

## Kinetic resolution of 2-methoxycarbonylalk-3-enols through a stereoselective cyclofunctionalization promoted by an enantiomerically pure electrophilic selenium reagent

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Dedicated to Prof. Jacek Młochowski on the occasion of his 80th birthday

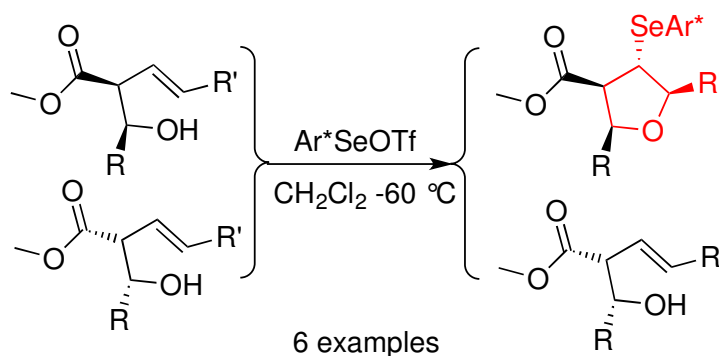
Received 08-02-2016

Accepted 09-15-2016

Published on line 09-29-2016

### Abstract

In this manuscript the kinetic resolution of 2-methoxycarbonylalk-3-enols is reported through a stereoselective selenocyclization promoted by an electrophilic sulfur-containing selenium reagent. Reacting one equivalent of the selenenylating agent with two equivalents of racemic starting material afforded a mixture of a stereoselectively enriched tetrahydrofuran and the corresponding enantiomerically enriched alkenols.



**Keywords:** Selenium, electrophile, cyclization, tetrahydrofurans, alkenols

## Introduction

Electrophilic organoselenium derivatives are widely studied reagents that can be efficiently used in a number of transformations enabling the chemo- and stereoselective synthesis of variously functionalized compounds.<sup>1-3</sup>

During the last decades, the synthesis of enantiomerically pure diselenides and their use as precursors of the corresponding electrophilic reagents, has been shown to be a practical and powerful tool for the stereoselective preparation of enantiomerically enriched chiral molecules.<sup>1-8</sup> Some years ago we introduced a new class of enantiopure sulfur-containing diselenides exploring their synthetic applications in enantioselective selenium addition reactions to unsaturated substrates.<sup>9</sup> Electrophilic reagents generated starting from these diselenides were successfully employed in the synthesis of enantiomerically enriched alcohols,<sup>10</sup> ethers,<sup>10</sup> azides,<sup>11</sup> heterocycles<sup>12,13</sup> and, very interestingly, in the kinetic resolution of racemic allylic alcohols through a methoxyselenenylation reaction. To the best of our knowledge this was the first example of non-enzymatic kinetic resolution promoted by organoselenium reagents.<sup>14</sup> More recently, highly enantioselective selenocyclization reactions were achieved from the dynamic kinetic resolution of seleniranium ions through anion-binding catalysis.<sup>15</sup>

In all the explored reactions the sulfur atom, which is suitably positioned to establish a non-bonding interaction with the electrophilic selenium atom, showed a very high facial selectivity, higher than those obtained with similar nitrogen- or oxygen-containing reagents. Here we explore the possibility of applying the same protocol to the kinetic resolution of 2-methoxycarbonyl-3-alkenols. We demonstrated that these substrates are interesting precursors for the stereoselective synthesis of tetrasubstituted tetrahydrofurans bearing synthetically manipulable functional groups. The possibility to prepare these substrates in a stereocontrolled manner is particularly attractive on account of the presence of four contiguous stereocenters<sup>12</sup> (Figure 1).

