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Biotransformations on organic selenides and tellurides: synthetic applications

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Contents

1. Introduction

The chemistry of organoselenium compounds experienced remarkable progress in the 1970s,[1] and the same occurred with the organic tellurium chemistry in the 1980s.[2] However, at that time the chirality of the organochalcogen compounds was not addressed as a fundamental aspect for their application in organic synthesis. In contrast, due to the importance of the chirality in biological processes, nowadays racemic compounds are hardly considered for synthetic purposes. Besides the use of compounds from the natural chiral pool, two main approaches are considered in the preparation of enantiomericaly pure compounds, chiral homogeneous catalysis and biocatalysis.[3] Despite the resistance of synthetic organic chemists to employ biological materials as reagents,[4] some biocatalytic strategies, such as the enzymatic kinetic resolution of alcohols, are now routinely used in synthetic chemistry laboratories.[5] Notwithstanding this fact, until recently, the use of biocatalytic methods to prepare enantiomericaly enriched organoselenium and organotellurium compounds were very scarce.

At this point it is important to mention that the use of organoselenium and, to a larger extent, organotellurium compounds, is avoided by synthetic organic chemists, who very often believe that they are very bad smelling compounds, and claim that tellurium-based compounds are unstable to the light and air. These observations are indeed true for low molecular weight alkyl selenides and tellurides, especially for the non-functionalized ones. Introduction of additional functional groups to the structure of a bad smelling selenide or telluride very often produces a neutral smelling derivative as illustrated in Figure 1.

All the compounds commented in this article present an odor not more unpleasant than the organic compounds usually employed in an organic synthesis laboratory. Additionally, they are air- and light-stable compounds that can be purified by column

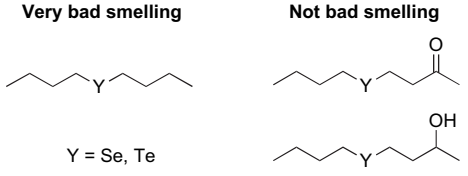

Figure 1.

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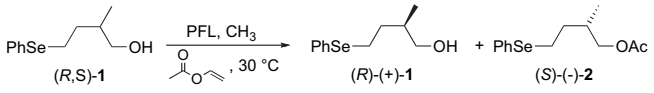
chromatography. When stored under refrigeration, the selenides do not degrade to an observable extent; however, the tellurides are less stable, and after a few days some decomposition can be detected by the darkening of the samples. When in solution in the presence of the air, the tellurides are slowly transformed into amorphous white solids, presumably oxidation products. However, by taking the proper care, evaporating the solvent immediately after the work-up, the tellurides can be safely manipulated in the presence of light and air.

The article is organized in four sections: (a) Kinetic enzymatic resolution of alcohols and amines containing selenium and tellurium in their structure; (b) Enzymatic oxidation of selenium and tellurium containing substrates; (c) enzymatic reduction of selenium and tellurium containing substrates; (d) miscellanea.

2. Kinetic enzymatic resolution of hydroxyselenides and hydroxytellurides

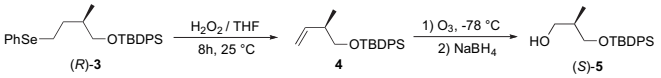
The kinetic enzymatic resolution of secondary alcohols is one of the most investigated enzymatic transformations used in organic synthesis laboratories.[5] Although less studied, the enzymatic resolution of chiral alcohols that have the hydroxy group bonded in a remote location from the chiral center also gives good enantiomeric excesses.[5] The first report of an enzymatic resolution involving a hydroxyselenide describes the resolution of a primary alcohol with the chiral center α to the carbinol carbon.[6] Compound **1** was selectively esterified by reaction with vinyl acetate in chloroform at 30 °C in the presence of *Pseudomonas fluorescens lipase* (PFL). At 60% conversion, the alcohol (*R*)-(+)-**1** was obtained in 38% yield and 98% ee (Scheme 1). At 40% conversion, the acetate (*S*)-(−)-**2**, was obtained in 36% yield and **3** was treated with hydrogen peroxide giving **4**, which on ozonolysis furnished (*R*)-**5**, a chiral building block used in asymmetric synthesis (Scheme 2).



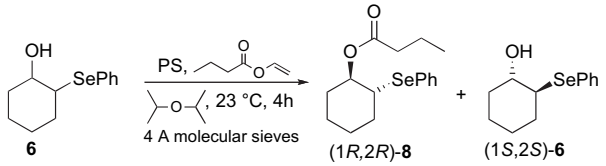
PFL = *Pseudomonas fluorescens lipase*

	(*R*)-(+)-1	(*S*)-(-)-2
e.e. (%)	98	>98
Yield (%)	38	36
Conversion (%)	60	40

Scheme 1.[6]

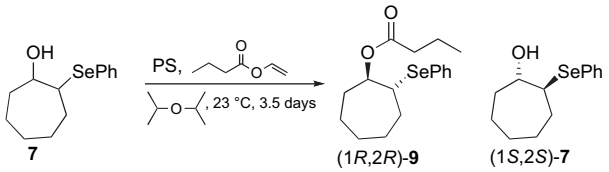


Scheme 2.[6]



	(1*R*,2*R*)-8	(1*S*,2*S*)-6
e.e. (%)	>99	96
Yield (%)	41	52

Scheme 3.[7]



	(1*R*,2*R*)-9	(1*S*,2*S*)-7
e.e. (%)	>99	88
Yield (%)	43	50

Scheme 4.[8]

trans-2-(Phenylseleno)-cyclohexan-2-ol **6**[7] and *trans*-2-(phenylseleno)-cycloheptan-1-ol **7**[8] were selectively acylated with vinyl acetate and vinyl butyrate in the presence of *Pseudomonas cepacia lipase* (PS), *Porcine pancreatic lipase* (PPL) and *Candida cylidracea lipase* (CCL). The best results were obtained with vinyl butyrate and PS, under the reaction conditions shown in Schemes 3 and 4. Under these conditions the alcohols (1*S*,2*S*)-**6** and (1*S*,2*S*)-**7** were obtained in 96% and 88% ee, respectively, and the acetates (1*R*,2*R*)-**8** and (1*R*,2*R*)-**9** were obtained in >99% ee. The selenide oxidation/elimination of the enantiomericaly enriched alcohols **6** and **7**, followed by the hydrolysis of the enantiomericaly pure esters **8** and **9**, make these compounds synthetic equivalents of the corresponding chiral allyl alcohols **10** and **11** (Fig. 2).

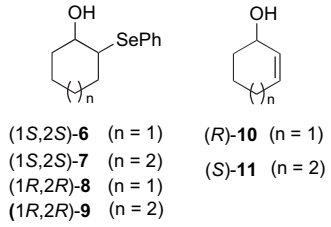


Figure 2.

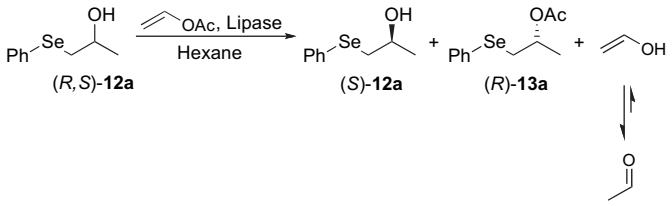
Recently, a more detailed study on the influence of the selenide structure, temperature, solvent and enzyme in the kinetic enzymatic resolution of β-hydroxyselenides has been published.[9]

The influence of the temperature was studied using PPL, PSL and CALB in typical experiments at 5, 10, 20, 32 and 40 °C. Table 1 shows the effects of temperature and enzymes in the resolution of racemic **12a**. The enzymatic activity depends on the temperature employed. The temperature also had considerable effect on the enantioselectivity, but no influence in the stereochemical preference for the (*R*)-1-phenylselanyl-propan-2-ol (*R*)-**12a** enantiomer. The enantiopreference agrees with the Kazlauskas's rule, an extension of Prelog's rule for hydrolases.[10]

The highest stereoselectivities were obtained using PSL and CALB at 20–40 °C, and the best relation between enantiomeric excess and conversion was observed at 32 °C. In the reaction with PSL, both (*S*)-**12a** and (*R*)-**13a** were obtained in more than 92% ee at 32 °C (Table 1, entries 11 and 12). On the other hand, the best enantioselectivity was achieved in the reaction with CALB at 32 °C, when both (*S*)-**12a** and (*R*)-**13a** were obtained in more than 98% ee (Table 1, entries 18 and 19). Control of the reaction time and temperature, when PSL or CALB were used as biocatalysts, allowed the isolation of both (*S*)-**12a** and (*R*)-**13a** with >99% ee (Table 1, entries 9, 12, 17 and 19).

