	47	44	46			4
4[c,e]		60	15	0	0			—
5[c,f]		24	<5	n.d.	72			—
6	(±)-**1b**	48	50	58	58	(*S*)	(*R*)	7
7	(±)-**1c**	1	50	>99	>99	(*S*,*S*)	(*R*,*R*)	>200
8	(±)-**1d**	48	50	>99	>99	(*S*,*S*)	(*R*,*R*)	>200
9	(±)-**1e**	1.7	50	>99	>99	(*S*,*S*)	(*R*,*R*)	>200
10	(±)-**1f**	120	0	—	—			—
11[c,d]		73	19	22	96	(*S*,*S*)	(*R*,*R*)	61
12[c,d]		161	31	34	76			10
13	(±)-**1g**	30	45	82	>99	(*S*,*S*)	(*R*,*R*)	>200
14	(±)-**1h**	0.33	25	31	93	(*S*)	(*R*)	37
15		2.5	50	80	80			22
16	(±)-**1i**	4	51	>99	94	(*S*)	(*R*)	146
17	(±)-**1j**	4	24	30	95	(*S*)	(*R*)	52
18		25	49	85	89			47
19	(±)-**1k**	0.5	22	27	96	(*S*)	(*R*)	64
20		2.5	47	84	95			104

[a] Conditions: **1** (0.4 mmol), lipase (50 mg), vinyl acetate (3 equiv), toluene (0.9 mL), 30 °C.
[b] $E = \ln [1 - c(1 + \text{ee}(\mathbf{2}))]/\ln [1 - c(1 - \text{ee}(\mathbf{2}))]$, where $c = \text{ee}(\mathbf{1})/[\text{ee}(\mathbf{1}) + \text{ee}(\mathbf{2})]$.
[c] Lipase (100 mg), vinyl acetate (5 equiv).
[d] Temperature 60 °C.
[e] Novozym 435.
[f] CRL.

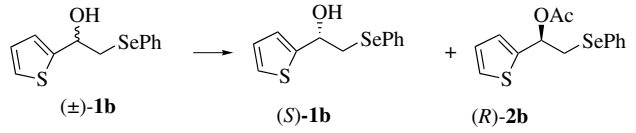
removal of the SePh group. Such investigations showed that resolutions gave (*S*)-alcohols **1** and (*R*)-esters **2**, except for **1a**. Thus for compounds **1c**, **1e**, **1g**–**k** it was assumed that the CHRSePh group was the large substituent.

The configuration of enantiomerically enriched alcohol **1a** was determined by the comparison of the specific optical rotation of (*S*)-1-phenyl-2-(phenylseleno)ethanol ([α] = +14.4)[14a] with the enantiomerically enriched alcohol obtained by us. This comparison proved that the enzyme showed an enantiopreference for the (*S*)-alcohol, giving enantiomerically enriched (*R*)-alcohol **1a** and (*S*)-ester **2a** (Scheme 4).



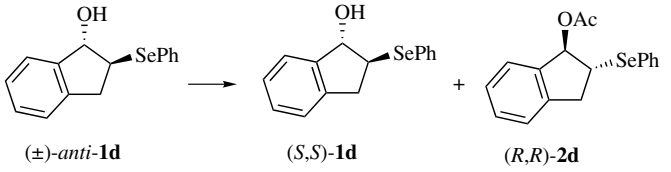
Scheme 4. Lipase-catalyzed resolution of (±)-**1a**.

For enantiomerically enriched **1b** (Scheme 5), we tried a correlation with enantiopure 1-thiophen-2-yl-ethanol however, the reductive elimination of the SePh group with Bu_3SnH and AIBN did not afford the expected product. However, it has been reported that 2-ethylthio-1-thiophen-2-yl-ethanol was resolved with *Humicola lanuginosa*, a lipase, which follows the Kazlauskas's rule, to give (*S*)-alcohol and (*R*)-ester.[38] Moreover, compounds (*R*)-**1a** and (*S*)-**1b** showed an opposite Cotton effect.



Scheme 5. Lipase-catalyzed resolution of (±)-**1b**.

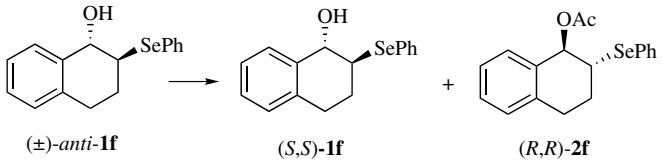
The configuration of enantiomerically pure alcohol (*S*,*S*)-**1d** (Scheme 6) was proved by comparison of specific rotation of 1-indanol, obtained after reductive elimination of (*S*,*S*)-**1d** with Bu_3SnH and AIBN.



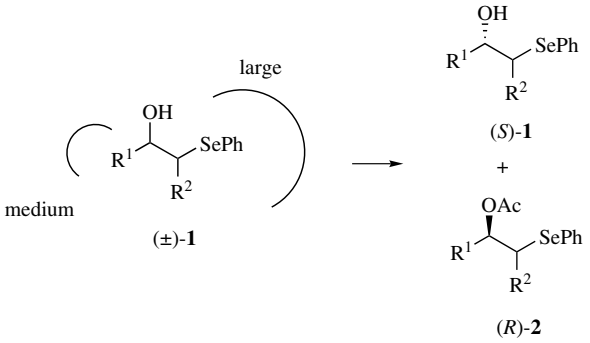
Scheme 6. Lipase-catalyzed resolution of (±)-**1d**.

