Tetrahedron: *Asymmetry* 19 (2008) 1175–1181

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: http://www.elsevier.com/locate/tetasy

First chemoenzymatic synthesis of organoselenium amines and amides

Leandro H. Andrade *, Alexandre V. Silva

Institute of Chemistry, University of São Paulo, Av. Prof. Lineu Prestes, 748, CEP 05508-900, São Paulo, SP, Brazil

ARTICLE INFO

Article history:
Received 21 January 2008
Accepted 2 April 2008
Available online 26 May 2008

ABSTRACT

A series of organoselenium amines have been synthesized and submitted to the enzymatic kinetic resolution by acetylation mediated by CAL-B (Novozym 435) to give the corresponding chiral amides in an enantiomerically pure form. After evaluating the appropriate lipase, solvent, temperature, and lipase/substrate ratio in the kinetic resolution, the chiral organoselenium amides were obtained with enantiomeric excess of up to 99%.

1. Introduction

In recent years chiral organoselenium compounds have been prepared by several methods ranging from selenocyclization to biocatalysis.[1–9] The constant interest in this area can be devoted to the wide application of selenium to organic synthesis and biological chemistry. For example, we mention that compounds containing a selenium atom have important antioxidant and anti-inflammatory activities.[10,11] Besides those biological applications, this class of compounds has been intensively applied as ligands for asymmetric catalysis, such as asymmetric hydrosilylation of ketones and imines, enantioselective addition of diorganozinc reagents to aldehydes, enantioselective conjugate addition of organometallic reagents to enones, and palladium-catalyzed asymmetric allylic alkylation.[12–14] Among the chiral selenium compounds found as ligands, we observe that amino selenides and diselenides,[15,16] selenium-oxazolidines,[17] chiral selenium-imine,[18,19] and, more recently, chiral β-organoselenium amides[20,21] have been demonstrated to be excellent catalysts. Notwithstanding the intense activity in the field of organoselenium chemistry over the last three decades, to our knowledge, no synthetic studies employing biocatalysis to prepare organoselenium amines have been published to date. As part of our current interest in biocatalytic reactions applied to the selenium chemistry, we decided to develop a chemoenzymatic methodology to synthesize chiral organoselenium amines and amides without the use of organolithium or organomagnesium reagents. Herein we report the incorporation of the selenium atom to aromatic ketones by the use of reactions of potassium selenocyanate and diazonium salts to yield selenocyanate acetophenones. These ketones were alkylated with alkyl halides to result in organoselenium acetophenones which were converted into their corresponding racemic organoselenium amines by reductive amination. Finally, we carried out the enzymatic kinetic resolution (EKR) of the racemic organoselenium amines by their acetylation mediated by lipases to yield the corresponding chiral organoselenium amines and amides in an enantiomerically pure form.

2. Results and discussion

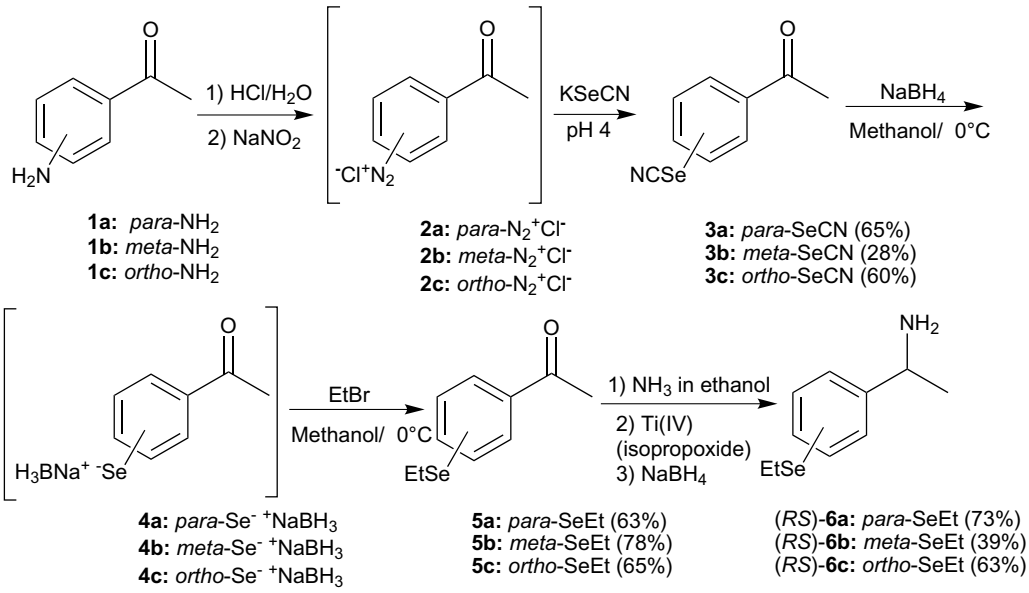
2.1. Synthesis of the organoselenium amines

The methodology of choice for the synthesis of organoselenium amines **6a–c** was the reductive amination of organoselenium ketones. In this way, in order to avoid organolithium or organomagnesium compounds for the insertion of a selenium atom in the acetophenones[5,22,23] an easy synthetic methodology was developed by using the reaction of KSeCN and diazonium salts (Scheme 1). The first step was the preparation of diazonium salts **2a–c** from *ortho*-, *meta*-, and *para*-aminoacetophenones followed by the addition of KSeCN to produce the corresponding selenocyanate acetophenones **3a–c** (yields, 28–65%) as described in Scheme 1. As KSeCN has low stability in acid conditions, needed for the diazotization reaction, and under light exposure, elemental selenium was formed during the reaction affecting the final yield.[24,25]