The influence of the solvent was also evaluated in the acylation of (*R*,*S*)-**12a** using PSL and CALB at 32 °C in some dry solvents

Table 1
Influence of temperature and enzyme in the kinetic enzymatic resolution of (*R*,*S*)-**12a**[9]



Entry	Lipase	Temp (°C)	*t* (h)	*c* (%)	(*S*)-**12a** ee (%)	(*R*)-**13a** ee (%)	*E*
1	PPL	5	24	39	40	94	47
2		10	24	39	57	90	33
3		20	24	41	63	89	32
4		32	24	40	59	88	28
5		32	98	49	81	84	28
6		40	34	34	46	88	24
7	PSL	5	24	27	37	99	>200
8		10	24	28	39	99	>200
9		20	24	31	45	>99	>200
10		32	24	45	80	97	161
11		32	49	51	98	95	179
12		32	72	52	>99	92	>125
13		40	24	47	85	95	106
14	CALB	5	6	43	76	>99	>200
15		10	6	47	88	>99	>200
16		20	6	48	90	>99	>200
17		32	2	45	80	>99	>200
18		32	4	49	98	99	>200
19		32	6	50	>99	99	>200
20		40	5	51	>99	98	>200

(Fig. 3). It was observed that different solvents had different influences on the conversion of the substrate (enzymatic activity), but had no effect in the enzyme enantioselectivity and enantiopreference, showing the same preference for the (*R*)-1-phenylselanyl-propan-2-ol [(*R*)-**12a**] enantiomer. In all solvents (*R*)-**13a** was obtained in more than 97% ee using PSL, and in more than 99% ee using CALB. The highest enzymatic activities were observed in non polar solvents such as hexane and cyclohexane, while in polar solvents the enzymatic activity decreased.

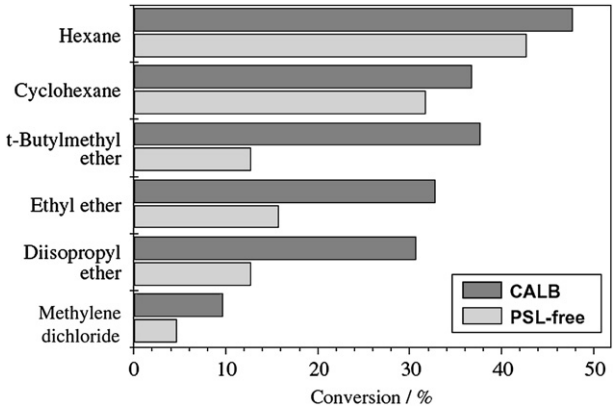


Figure 3. Influence of the solvent in the kinetic resolution of (*R*,*S*)-**12a** with CALB and PSL free.[9]

The influence of the support was evaluated by the reaction of compound (*R*,*S*)-**12a** with supported enzymes, under the same experimental conditions used for the free enzyme reaction. The results showed the dependence of the enzymatic activity on the kind of support employed (Fig. 4). No product was detected using PSL immobilized in agar gel and montmorillonite K10, while using silica or sodium caseinate films as the support the enzymatic activity decreased. However, the immobilization of PSL in PEO

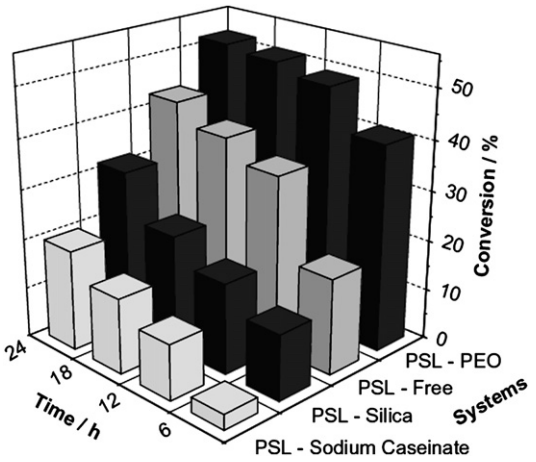


Figure 4. Influence of the support in the kinetic resolution of (*R*,*S*)-**12a**.[9]

[poly(ethylene oxide)] increased its activity. In all employed systems (*R*)-**13a** was obtained in more than 92% ee at 35 °C. The product (*R*)-**13a** was obtained with 92% ee and the unreacted substrate (*S*)-**12a** with >99% ee with 52% of conversion within 24 h reaction time (entry12, Table 1), while 45% of conversion and 80% ee for (*S*)-**12a** and 97% ee for (*R*)-**13a** were obtained using the free lipase (entry 10, Table 1). The stereochemical preference for the (*R*)-1-phenylselanyl-propan-2-ol [(*R*)-**12a**] enantiomer, leading to the acetate (*R*)-**13a**, is the same with PSL-free or immobilized, regardless of the support used.

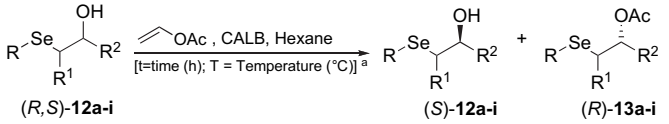
The study discussed above established that CALB in hexane is the system of choice to perform the kinetic resolution of (*R*,*S*)-**12a**. Therefore, a number of β-hydroxyselenides were submitted to the same reaction conditions to evaluate the influence of the substituents in the resolution parameters. The best results are summarized in Table 2 and show that, in all cases, the stereochemical preference for the *R* enantiomer is observed.

The results in Table 2 show that the reaction time and the enantioselectivity are affected by the size of the R^2 group. The presence of a large substituent (compounds **12e**, **12f**) or branching substituents (compound **12g**) had a negative influence on the kinetic resolution and, in the case of compound **12h** no acetylated product could be detected. These results showed that the $PhSeCH_2$ group behaves as a large substituent in the Kazlauskas's rule.[10] This conclusion was confirmed when compound **12i** was submitted to kinetic resolution. In this case, a stereochemical preference for the (*S*)-enantiomer was observed, in contrast to other compounds in Table 2. In this case, the methylseleno group behaved as a medium-sized group in the Kazlauskas's rule.[10] Considering the above commented results it was concluded that β-hydroxyselenides need a medium-sized substituent smaller than the ethyl group like the methyl group in **12a**–**12d** (Table 2) in order to be successfully resolved by CALB.

A number of acyclic β-hydroxyselenides were submitted to the kinetic enzymatic resolution with PS-C II Amano lipase and vinyl acetate in toluene at 30 °C.[11] The results are shown in Table 3.

In most cases, as can be observed in Table 3, under the reaction conditions employed the β-hydroxyselenides **12j**–**12n** behaved similarly to the ones in Table 2. The $PhSeCH_2$ group behaved as the large group in the Kazlauskas's rule.[10] Compound **12h** presented a low conversion and gave the inverse stereoselectivity, similar to the results presented in Table 2 for compound **12i**.[9] A number of cyclic β-hydroxyselenides were submitted to the kinetic enzymatic resolution with PS-CII in toluene.[11] The results are shown in Table 4.

Table 2
Enzymatic kinetic resolution of β-hydroxyselenides[9]



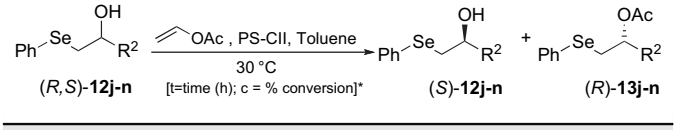
(*R*,*S*)-**12a-i** (*S*)-**12a-i** (*R*)-**13a-i**

(*S*)-**12a**	(*R*)-**13a**	(*S*)-**12e**	(*R*)-**13e**
>99%*e.e.*	99%*e.e.*	>99%*e.e.*	70%*e.e.*
(t = 6; T = 32)		(t = 9; T = 32)	
(*S*)-**12b**	(*R*)-**13b**	(*S*)-**12f**	(*R*)-**13f**
>99%*e.e.*	>99%*e.e.*	>42%*e.e.*	33%*e.e.*
(t = 25; T = 32)		(t = 9; T = 40)	
(*S*)-**12c**	(*R*)-**13c**	(*S*)-**12g**	(*R*)-**13g**
>93%*e.e.*	>99%*e.e.*	69%*e.e.*	86%*e.e.*
(t = 50; T = 32)		(t = 20; T = 40)	
(*S*)-**12d**	(*R*)-**13d**	(*S*)-**12h**	(*R*)-**13h**
>92%*e.e.*	>99%*e.e.*	n.c.[b]	n.c.[b]
(t = 72; T = 32)		(t = 20; T = 40)	
(*R*)-**12i**	(*S*)-**13i**		
41%*e.e.*	74%*e.e.*		
(t = 20; T = 40)			

[a]Only the best results are shown. The reactions were performed at several reaction times, with different conversions and enantiomeric excesses.
[b]n.c.=no conversion.