Following the same procedure we proved that in the case of compound (±)-**1f**, the lipase showed the same enantiopreference. Indeed, we obtained (*S*,*S*)-alcohol **1f** and (*R*,*R*)-ester **2f** (Scheme 7).

These substrates follow the Kazlauskas's rule,[2c] in which the CH_2SePh or CHSePh was the larger substituent (Scheme 8).



Scheme 7. Lipase-catalyzed resolution of (±)-**1f**.



Scheme 8. Kazlauskas's rule.

Only in the case of alcohol (±)-**1a** did the resolution give an opposite enantiopreference. At lower temperatures the bulky substituents of compound (±)-**1a** cause severe steric repulsions. Indeed, on increasing the temperature, the protein can fluctuate to relieve steric repulsion.

The CH_2SePh group should be bulkier than the Ph group, as can be seen by the comparison of the relevant M_R values (37.93 and 25.36, respectively).[39] However, in the case of compound (±)-**1a** the CH_2SePh group was preferentially fitted as a medium group, probably because of the free rotation of the CH_2 group. By changing the phenyl with thiophen-2-yl, the enantiopreference was reversed. The resolution of 2-ethylthio-1-thiophen-2-yl-ethanol showed that the $CH_2SCH_2CH_3$ group acted as a large substituent whereas the thiophen-2-yl acted as a medium one.[38] We believe that, in our case, the CH_2SePh group was the preferred large substituent. The steric requirement of the thiophen-2-yl group is slightly smaller than that of a phenyl ring (M_R values 24.04 and 25.36, respectively).[39] This may explain the different behaviour between (±)-**1a** and (±)-**1b** (Fig. 1).

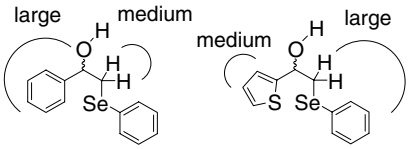


Figure 1. Size of substituents in compounds (±)-**1a** and (±)-**1b**.

The annelation in compound (±)-**1d** gave a more rigid molecule. In this case, the absence of rotation, makes the CHSePh group bulkier than the fused phenyl ring.

Recently, a new transition-state model for the lipase-catalyzed kinetic resolutions of secondary alcohols has been proposed.[40] In this model the C–O bond of the substrate

takes a *gauche* conformation with respect to the breaking C–O bond, due to stereoelectronic effects, and the H atom attached to the asymmetric C atom of the substrate is *syn*-oriented towards the carbonyl O atom of the acetyl group. In this model the faster-reacting enantiomer can direct the larger substituent towards the external solvent (Fig. 2).

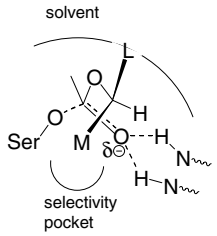


Figure 2. Ema's model.

On the grounds of the PCL structure,[41,42] this model and simple computer molecular models, it could be seen that **1d** fits very well into the enzyme pocket giving excellent enantiopreference.

Also in the case of compound (±)-**1f**, the annelation makes the CHSePh group bulkier than the fused phenyl ring giving good enantiopreference but, at low conversion. Indeed, compound (±)-**1f** showed an intermediate behaviour between (±)-**1a** and (±)-**1d** both in terms of reactivity and enantiopreference. Because of the annelation with the more flexible cyclohexane ring in compound (±)-**1f**, the phenyl ring can be considered a bulkier substituent than the phenyl ring of compound (±)-**1d**. As a consequence it does not fit well (Fig. 3). In fact, no reaction was observed at 30 °C, whereas at 60 °C the reaction was slow. Following Ema's model, the large substituent is directed towards the external solvent pool, whereas in the case of (±)-**1d** the almost planar medium substituent fits perfectly in the selectivity pocket. In the case of (±)-**1f** the medium substituent does not fit.

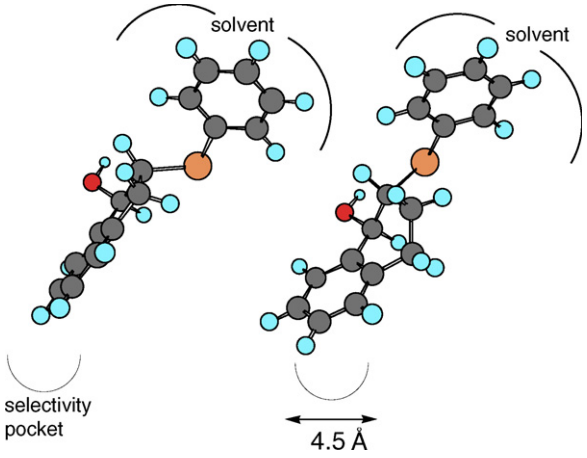
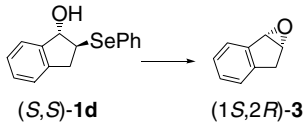


Figure 3.