The next step was the alkylation of the selenium atom in the ketones **3a–c** using $NaBH_4$ and ethyl bromide to give *ortho*-, *meta*-, and *para*-ethylselenium acetophenones (63–78% yield). An interesting feature of this methodology is the facility to prepare several organoselenium ketones by simply changing the alkylating agent. After the alkylation step, we carried out the reductive amination of the organoselenium ketones **5a–c** to afford the (*RS*)-organoselenium amines **6a–c** (39–73% yield). The protocol chosen involved the use of ammonia, titanium(IV) isopropoxide, and ketones **5a–c** to give a titanium(IV) complex,[26] followed by the addition of $NaBH_4$. The reducing agent ($NaBH_4$), under these conditions, can also reduce the unreacted ketone **5a–c**, consequently, decreasing the yield of desired amines **6a–c**.

* Corresponding author. Tel.: +55 11 3091 2287; fax: +55 11 3815 5579.
E-mail address: leandroh@iq.usp.br (L. H. Andrade).

0957-4166/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2008.04.026



Scheme 1. Synthesis of organoselenium amines **6a–c**.

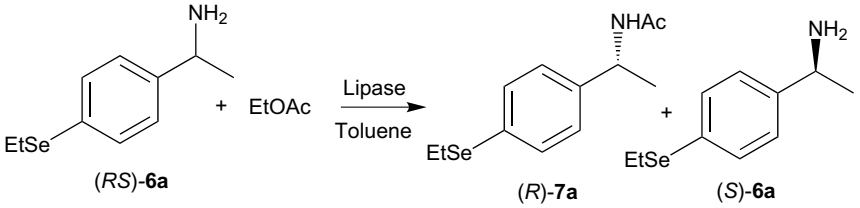
2.2. Kinetic resolution of organoselenium amines catalyzed by lipases

Having in hands the organoselenium amines **6a–c**, we have chosen (*RS*)-1-[4-(ethylselanyl)phenyl]ethanamine **6a** as a model substrate for the study of kinetic resolution. In this study, we have screened for appropriate lipases, solvent, temperature, and lipase/substrate ratio. Initially, we carried out a screening test using 14 lipases for kinetic resolution of (*RS*)-organoselenium amine **6a** with ethyl acetate as an acyl donor and toluene as a solvent at 40 °C (Table 1).

According to the screening test, the lipase which exhibited the highest enantioselectivity was CAL-B (lipase B from *Candida antarctica*, Novozyme 435). This lipase catalyzed the preferential acetylation of the (*R*)-enantiomer of the racemic organoselenium amine **6a** to give the organoselenium amide (*R*)-**7a** in 96% enantiomeric excess. The remaining lipases did not give satisfactory results. For example, when the reaction was performed by lipase Amano M, the amide **7a** was obtained in 69% of conversion (C) with very low enantioselectivity (E) (Table 1, entry 11). On the other hand, the lipase of *Pseudomonas* sp. conducted the preferential acetylation of the (*R*)-organoselenium amine **6a** with 65% ee in low conversion (Table 1, entry 14).

In order to achieve higher enantioselectivity for the process, we decided to evaluate the kinetic resolution of **6a** with CAL-B in different solvents (Table 2, hexane, toluene, ethyl acetate, and

Table 1
Screening of lipases for the kinetic resolution of (*RS*)-**6a**[a]



Entry	Lipase	Product (*R*)-amide ee[b] (%)	Substrate (*S*)-amine ee[c] (%)	Conv.[d]	*E*[e]
1	Porcine pancreatic	21	1	5	2
2	*Candida cylindracia*	8	1	11	1
3	Amano AK	25	1	4	2
4	*Candida rugosa*	16	1	16	1
5	Lipozyme IM	11	1	8	1
6	Amano PS-C II	62	1	2	4
7	Amano A (Aldrich)	29	1	3	2
8	Lipolase 100T	31	3	9	2
9	CAL-B	96	52	35	82
10	Amano PS-DI	59	2	3	4
11	Amano M	4	9	69	1
12	Amano PS	35	1	3	2
13	Amano G	59	3	5	4
14	*Pseudomonas* sp.	65	1	2	5

[a] Reaction conditions: Selenium amine (0.2 mmol); lipase (20 mg); ethyl acetate (0.8 mmols); toluene (1 mL); 40 °C; 48 h.
[b] Ee determinated by HPLC (OD column).
[c] Ee determinated by HPLC after derivatization of the amine using acetic anhydride.
[d] Conversion: $c = ee_s/(ee_s + ee_p)$.[27]
[e] $E = \{\ln[ee\mathbf{P}(1 - ee\mathbf{S})]/(ee\mathbf{P} + ee\mathbf{S})\}/\{\ln[ee\mathbf{P}(1 + ee\mathbf{S})]/(ee\mathbf{P} + ee\mathbf{S})\}$.[27]

Table 2
Evaluation of the enzymatic kinetic resolution of (*RS*)-**6a** under different reaction conditions[a]