As can be observed, most of the cyclic compounds afforded high stereoselectivity, following Kazlauskas's rule.[10] The PhSe moiety behaved as a large group. Compound **14d** presented a low conversion after a long reaction time, and the (*S*,*S*)-**14d** alcohol was obtained in low ee. Several arylselenoethanols were submitted to the kinetic enzymatic resolution in hexane catalyzed by *Candida antartica* (CALB Novozym 435) lipase.[12,13] The results are presented in Table 5. A standard 24 h reaction time was adopted. Both the non-acetylated alcohols (*S*)-**16** and the acetates (*R*)-**17** were obtained in 99% ee, except for compounds (*R*)-**17a** and (*R*)-**17e** which were obtained in 97% and 99% ee, respectively. The isolated yields for both alcohols and acetates ranged from 36% to 45%. As expected, the stereopreference once again followed Kazlauskas's rule.[10]

Table 3
Enzymatic kinetic resolution of β-hydroxyselenides[11]



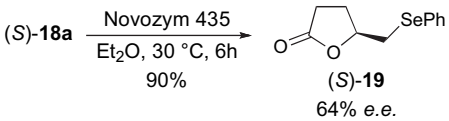
(*R*,*S*)-**12j-n** (*S*)-**12j-n** (*R*)-**13j-n**

(*S*)-**12j**	(*R*)-**13j**	(*S*)-**12m**	(*R*)-**13m**
31%*e.e.*	99%*e.e.*	84%*e.e.*	95%*e.e.*
(t = 0.33; c = 25)		(t = 25; c = 47)	
(*S*)-**12k**	(*R*)-**13k**	(*S*)-**12n**	(*R*)-**13n**
>99%*e.e.*	>94%*e.e.*	58%*e.e.*	58%*e.e.*
(t = 4; c = 51)		(t = 48; c = 50)	
(*S*)-**12l**	(*R*)-**13l**	(*S*)-**12h**	(*R*)-**13h**
85%*e.e.*	>89%*e.e.*	62%*e.e.*	14%*e.e.*
(t = 25; c = 49)		(t = 48; c = 17)	

*Only the best results are shown. The reactions were performed at several reaction times, with different conversions and enantiomeric excesses.

A special case of kinetic enzymatic resolution of a hydroxyselenide involved the internal transesterification of compound (*R*,*S*)-**18** (Scheme 5 and Table 6).[14]

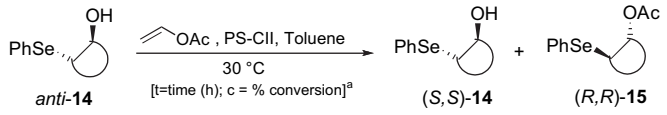
Racemic **18** was submitted to lactonization promoted by PPL, PSL, MML, CRL, CALB and Novozym 435 lipases in diethyl ether at 30 °C. The most efficient enzyme to perform the lactonization was Novozym 435, which after 3 h led to 97% conversion, but with no enantiomeric excess. The best enzyme in terms of enantioselectivity was found to be PPL, which transformed (*R*,*S*)-**18** into (*R*)-**19** in 74% ee (Table 5, entry 3). In an attempt to improve the ee of the lactonization, compound **18a** was allowed to react with PPL in hexane, cyclohexane, toluene and ^{t}butyl methyl ether, but these reactions presented inferior results. In addition, calculated *E* values for **18a**–**18c** showed that the lactonization was not dependent on the size of the R group.[14] Compound (*S*)-**18a** was transformed into (*S*)-**19** in 90% yield and 64% ee by reaction with Novozym 435 in diethyl ether at 30 °C for 6 h[14] (Eq. 1).

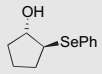
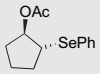
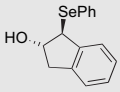
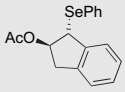
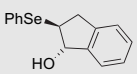
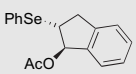
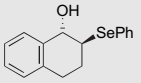
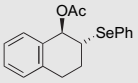
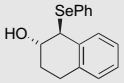
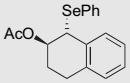


(1)

Recently, a study on the kinetic enzymatic resolution of arylselenoethyl amines was reported.[15] A number of lipases were tested using toluene as the solvent and ethyl acetate as the acetylating agent. The best result in terms of ee was obtained with CALB as the enzyme and hexane as the solvent. The acetylated amines (*R*)-**21** were obtained with good ee (96–99%), however the free amines (*S*)-**20** presented poor ee (8–52%). In some cases, the isolated yields for

Table 4
Enzymatic kinetic resolution of cyclic β-hydroxyselenides[11]



 (*S*)-14a[b]	 (*R*)-15a[b]	 (*S*)-14c[b]	 (*R*)-15c[b]
>99%*e.e.*	>99%*e.e.*	>99%*e.e.*	>99%*e.e.*
(t = 1; c = 50)		(t = 1.7;c = 50)	
 (*S*)-14b[b]	 (*R*)-15b[b]	 (*S*)-14d[b]	 (*R*)-15d[b]
>99%*e.e.*	>94%*e.e.*	22%*e.e.*	96%*e.e.*
(t = 48; c = 50)		(t = 73; c = 19)	
 (*S*)-14e[b]	 (*R*)-15e[b]		
82%*e.e.*	>99%*e.e.*		
(t = 30; c = 45)			

[a]only the best results are shown. The reactions were performed at several reaction times, with different conversions and enantiomeric excesses.
[b]for the sake of clarity, only the carbinol center configuration is indicated.

the acetamides were also poor (8–30%).[15a] Recently an improvement of this resolution reaction was published. [15b] The arylselenoamines (*R,S*)-**20** were submitted to a dynamic kinetic resolution (DKR) with CAL-B, Pd/$BaSO_4$. High yields and ee >99% were observed in most cases (Table 7).

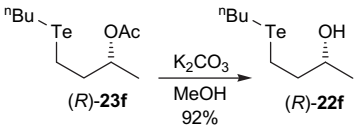
A systematic study on the kinetic enzymatic resolution of hydroxytellurides was published,[16] which described a screening to determine the more efficient enzyme for the resolution of the telluride **22a**. The best results were obtained with CALB in hexane at 30 °C, as shown in Table 8. The enantiopreference of CALB, PSL and PPL was for (*R*)-**22**, whilst that of CRL was for (*S*)-**22** (Table 8, entries 5 and 6).

The influence of the solvent was studied with CALB and CRL. The solvents investigated were those commonly used in kinetic resolution studies, and are shown in Figure 5. The experiments were performed at 30 °C, and the conversions determined after 3 h for CLR and after 1 h for CALB.

The most efficient solvent in terms of stereoselectivity was found to be hexane. This solvent was used to test the influence of the substituents on the kinetic resolution of a number of hydroxytellurides (Table 9).

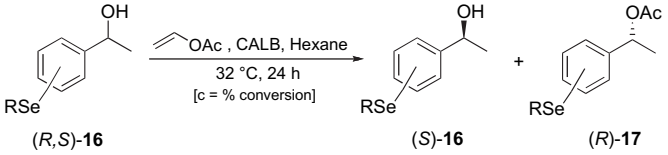
No acetylated products were detected for **22b**, **22c** and **22d**. In the case of hydroxytelluride **22e**, when the resolution was performed in hexane, good yield and enantioselectivity was observed. In the same solvent, good enantioselectivity and good conversion was observed for the telluride **22f**, but the acetate **23f** was isolated in less than 5% yield. This result was attributed to the low solubility of **22f** in hexane; when the resolution of **22f** was performed in THF the reaction time increased, but gave the derivative **23f** in 36% yield and in high ee.[16]

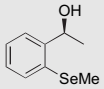
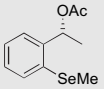
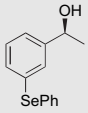
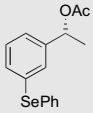
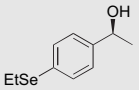
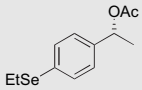
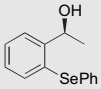
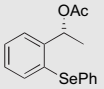
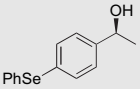
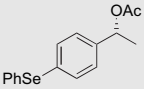
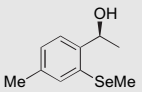
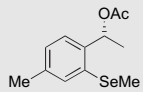
Enantiomericaly pure (*R*)-**22f** was obtained by hydrolysis of (*R*)-**23f** (Eq. 2).[16]

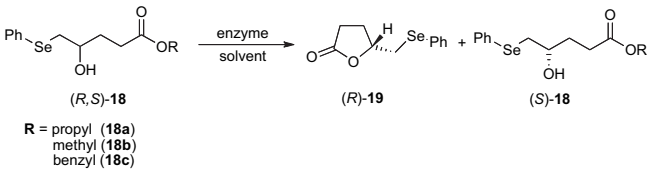


(2)

Table 5
Enzymatic kinetic resolution of arylselenoethanols[12,13]