In compound (±)-**1e**, the large substituent is the PhSe group whereas the methylene group is the medium one. The great difference in size for both groups may explain the high enantioselectivity observed. Moreover, for the same reason, (±)-**1e** reacted faster as compared to (±)-**1d**. A similar behaviour has been observed with compound (±)-**1g**. Indeed, for the same reason it reacted at 30 °C while no reaction was observed for (±)-**1f** at the same temperature. Moreover, the resolution of (±)-**1g** was slower than (±)-**1e**, as expected. It should also be noted that compounds (±)-**1c** and (±)-**1e** showed very similar behaviour indicating that the fused phenyl ring plays a minor role.

Among compounds (±)-**1h–j**, the higher *E* value has been obtained with allyl substituted hydroxy selenide **1i**. Also the homoallyl group fits quite well in the stereoselectivity pocket, while lower *E* values have been obtained with the smaller vinyl group. It is interesting to note that compound (±)-**1k**, which possesses a substituent similar in size to the vinyl group (M_R vinyl: 10.99; M_R CH_2Cl 10.49) showed a similar reactivity, but better resolution (*E* **1h** 22; *E* **1k**: 104).

As a demonstration of the utility of enantiopure β-hydroxy selenides, compound (*S*,*S*)-**1d** was transformed into enantiopure (1*S*,2*R*)-indene oxide **3** (Scheme 9). This product can be obtained by oxidation with oxone.[43] We obtained the indene oxide after the reaction with Me_3OBF_4 followed by treatment with NaOH (75%).[4]



Scheme 9. Synthesis of enantiopure indene oxide.

Enantiopure (1*S*,2*R*)-indene oxide can be transformed into *cis*-1-amino-2-indanol,[44] which has been used as a chiral auxiliary for asymmetric synthesis[45–48] and is an important component of Crixivan®,[49] a potent inhibitor of the protease of human immunodeficiency virus (HIV).[50,51]

3. Conclusion

In conclusion we have shown that racemic β-hydroxy selenides can be successfully resolved by lipase-catalyzed acetylation using PS-C II lipase in the presence of vinyl acetate with ee values up to >99%. These results allow us to broaden the poor set of examples reported in the literature. Moreover, this study pointed out that bulky substituents, such as phenyl and CH_2SePh, have a detrimental effect both on the reactivity and enantiopreference. However, when the annelation reduces the steric hindrance of the phenyl group, it leads to higher enantiopreference. Moreover, regioisomeric annelated compound having a greater difference in sizes for substituents at the carbinol atom showed high enantiopreference. Good enantiopreferences were also observed in acyclic β-hydroxy selenides having a vinyl, allyl, homoallyl and chloromethyl group. Finally, even if the ee values were low, the opposite enantiopreference shown by phenyl and thiophen-2-yl substituted compounds should be noted. This methodology offers an interesting method for the synthesis of enantiopure β-hydroxy selenides that are useful building blocks.

4. Experimental

4.1. General

NMR spectra were recorded on a Bruker AC-E series 250 MHz spectrometer using $CDCl_3$ as solvent. FT-IR spectra were registered with a Shimadzu FTIR 8300 infrared spectrophotometer. Carbon and nitrogen content were determined by combustion analysis in a Fisons EA 1108 elemental analyzer. Optical rotations were measured in chloroform on a Jasco P1010 polarimeter. Chiral HPLC was performed using a Shimadzu LC-10AD pump with a SPD-M10A UV detector and Daicel column (OD-H).

4.2. Enzymatic resolution procedure

To a solution of alcohol (±)-**1** (0.4 mmol) in toluene (0.9 mL) at 30 °C, vinyl acetate (1.2 mmol) and PS-C II lipase (50 mg) were added. The reaction was monitored by HPLC, then taken up with diethyl ether, filtered and the solvent removed under reduced pressure. The residue was checked by NMR then purified by silica gel chromatography using light petroleum/ethyl acetate as eluent.

4.2.1. (*R*)-1-Phenyl-2-(phenylseleno)ethanol 1a. $[\alpha]_D^{26} = -8.6$ (*c* 0.90, $CHCl_3$); 44% ee. HPLC: (*R*)-**1a** 12.22 min, (*S*)-**1a** 11.56 min (*n*-hexane/*i*-PrOH 90/10; 1 mL/min). ^{1}H NMR (250 MHz): δ 3.21 (dd, $J = 12.6$ and 8.9 Hz, 1H), 3.32 (dd, $J = 12.6$ and 4.1 Hz, 1H), 3.40 (s, 1H, OH), 4.82 (dd, $J = 8.9$ and 4.1 Hz, 1 H), 7.31–7.39 (m, 8H), 7.57–7.61 (m, 2H); ^{13}C NMR (62.5 MHz): δ 38.2, 72.6, 126.1, 127.3, 128.0, 128.6, 129.4, 129.8, 133.1, 142.9. IR (liquid film) 3418, 1577, 1493, 1477, 1437 cm^{-1}. Anal. Calcd for $C_{14}H_{14}OSe$: C, 60.66; H, 5.09. Found: C, 60.49; H, 5.01.