Entry	Solvent	Temperature (°C)	Product (*R*)-amide ee[b] (%)	Substrate (*S*)-amine ee[c] (%)	Conv.[d]	*E*[e]
1	Ethyl ether	40	78	7	8	8.7
2	Toluene	40	96	52	35	82
3	Ethyl acetate	40	29	50	63	2.8
4	Hexane	40	97	58	37	118
5	Hexane	50	94	91	49	102
6	Toluene	50	94	77	45	75
7	Hexane	60	76	28	27	10
8	Toluene	60	77	70	48	15
9	Hexane	30	98	29	23	131
10	Toluene	30	97	20	17	79
11	Hexane[f]	30	98	40	29	146
12	Toluene[f]	30	95	33	26	53
13	Hexane[g]	30	99	22	18	>200
14	Toluene[g]	30	98	46	32	156
15	Hexane[h]	30	98	32	25	135
16	Toluene[h]	30	98	33	25	136
17	Hexane[i]	30	99	25	20	>200
18	Toluene[i]	30	97	12	11	73

[a] Reaction conditions: Selenium amine (0.2 mmol); CAL-B (20 mg); ethyl acetate (0.8 mmols); hexane or toluene (1 mL); temperature (°C); 48 h.
[b] Ee determinated by HPLC (OD column).
[c] Ee determinated by HPLC after derivatization of the amine using acetic anhydride.
[d] Conversion: $c = ee_s/(ee_s + ee_p)$.[27]
[e] $E = \{\ln[ee\mathbf{P}(1 - ee\mathbf{S})]/(ee\mathbf{P} + ee\mathbf{S})\}/\{\ln[ee\mathbf{P}(1 + ee\mathbf{S})]/(ee\mathbf{P} + ee\mathbf{S})\}$.[27]
[f] CAL-B (40 mg).
[g] CAL-B (60 mg).
[h] CAL-B (80 mg).
[i] CAL-B (100 mg).

diethyl ether; entries 1–4). As we can see in Table 2, the lipase CAL-B showed the highest enantioselectivity in hexane ($E = 118$), in spite of the low solubility of the compound **6a** in this solvent. When toluene was used as solvent, the enantioselectivity was also good ($E = 82$) and no problems with solubility were observed. However, when the reactions were performed with diethyl ether and ethyl acetate as solvent, a significant decrease in the enantioselectivity was observed (Table 2, $E = 8.7$ and $E = 2.8$; entries 1 and 3, respectively).

Based on these results, we decided to evaluate the effect of different temperature and enzyme amount on the kinetic resolution of (*RS*)-1-[4-(ethylselanyl)phenyl]ethanamine **6a** using hexane and toluene as solvents (Table 2, entries 5–18).

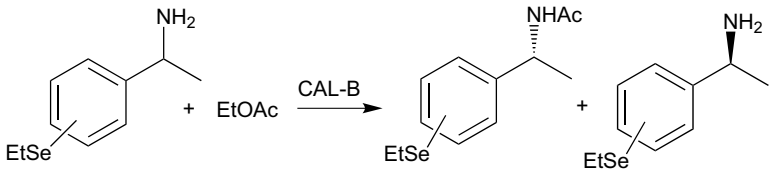
Initially, we evaluated the influence of the temperature (Table 2, entries 2 and 4–10). The reactions were carried out at 30, 40, 50, and 60 °C. The best results were obtained at 30 °C for both solvents (Table 2, entries 9 and 10). According to this study, it was observed that the increase of temperature yielded a higher conversion accomplished with the decrease of enantioselectivity. For example, when the kinetic resolution was performed using hexane at 30 °C, the *E* was 131 (Table 2, entry 9), however, at 60 °C the *E* dropped to 10 (Table 2, entry 7). In toluene, the enantioselectivity observed at 30 °C was 79 (Table 2, entry 10) but, at 60 °C, this *E* value dropped to 15 (Table 2, entry 8). These results showed that the best conditions were obtained at 30 °C for both solvents (hexane and toluene).

A study to choose the appropriated amount of CAL-B was carried out at 30 °C using hexane and toluene as solvents. The reaction was performed using 20, 40, 60, 80, and 100 mg of CAL-B to 0.2 mmol of (*RS*)-organoselenium amine **6a** (Table 2, entries 9–18).

As it can be seen in Table 2, entries 9–18, the increase of the amount of CAL-B did not improve the conversion of the kinetic resolution. However, the enantiomeric purity of the amides formed was poorly affected, especially when hexane was used as a solvent. For the reactions in hexane, the highest conversion was obtained using 40 mg of CAL-B (Table 2, $c = 29$, entry 11) but the highest enantioselectivities were observed using 60 mg and 100 mg of CAL-B (Table 2, $E > 200$, entries 13 and 17). According to these results, we can conclude that the best amount of CAL-B was 60 mg from 0.2 mmol of (*RS*)-organoselenium amine **6a**. After the best conditions for EKR for compound **6a** were established, this methodology has been employed on the organoselenium amine derivatives **6b** and **6c**. The results of EKR for these organoselenium amines are shown in Table 3.