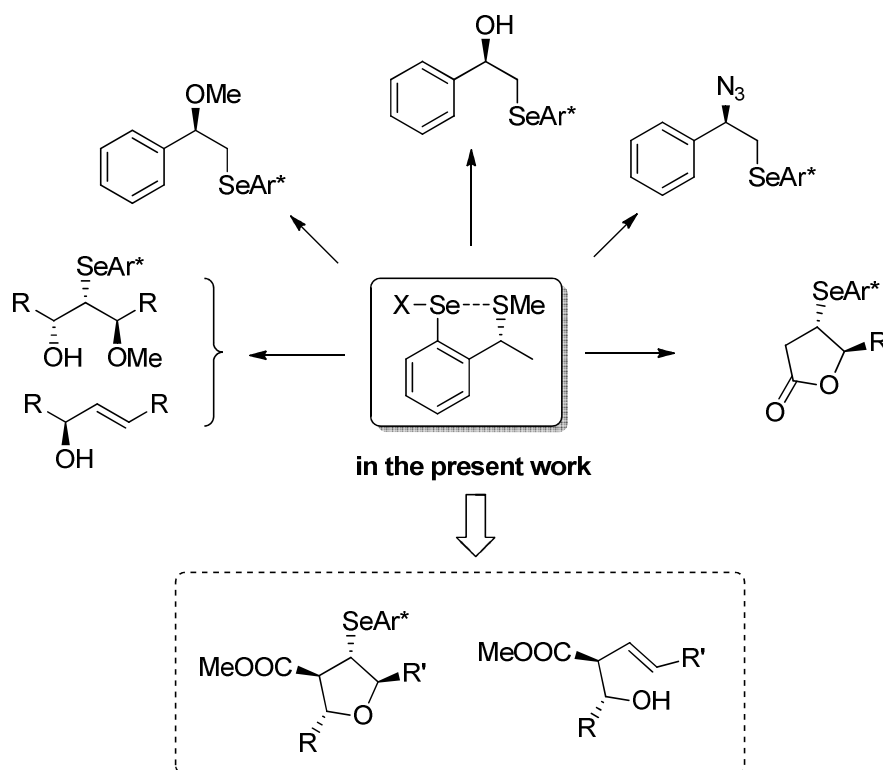


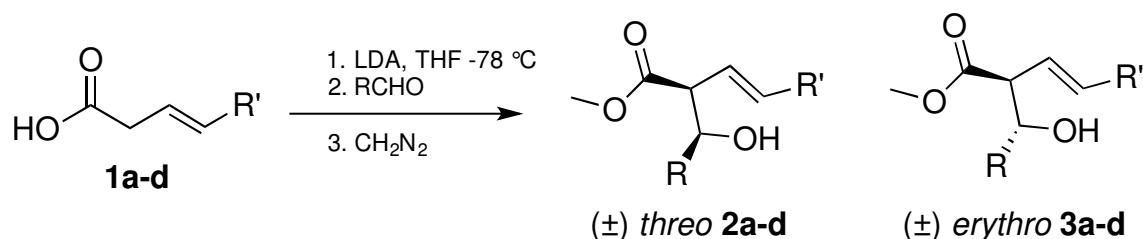
Figure 1

## Results and Discussion

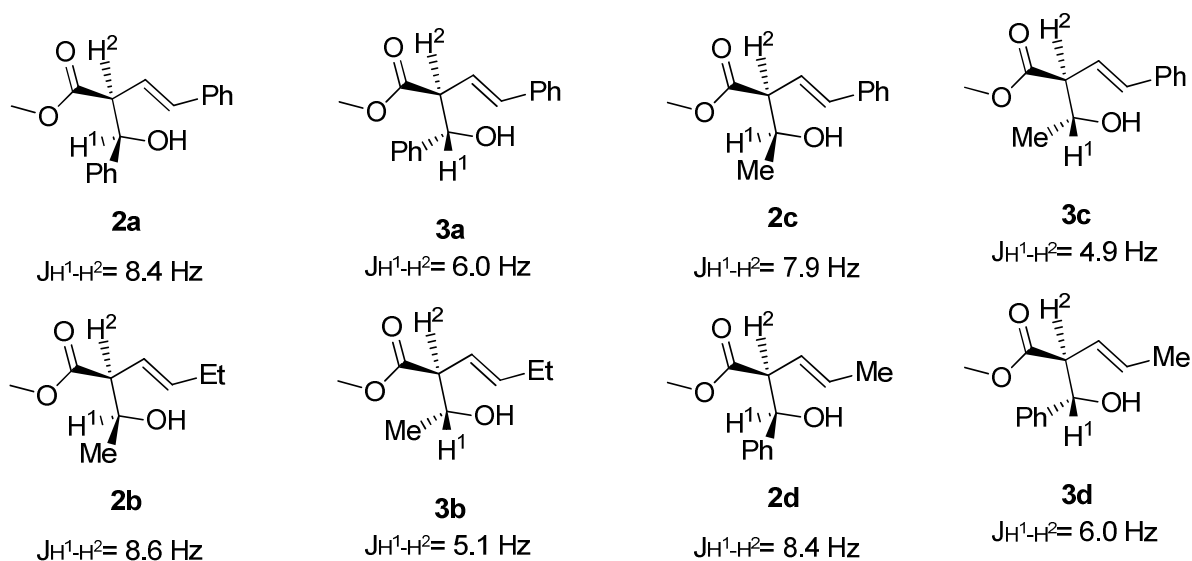
Substrates **2a-d** and **3a-d** used for the present investigation were easily prepared starting from commercially available carboxylic acids **1a-d** following the procedure reported in literature.<sup>12</sup> Treatment of the alkenoic acid **1a-d** with LDA at -78 °C in THF and then reaction of the corresponding dianion with an aldehyde afforded in all the cases a pair of diastereoisomers that were purified by flash chromatography. Diastereomeric ratios were measured by proton NMR of the crude and yields, reported in Table 1, refer to isolated products. The relative configurations for the *threo* isomers (**2a-d**) and the *erythro* isomers (**3a-d**) were assigned on the basis of the coupling constants values between H<sup>1</sup> and H<sup>2</sup> by comparison with those reported in the literature for the known compounds **2b-c** and **3b-c**<sup>12</sup> (Figure 2).

Unfortunately, alkenols **3a** and **3d** were not obtained in a suitable amount and purity for further investigation in kinetic resolution.