 (*S*)-16a	 (*R*)-17a	 (*S*)-16e	 (*R*)-17e
>99%*e.e.*[12]	97%*e.e.*[12]	99%*e.e.*[13]	99%*e.e.*[13]
(c = 50)		(c = 50)	
 (*S*)-16b	 (*R*)-17b	 (*S*)-16f	 (*R*)-17f
99%*e.e.*[13]	99%*e.e.*[13]	99%*e.e.*[13]	99%*e.e.*[13]
(c = 57)		(c = 50)	
 (*S*)-16c	 (*R*)-17c	 (*S*)-16g	 (*R*)-17g
99%*e.e.*[12]	88%*e.e.*[12]	99%*e.e.*[13]	99%*e.e.*[13]
(c = 53)		(c = 40)	
 (*S*)-16d	 (*R*)-17d		
99%*e.e.*[13]	99%*e.e.*[13]		
(c = 50)			



Scheme 5. Enantioselective lactonization of a hydroxyselenide.[14]

Table 6
Enantioselective lactonization of (*R,S*)-**18**[14]

Entry	Enzyme	R	Solvent	Time (h)	Conversion (%)	(*R*)-**19** ee (%)	*E*
1	*Pseudomonas* sp.	Propyl (**18a**)	Diethyl ether	180	31	32	2.2
2	*Mucor miehei*	Propyl (**18a**)	Diethyl ether	14	47	43	3.6
3	PPL	Propyl (**18a**)	Diethyl ether	39	46	74	12
4	*Candida rugosa*	Propyl (**18a**)	Diethyl ether	160	4	0	—
5	*C. antartica, B*	Propyl (**18a**)	Diethyl ether	160	11	22	1.6
6	*Novozym* 435	Propyl (**18a**)	Diethyl ether	3	97	0	—
7	PPL	Propyl (**18a**)	Hexane	50	40	61	6.1
8	PPL	Propyl (**18a**)	Toluene	42	42	70	9.3
9	PPL	Propyl (**18a**)	Cyclohexane	40	47	68	9.6
10	PPL	Propyl (**18a**)	^{t}BuOMe	40	50	64	8.6
11	PPL	Propyl (**18a**)	Diethyl ether	33	43	71	10
12	PPL	Methyl (**18b**)	Cyclohexane	16	47	64	7.9
13	PPL	Benzyl (**18c**)	Diethyl ether	13	49	66	9.2
14	PPL	Benzyl (**18c**)	Cyclohexane	14	50	64	8.6
15	PPL	Benzyl (**18c**)	Hexane	15	43	64	7.8

Enantiomericaly pure (*S*)-**22f** and (*R*)-**22f** were transformed into the corresponding lithium dianions **24** by reaction with ^{n}BuLi. Subsequent treatment with carbon dioxide afforded (*S*)- and (*R*)-valerolactone **25** (Scheme 6).[16]

Upon treatment of (*R*)-**24** with $CeCl_3$, followed by reaction of the resulting dicerium species (*R*)-**26** with (*S*)-**25**, the spiroketals **27** were obtained in 65% isolated yield (Scheme 7).[17]

Treatment of (*S*)-**24** with CuCN gave (*S*)-**28** which, through the reaction with the tosylate **29** gave the pheromone **30**. The same reaction sequence when applied to tosylates **31** and **33**, followed by acetylation, gave the pheromones **32** and **34** (Scheme 8).[18]

The lithium dianion (*S*)-**24** was transmetallated to the zinc analogue (*S*)-**35**, which on reaction with benzoyl chloride gave the Ipomeanol analogue (*S*)-**36**[22] in 70% yield and 99% ee (Scheme 9).[23]

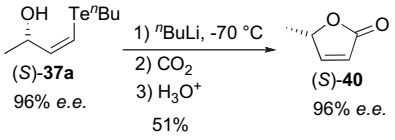
The results commented above show that the enantiomericaly pure hydroxytellurides (*R*)-**22f** and (*S*)-**22f** are efficient synthetic equivalents of (*R*) and (*S*) dianions of type **24** (Scheme 6), **26** (Scheme 7), **28** (Scheme 8) and **35** (Scheme 9).

The vinylic telluride (*R,S*)-**37** was submitted to an enzymatic screening aiming to perform its kinetic resolution. Three lipases were investigated, PPL, PSL and CALB in three solvent systems. The results are summarized in Table 10.[24]

The acetate (*R*)-**38a** was obtained in high enantiomeric excess using CALB and PRL in different solvent systems (entries 1–11, Table 10). Modest and poor ee values were obtained for the acetate (*R*)-**38a** and alcohol (*S*)-**37a** when PSL was employed as the biocatalyst (entries 12 and 13, Table 10). In the presence of CAL-B, the ee for the unreacted alcohol (*S*)-**37a** was good in the presence of hexane (entry 3, Table 10), but only moderate in a 1:1 mixture of THF/hexane (entry 5, Table 10). In all other cases the optical purity of (*S*)-**37a** was modest.

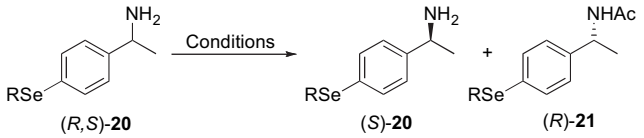
In view of the easy Li/Te exchange in vinylic tellurides,[2] compounds (*S*)-**37a** and (*R*)-**38a** can be considered synthetic equivalents of (*S*) and (*R*) dilithium species (*S*)-**39a** and (*R*)-**39a**, of *Z* configuration (Fig. 6).[24]

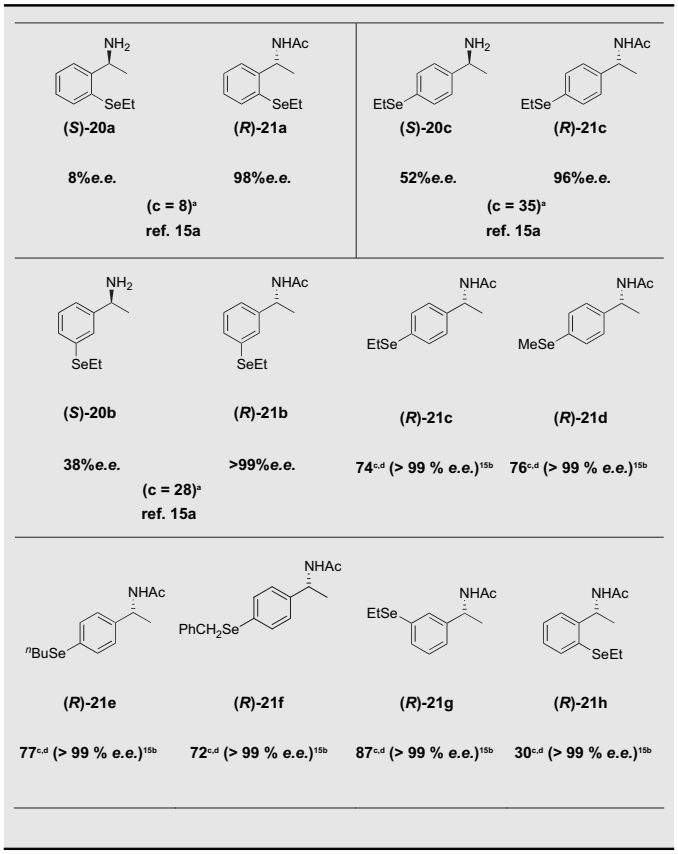
This assumption was confirmed by transforming (*S*)-**37a** into (*S*)-Angelicalactone (*S*)-**40** (Eq. 3).[24]



(3)

Table 7
Enzymatic kinetic resolution of arylselenoamines[15]





[a] *c*=conversion.
[b] Conditions: EtOAc, CAL-B, Hexane, 30 °C, 48 h.[15a]
[c] Conditions: Pd-$BaSO_4$, (10 mol %), CAL-B, EtOAc, Toluene, H_2 (1 atm), 70 °C, 48 h.[15b]
[d] isolated yield.[15b]

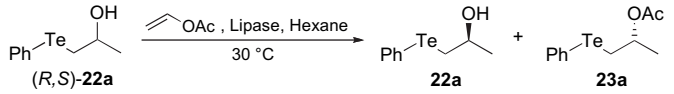
Other vinylic tellurides were submitted to the same reaction sequence, leading to enantiomericaly enriched γ-butyrolactones (**41a**–**41d**, Scheme 10).[25]

In conclusion, the enzymatic kinetic resolution of hydroxyselenides and hydroxytellurides is a useful technique to obtain enantiomericaly enriched selenium- and tellurium containing synthetic building blocks, and can be routinely performed in an organic synthesis laboratory.

3. Enzymatic oxidation of selenium and tellurium containing substrates

The interaction of inorganic selenium and tellurium species with enzymes present in microorganisms and plants is well known.[30] However, chemical transformations of selenium and tellurium organic substrates, promoted by living organisms remain very scarcely investigated, especially when applied to organic synthesis.