As we can see in Table 3, the kinetic resolution of organoselenium amines **6b** and **6c** mediated by CAL-B, ethyl acetate as an acyl donor, and hexane as a solvent afforded the organoselenium amides **7b** and **7c** with 99% and 98% enantiomeric excesses, respectively (Table 3, entries 1 and 3). The low conversion for the kinetic resolution of **6c** can be attributed to the known selenium–nitrogen interaction (Se–N).[28] Due to this interaction, the nucleophilicity of the amine group decreases and, consequently, a low conversion was observed. The same interaction cannot occur when the selenium atom is at the *para* or *meta* position in the aromatic ring.

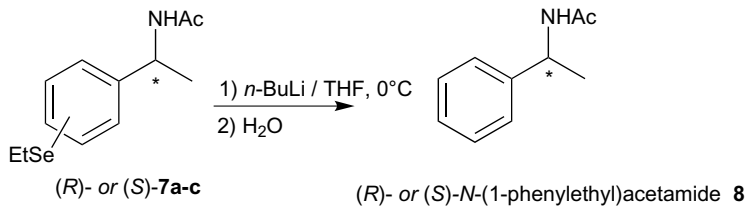
Table 3
Enzymatic kinetic resolution of (*RS*)-**6b**–**c** mediated by CAL-B[a]



(*RS*)-**6b-c** (*R*)-**7b** *meta*-SeEt (*R*)-**7c** *ortho*-SeEt (*S*)-**6b-c**

Entry	Selenium amine/solvent	Product (*R*)-amide ee[b] (%)	Substrate (*S*)-amine ee[c] (%)	Conv.[d]	*E*[e]
1	**6b**: *meta*-SeEt/hexane	99	38	28	>200
2	**6b**: *meta*-SeEt/toluene	96	16	14	57
3	**6c**: *ortho*-SeEt/hexane	98	8	8	107
4	**6c**: *ortho*-SeEt/toluene	82	7	8	10

[a] Reaction conditions: Selenium amine (0.2 mmol); CAL-B (60 mg); ethyl acetate (0.8 mmols); hexane or toluene (1 mL); temperature (30 °C); 48 h.
[b] Ee determinated by HPLC (OD column).
[c] Ee determinated by HPLC after derivatization of the amine using acetic anhydride.
[d] Conversion: $c = ee_s/(ee_s + ee_p)$.[27]
[e] $E = \{\ln[ee\mathbf{P}(1 - ee\mathbf{S})]/(ee\mathbf{P} + ee\mathbf{S})\}/\{\ln[ee\mathbf{P}(1 + ee\mathbf{S})]/(ee\mathbf{P} + ee\mathbf{S})\}$.[27]



Scheme 2. Chemical reaction performed to transform organoselenium amides **7a–c** into (*R*)-and (*S*)-*N*-(1-phenylethyl)acetamide **8**.

2.3. Determination of the enantiomeric excesses and absolute configuration for 6a–c and 7a–c

The enantiomeric excesses of organoselenium amines **6a**, **6b**, and **6c** were calculated from the chiral HPLC chromatograms after derivatization with acetic anhydride (see Section 4.7). The enantiomeric excesses of selenium amides **7a**, **7b**, and **7c** were also calculated from the chiral HPLC chromatograms. The absolute configuration of the amides were attributed by chiral GC chromatographic comparison with authentic samples of (*R*)- and (*S*)-*N*-(1-phenylethyl)acetamide **8** after removing the organoselenium group from organoselenium amides **7a–c** by *n*-butyllithium in THF as shown in Scheme 2.

It was supposed that the lithium–selenium exchange reaction did not affect the stereogenic center of the compounds **7a**, **7b**, and **7c**. To support this assumption, (*R*)-*N*-(1-phenylethyl)acetamide **8** (ee >99%) was also reacted with *n*-butyllithium in THF using the same methodology described above, and an identical enantiomeric excess (ee >99%) was observed at the end of the process. The results obtained showed that the stereochemical preference of CAL-B for the acylation of the organoselenium amines is in accordance with Kazlauska's rule.[29]

3. Conclusion

In order to develop a chemoenzymatic methodology to synthesize chiral organoselenium amines/amides without the use of organolithium or organomagnesium reagents, we have shown that the selenium atom can be incorporated onto an aromatic ketone by using the reaction of potassium selenocyanate and diazonium salts to obtain the selenocyanate acetophenones **3a–c**. These ketones were alkylated with ethyl bromide to give the organoselenium acetophenones **5a–c** which were converted into their corresponding racemic organoselenium amines **6a–c** by reductive amination in good yields. At the end of the process, we employed the kinetic resolution of these racemic organoselenium amines by their acetylation mediated by lipases to give the corresponding chiral amides/amines in an enantiomerically pure form (up to 99% ee). The stereochemistry of the resolved organoselenium amines and their acetates is in accordance with Kazlauska's rule.