**Table 1.** Synthesis of *threo*- and *erythro*-hydroxy-esters **2** and **3**



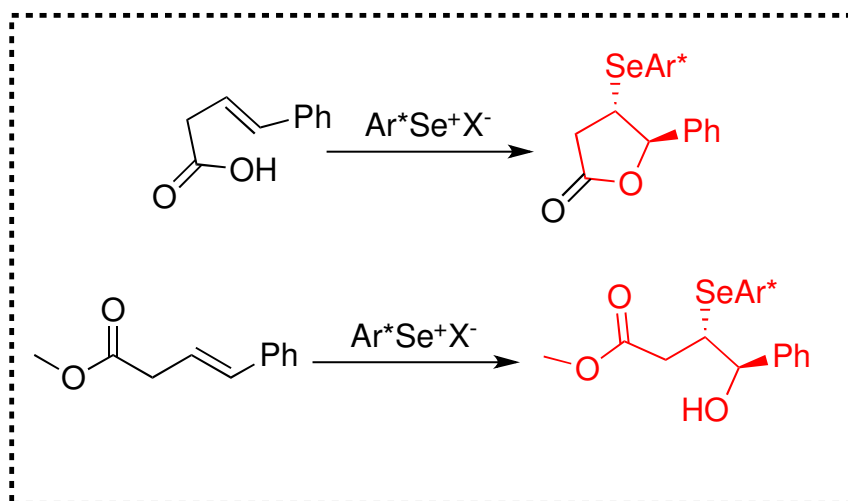
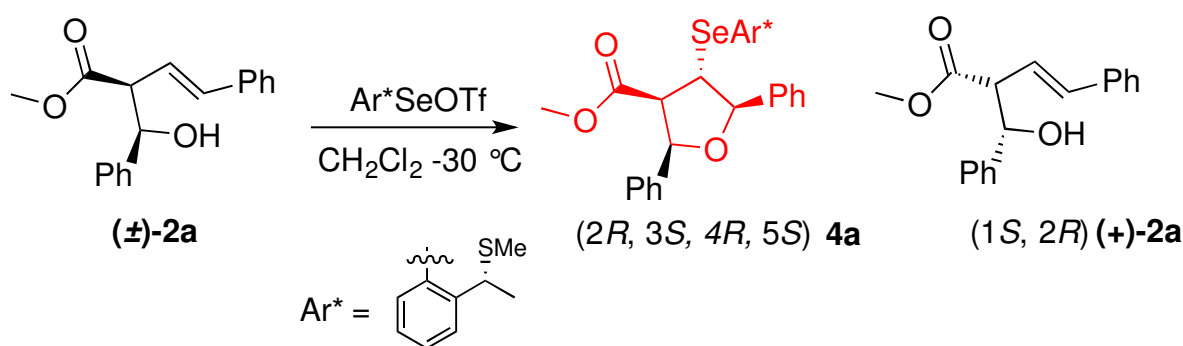
Entry	R	R'	2/3	Yield %
a	Ph	Ph	82:18	88
b	Me	Et	50:50	60
c	Me	Ph	50:50	67
d	Ph	Me	70:30	30



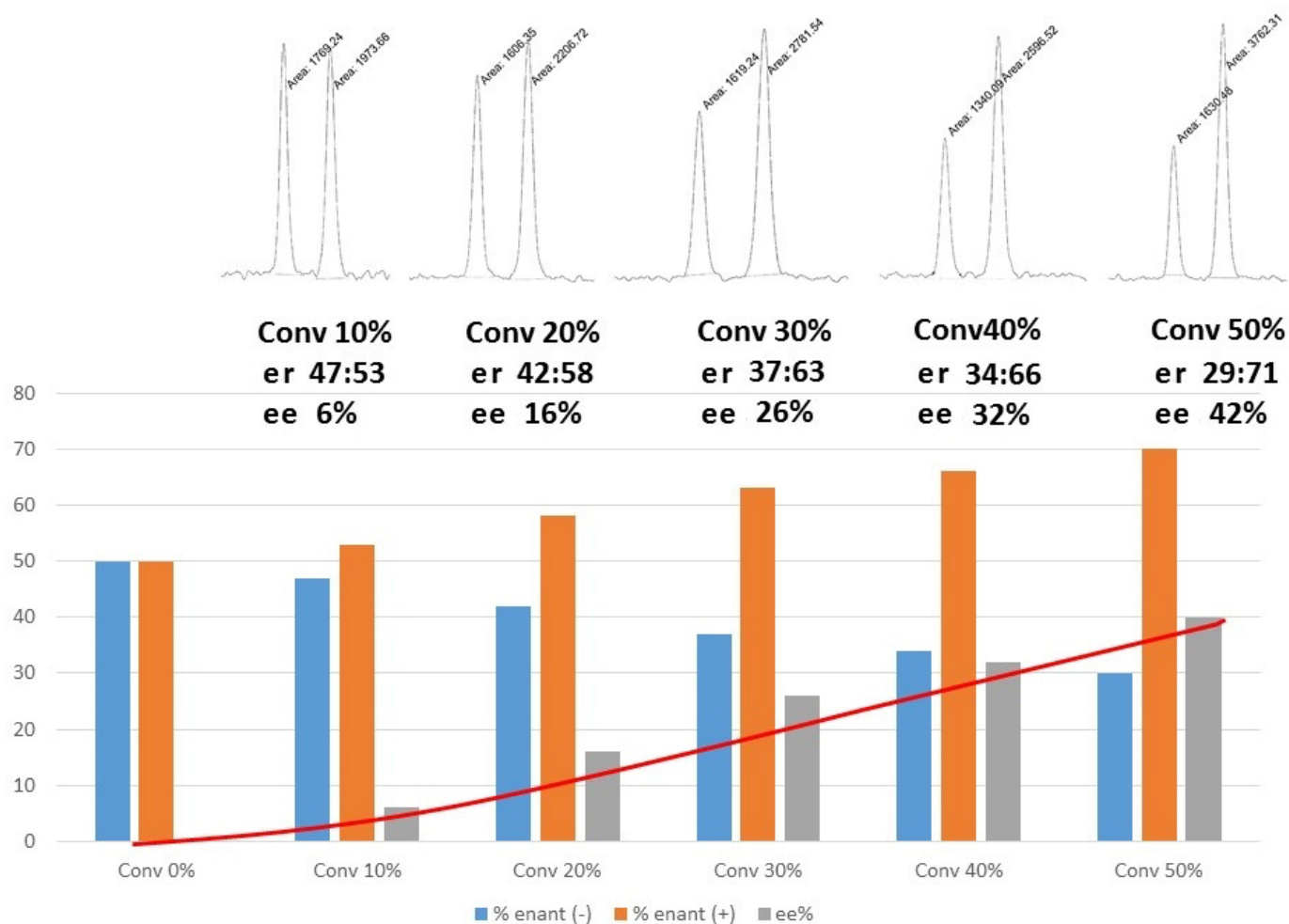
**Figure 2.** Assignment by *J* values.