Table 8
Enzymatic kinetic resolution of a β-hydroxytellurides[16]



Entry	Lipase	*t* (h)	*c* (%)	**22a** ee (%)	**23a** ee (%)	Absolute configuration of **23a**	*E*
1	PPL	6	32	44	93	(*R*)	—
2		24	41	63	91	(*R*)	40
3	PSL	6	36	56	98	(*R*)	—
4		24	49	94	96	(*R*)	174
5	CRL	1	21	13	48	(*S*)[a]	—
6		3	46	35	41	(*S*)[a]	3.3
7	CALB	2	50	>99	98	(*R*)	>200

[a] In this case the enantiopreference was reversed; (*S*)-**23a** was formed.

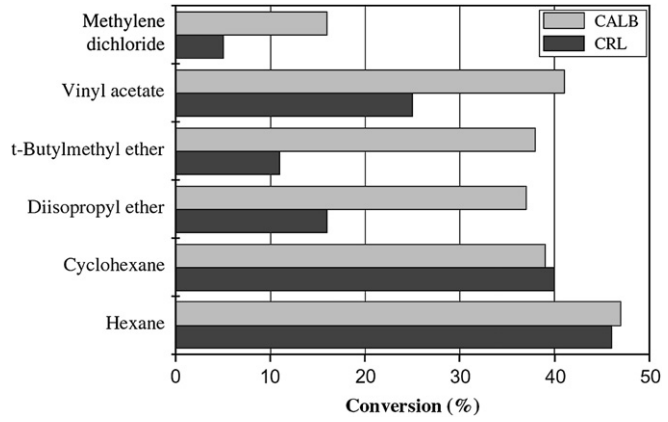
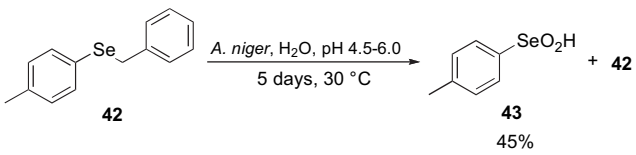


Figure 5. Effect of the solvent in the lipase-catalyzed kinetic resolution of (*R,S*)-**22a** at 30 °C.[16]

However, due to the importance of the microbial transformations in synthetic processes,[3] associated with the use of organoselenium[1] and organotellurium[2] compounds as building blocks[17,24] or chiral ligands[31] in asymmetric synthesis, this is an exciting field for investigation. In view of the tendency of the selenium atom to oxidize, this is the most obvious transformation to be studied under a synthetic point of view. Besides the oxidation of the selenium atom, the oxidation of other sites of a selenium containing molecule must be considered. Notwithstanding the potential of the field, very few studies have been undertaken on the enzymatic oxidation of organic selenides and tellurides, very probably due to the disappointing results obtained in the early investigations on the subject.

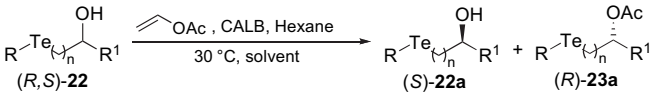
In an early report,[32] compound **42** was incubated with *A. niger* in water at pH 4.5–6 (Eq. 4). This microorganism is known to transform sulfides into sulfoxides.[32,33] After shaking the mixture of the microorganism and **42** for 5 days at 30 °C, seleninic acid **43** was isolated in 45% yield and **42** was recovered in 15% yield. No selenoxide was detected.[32]

In another investigation, phenyl methyl selenide was incubated with *A. niger*, *A. foetidus*, *M. isabelina* and *Helmithosporium sp.* These fungi promote the oxidation of sulfides to chiral

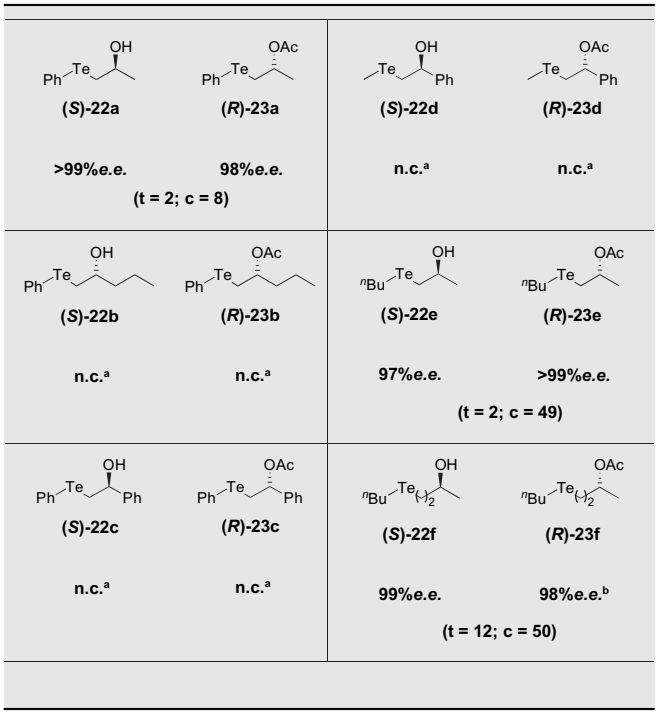


(4)

Table 9
Enzymatic kinetic resolution of hydroxytellurides[16]



22a R = Ph, n = 1, R^1 = CH_3
22b R = Ph, n = 1, R^1 = $(CH_2)CH_3$
22c R = Ph, n = 1, R^1 = Ph
22d R = CH_3, n = 1, R^1 = Ph
22e R = ^{n}Bu, n = 1, R^1 = CH_3
22f R = ^{n}Bu, n = 2, R^1 = CH_3

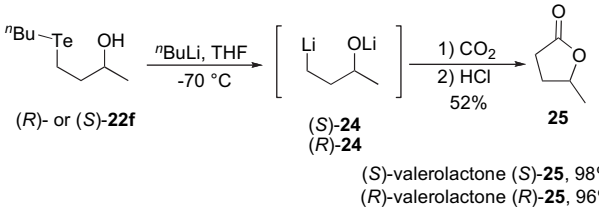


[a]n.c.=no conversion.
[b]Reaction performed in THF.

sulfoxides,[33] but no selenoxide was identified after 48 h incubation.[34]

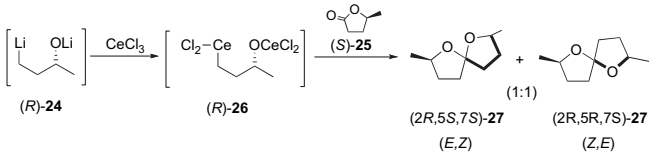
Phenyl propargyl selenide (**44**) was transformed into a-phenylselenoacrolein (**47**) upon contact with cyclohexanoneoxygenase. This result was rationalized as an oxidation of **44** to the selenoxide **45**, followed by a 2,3-sigmatropic rearrangement to **46** and a fragmentation of **46** followed by recombination leading to **47** (Scheme 11).[35]

cis-Hex-2-enyl phenyl selenide (**48**) in the presence of cyclohexanoneoxygenase gave hex-1-en-3-ol (**50**) (Scheme 12),[35] pre-

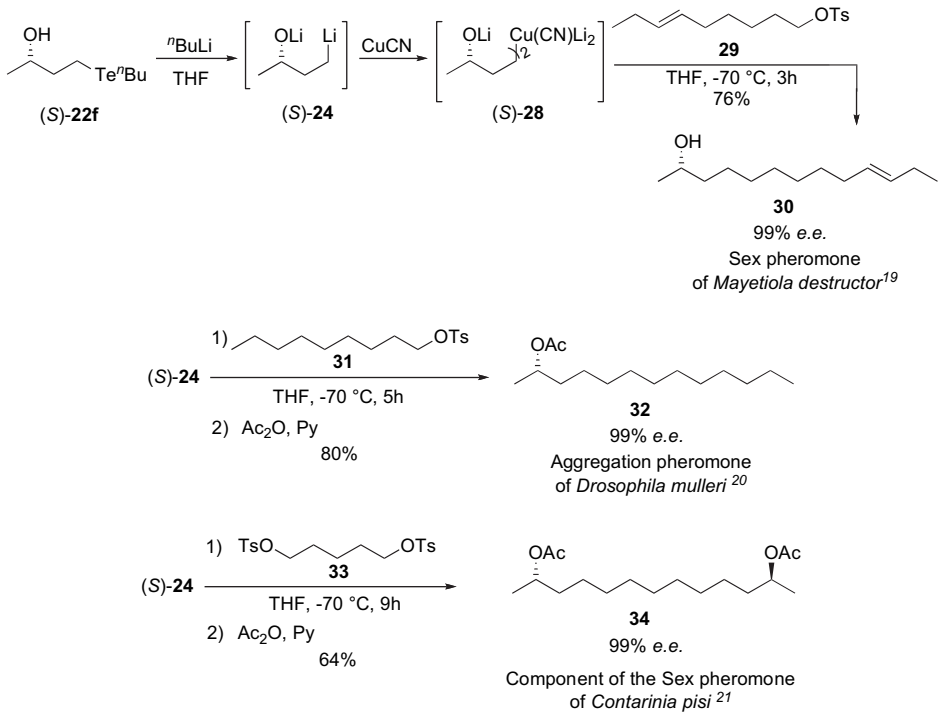


(*S*)-valerolactone (*S*)-**25**, 98% *e.e* [16]
(*R*)-valerolactone (*R*)-**25**, 96% *e.e* [17]

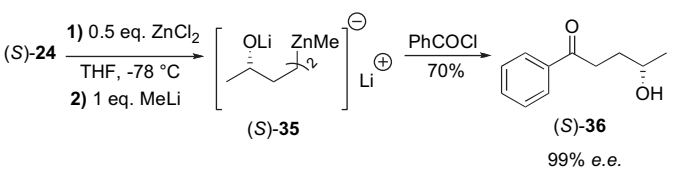
Scheme 6.