4.2.2. (*S*)-1-Phenyl-2-(phenylseleno)ethyl acetate 2a. $[\alpha]_D^{26} = +13.2$ (*c* 1.38, $CHCl_3$); 46% ee. HPLC: (*S*)-**2a** 6.09 min, (*R*)-**2a** 6.60 min (*n*-hexane/*i*-PrOH 90/10; 1 mL/min). ^{1}H NMR (250 MHz): δ 2.00 (s, 3H), 3.21 (dd, $J = 12.8$ and 6.0 Hz, 1H), 3.36 (dd, $J = 12.8$ and 7.9 Hz, 1H), 5.93 (dd, $J = 7.9$ and 6.0 Hz, 1H), 7.22–7.32 (m, 8H), 7.47–7.51 (m, 2H); ^{13}C NMR (62.5 MHz): δ 21.0, 33.4, 75.2, 126.6, 127.2, 128.4, 128.5, 129.1, 129.9, 133.1, 139.5, 169.5. IR (liquid film) 1740, 1577, 1493, 1477, 1454, 1437, 1234 cm^{-1}. Anal. Calcd for $C_{16}H_{16}O_2Se$: C, 60.19; H, 5.05. Found: C, 60.30; H, 5.17.

4.2.3. (*S*)-2-(Phenylseleno)-1-thiophen-2-yl-ethanol 1b. $[\alpha]_D^{25} = +4.1$ (*c* 0.73, $CHCl_3$); 58% ee. HPLC: (*S*)-**1b** 52.85 min, (*R*)-**1b** 57.95 min (*n*-hexane/*i*-PrOH 98/2; 1 mL/min). ^{1}H NMR (250 MHz): δ 3.22 (s, 1H, OH), 3.28–3.45 (m, 2H), 5.05 (dd, $J = 8.2$ and 4.6 Hz, 1H), 6.96–6.99 (m, 2H); 7.24–7.33 (m, 4H), 7.53–7.59 (m, 2H); ^{13}C NMR (62.5 MHz): δ 38.1, 68.8, 124.1, 124.9, 126.8, 127.5, 129.3, 133.2, 146.6. IR (liquid film) 3408, 1577, 1493, 1477, 1437 cm^{-1}. Anal. Calcd for $C_{12}H_{12}OSSe$: C, 50.88; H, 4.27. Found: C, 50.69; H, 4.21.

4.2.4. (*R*)-2-(Phenylseleno)-1-thiophen-2-yl-ethyl acetate 2b. $[\alpha]_D^{26} = -20.4$ (*c* 0.93, $CHCl_3$); 58% ee. HPLC: (*R*)-**2b** 6.50 min, (*S*)-**2b** 6.30 min (*n*-hexane/*i*-PrOH 90/10; 1 mL/min). ^{1}H NMR (250 MHz): δ 2.00 (s, 3H), 3.32 (dd, $J = 12.7$ and 6.1 Hz, 1H), 3.46 (dd, $J = 12.7$ and 7.9 Hz, 1H), 6.24 (dd, $J = 7.9$ and 6.1 Hz, 1H), 6.98 (dd, $J = 5.3$ and 3.5 Hz, 1H), 7.08 (d, $J = 3.5$ Hz, 1H), 7.25–7.30 (m, 4H), 7.53–7.57 (m, 2H); ^{13}C NMR (62.5 MHz): δ 20.9, 33.2, 70.6, 125.6, 126.2, 126.6, 127.3, 129.1, 129.5, 133.1, 142.0, 169.8. IR (liquid film) 1740, 1577, 1535, 1477, 1437, 1229 cm^{-1}. Anal. Calcd for $C_{14}H_{14}O_2SSe$: C, 51.69; H, 4.34. Found: C, 51.40; H, 4.25.

4.2.5. (*S*,*S*)-2-(Phenylseleno)-cyclopentanol 1c. $[\alpha]_D^{28} = +19.7$ (*c* 0.81, $CHCl_3$); >99% ee. HPLC: (*S*,*S*)-**1c** 7.40 min, (*R*,*R*)-**1c** 5.80 min (*n*-hexane/*i*-PrOH 90/10; 1 mL/min). ^{1}H NMR (250 MHz): δ 1.52–1.81 (m, 4H), 1.96–2.10 (m, 1H), 2.18–2.30 (m, 1H), 2.80 (s, 1H, OH), 3.39–3.46 (m, 1H), 4.12–4.17 (m, 1H), 7.17–7.34 (m, 3H), 7.52–7.58 (m, 2H); ^{13}C NMR (62.5 MHz): δ 21.9, 31.0, 32.7, 49.4, 78.5, 127.1, 128.9, 129.4, 133.8. IR (liquid film) 3332, 1577, 1477, 1437 cm^{-1}. Anal. Calcd for $C_{11}H_{14}OSe$: C, 54.78; H, 5.85. Found: C, 54.60; H, 5.66.