Preliminary investigations were carried out using alkenol **2a** and the best reaction conditions optimized for the kinetic resolution of allylic alcohols (using triflate as anion at  $-30\text{ }^{\circ}\text{C}$ ).<sup>14</sup> The reaction was monitored by chiral HPLC at various states of conversion, evidencing also in this case that the cyclization reaction occurs preferentially on the (-)-**2a** producing a progressive enrichment of the unreacted (+)-**2a** reaching 50% of conversion an enantiomeric ratio of (+)-**2a**/(-)-**2a** = 71:29 (42% ee) (Scheme 1 and Figure 3).

Assignment of the absolute configuration can be deduced by comparison with the stereoselectivity obtained in some reactions similar to those reported (box in Scheme 1). It is reasonable to speculate that the selenium atom attack the double bond with the same facial discrimination observed for the analogous series of selenenylating reagents in the cyclofunctionalization of *trans*-3-hexenoic acid and in the hydroxyselenenylation of (*E*)-methyl 4-phenylbut-3-enoate. This allows us to assign the absolute configuration at carbons 4 and carbon 5 of the ring and, consequently, considering the stereoselectivity obtained with diphenyl diselenide,<sup>10</sup> to assign to (+)-**2a** the absolute configuration 1*S*, 2*R*.<sup>9,13</sup>



**Scheme 1.** Kinetic resolution of **2a**.



**Figure 3.** HPLC chiral resolution of **2a** using Chiralpak AD-H (250 x 4.6 nm) column, hexane-IPA 92:8, 1.0 mL/min,  $\lambda$  230 nm,  $t$  (minor) 23.6 min,  $t$  (major) 26.4 min (upper panel). Trend of enantiomeric excesses related to the conversion % (lower panel).

An optimization of the reaction conditions was attempted using  $\text{Ar}^*\text{SeX}$  having  $\text{R} = \text{H}$  (see Scheme 1) and exploring different anions ( $\text{X}$ ) at different temperatures. In the case of bromide, reaction did not occur at  $0^\circ\text{C}$  and the reaction with chloride proved to be very slow and only slightly more selective as compared with triflate. The reactivity of the triflate allowed us to decrease the temperature to  $-60^\circ\text{C}$  obtaining (+)-**2a** in 120 hours with 52% ee (Table 2).

**Table 2.** Preliminary investigation

Electrophile	$T^\circ\text{C}$	Time (h)	(+)- <b>2a</b> e.r. <sup>a</sup>
$\text{Ar}^*\text{SeBr}$	0	120	nr
$\text{Ar}^*\text{SeCl}$	0	120	58:42
$\text{Ar}^*\text{SeOTf}$	0	3	52:48
$\text{Ar}^*\text{SeOTf}$	-30	96	71:29
$\text{Ar}^*\text{SeOTf}$	-60	120	76:24

<sup>a</sup> Calculated from NMR measurements using EuFod as Chiral Shift Reagent.

Having established the optimum conditions, we explored the scope of the kinetic resolution of racemic alkenols **2a-d** and **3b,c**. With only the exception of **2d** all the reactions reached 50% of conversion after 120 hours and the conversion was confirmed by integration of diagnostic signals in the  $^1\text{H-NMR}$  spectra of the crude products after complete consumption of the selenenylating reagent.

According to our previous results,<sup>12</sup> obtained using diphenyl diselenide as selenenylating reagent, we can assume that in all the cases the cyclization afforded as major isomer those bearing -SePh and -COOMe groups on the opposite faces of the tetrahydrofuran. This selectivity is here reasonably increased by the higher steric requirement of the aryl moiety, like the effect described by Lipshutz using 2,4,6-triisopropylphenyl diselenide.<sup>16</sup> Consequently, based on the kinetic resolution, a pair of the diastereoisomeric tetrahydrofurans and enantiomerically enriched unreacted starting material were recovered after the reaction. As an example, starting from ( $\pm$ )-**2a**, reaction with half an equivalent of selenenylating reagent afforded mainly a pair of isomers in a ratio of 77:23 that is very close to the enantiomeric ratio measured on the kinetically resolved starting material (76:24). The major cyclization product is indicated in the Table 3 as **4a** and is reasonably derived from the cyclization of (-)-**2a** producing the (2*R*,3*S*,4*S*,5*R*) tetrahydrofuran ring. On the contrary, the minor product (not indicated in the Table 3) derives from the cyclization of (+)-**2a** affording the (2*S*,3*R*,4*R*,5*S*) diastereoisomer. The presence of the other possible pair of compounds (2*R*,3*S*,4*R*,5*S*) and (2*S*,3*R*,4*S*,5*R*) cannot be clearly confirmed nor excluded by the analysis of the spectra of the crude product, and in some cases also after chromatographic purifications, they could represent the minor impurities that could not be completely removed from the main pair of compounds.

In some cases, the relative configurations were confirmed by NOESY experiments. After chromatographic purification the enantiomeric ratios of the resolved alcohols were measured by NMR using  $\text{Eu}(\text{fod})_3$  as chiral shift reagent and, in selected examples, they proved to be in perfect agreement with those obtained by HPLC. The yields reported in Table 3 refer to the amount of the product isolated after chromatography as pure compounds (**2** or **3**) or as mixtures of isomers (**4,5**).