4. Experimental

4.1. General methods

Lipase B from *C. antarctica*, Novozym 435, was a gift from Novozymes A/S. Solvents were purified by standard procedures. All other reagents are commercially available and were used without further purification. Thin-layer chromatography (TLC) was performed using precoated plates (Aluminum foil, Silica Gel 60 F_{254} Merck, 0.25 mm). Silica gel (0.035–0.070 mm, Acros) was used for column chromatography. GC analyses were performed in a Shimadzu GC-17A instrument with a FID detector, using hydrogen as a carrier gas (100 kPa). The GC chiral column used was a Chirasil-Dex CB β-cyclodextrin (25 m × 0.25 mm) for determination of the enantiomeric excesses. Low Resolution Mass Spectra (LRMS) were recorded on a Shimadzu GCMS P5050A (70 eV) spectrometer. HPLC analyses were performed in a Shimadzu SPD-10AV instrument with a UV–vis detector. The HPLC chiral column used was a Chiralcel OD-H (0.46 cm × 25 cm) for determination of the enantiomeric excesses. Optical rotations were determined on a JASCO DIP-378 polarimeter. Infrared spectra were recorded on a Perkin–Elmer 1750-FT-IR spectrometer. NMR spectra were recorded on Bruker DPX 500, DPX 300 or DPX 200 instrument. For ^{1}H (instrument operating at 500.13 MHz, 300 MHz, or 200 MHz) δ values are referenced to $(CH_3)_4Si$ (0 ppm) and for ^{13}C (instrument operating at 125.77 MHz, 75.5 MHz, or 50 MHz) δ values are referenced to $CDCl_3$ (77.0 ppm). Chemical shifts are given in ppm and coupling constants are given in Hertz (s = singlet, d = doublet, dd = double doublet, t = triplet, quart. = quartet, m = multiplet). High resolution mass spectra (HRMS) analyses were performed in a LCMS-Bruker Daltonik Microtof with ESI ionization.

4.2. Synthesis of 1-((selenocyanate)phenyl)ethanones 3a–c

The procedure was adopted from that reported by Kirmse et al.[25] To an Erlenmeyer flask, aminoacetophenones **1a–c** (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 inorganic salt 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 (8:2) as solvent. The solvent was removed to give the selenocyanate acetophenones **3a–c**.

4.2.1. 1-((4-Selenocyanate)phenyl)ethanone 3a

Yield: 65%. IR (KBr) cm^{-1}: 3434, 3342, 2964, 2920, 2151, 1685, 1586, 1394, 1360, 1266, 1185, 960, 816, 587, 520, 464. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.99–7.95 (d, *J* = 8.3 Hz, 2H), 7.73–7.68 (d, *J* = 8.8 Hz, 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.

4.2.2. 1-((3-Selenocyanate)phenyl)ethanone 3b

Yield: 28%. IR (KBr) cm^{-1}: 3430, 3332, 2151, 1675, 1563, 1414, 1359, 1256, 959, 900, 799, 684, 592, 523. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.20 (s, 1H), 8.01–7.98 (d, J = 7.8 Hz, 1H), 7.87–7.84 (m, 1H), 7.57–7.52 (t, *J* = 7.8 Hz, 1H), 2.63 (s, 3H). ^{13}C NMR (75 MHz) δ: 196.36, 138.79, 136.81, 132.16, 130.71, 129.53, 122.89, 100.87,

26.63. LRMS [EI], *m*/*z* (relative abundance): 225 (M^+, 36), 210 (87), 182 (35), 156 (11), 76 (25), 63 (14), 43 (100). HRMS [ESI(+)], calcd for $[C_9H_7NOSe+Na]^+$: 247.9591, found 247.9587.

4.2.3. 1-((2-Selenocyanate)phenyl)ethanone 3c

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 (t, J = 7.5 Hz, 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.

4.3. Synthesis of 1-((ethylselanyl)phenyl)ethanones 5a–c

To a two-necked round-bottomed flask, selenocyanate acetophenones **3a**–**c** (225 mg, 1 mmol) and methanol (5 mL) under N_2 were added. The solution was cooled to 0 °C and ethyl bromide (300 μL, 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 the 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 (8:2) as solvent. The solvent was removed to give the ethylselenium acetophenones **5a**–**c**.

4.3.1. 1-(4-(Ethylselanyl)phenyl)ethanone 5a

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: 7.84–7.80 (d, J = 8.3 Hz, 2 H), 7.50–7.45 (d, J = 8.8 Hz, 2H), 3.07–2.95 (quart., J = 7.5 Hz, 2H), 2.57 (s, 3H), 1.52–1.45 (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.

4.3.2. 1-(3-(Ethylselanyl)phenyl)ethanone 5b

Yield: 78%. IR (KBr) cm^{-1}: 3526, 3354, 3057, 2962, 2923, 2867, 1686, 1568, 1413, 1355, 1254, 962, 908, 788, 687, 588, 467. ^1H NMR (200 MHz, $CDCl_3$) δ: 8.06 (s, 1H), 7.82–7.78 (m, 1H), 7.69–7.64 (m, 1H), 7.39–7.32 (t, J = 7.7 Hz, 1H), 3.03–2.92 (quart., J = 7.5 Hz, 2H), 2.60 (s, 3H), 1.49–1.41 (t, J = 7.5 Hz, 3H). ^{13}C NMR (50 Hz) δ: 197.63, 137.63, 136.68, 131.79, 131.27 129.01, 126.51, 26.60, 21.41, 15.34. LRMS [EI], *m*/*z* (relative abundance): 228 (M^+, 63), 213 (34), 185 (42), 156 (15), 117 (7), 105 (12), 91 (7), 77 (17), 51 (9), 43 (100). HRMS [ESI(+)], calcd for $[C_{10}H_{12}OSe+H]^+$: 229.0131, found 229.0123; $(M+Na)^+$; for $[C_{10}H_{12}OSe+Na]$: 250.9951, found 250.9952.