Scheme 7.



Scheme 8.[18]



Scheme 9.[23]

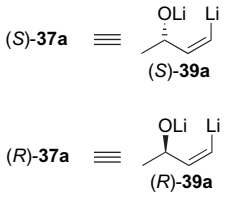
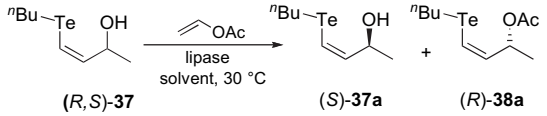


Figure 6.

Table 10
Enzymatic kinetic resolution of vinylic tellurides[24]



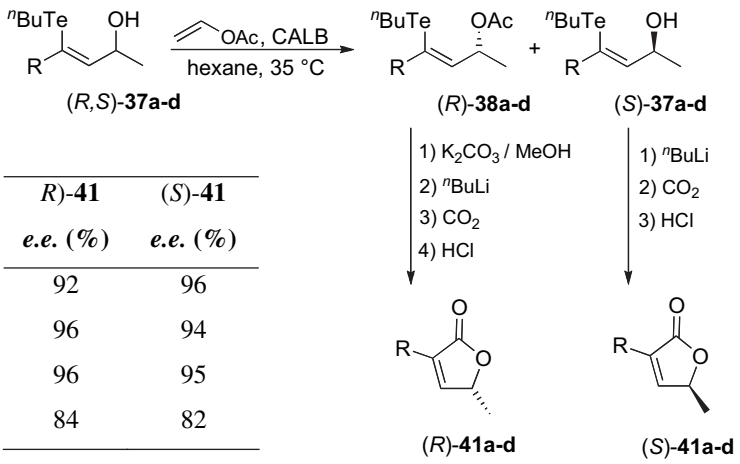
Entry	Enzyme	Solvent	Time (h)	*c* (%)	(*S*)-**37a** ee (%)	(*R*)-**38a** ee (%)	Yield (%) [(*S*)-**37a**; (*R*)-**38a**]	*E*
1	CALB	Hexane	2	39	62	>99		
2			3	45	79	98		
3			4	49	96	98	36; 32	>200
4		THF	6	27	37	99		
5			24	28	38	99	36; 26	
6			48	36	54	96		84
7		Hexane/THF	4	29	40	99		
8			6	32	46	97		
9			24	48	89	98	36; 49	>200
10	PPL	Hexane	2	9	10	98		
11			5	26	35	98		139
12	PSL	Hexane	2	4	3	65		
13			6.5	12	9	64		5

sumably following a mechanism similar to the one depicted in Scheme 11. The 2,3-sigmatropic rearrangement of the selenoxide **49** occurred with no chirality transfer,[35] and the reaction yield was not reported.

Recently, more encouraging results on the enzymatic oxidation of selenides were published. One of these reports described a study on the incubation of diphenyldiselenide (**51**), benzeneseleninic acid (**43**) and hydroxyselenides **12a**, **12h**, **12e** and **12g** (for the structures see Table 2) with *Aspergillus terreus*. Incubation of **51** and **43** with *A. terreus* CCT 3320 gave methyl phenyl selenide (**53**) with high conversion (100% for **51** and 90% for **43**). These transformations could be rationalized as shown in Scheme 13.[36]

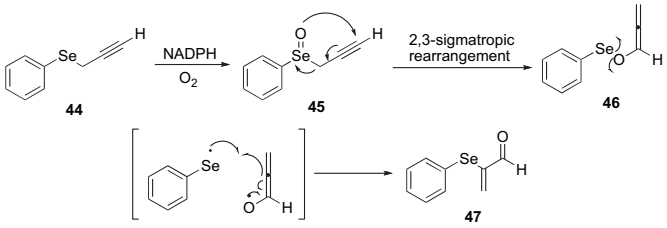
The biomethylation of inorganic species of selenium is well known.[30] However, similar transformations involving organoselenium substrates are scarcely reported. Incubation of (*R,S*)-**12a** with *A. terreus* URM 3571 for 3 days gave (*R*)-**12a** in 50% isolated yield (>99% *e.e*) and phenyl methyl selenide (**53**) in 40% isolated yield. This result was rationalized as shown in Scheme 14.[36]

As is observed, the hydroxyselenide **12a** was enantiodiscriminated by *A. terreus*. Only the (*R*)-**12a** enantiomer was oxidized, while (*S*)-**12a** was recovered intact with high yield and enantiomeric excess. Two mechanistic pathways were proposed to account for this transformation. In path A, (*R*)-**12a** is selectively oxidized by *A. terreus* to give the selenoxide **54**, which suffers spontaneous elimination of volatile propanone to produce benzeneselenenic acid (**52**). This intermediate may be transformed into **53** through direct biomethylation catalyzed by *A. terreus*, or via the formation of **43** catalyzed by *A. terreus*, followed by biomethylation. Although the suggested intermediates **52** and **54** have not been isolated, the finding that whole cells of *A. terreus* efficiently transformed **43** into **53** (Scheme 13) supports the proposed mechanism. In path B, it is

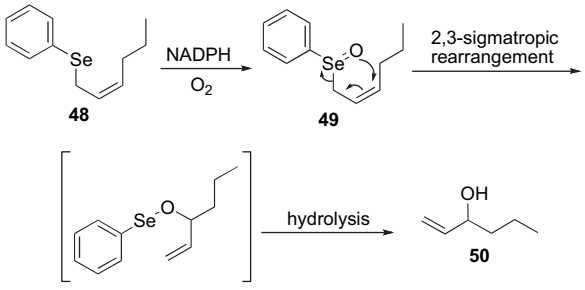


		(*R*)-**41** *e.e.* (%)	(*S*)-**41** *e.e.* (%)
R =	Me (**41a**)[26]	92	96
	^{n}Bu (**41b**)[27]	96	94
	^{n}Hex (**41c**)[28]	96	95
	Ph (**41d**)[29]	84	82

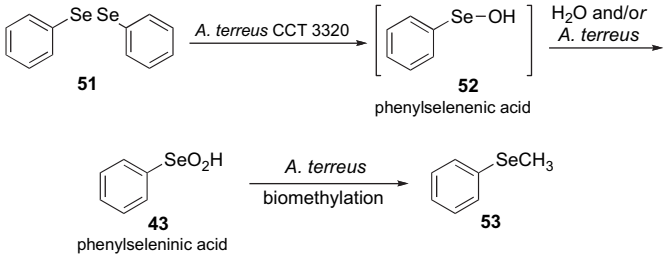
Scheme 10.[25]



Scheme 11.[35]



Scheme 12.[35]



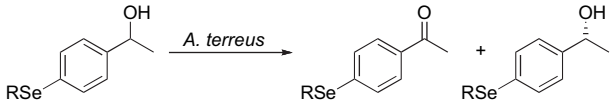
Scheme 13.[36]

proposed a hydroxylation of (*R*)-**12a** to hemiselenoacetal **55**, followed by the decomposition of **55** into selenophenol (**56**). Oxidation of **56** to **43** and biomethylation of **43** should give **53**.

After 5 days incubation of (*R*,*S*)-**12g** with *A. terreus* CCT 3320, (*S*)-**12g** was obtained with 95% conversion and 90% ee. On the other hand, *A. terreus* URM 3571 did not promote the biotransformation of (*R*,*S*)-**12g**. The biotransformation of (*R*,*S*)-**12e** with *A. terreus* strains CCT 3320 and URM 3571 led to the exclusive formation of **53**, whilst (*R*,*S*)-**12h** was not efficiently transformed into products by either strain.[36]

Three arylselenoethanols (*R*,*S*)-**57**, **16f** and **16g**, (Eq. 5) were incubated with *A. terreus*, leading to deracemization in some cases.[37]

The selenoacetophenones **58a**–**c** were detected as intermediates in all cases. The best result in terms of conversion and enantiomeric excess was obtained with **57**. The deracemization process for this compound is rationalized in Scheme 15.