**Table 3.** Scope of the reaction

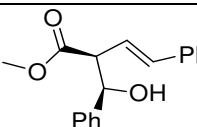
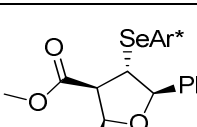
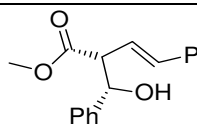
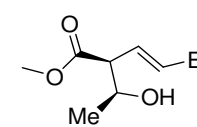
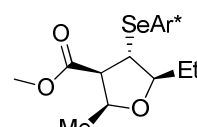
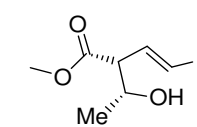
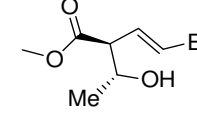
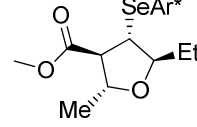
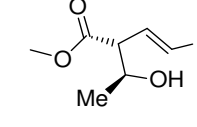
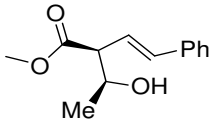
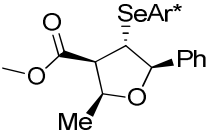
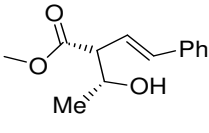
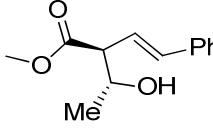
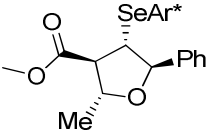
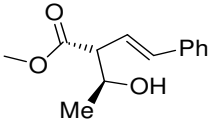
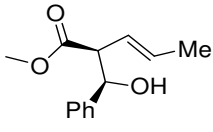
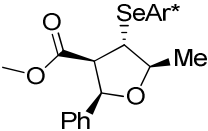
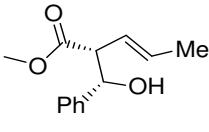
( $\pm$ )- <b>2, 3</b>	Conv %	<b>4, 5</b>	dr yield	resolved (2 or 3)	er yield	$[\alpha]_D$
 ( $\pm$ )- <b>2a</b>	50	 <b>4a</b>	77:23 45%	 (+)- <b>2a</b>	76:24 45%	$[\alpha]_D^{29.2} = +34,21$ (c 0.48, $\text{CHCl}_3$ )
 ( $\pm$ )- <b>2b</b>	50	 <b>4b</b>	88:12 38%	 (-)- <b>2b</b>	89:11 46%	$[\alpha]_D^{23.2} = -1.12$ (c 1.53, $\text{CHCl}_3$ )
 ( $\pm$ )- <b>3b</b>	50	 <b>5b</b>	91:9 42%	 (-)- <b>3b</b>	82:18 40%	$[\alpha]_D^{23.2} = -4.26$ (c 0.36, $\text{CHCl}_3$ )

Table 3. Continued

(±)- <b>2</b> , <b>3</b>	Conv %	<b>4</b> , <b>5</b>	dr yield	resolved (2 or 3)	er yield	$[\alpha]_D$
 (±)- <b>2c</b>	50	 <b>4c</b>	75:25 40%	 (+)- <b>2c</b>	70:30 42%	$[\alpha]_D^{22.8} = +27.66$ (c 0.46, CHCl <sub>3</sub> )
 (±)- <b>3c</b>	50	 <b>5c</b>	88:12 38%	 (+)- <b>3c</b>	90:10 44%	$[\alpha]_D^{26.5} = +66.64$ (c 0.83, CHCl <sub>3</sub> )
 (±)- <b>2d</b>	30	 <b>4d</b>	87:13 24%	 (+)- <b>2d</b>	65:35 66%	$[\alpha]_D^{26.7} = +23.97$ (c 0.29, CHCl <sub>3</sub> )

Moderate to good levels of enantioresolution (ranging from 40% to 80% ee) were obtained for **2a-c** with the only exception of the substrate **2d**. In this case only 30% of conversion was achieved after 120 hours at -60 °C, and consequently the unreacted alkenol was recovered in 66% of yield and low enantiomeric excess. (30% ee).

## Experimental Section

**General.** Solvents and reagents were used as received unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F254 precoated aluminum foil sheets and visualized by UV irradiation or by KMnO<sub>4</sub> staining. Silica gel Kieselgel 60 (70–230 mesh) was used for column chromatography. NMR experiments were conducted at 25 °C with a Bruker DPX 200 spectrometer operating at 200 MHz for <sup>1</sup>H and 50.31 MHz for <sup>13</sup>C experiments or with a Bruker DRX spectrometer operating at 400 MHz for <sup>1</sup>H and 100.62 MHz for <sup>13</sup>C experiments. <sup>1</sup>H and <sup>13</sup>C chemical shifts (δ) are reported in parts per million (ppm), relative to TMS (δ = 0.0 ppm) and the residual solvent peak of CDCl<sub>3</sub> (δ = 7.26 and 77.00 ppm in <sup>1</sup>H and <sup>13</sup>C NMR, respectively). Data are reported as: chemical shift (multiplicity, coupling constants where applicable, number of hydrogen atoms). Abbreviations are: s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), dt (double triplet), tt (triple triplet), m (multiplet), br. s (broad signal). Coupling constant (*J*) quoted in Hertz (Hz) to the nearest 0.1 Hz. Spectroscopic data for **2a**,<sup>17</sup> **2c**, **3c** and **2d**<sup>12</sup> were compared with those reported in literature and, in the cases of tetrahydrofurans **5a-d** and **6b,c** the spectral data of the major isomer were extrapolated by the <sup>1</sup>H-NMR and <sup>13</sup>C-NMR of a mixture of diastereoisomers. Optical rotations were measured with a Jasco DIP-1000 digital polarimeter. Elemental analyses were carried out on a Carlo Erba 1106 Elemental Analyzer.