4.2.6. (*R*,*R*)-2-(Phenylseleno)-cyclopentyl acetate 2c. $[\alpha]_D^{28} = -2.2$ (*c* 1.02, $CHCl_3$); >99% ee. HPLC: (*R*,*R*)-**2c** 5.45 min, (*S*,*S*)-**2c** 5.35 min (*n*-hexane/*i*-PrOH 98/2; 1 mL/min). ^{1}H NMR (250 MHz): δ 1.65–1.80 (m, 4H), 1.94 (s, 3H), 2.14–2.25 (m, 2H), 3.58–3.65 (m, 1H), 5.10–5.16 (m, 1H), 7.25–7.29 (m, 3H), 7.55–7.59 (m, 2H); ^{13}C NMR (62.5 MHz): δ 21.1, 22.5, 30.9, 31.1, 45.8, 81.4, 127.5, 129.0, 129.2, 134.2, 170.2. IR (liquid film) 1738, 1577, 1477, 1437, 1371, 1238 cm^{-1}. Anal. Calcd for $C_{13}H_{16}O_2Se$: C, 55.13; H, 5.69. Found: C, 55.32; H, 5.87.

4.2.7. (*S*,*S*)-2,3-Dihydro-2-(phenylseleno)-1*H*-inden-1-ol 1d. $[\alpha]_D^{26} = +3.7$ (*c* 0.83); >99% ee. HPLC: (*S*,*S*)-**1d** 15.48 min, (*R*,*R*)-**1d** 9.04 min (*n*-hexane/*i*-PrOH 90/10; 1 mL/min). Mp 101 °C. ^{1}H NMR (250 MHz): δ 2.26 (s, 1H, OH), 2.96 (dd, $J = 16.3$ and 7.6 Hz, 1H), 3.46 (dd, $J = 16.3$ and 7.7 Hz, 1H), 3.78 (ddd, $J = 7.7$, 7.6 and 5.8 Hz, 1H), 5.19 (d, $J = 5.8$ Hz, 1H), 7.18–7.40 (m, 7H), 7.63–7.67 (m, 2H); ^{13}C NMR (62.5 MHz): δ 37.7, 49.3, 81.5, 124.2, 124.5, 127.2, 127.7, 128.6, 129.2, 134.7, 141.0, 143.1. IR (nujol) 3248, 1336, 1068 cm^{-1}. Anal. Calcd for $C_{15}H_{14}OSe$: C, 62.29; H, 4.88. Found: C, 62.40; H, 4.80.

4.2.8. (*R*,*R*)-2,3-Dihydro-2-(phenylseleno)-1*H*-inden-1-yl acetate 2d. $[\alpha]_D^{25} = -83.6$ (*c* 1.95, $CHCl_3$); >99% ee determined as alcohol. ^{1}H NMR (250 MHz): δ 1.94 (s, 3H), 2.92 (dd, $J = 16.6$ and 5.4 Hz, 1H), 3.50 (dd, $J = 16.6$ and 7.5 Hz, 1H), 3.78 (ddd, $J = 7.5$, 5.4 and 4.2 Hz, 1H), 6.24 (d, $J = 4.2$ Hz, 1H), 7.14–7.31 (m, 7H), 7.54–7.58 (m, 2H). ^{13}C NMR (62.5 MHz): δ 20.9, 37.8, 44.8, 82.7, 124.6, 125.5, 127.1, 127.8, 128.3, 129.0, 129.1, 134.9, 139.9, 142.2. IR (liquid film) 1732, 1608, 1577, 1437, 1232 cm^{-1}. Anal. Calcd for $C_{17}H_{16}O_2Se$: C, 61.64; H, 4.87. Found: C, 61.74; H, 4.99.

4.2.9. (*S*,*S*)-2,3-Dihydro-1-(phenylseleno)-1*H*-inden-2-ol 1e. $[\alpha]_D^{26} = -58.1$ (*c* 1.01, $CHCl_3$); >99% ee determined as ester. Mp 62 °C. ^{1}H NMR (250 MHz): δ 2.73 (d, $J = 16.6$ Hz, 1H), 3.22 (dd, $J = 16.6$ and 5.3 Hz, 1H), 3.40 (s, 1H, OH), 4.50 (d, $J = 5.3$ Hz, 1H), 4.63 (s, 1H), 7.25–7.40 (m, 7H), 7.56–7.58 (m, 2H); ^{13}C NMR (62.5 MHz): δ 39.6,

53.4, 78.2, 124.9, 125.4, 126.7, 127.3, 127.6, 128.7, 129.2, 133.8, 140.4, 140.6. IR (film) 3346, 1577, 1477 cm^{-1}. Anal. Calcd for $C_{15}H_{14}OSe$: C, 62.29; H, 4.88. Found: C, 62.44; H, 4.79.

4.2.10. (*R*,*R*)-2,3-Dihydro-1-(phenylseleno)-1*H*-inden-2-yl acetate 2e. $[\alpha]_D^{27} = +25.6$ (*c* 1.19, $CHCl_3$); >99% ee. HPLC: (*R*,*R*)-**2e** 6.90 min, (*S*,*S*)-**2e** 7.30 min (*n*-hexane/*i*-PrOH 98/2; 1 mL/min). Mp 58 °C. ^1H NMR (250 MHz): δ 1.97 (s, 3H), 2.85 (d, $J = 17.3$ Hz, 1H), 3.28 (dd, $J = 17.3$ and 5.7 Hz, 1H), 4.78 (d, $J = 1.4$ Hz, 1H), 5.54 (ddd, $J = 17.3$, 5.7 and 1.4 Hz, 1H), 7.19–7.36 (m, 7H), 7.51–7.55 (m, 2H); ^{13}C NMR (62.5 MHz): δ 21.1, 37.7, 50.6, 81.1, 124.6, 125.3, 127.1, 128.0, 128.1, 128.4, 128.9, 135.1, 140.6, 140.8, 170.4. IR (film) 1738, 1577, 1475, 1371, 1238 cm^{-1}. Anal. Calcd for $C_{17}H_{16}O_2Se$: C, 61.64; H, 4.87. Found: C, 61.79; H, 5.01.

