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Efficient asymmetric selenocyclizations of alkenyl oximes into cyclic nitrones and 1,2-oxazines promoted by sulfur containing diselenides

Marcello Tiecco,* Lorenzo Testaferri, Luana Bagnoli, Valentina Purgatorio, Andrea Temperini, Francesca Marini and Claudio Santi

Dipartimento di Chimica e Tecnologia del Farmaco, Sezione di Chimica Organica, Università di Perugia, I-06123 Perugia, Italy

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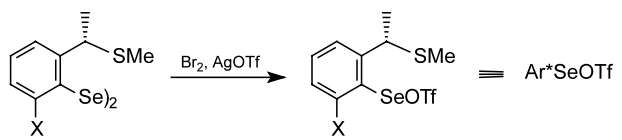
Abstract—Treatment of the di-2-[(1*S*)-1-(methylthio)ethyl]phenyl diselenide or of the di-2-methoxy-6-[(1*S*)-1-methylthio)-ethyl]phenyl diselenide with bromine and silver triflate afforded the corresponding electrophilic selenylating triflates which were used in situ to promote the asymmetric selenocyclization of γ-alkenyl oximes and δ-phenyl-γ-alkenyl oximes. The course of these reactions and hence the structures of the cyclization products were dictated by the (*E*)- or (*Z*)-geometry of the starting oximes. The two types of cyclization products were either the cyclic nitrones or the 1,2-oxazines; in both cases the reactions proceeded with excellent yields, complete regioselectivity and good diastereoselectivity.

1. Introduction

We have recently reported the synthesis of the two new sulfur containing diselenides di-2-[(1*S*)-1-(methylthio)-ethyl]phenyl diselenide **1**[1] and di-2-methoxy-6-[(1*S*)-1-methylthio)ethyl]phenyl diselenide **2**.[2] Upon treatment with bromine and with silver triflate, **1** and **2** can be easily converted into the electrophilic selenylating reagents **3** and **4** (Scheme 1), which were employed to effect the selenomethoxylation and seleno-hydroxylation[2] of alkenes. Excellent facial differentiations were observed in both cases.

Similarly, cyclic ethers,[2,3] lactones,[2,3] lactams, *N*-protected pyrrolidines[3] and isoxazolidines[4] were also



1 : X = H
2 : X = OMe

3 : X = H
4 : X = OMe

Scheme 1.

obtained with high diastereoselectivity from the asymmetric selenocyclization of alkenes containing oxygen or nitrogen atoms as internal nucleophiles. The diastereoselectivities observed in these reactions were comparable or even better than those obtained with the most efficient, but not so readily available, diselenides which have been described in the literature.[5–16] On the basis of several experimental evidences[17–19] it has been proposed that the high stereoselectivity observed with the previously described optically active diselenides is due to a non-bonded interaction between the selenium atom and an oxygen or nitrogen atom positioned in the close proximity. The excellent results obtained with the diselenides **1** and **2** seem to indicate that interaction of the selenium with sulfur is probably more important than those with oxygen or with nitrogen.

From the results accumulated so far it can be anticipated that the diselenides **1** and **2** can be successfully employed to effect the asymmetric synthesis of nitrogen-containing heterocyclic compounds starting from properly substituted alkenes. Despite the numerous examples of selenium-promoted cyclization reactions reported in the literature, few of their applications to the syntheses of nitrogen containing heterocycles have been described.[8,9,11–14] It therefore seemed of some interest to test the efficiency of the electrophilic reagents **3** and **4** to promote such cyclization reactions.

* Corresponding author. Tel.: +39 075 5855100; fax: +39 075 5855116; e-mail: tiecco@unipg.it

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2. Results and discussion

We report herein that the cyclization of γ-alkenyl oximes **5a**–**b** or of δ-phenyl-γ-alkenyl oximes **5c**–**d** (Scheme 2), promoted by **3** or **4**, represents a convenient method for the stereoselective preparation of 1,2-oxazines **7a**–**b** or **11a**–**b** and/or five-membered **8a**–**b** or **12a**–**b** or six-membered cyclic nitrones **9c**–**d** or **13c**–**d**. Compounds **6**, **7**, **8** and **9** were obtained using the reagent **3** and compounds **10**, **11**, **12** and **13** using the reagent **4**. In every case the reaction products were obtained as a mixture of two enantiomerically pure diastereoisomers.