4.3.3. 1-(2-(Ethylselanyl)phenyl)ethanone 5c

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: 7.93–7.90 (dd, J = 7.5Hz, J = 1.5 Hz, 1H), 7.51–7.48 (m, 1H), 7.44–7.38 (m, 1H), 7.27–7.22 (m, 1H), 2.90–2.82 (quart., J = 7.5 Hz, 2H), 2.63 (s, 3H), 1.50–1.45 (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.

4.4. Synthesis of (*RS*)-1-((ethylselanyl)phenyl)ethanamines 6a–c

The procedure was carried out in a way similar to that reported by Bhattacharyya et al.[26] To a two-necked round-bottomed flask, ethylselenium acetophenones **5a**–**c** (228 mg, 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) under N_2 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 acid 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 in a pure form. These compounds were employed directly in the enzymatic kinetic resolution.

4.4.1. (*RS*)-1-(4-(Ethylselanyl)phenyl)ethanamine 6a

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: 7.47–7.43 (d, J = 8.3 Hz, 2 H), 7.26–7.22 (d, J = 8.3 Hz, 2H), 4.13–4.04 (quart., J = 6.5 Hz, 1H), 2.95–2.84 (quart., J = 7.5 Hz, 2H), 1.81 (s, 2H), 1.46–1.39 (t, J = 7.0 Hz, 3H), 1.39–1.35 (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.

4.4.2. (*RS*)-1-(3-(Ethylselanyl)phenyl)ethanamine 6b

Yield: 38%. IR (KBr) cm^{-1}: 3358, 3285, 3052, 2961, 2923, 2866, 1589, 1570, 1448, 1372, 1231, 887, 786, 700, 445. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.47 (s, 1H), 7.36–7.33 (m, 1H), 7.22–7.19 (m, 2H), 4.11–4.05 (quart., J = 6.6 Hz, 1H), 2.98–2.89 (quart., J = 7.5 Hz, 2H), 2.03 (s, 2H), 1.46–1.41 (t, J = 7.5 Hz, 3H), 1.39–1.37 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz) δ: 148.32, 130.72, 130.49, 129.77, 129.09, 124.15, 51.15, 25.49, 21.23, 15.48. LRMS [EI], *m*/*z* (relative abundance): 229 (M^+, 43), 214 (100), 185 (43), 120 (12), 104 (19), 78 (28), 44 (84). HRMS [ESI(+)], calcd for $[C_{10}H_{15}NSe{-}NH_2]^+$: 213.0182, found 213.0167; calcd for $[C_{10}H_{15}NSe+H]^+$: 230.0448, found 230.0441.

4.4.3. (*RS*)-1-(2-(Ethylselanyl)phenyl)ethanamine 6c

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), 4.63–4.56 (quart., J = 6.6 Hz, 1H), 2.95–2.87 (quart., J = 5.7 Hz, 2H), 2.21 (s, 2H), 1.46–1.41 (t, J = 7.5 Hz, 3H), 1.40–1.38 (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.

4.5. Synthesis of *N*-(1-((ethylselanyl)phenyl)ethyl)acetamides 7a–c

To a Schlenck-flask, organoselenium amines **6a–c** (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 **7a–c**.

4.5.1. (*RS*)-*N*-(1-(4-(Ethylselanyl)phenyl)ethyl)acetamide 7a

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: 7.46–7.44 (d, J = 8.1 Hz, 2H), 7.22–7.20 (d, J = 8.1 Hz, 2H), 5.98 (s, 1H), 5.11–5.06 (quart., J = 7.2 Hz, 1H), 2.94–2.87 (quart., J = 7.0 Hz, 2H), 2.01 (s, 3 H), 1.49–1.46 (d, J = 7.0 Hz, 3H), 1.45–1.40 (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.

4.5.2. (*RS*)-*N*-(1-(3-(Ethylselanyl)phenyl)ethyl)acetamide 7b

Yield: 92%. IR (KBr) cm^{-1}: 3284, 3064, 2975, 2926, 2867, 1712, 1651, 1549, 1374, 1232, 885, 786, 701, 620, 450. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.43–7.35 (m, 2H), 7.27–7.16 (m, 2H), 6.01 (s, 1H), 5.13–5.04 (quart., J = 7.2 Hz, 1H), 2.97–2.89 (quart., J = 7.5 Hz, 2H), 2.00 (s, 3H), 1.49–1.46 (d, J = 7.2 Hz, 3H), 1.46–1.41 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz) δ: 169.46, 143.91, 131.18, 130.87, 130.10, 129.27, 124.64, 48.75, 23.32, 21.72, 21.33, 15.44. LRMS [EI], m/z (relative abundance): 271 (M^+, 100), 256 (12), 228 (21), 214 (94), 200 (27), 183 (24), 120 (67), 104 (36), 77 (26), 43 (92). HRMS [ESI(+)], calcd for $[C_{12}H_{17}NOSe+H]^+$: 272.0554, found 272.0551.

4.5.3. (*RS*)-*N*-(1-(2-(Ethylselanyl)phenyl)ethyl)acetamide 7c

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: 7.53–7.51 (dd, J = 4.5 Hz, J = 0.6 Hz, 1H), 7.33–7.31 (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), 5.49–5.44 (quart., J = 4.2 Hz, 1H), 2.95–2.93 (quart., J = 4.2 Hz, 2H), 2.02 (s, 3H), 1.50–1.48 (d, J = 4.2 Hz, 3H), 1.44–1.40 (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.