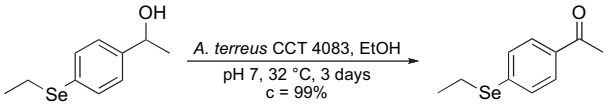
R = Me (*R*,*S*)-**57**; Et (*R*,*S*)-**16f**; Ph (*R*,*S*)-**16g**

R = Me **58a**; Et **58b**; Ph **58c**

(*R*)-**57**; (*R*)-**16f**; (*R*)-**16g**

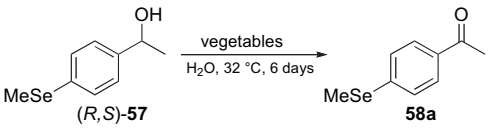
In the first step (*S*)-**57** was rapidly oxidized to the selenoacetophenone **58a**. The isomer (*R*)-**57** was oxidized slowly to **58a**. In a second step, **58a** was reduced slowly to (*S*)-**57**, but more rapidly to (*R*)-**57**. In this way, the sample of **57** became enriched in the isomer (*R*)-**57**, as shown in Scheme 15.

Under certain conditions, the selenoacetophenone **58** was the main product. For example, compound **16f** was transformed into **58b** with 99% conversion after incubating with *A. terreus* CCT 4083 at 32 °C for 3 days at pH 7 (Eq. 6).[37]



(*R*,*S*)-**16f** **58b**

The use of vegetables as chemical reagents appears as an alternative to classical methods, due to economical and ecological implications.[38] In the context of inorganic selenium and tellurium compounds, plants have been used for their volatilization from contaminated soils.[30,39] A few examples were recently disclosed showing that vegetables can be used to make transformations in selenium containing organic substrates. The functional groups were transformed, leaving the selenium atom intact. Compound **57** was transformed into **58b** with high conversion through the reaction with some vegetables. The best results were obtained with *Allium schoenoprasum* (88% conversion), *Coriandrum sativum* (100% conversion) and *Zingiber officinale* (100% conversion) (Eq. 7).[40]

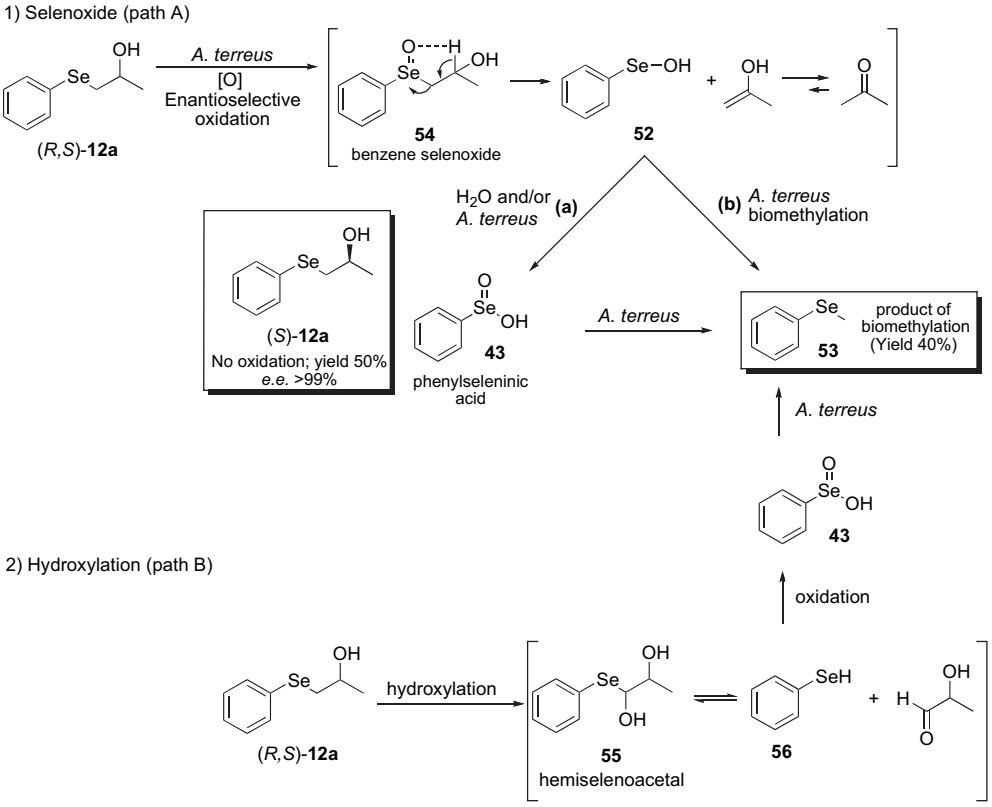


(7)

vegetables: *Allium schoenoprasum* (c = 88%)
Coriandrum sativum (c = 100%)
Zingiber officinale (c = 100%)

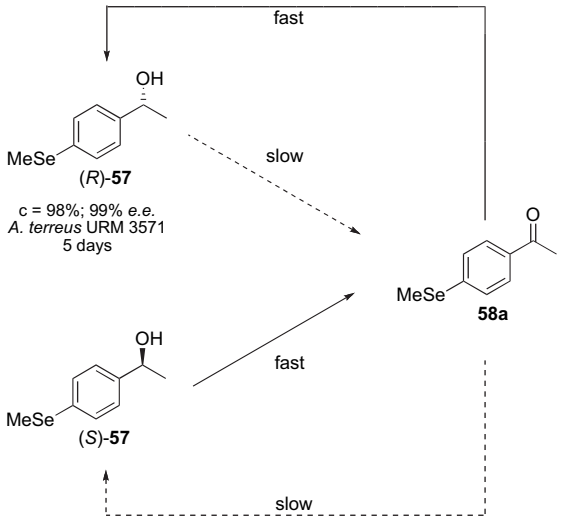
4. Enzymatic reduction of selenium and tellurium containing substrates

The enzymatic reduction of selenium containing substrates has been studied with fungi[41,42] and vegetables.[12,37] In most cases, the main transformation was a carbonyl reduction, a biotransformation of wide application in organic synthesis.[43] The substrates studied are shown in Scheme 16.

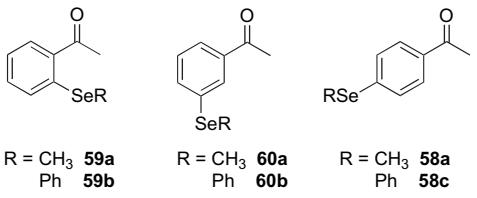


Scheme 14.[36]

As can be deduced by the results described in this section, the oxidation of selenium containing substrates by enzymes is a promising field for investigation. Similar transformations involving tellurium species were not yet described.



Scheme 15. Deracemization of **57** by whole cells of Aspergilus terreus URM 3571 at pH=4 in the presence of ethanol at 32 °C.



Scheme 16. Selenoacetophenones used in the enzymatic reduction studies.

Four fungi strains were used, namely *Rhizopus oryzae* CCT 4964, *A. terreus* CCT 4083, *A. terreus* CCT 3320 and *Emericella nidulans* CCT 3119. The results obtained are summarized in Table 11.[41]

The selenoacetophenones **59a** and **59b** were unreactive toward the four fungi investigated. The same fungi strains reduced *o*-fluoroacetophenones efficiently.[44] This fact led to the conclusion that some steric constraint is operating in the case of **59a** and **59b**. This assumption was supported by the reduction of **60a** by the four fungi strains with good conversion and ee. Similar results were obtained with **58a**. Compound **58c** gave low conversion and ee with all fungi tested, except with *R. oryzae* CCT 4964, which transformed **58c** into the corresponding alcohol with 85% conversion and 71% ee. In most cases, the enantioselectivity was in accordance with Prelog's rule. Interestingly, the reduction of **58a** with some fungi strains showed also the anti-Prelog stereoselectivity. For example, **58a** was transformed into (*S*)-**57** by *R. oryzae* CCT 4964, but *E. nidulans* CCY 3119

Table 11
Asymmetric bioreduction of selenoketones by whole fungal cells[41]

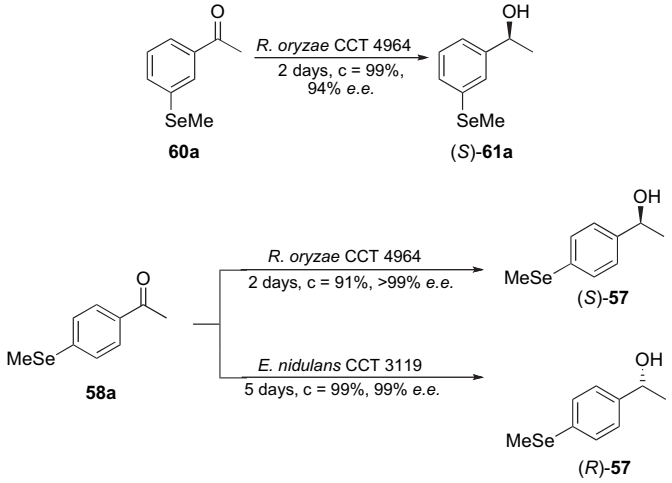
o-MeSe	**59a**	*o*-MeSe	**16a**
o-PhSe	**59b**	*o*-PhSe	**16b**
m-MeSe	**60a**	*m*-MeSe	**61a**
m-PhSe	**60b**	*m*-PhSe	**16e**
p-MeSe	**58a**	*p*-MeSe	**57**
p-PhSe	**58c**	*p*-PhSe	**16g**