4.2.11. (*S*,*S*)-1,2,3,4-Tetrahydro-2-(phenylseleno)naphthalen-1-ol 1f. $[\alpha]_D^{28} = -9.7$ (*c* 1.27, $CHCl_3$); 34% ee determined as ester. ^1H NMR (250 MHz): δ 1.97 (dddd, $J = 20.2$, 13.6, 8.1 and 6.7 Hz, 1H), 2.37–2.49 (m, 1H), 2.77 (s, 1H, OH), 2.83–2.94 (m, 2H), 3.49 (ddd, $J = 10.3$, 7.8 and 3.3 Hz, 1H), 4.71 (d, $J = 7.8$ Hz, 1H), 7.06–7.10 (m, 1H), 7.20–7.35 (m, 5H), 7.50–7.55 (m, 1H), 7.61–7.66 (m, 2H); ^{13}C NMR (62.5 MHz): δ 27.6, 28.7, 48.7, 71.7, 126.4, 127.2, 127.6, 128.1, 128.2, 128.6, 129.2, 135.5, 135.6, 136.9. IR (liquid film) 3385, 1577, 1477, 1437 cm^{-1}. Anal. Calcd for $C_{16}H_{16}OSe$: C, 63.37; H, 5.32. Found: C, 63.50; H, 5.37.

4.2.12. (*R*,*R*)-1,2,3,4-Tetrahydro-2-(phenylseleno)naphthalen-1-yl acetate 2f. $[\alpha]_D^{26} = -51.2$ (*c* 0.26, $CHCl_3$); 96% ee. HPLC: (*R*,*R*)-**2f** 7.70 min, (*S*,*S*)-**2f** 9.90 min (*n*-hexane/*i*-PrOH 98/2; 1 mL/min). ^1H NMR (250 MHz): δ 2.01–2.10 (m, 1H, overlapped with 2.04 s, 3H), 2.40–2.52 (m, 1H), 2.86–3.05 (m, 2H), 3.77 (ddd, $J = 8.4$, 5.1 and 3.2 Hz, 1H), 6.13 (d, $J = 5.1$ Hz, 1H), 7.14–7.34 (m, 7H), 7.62–7.66 (m, 2H); ^{13}C NMR (62.5 MHz): δ 21.2, 25.5, 26.9, 43.2, 73.1, 126.4, 127.7, 128.3, 128.4, 128.9, 129.1, 129.8, 133.0, 134.6, 136.6, 170.5. IR (liquid film) 1732, 1577, 1477, 1369, 1232 cm^{-1}. Anal. Calcd for $C_{18}H_{18}O_2Se$: C, 62.61; H, 5.25. Found: C, 62.79; H, 5.14.

4.2.13. (*S*,*S*)-1,2,3,4-Tetrahydro-1-(phenylseleno)naphthalen-2-ol 1g. $[\alpha]_D^{22} = -20.9$ (*c* 0.37, $CHCl_3$); 82% ee. HPLC: (*S*,*S*)-**1g** 28.1 min, (*R*,*R*)-**1g** 48.4 min (*n*-hexane/*i*-PrOH 98/2; 1 mL/min). ^1H NMR (250 MHz): δ 1.18–1.94 (m, 1H), 2.35 (s, 1H, OH), 2.38–2.51 (m, 1H), 2.76 (ddd, $J = 17.2$, 5.8 and 5.8 Hz, 1H), 2.95 (ddd, $J = 17.2$, 9.2 and 5.8 Hz, 1H), 4.12–4.18 (m, 1H), 4.50 (d, $J = 4.7$ Hz, 1H), 7.08–7.33 (m, 7H), 7.53–7.58 (m, 2H); ^{13}C NMR (62.5 MHz): δ 24.7, 26.1, 50.5, 69.8, 126.1, 126.9, 127.9, 128.7, 129.1, 129.4, 131.4, 133.8, 134.5, 136.2. IR (liquid film) 3385, 1577, 1493, 1475, 1452, 1437 cm^{-1}. Anal. Calcd for $C_{16}H_{16}OSe$: C, 63.37; H, 5.32. Found: C, 63.30; H, 5.29.