4.6. Enzymatic kinetic resolution of (*RS*)-1-((ethylselanyl)-phenyl)ethanamines 6a–c

4.6.1. Screening reactions

To a Schlenk-flask, solvent (1 mL, see Table 2), ethyl acetate (78 μL, 0.8 mmol), lipase (amount indicated in Table 2), and the appropriated organoselenium amines **6a–c** (46 mg, 0.2 mmol) were added. The reaction mixture was stirred on a rotary shaker (temperature indicated in Table 2, 160 rpm) for 48 h. After this period, the enzyme was filtered off and washed with CH_2Cl_2 (5 mL). The organic phase was extracted with an aqueous HCl solution (3 × 2 mL, 1 M), washed with brine (3 mL), and dried over $MgSO_4$. The solvent was removed in vacuum and the residue, containing the organoselenium amides **7a–c**, was readily analyzed by HPLC (see Section 4.6).

A saturated aqueous NaOH solution was added to the combined aqueous solution until pH 10. The resulting solution was extracted with CH_2Cl_2 (3 × 2 mL). The organic phases were combined and washed with brine (3 mL), dried over $MgSO_4$. The solvent was removed in vacuum and the residue, containing the organoselenium amines **6a–c**, was acetylated with acetic anhydride for further HPLC analysis (see Section 4.5).

4.6.2. Small scale reaction

To a Schlenk-flask, hexane (2.5 mL), ethyl acetate (195 μL, 2.5 mmol), CAL-B, Novozym 435, (150 mg) and the appropriate organoselenium amines **6a–c** (115 mg, 0.5 mmol) was added. The reaction mixture was stirred on a rotary shaker (30 °C, 160 rpm) for 48 h. After this time, the enzyme was filtered off and washed with CH_2Cl_2 (10 mL). The organic phase was extracted with an aqueous HCl solution (3 × 5 mL, 1 M), washed with brine (5 mL) and dried over $MgSO_4$. The solvent was removed in vacuum and the residue purified by silica gel column chromatography, using ethyl acetate as a solvent. The solvent was removed to give the organoselenium amides **7a–c**, which were readily analyzed by HPLC (see Section 4.7).

A saturated aqueous NaOH solution was added to the combined aqueous solution until pH 10. The resulting solution was extracted with CH_2Cl_2 (3 × 5 mL). The organic phases were combined and washed with brine (5 mL), dried over $MgSO_4$. The solvent was removed in vacuum to give the organoselenium amines **6a–c**. The enantiomeric purities of the compounds **6a–c** were measured by HPLC analysis (see Section 4.7) after derivatization with acetic anydride (see Section 4.5).

4.6.2.1. 1-((Ethylselanyl)phenyl)ethanamines 6a–c.

(*S*)-**6a**: Yield = 57%, $[\alpha]_D^{26} = -5.0$ (*c* 0.5, ethyl acetate), ee = 22%;
(*S*)-**6b**: Yield = 62%, $[\alpha]_D^{26} = -5.8$ (*c* 2.24, ethyl acetate), ee = 34%;
(*S*)-**6c**: Yield = 51%, $[\alpha]_D^{26} = -2.5$ (*c* 3.49, ethyl acetate), ee = 8%.

4.6.2.2. *N*-(1-(4-(Ethylselanyl)phenyl)ethyl)acetamides 7a–c.

(*R*)-**7a**: Yield = 19%, $[\alpha]_D^{24} = +102.8$ (*c* 0.59, ethyl acetate), ee = 99%;
(*R*)-**7b**: Yield = 30%, $[\alpha]_D^{24} = +88.7$ (*c* 0.21, ethyl acetate), ee = 98%;
(*R*)-**7c**: Yield = 08%, $[\alpha]_D^{24} = +21.8$ (*c* 0.50, ethyl acetate), ee = 99%.

4.7. HPLC analysis for determination of the enantiomeric excess (ee)

The enantiomeric purities of the organoselenium amides **7a–c** were measured by HPLC analysis. The analysis was carried out on Chiralcel OD-H column and the peaks were detected by a UV detector at 254 nm. Eluent: hexane/isopropanol (95:05), flow rate: 1.0 mL/min. Retention times for:

(*RS*)-*N*-(1-(4-(Ethylselanyl)phenyl)ethyl)acetamide **7a**: [(*R*)-**7a** = 20.44 min; (*S*)-**7a** = 24.93 min].
(*RS*)-*N*-(1-(3-(Ethylselanyl)phenyl)ethyl)acetamide **7b**: [(*R*)-**7b** = 19.19 min; (*S*)-**7b** = 28.29 min].
(*RS*)-*N*-(1-(2-(Ethylselanyl)phenyl)ethyl)acetamide **7c**: [(*R*)-**7c** = 16.92 min; (*S*)-**7c** = 44.46 min].

4.8. GC analysis for determination of the enantiomeric excess of *N*-(1-phenylethyl)acetamide 8

The enantiomeric excess of (*RS*)-*N*-(1-phenylethyl)acetamide **8** and the products of the reactions shown in Section 4.9 were analyzed by GC/FID in a chiral capilary column (Chirasil-Dex CB-Var-

ian). GC conditions: Injector 220 °C; detector: 220 °C; pressure: 100 kPa. Column temperature: 70 °C, 3 °C/min up to 180 °C. Retention times for (*RS*)-*N*-(1-phenylethyl)acetamide **8**: [(*R*)-**8** = 25.06 min, (*S*)-**8** = 24.21 min].