Preparation of selenenylating reagents: (1S)-[2-(1-methylthioethyl)phenyl]selenenyl chloride, (1S)-[2-(1-methylthioethyl)phenyl]selenenyl bromide and: (1S)-[2-(1-methylthioethyl)phenyl]selenenyl triflate were carried out according literature.<sup>9,10</sup> Chiral HPLC analyses were performed on an HP 1100 series instrument equipped with Chiralpak AD-H (250 x 4.6 nm) column and an UV detector.

**Synthesis of 2-methoxycarbonyl-3-alkenols (2a-d and 3a-d).**<sup>12</sup> 2.1 mmoles of BuLi (1,6M solution in hexane) were added dropwise to a solution of diisopropylamine (2.1 mmol) in THF (2mL) at 0 °C under inert conditions. After 15 minutes the reaction mixture was cooled at -78 °C and stirred for additional 30 minutes. Carboxylic acid **1a-d** (1 mmol), dissolved in freshly distilled THF (1 mL), was then slowly added observing a deep yellow/orange coloration of the solution. 2 h a stoichiometric amount of aldehyde was added and the mixture stirred at rt for 6 h. The reaction mixture was poured into aq NH<sub>4</sub>Cl (10%) and extracted with Et<sub>2</sub>O (3 × 10 mL). The aqueous layers washed with aq NaHCO<sub>3</sub> (10%), acidified with HCl and extracted again with Et<sub>2</sub>O (3 × 10 mL). The organic layers were dried and the organic solvent was removed under vacuum. The crude was treated with an ethereal solution of CH<sub>2</sub>N<sub>2</sub> and purified by silica flash chromatography (Et<sub>2</sub>O /petroleum ether 10%)

**(RS,E)-Ethyl 2-((SR)-hydroxy(phenyl)methyl)-4-phenylbut-3-enoate (±-2a).** Oil; <sup>1</sup>H-NMR: δ 7.50-7.20 (10H, m), 6.36 (1H, d, *J* 15.9 Hz), 6.12 (1H, dd, *J* 15.9 and 8.8 Hz), 5.09 (dd, 1H, *J* 8.4 and 4.8 Hz), 3.80 (3H, s), 3.65 (1H, dd, *J* 8.8 and 8.4 Hz), 3.29 (1H, d, *J* 4.8 Hz) ppm; <sup>13</sup>C-NMR: δ 173.9, 141.6, 136.9, 134.8, 128.9, 128.8, 128.5, 128.2, 127.0, 126.8, 123.8, 76.0, 57.7, 52.7 ppm. Elemental analysis. calc. for C<sub>18</sub>H<sub>18</sub>O<sub>3</sub>: C, 76.57; H, 6.43. Found: C, 76.57; H, 6.45%.

**(RS,E)-Methyl 2-((RS)-1-hydroxyethyl)hex-3-enoate (±-2b).** Oil; <sup>1</sup>H-NMR: δ 5.68 (1H, dt, *J* 15.4, and 6.3 Hz), 5.38 (1H, ddt, *J* 15.5, 9.2 and 1.7 Hz), 4.03-3.97 (1H, m), 3.7 (3H, s), 2.98 (1H, dd, *J* 9.2, 8.6 Hz), 2.51 (1H, s), 2.10-2.00 (2H, m), 1.17 (3H, d, *J* 6.4 Hz), 0.98 (3H, t, *J* 7.5 Hz) ppm; <sup>13</sup>C-NMR: δ 174.1, 137.2, 123.2, 68.5, 57.5, 51.7, 25.4, 20.6, 13.1 ppm. Elemental analysis calc. for C<sub>9</sub>H<sub>16</sub>O<sub>3</sub>: C, 62.77; H, 9.36. Found: C, 62.68; H, 9.31 %.

**(RS,E)-Methyl 2-((SR)-1-hydroxyethyl)hex-3-enoate (±-3b).** Oil; <sup>1</sup>H-NMR: δ 5.73 (1H, dt, *J* 15.4 and 6.3 Hz), 5.53 (1H, ddt, *J* 15.4, 9.3 and 1.5 Hz), 4.05 (1H, ddq, *J* 2.7, 5.1 and 6.3 Hz), 3.73 (3H, s), 2.97 (1H, dd, *J* 9.3, and 5.1 Hz), 2.60 (1H, d, *J* 2.7 Hz), 2.20-2.00 (2H, m), 1.18 (3H, d, *J* 6.3 Hz), 1.03 (3H, t, *J* 7.4 Hz) ppm; <sup>13</sup>C-NMR: δ 173.9, 138.5, 122.1, 67.6, 56.1, 51.7, 25.5, 19.9, 13.3 ppm. Elemental analysis. calc. for C<sub>9</sub>H<sub>16</sub>O<sub>3</sub>: C, 62.77; H, 9.36. Found: C, 62.78; H, 9.35%.