4.2.14. (*R*,*R*)-1,2,3,4-Tetrahydro-1-(phenylseleno)naphthalen-2-yl acetate 2g. $[\alpha]_D^{21} = -66.4$ (*c* 0.33, $CHCl_3$); >99% ee. HPLC: (*R*,*R*)-**2g** 12.70 min, (*S*,*S*)-**2g** 13.53 min (*n*-hexane/*i*-PrOH 99.5/0.5; 1 mL/min). ^1H NMR (250 MHz): δ 1.95 (s, 3H), 1.95–2.08 (m, 1H), 2.46–2.60 (m, 1H), 2.76 (ddd, $J = 16.9$, 6.1 and 2.5 Hz, 1H), 2.97 (ddd, $J = 16.9$, 12.0 and 6.0 Hz, 1H), 4.70 (s, 1H), 5.31–5.35 (m, 1H), 7.07–7.20 (m, 3H), 7.30–7.42 (m, 4H), 7.61.7.65 (m 2H); ^{13}C NMR (62.5 MHz): δ 21.2, 22.5, 24.0, 44.7, 72.5, 126.1, 127.0, 128.0, 128.8, 129.2, 129.8, 131.2, 133.4, 134.4, 136.0, 170.5. IR (liquid film) 1732, 1577, 1493, 1477, 1454, 1437, 1373, 1234 cm^{-1}. Anal. Calcd for $C_{18}H_{18}O_2Se$: C, 62.61; H, 5.25. Found: C, 62.75; H, 5.31.

4.2.15. (*S*)-1-(Phenylseleno)-but-3-en-2-ol (1h). $[\alpha]_D^{26} = +40.4$ (*c* 0.51, $CHCl_3$); 80% ee determined as ester. ^1H NMR (250 MHz): δ 2.55 (s, 1H, OH), 3.00 (dd, $J = 12.6$ and 8.0 Hz, 1H), 3.14 (dd, $J = 12.6$ and 4.5 Hz, 1H), 4.19–4.27 (m, 1H), 5.16 (ddd, $J = 10.4$, 1.5 and 1.5 Hz, 1H), 5.30 (ddd, $J = 17.0$, 1.5 and 1.5 Hz, 1H), 5.88 (ddd, $J = 17.0$, 10.4 and 5.7 Hz, 1H), 7.24–7.30 (m, 3H), 7.53–7.57 (m, 2H); ^{13}C NMR (62.5 MHz): δ 35.6, 70.8, 115.6, 126.9, 128.9, 129.3, 132.6, 138.7. IR (liquid film) 3387, 1577, 1477, 1437 cm^{-1}. Anal. Calcd for $C_{10}H_{12}OSe$: C, 52.87; H, 5.32. Found: C, 53.00; H, 5.37.

4.2.16. (*R*)-1-(Phenylseleno)-but-3-en-2-yl acetate 2h. $[\alpha]_D^{26} = -5.4$ (*c* 0.99, $CHCl_3$); 80% ee. HPLC: (*R*)-**2h** 5.20 min, (*S*)-**2h** 4.69 min (*n*-hexane/*i*-PrOH 90/10; 1 mL/min). ^1H NMR (250 MHz): δ 2.00 (s, 3H), 3.04–3.20 (m, 2H), 5.24 (d, $J = 10.7$ Hz, 1H), 5.31 (d, $J = 16.8$ Hz, 1H), 5.40–5.48 (m, 1H), 5.86 (ddd, $J = 16.8$, 10.7 and 6.0 Hz, 1H), 7.24–7.29 (m, 3H), 7.51–7.57 (m, 2H); ^{13}C NMR (62.5 MHz): δ 20.9, 31.4, 73.8, 117.9, 127.2, 129.1, 129.8, 133.0, 135.2, 169.9. IR (liquid film) 1736, 1577, 1477, 1437, 1236 cm^{-1}. Anal. Calcd for $C_{12}H_{14}O_2Se$: C, 53.54; H, 5.24. Found: C, 53.62; H, 5.14.

4.2.17. (*S*)-1-(Phenylseleno)-pent-4-en-2-ol 1i. $[\alpha]_D^{26} = +30.65$ (*c* 0.65, $CHCl_3$); >99% ee. HPLC: (*S*)-**1i** 19.25 min, (*R*)-**1i** 18.40 min (*n*-hexane/*i*-PrOH 98/2; 1 mL/min). ^1H NMR (250 MHz): δ 2.30–2.41 (m, 2H), 2.82 (s, 1H, OH), 2.94 (dd, $J = 12.7$ and 7.9 Hz, 1H), 3.11 (dd, $J = 12.7$ and 4.3 Hz, 1H), 3.75–3.85 (m, 1H), 5.07–5.15 (m, 2H), 5.72–5.87 (m, 1H), 7.22–7.26 (m, 3H), 7.51–7.55 (m, 2H); ^{13}C NMR (62.5 MHz): δ 35.6, 40.6, 69.2, 117.8, 126.9, 128.9, 129.3, 132.6, 133.9. IR (liquid film) 3423, 1577, 1477, 1437 cm^{-1}. Anal. Calcd for $C_{11}H_{14}OSe$: C, 54.78; H, 5.85. Found: C, 54.90; H, 5.92.

4.2.18. (*R*)-1-(Phenylseleno)-pent-4-en-2-yl acetate 2i. $[\alpha]_D^{26} = -16.2$ (*c* 0.87, $CHCl_3$); 94% ee. HPLC: (*R*)-**2i** 4.90 min, (*S*)-**2i** 4.62 min (*n*-hexane/*i*-PrOH 90/10; 1 mL/min). ^1H NMR (250 MHz): δ 1.94 (s, 3H), 2.22–2.54 (m, 2H), 3.07–3.10 (m, 2H), 5.07–5.12 (m, 2H), 5.65–5.80 (m, 1H), 7.24–7.28 (m, 3H), 7.53–7.57 (m, 2H); ^{13}C NMR (62.5 MHz): δ 20.9, 30.9, 38.1, 72.5, 118.4, 127.1, 129.1, 129.9, 132.9, 170.3. IR (liquid film) 1740, 1577, 1477, 1493, 1436, 1371, 1234 cm^{-1}. Anal. Calcd for $C_{13}H_{16}O_2Se$: C, 55.13; H, 5.69. Found: C, 55.24; H, 5.84.