Entry	Substrate	Whole fungal cells	Time (days)	*c* (%)	Products ee (%)
1	**59a**	*R. oryzae* CCT 4964	7	n.c.	—
2	**60a**	*R. oryzae* CCT 4964	2	99	94 (*S*)-**61a**
3	**58a**	*R. oryzae* CCT 4964	2	91	96 (*S*)-**57**
4	**59b**	*R. oryzae* CCT 4964	7	n.c.	—
5	**60b**	*R. oryzae* CCT 4964	7	90	87 (*S*)-**16e**
6	**58c**	*R. oryzae* CCT 4964	7	85	71 (*S*)-**16g**
7	**59a**	*A.terreus* CCT 4083	7	n.c.	—
8	**60a**	*A.terreus* CCT 4083	2	76	90 (*S*)-**61a**
9	**58a**	*A. terreus* CCT 4083	2	86	55 (*R*)-**57**
10	**59b**	*A. terreus* CCT 4083	7	n.c.	—
11	**60b**	*A. terreus* CCT 4083	9	21	47 (*S*)-**16e**
12	**58c**	*A. terreus* CCT 4083	9	12	45 (*S*)-**16g**
13	**59a**	*A. terreus* CCT 3320	7	n.c.	—
14	**60a**	*A. terreus* CCT 3320	2	75	86 (*S*)-**61a**
15	**58a**	*A. terreus* CCT 3320	10	75	95 (*R*)-**57**
16	**59b**	*A. terreus* CCT 3320	7	n.c.	—
17	**60b**	*A. terreus* CCT 3320	7	41	99 (*S*)—**16g**
18	**58c**	*A. terreus* CCT 3320	7	n.c.	—
19	**59a**	*E. nidulans* CCT 3119	7	n.c.	—
20	**60a**	*E. nidulans* CCT 3119	3	9	67 (*S*)-**61a**
21	**58a**	*E. nidulans* CCT 3119	5	99	99 (*R*)-**57**
22	**59b**	*E. nidulans* CCT 3119	7	n.c.	—
23	**60b**	*E. nidulans* CCT 3119	10	n.c.	—
24	**58c**	*E. nidulans* CCT 3119	7	n.c.	—

n.c.: no conversion.

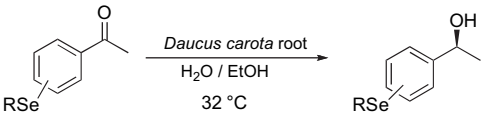
transformed it into (*R*)-**57**. The most interesting results of this study are shown in Scheme 17.

The same ketones shown in Scheme 16 were incubated with carrot roots (*Daucus carota*), [12] and the results obtained were similar to the ones described for the reduction with fungi. Interestingly, the *o*-organoselenoacetophenones **59a** and **59b** were not reduced, even after three days in contact with the biocatalyst. In contrast, the *meta* and *para*-organochalcogenoacetophenones (**60a**, **60b**, **58a**, **58c**) were transformed into (*S*)-**61a**, (*S*)-**57**, (*S*)-**61a** and (*S*)-**16g**, respectively, with excellent enantioselectivity (>99% ee) and high conversion. In all cases, the enantioselectivity was in accordance with Prelog's rule, giving the alcohol with *S* configuration. The results are summarized in Table 12.[12]



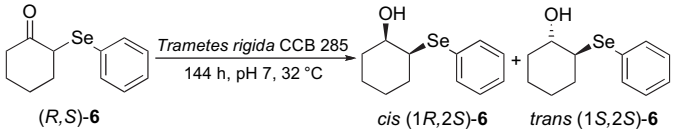
Scheme 17. Reduction of selenoacetophenones **60a** and **58a** by fungi.[41]

Table 12
Reduction of selenoacetophenones **58a**, **58c**, **59**, **60** using *D. carota* root[12]



Entry	Chalcogeno ketone	Chalcogeno alcohol	Time (h)	*c* (%)	ee (%)
1	**59a**=*o*-MeSe	(*S*)-**16a**	72	n.c.	—
2	**60a**=*m*-MeSe	(*S*)-**61a**	48	96	>99
3	**58a**=*p*-MeSe	(*S*)-**57**	48	83	>99
4	**59b**=*o*-PhSe	(*S*)-**16c**	72	n.c.	—
5	**60b**=*m*-PhSe	(*S*)-**61b**	72	95	>99
6	**58c**=*p*-PhSe	(*S*)-**16g**	72	72	>99

Whole cells of basidiomycetes catalyse the reduction of a-phenylselenocyclohexanone (*R,S*)-**6**. Only (*S*)-**6** was reduced giving *cis*-(1*R*,2*S*)-**6** and *trans*-(1*S*,2*S*)-**6**. Several *basidiomycetes* strains were effective, but the best results were obtained with *Trametes rigida* CCB 285. After incubation in a phosphate buffer at 32 °C for 6 days, (*R,S*)-**6** led to *cis*-(1*R*,2*S*)-**6** and *trans*-(1*S*,2*S*)-**6**, which were separated by column chromatography on silica gel (Scheme 18).[42]

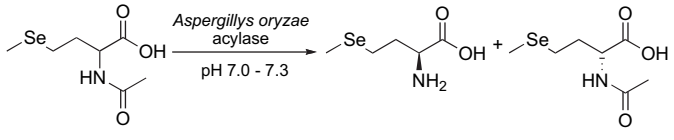


Scheme 18. Reduction of (*S*)-**6** by *Trametes rigida* CCB 285.[42]

In conclusion, the bioreduction of the carbonyl group of ketones, bearing an organoseleno group in their structures, is a useful method to access enantiomericaly enriched hydroxyselenides. Similar transformations were not yet described for ketones bearing an organotellurium group.

5. Miscellanea

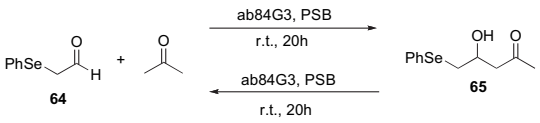
L-Selenomethionine L-**63**, which was described as suitable for treatment of Alzheimer's disease and Parkinson's syndrome, was obtained in 99.6% ee by enantioselective deacylation of DL-selenomethionine (DL-**62**) by acylase of *Aspergillus oryzae* (Scheme 19).[45]

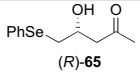
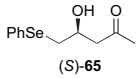


Scheme 19. Enantioselective deacylation of DL-Selenomethionine (DL-**62**) by acylase of *A. oryzae*.[45]

The aldolase antibody 84G3 (ab84G3) in a phosphate buffer solution (PBS) at room temperature catalyzed the aldol reaction of

phenylselenoacetaldehyde **64** with acetone. The same antibody catalyzed the retro-aldol reaction of **65**. In both cases, **65** was obtained with low ee (Scheme 20).[46]



Product	c (%)	*e.e.* (%)
 (*R*)-**65**	**Aldol (65)**	**64**
 (*S*)-**65**	**Retroaldal (66)**	**66**

Scheme 20. Aldol and retroaldol reaction catalyzed by ab84G3.[46]

6. Conclusion

Some biotransformations of organic selenides and organic tellurides can already be considered well established, as the enzymatic kinetic resolution of selenides and tellurides by commercially available lipases, and the reduction of selenoacetophenones by *D. carota*. Other biotransformations, such as deracemization and oxidation of arylselenoethanols with plants and fungi, as well as the reduction of selenoketones with fungi, although potentially useful, still require more studies to be applied in synthesis. However, the demonstration that selenides and tellurides do not deactivate isolated enzymes or enzymes found in plants or fungi, open the perspective for further studies in this area. Noteworthy is the observation that these enzymes are able to perform chemical transformations in functional groups present in selenides, leaving the selenium atom intact. The transformation of organic tellurides by plants and fungi is still an open field for investigation. Organic telluranes are active toward some classes of enzymes and some of them are very effective as protease inhibitors.[47] This subject has been studied under the biochemical point of view, with no connection to the organic synthesis.

In conclusion, this branch of organic chemistry is still in its infancy, but shows great potential. Considering the prejudice involving selenium and tellurium compounds, it is worth elucidating the properties of the compounds of these elements, destroying some negative myths in the process that hamper their use in chemistry.

Acknowledgements

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