**(RS,E)-Methyl 2-((RS)-1-hydroxyethyl)-4-phenylbut-3-enoate (±-2c).** Oil; <sup>1</sup>H-NMR: δ 7.40-7.20 (5H, m), 6.55 (1H, d, *J* 15.9 Hz), 6.15 (1H, dd, *J* 15.9 and 9.3 Hz), 4.10 (dq, 1H, *J* 7.9 and 6.4 Hz), 3.70 (3H, s), 3.20 (1H, dd, *J* 9.3 and 7.9 Hz), 1.20 (3H, d, *J* 6.4 Hz) ppm; <sup>13</sup>C-NMR: δ 173.5, 134.3, 128.5, 127.8, 126.3, 123.9, 68.8, 57.7, 52.0, 20.9 ppm. Elemental analysis. calct. for C<sub>13</sub>H<sub>16</sub>O<sub>3</sub>: C, 70.89; H, 7.32. Found C, 70.93; H, 7.35%.

**(RS,E)-Methyl 2-((SR)-1-hydroxyethyl)-4-phenylbut-3-enoate (±-3c).** Oil; <sup>1</sup>H-NMR: δ 7.40-7.20 (5H, m), 6.55 (1H, d, *J* 16.0 Hz), 6.3 (1H, dd, *J* 9.3 and 16.0 Hz), 4.15 (1H, dq, *J* 4.9 and 7.3 Hz), 3.7 (3H, s), 3.15 (1H, dd, *J* 4.9 and 9.3 Hz), 2.80 (1H, s), 1.2 (3H, d, *J* 7.3 Hz) ppm; <sup>13</sup>C-NMR: δ 173.6, 136.4, 135.4, 128.5, 127.8, 126.4, 122.9, 68.0, 56.4, 52.0, 20.2 ppm. Elemental analysis. calct. for C<sub>13</sub>H<sub>16</sub>O<sub>3</sub>: C, 70.89; H, 7.32. Found C, 70.81; H, 7.40%.

**(RS,E)-methyl 2-((SR)-hydroxy(phenyl)methyl)pent-3-enoate (±-2d)** oil; <sup>1</sup>H-NMR: δ 7.40-7.20 (5H, m), 5.45-5.3 (2H, m), 4.85 (1H, d, *J* 8.4 Hz), 3.65 (3H, s), 3.33 (2H, m), 1.5 (3H, d, *J* 4.8 Hz) ppm; <sup>13</sup>C-NMR: δ 173.7, 141.4, 130.3, 128.0, 127.6, 126.5, 124.7, 75.3, 56.9, 51.7, 17.7 ppm. Elemental analysis. calct. for C<sub>13</sub>H<sub>16</sub>O<sub>3</sub>: C, 70.89; H, 7.32. Found: C, 70.89; H, 7.35%.



**Kinetic resolution of 2a-d and 3b-c**

0.5 mmol of Ar\*SeCl prepared according to the literature<sup>10</sup> were treated with 0.5 mmol of AgOTf in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) at 0 °C. The white precipitate was removed by filtration and the organic solution was cooled to -60 °C and reacted with 1 mmol of **2a-d** or **3b-c**. The reaction was monitored by TLC and at complete consumption of the selenenylating reagent the mixture was poured into aq NaHCO<sub>3</sub> (10%) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 5 mL). The organic layer was washed with brine, dried Na<sub>2</sub>SO<sub>4</sub>, and solvent removed under vacuum. The crude material was purified by flash chromatography using as eluent a mixture of Et<sub>2</sub>O/petroleum ether 15:85. Tetrahydrofurans were obtained as mixtures of isomers, and in all the cases the spectral data of the major isomer are here extrapolated from the spectra of the mixture.

**(2R,3S,4S,5R)-Methyl 4-({2-[(S)-1-(methylthio)ethyl]phenyl}selanyl)-2,5-diphenyltetrahydrofuran-3-carboxylate (4a).** Oil, <sup>1</sup>H-NMR: δ 7.70-7.50 (2H, m), 7.50-7.20 (11H, m), 7.10-6.90 (1H, m), 5.30 (1H, d, *J* 8.6 Hz), 4.90 (1H, d, *J* 9.3 Hz), 4.25 (1H, q, *J* 7.2 Hz), 4.10 (1H, dd, *J* 9.3 and 6.9 Hz), 3.70 (1H, dd, *J* 6.9 and 8.6 Hz), 3.10 (3H, s), 1.90 (3H, s), 1.25 (3H, d, *J* 7.2 Hz) ppm; <sup>13</sup>C-NMR: δ 171.5, 145.9, 138.2, 137.4, 136.0, 133.5, 128.6, 128.5, 128.4, 128.2, 128.1, 127.9, 127.3, 127.0, 126.5, 87.1, 59.0, 51.5, 49.7, 43.9, 21.2, 13.9 ppm.

**(2R,3S,4S,5R)-Methyl 5-ethyl-2-methyl-4-({2-[(S)-1-(methylthio)ethyl]phenyl}selanyl)tetrahydrofuran-3-carboxylate (4b).** Oil <sup>1</sup>H-NMR: δ 7.61 (1H, dd, *J* 1.5, 7.8 Hz), 7.53 (1H, dd, *J* 1.5, 7.8 Hz), 7.34 (1H, dt, *J* 1.2, 7.8 Hz), 7.16 (1H, dt, *J* 1.5, 7.8 Hz), 4.62 (1H, q, *J* 7.0 Hz), 4.25 (1H, dq, *J* 7.9, 6.4 Hz), 3.73 (1H, ddd, *J* 3.4, 7.5, 8.8 Hz), 3.66 (1H, dd, *J* 6.5, 8.8 Hz), 3.65 (3H, s), 3.18 (1H, dd, *J* 6.5, 7.9 Hz *CHCO*), 1.97 (3H, s), 1.78 (2H, m), 1.60 (3H, d, *J* 6.5, 7.9 Hz), 0.99 (3H, t, *J* 7.4 Hz) ppm; <sup>13</sup>C-NMR: δ 172.7, 146.5, 136.3, 129.7, 129.1, 127.8, 127.7, 127.6, 86.4, 75.6, 56.9, 52.2, 47.0, 44.5, 26.6, 21.9, 17.4, 14.4, 10.7 ppm.