4.9. Determination of the absolute configurations of the organoselenium amines 6a–c and amides 7a–c

The absolute configurations of the organoselenium amides **7a**–**c** were assigned by chromatographic comparison with standard samples of (*R*)- and (*S*)-**8** after removing the organoselenium group from **7a**–**c** with *n*-butyllithium according to the procedure above.

To a two-necked round-bottomed flask, the chiral organoselenium amides **7a**–**c** (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 **8** (see Section 4.8).

Acknowledgments

The authors thank FAPESP and CNPq for financial support.

References

1. Zhu, C.; Huang, Y. *Curr. Org. Chem.* **2006**, *10*, 1905–1920.
2. Browne, D. M.; Wirth, T. *Curr. Org. Chem.* **2006**, *10*, 1893–1903.
3. Ferraboschi, P.; Grisenti, P.; Santaniello, E. *Synlett* **1990**, 545–546.
4. Da Costa, C. E.; Comasseto, J. V.; Crusius, I. H. S.; Andrade, L. H.; Porto, A. L. M. *J. Mol. Catal. B: Enzym.* **2007**, *45*, 135–139.
5. Comasseto, J. V.; Andrade, L. H.; Omori, A. T.; Assis, L. F.; Porto, A. L. M. *Tetrahedron: Asymmetry* **2007**, *18*, 1048–1053.
6. Clososki, G. C.; Costa, C. E.; Missio, L. J.; Cass, Q. B.; Comasseto, J. V. *Synth. Commun.* **2004**, *34*, 817–828.
7. Da Costa, C. E.; Clososki, G. C.; Comasseto, J. V.; Barchesi, H. B.; Zanotto, S. P.; Nascimento, M. G. *Tetrahedron: Asymmetry* **2004**, *15*, 3945–3954.
8. Braga, A. L.; Schneider, P. H.; Paixão, M. W.; Deobald, A. M.; Peppe, C.; Bottega, D. P. *J. Org. Chem.* **2006**, *71*, 4305–4307.
9. Tiecco, M.; Testaferri, L.; Bagnoli, L.; Marini, F.; Santi, C.; Temperini, A.; Scarponi, C.; Sternativo, S.; Terlizzi, R.; Tomassini, C. *Arkivoc* **2006**, *7*, 186–206.
10. Nogueira, C. W.; Zeni, G.; Rocha, J. B. T. *Chem. Rev.* **2004**, *104*, 6255–6285.
11. Mugesh, G.; Singh, H. B. *Chem. Soc. Rev.* **2000**, *29*, 347–357.
12. Braga, A. L.; Lüdtke, D. S.; Vargas, F.; Braga, R. C. *Synlett* **2006**, 1453–1466.
13. McGarrigle, E. M.; Myers, E. L.; IIIa, O.; Shaw, M. A.; Riches, S. L.; Aggarwal, V. K. *Chem. Rev.* **2007**, *107*, 5841–5883.
14. Braga, A. L.; Lüdtke, D. S.; Vargas, F. *Curr. Org. Chem.* **2006**, *10*, 1921–1938.
15. Wirth, T. *Tetrahedron Lett.* **1995**, *36*, 7849–7852.
16. Santi, C.; Wirth, T. *Tetrahedron: Asymmetry* **1999**, *10*, 1019–1023.
17. Helmchen, G.; Kudis, S.; Sennhenn, P.; Steinhagen, H. *Pure Appl. Chem.* **1997**, *69*, 513–518.
18. Braga, A. L.; Paixão, M. W.; Marin, G. *Synlett* **2005**, 1675–1678.
19. Zielinska-Blajet, M.; Siedlecka, R.; Skarzewski, J. *Tetrahedron: Asymmetry* **2007**, *18*, 131–136.
20. Braga, A. L.; Vargas, F.; Sehnem, J. A.; Wessjohann, L. A. *Eur. J. Org. Chem.* **2006**, *22*, 4993–4997.
21. Vargas, F.; Sehnem, J. A.; Galetto, F. Z.; Braga, A. L. *Tetrahedron* **2008**, *64*, 392–398.
22. Comasseto, J. V.; Omori, A. T.; Porto, A. L. M.; Andrade, L. H. *Tetrahedron Lett.* **2003**, *45*, 473–476.
23. Comasseto, J. V.; Omori, A. T.; Porto, A. L. M.; Andrade, L. H. *J. Mol. Catal. B: Enzym.* **2004**, *29*, 47–54.
24. Ganther, H. E. *Bioorg. Med. Chem.* **2001**, *9*, 1459–1466.
25. Kampf, M.; Richter, R.; Hennig, L.; Eidner, A.; Baldamus, J.; Kirmse, R. *Z. Anorg. Allg. Chem.* **2004**, *630*, 2677–2686.
26. Miriyala, B.; Bhattacharyya, S.; Williamson, J. S. *Tetrahedron* **2004**, *60*, 1463–1471.
27. Chen, C. S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294–7299.
28. Iwaoka, M.; Tomoda, S. *J. Am. Chem. Soc.* **1996**, *118*, 8077–8084.
29. Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656–2665.