4.2.19. (*S*)-1-(Phenylseleno)-hex-5-en-2-ol 1j. $[\alpha]_D^{24} = +36.3$ (*c* 0.83, $CHCl_3$); 85% ee. HPLC: (*S*)-**1j** 14.41 min, (*R*)-**1j** 15.67 min (*n*-hexane/*i*-PrOH 98/2; 1 mL/min). ^1H NMR (250 MHz): δ 1.59–1.69 (m, 2H), 2.08–2.25 (m, 2H), 2.93 (dd, $J = 12.4$ and 7.9 Hz, 1H), 3.10 (dd, $J = 12.4$ and 4.5 Hz, 1H), 3.13 (s, 1H, OH), 3.70–3.80 (m,

2H), 4.94–5.07 (m, 2H), 5.72–5.87 (m, 1H), 7.21–7.27 (m, 3H), 7.51–7.55 (m, 2H); ^{13}C NMR (62.5 MHz): δ 29.6, 35.3, 36.2, 69.2, 114.5, 126.6, 128.7, 129.4, 132.3, 137.7. IR (liquid film) 3414, 1639, 1577, 1477, 1437 cm^{-1}. Anal. Calcd for $C_{12}H_{16}OSe$: C, 56.47; H, 6.32. Found: C, 56.38, H, 6.25.

4.2.20. (*R*)-1-(Phenylseleno)-hex-5-en-2-yl acetate 2j. $[\alpha]_D^{25} = +3.2$ (*c* 0.49, $CHCl_3$); 95% ee. HPLC: (*R*)-**2j** 5.66 min, (*S*)-**2j** 4.80 min (*n*-hexane/*i*-PrOH 98/2; 1 mL/min). ^{1}H NMR (250 MHz): δ 1.76–1.84 (m, 2H), 1.95 (s, 3H), 2.03–2.13 (m, 2H), 3.09 (d, $J = 6.0$ Hz, 2H), 4.95–5.08 (m, 2H), 5.70–5.84 (m, 1H), 7.25–7.30 (m, 3H), 7.52–7.57 (m, 2H); ^{13}C NMR (62.5 MHz): δ 21.0, 29.5, 31.5, 32.9, 72.9, 115.2, 127.1, 129.1, 129.9, 132.9, 137.4, 170.5. IR (liquid film) 1740, 1641, 1577, 1477, 1437, 1371, 1238 cm^{-1}. Anal. Calcd for $C_{14}H_{18}O_2Se$: C, 56.57; H, 6.10. Found: C, 56.74; H, 6.22.

4.2.21. (*S*)-1-Chloro-3-(phenylseleno)-propan-2-ol 1k. $[\alpha]_D^{23} = +19.25$ (*c* 0.32, $CHCl_3$); 84% ee determined as ester. ^{1}H NMR (250 MHz): δ 2.66 (br s, 1H, OH), 3.07 (dd, $J = 12.8$ and 7.1 Hz, 1H), 3.16 (dd, $J = 13.2$ and 5.6 Hz, 1H), 3.68 (d, $J = 4.9$ Hz, 2H), 3.90–4.00 (m, 1H), 7.26–7.32 (m, 3H), 7.52–7.59 (m, 2H); ^{13}C NMR (62.5 MHz): δ 32.3, 48.3, 70.0, 127.5, 128.8, 129.3, 133.0. IR (liquid film) 3400, 1577, 1477, 1437 cm^{-1}. Anal. Calcd for $C_9H_{11}ClOSe$: C, 43.31; H, 4.44. Found: C, 43.44; H, 4.52.

4.2.22. (*R*)-1-Chloro-3-(phenylseleno)-propan-2-yl acetate 2k. $[\alpha]_D^{23} = -8.8$ (*c* 0.30, $CHCl_3$); 95% ee. HPLC: (*R*)-**2k** 6.27 min, (*S*)-**2k** 5.70 min (*n*-hexane/*i*-PrOH 90/10; 1 mL/min). ^{1}H NMR (250 MHz): δ 1.92 (s, 3H), 3.10 (d, $J = 6.3$ Hz, 2H), 3.70 ($J = 4.8$ Hz, 1H), 5.08 (dddd, $J = 6.3$, 6.3, 4.8 and 4.8 Hz, 1H), 7.18–7.24 (m, 3H), 7.49–7.52 (m, 2H); ^{13}C NMR (62.5 MHz): δ 20.8, 28.1, 44.9, 72.2, 127.5, 129.0, 129.3, 133.1, 170.1. IR (liquid film) 1738, 1578, 1478, 1438, 1372 cm^{-1}. Anal. Calcd for $C_{11}H_{13}ClO_2Se$: C, 45.30; H, 4.49. Found: C, 45.434; H, 4.52.

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