**(2R,3S,4S,5R)-Methyl 5-ethyl-2-methyl-4-({2-[(S)-1-(methylthio)ethyl]phenyl}selanyl)tetrahydrofuran-3-carboxylate (5b).** Oil <sup>1</sup>H-NMR: δ 7.67 (1H, dd, *J* 1.2, 7.8 Hz), 7.54 (1H, dd, *J* 1.2, 7.8 Hz), 7.35 (1H, dt, *J* 1.2, 7.8 Hz), 7.16 (1H, dt, *J* 1.2, 7.8 Hz), 4.67 (1H, q, *J* 7.0 Hz), 4.11 (1H, dq, *J* 6.0, 8.2 Hz), 3.98 (1H, dt, *J* 4.3, 7.8 Hz), 3.71 (1H, dd, *J* 7.8, 9.4 Hz), 3.60 (3H, s), 2.79 (1H, dd, *J* 8.2, 9.4 Hz), 1.97 (3H, s), 1.70-1.50 (2H, m), 1.60 (3H, d, *J* 7.0 Hz), 1.32 (3H, d, *J* 6.0 Hz), 0.94 (3H, t, *J* 7.4 Hz) ppm; <sup>13</sup>C-NMR: δ 172.5, 147.0, 137.1, 129.4, 129.3, 127.8, 127.6, 86.1, 77.6, 60.1, 52.6, 47.9, 44.5, 27.2, 22.0, 20.8, 14.5, 10.5 ppm.

**(2R,3S,4S,5R)-Methyl 2-methyl-4-({2-[(S)-1-(methylthio)ethyl]phenyl}selanyl)-5-phenyltetrahydrofuran-3-carboxylate (4c).** <sup>1</sup>H-NMR: δ 7.50-7.20 (8H, m), 6.97 (1H, dt, *J* 1.5, 7.4 Hz), 4.73 (1H, d, *J* 9.2 Hz), 4.5-4.3 (2H, m), 3.90 (1H, dd, *J* 7.2, 9.2 Hz), 3.66 (3H, s), 3.34 (1H, dd, *J* 7.2 e 8.0 Hz), 1.87 (3H, s), 1.43 (3H, d, *J* 7.0 Hz), 1.30 (3H, d, *J* 6.3 Hz) ppm; <sup>13</sup>C-NMR: δ 172.2, 145.8, 138.4, 135.9, 129.2, 128.6, 128.3, 127.4, 127.1, 126.9, 126.6, 86.9, 86.6, 75.8, 56.8, 51.9, 50.3, 43.9, 21.2, 17.2, 13.9 ppm.

**(2R,3S,4S,5R)-Methyl 2-methyl-4-({2-[(S)-1-(methylthio)ethyl]phenyl}selanyl)-5-phenyltetrahydrofuran-3-carboxylate (5c).** <sup>1</sup>H-NMR: δ 7.47 (1H, dd, *J* 1.1 e 7.7 Hz), 7.40 (1H, dt, *J* 1.1, 7.7 Hz), 7.39-7.20 (6H, m), 7.05 (1H, dt, *J* 1.1 e 7.7 Hz), 5.0 (1H, d, *J* 9.2 Hz), 4.5-4.3 (2H, m), 3.95 (1H, dd, *J* 9.2 e 10.1 Hz), 3.6 (3H, s), 3.00 (1H, dd, *J* 8.3 e 10.1 Hz), 1.89 (3H, s), 1.47 (3H, d, *J* 7.0 Hz), 1.43 (3H, d, *J* 6.1 Hz) ppm; <sup>13</sup>C-NMR: δ 171.7, 146.3, 139.7, 136.7, 128.6, 128.4, 128.3, 127.0, 126.9, 126.5, 85.8, 78.6, 60.1, 53.0, 51.4, 43.9, 24.4, 21.3, 14.0 ppm.

**(2R,3S,4S,5R)-Methyl 5-methyl-4-({2-[(S)-1-(methylthio)ethyl]phenyl}selanyl)-2-phenyltetrahydrofuran-3-carboxylate (4d).** <sup>1</sup>H-NMR: δ 7.67 (1H, dd, *J* 1.3, 7.7 Hz), 7.53 (1H, dd, *J* 1.5, 7.7 Hz), 7.35 (1H, dt, *J* 1.3, 7.7 Hz), 7.32-7.24 (5H, m), 7.17 (1H, dt, *J* 1.5, 7.7 Hz), 5.18 (1H, d, *J* 8.9 Hz), 4.66 (1H, q, *J* 7.0 Hz), 4.09 (1H, dq, *J* 9.2, 6.0 Hz), 3.74 (1H, dd, *J* 8.0, 9.2 Hz), 3.47 (1H, dd, *J* 8.0, 8.9 Hz), 3.11 (3H, s), 2.00 (3H, s), 1.60 (3H, d, *J* 7.0 Hz), 1.40 (3H, d, *J* 6.0 Hz) ppm; <sup>13</sup>C-NMR: δ 171.2, 146.3, 137.8, 136.4, 130.0, 129.0, 128.0, 127.9, 127.5, 127.2, 126.5, 81.6, 81.3, 58.2, 51.4, 47.9, 44.0, 21.4, 18.3, 13.9 ppm.

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