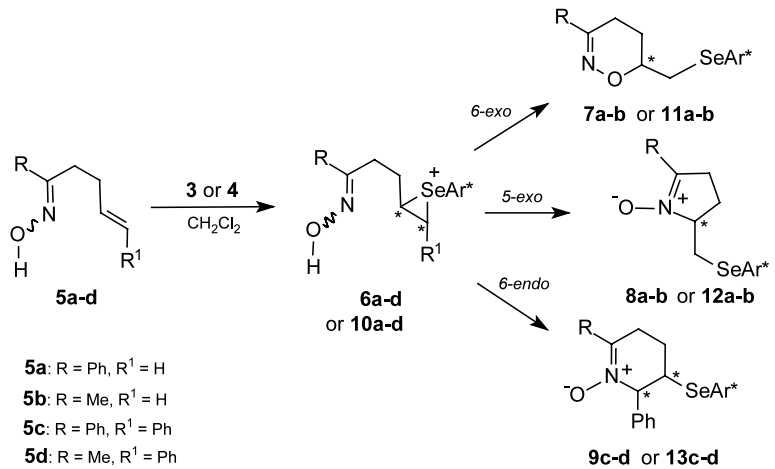
The formation of cyclic nitrones and/or 1,2-oxazines indicates that the oxime group, depending on its geometry, can act either as an oxy- or an aza-nucleophile in the intramolecular capture of the initially formed seleniranium intermediates **6a**–**d** or **10a**–**d**. This data is in agreement with the results reported by our research group in similar ring closure reactions of γ-alkenyl oximes promoted by phenylselenylating sulfate.[21]

The oximes **5a**–**d** (Table 1) were easily prepared according to the procedures described in the literature.[21,22] The single (*E*)-isomer was obtained in the case of **5c**. In all other cases mixtures of (*E*)- and (*Z*)-isomers were obtained which could be separated by column chromatography, the only exception being oxime **5b**, which was obtained as a 1:2 mixture of the (*Z*)- and (*E*)-isomers. In this case therefore the cyclization experiments were carried out using a mixture of the two isomers. The configurations of the geometrical isomers could be assigned on the basis of their ^{13}C NMR spectra.[21,22]

The cyclization reactions of these oximes were completed according to the following general procedure. Treatment of a stirred solution of the diselenide **1**, in dichloromethane at −78°C, with bromine and then with silver triflate afforded the selenylating reagent **3**. After 20 min one of the oximes **5a**–**d** was added at −78°C and the reaction temperature was allowed to increase gradually. The progress of the reaction was monitored by TLC, GC–MS and/or ^1H NMR spectroscopy. Reaction mixtures were worked-up in the usual way and compounds were purified by column chromatography. Reaction times, chemical yields and diastereomeric ratios are collected in Table 1. The cyclizations promoted by the ArSeOTf **4** were effected in the same way. The results of these reactions are reported in italics in Table 1. The results reported in Table 1 indicate that these cyclization reactions occur with excellent chemical yield, complete regioselectivity and good diastereoselectivity. The two diastereomeric 1,2-oxazines and the five- or six-membered cyclic nitrones could not be separated by column chromatography on silica gel. The diastereomeric ratios were determined by ^1H NMR spectroscopy.

As indicated in Scheme 2, the electrophilic selenylating reagent **3** attacks the double bond of the oximes **5a**–**d** giving rise to a mixture of two diastereomeric seleniranium intermediates **6a**–**d**. The facial selectivity of this attack determines the diastereoselectivity of the entire process. When the reaction was carried out starting from the γ-alkenyl oximes **5a**–**b** ($R^1 = H$) the intramolecular trapping can be effected either by the oxygen or by the nitrogen atoms affording 1,2-oxazines **7a**–**b** (6-*exo* cyclization) or five-membered cyclic nitrones **8a**–**b** (5-*exo* cyclization), respectively. The presence of the phenyl group in the δ-phenyl-γ-alkenyl oximes **5c**–**d** ($R^1 = Ph$) controls the regioselectivity of the process and the six-membered nitrones **9c**–**d** are the sole reaction products obtained (6-*endo* cyclization). In all cases the cyclization process was a stereospecific *anti* addition. A similar mechanism is proposed to operate in the cases in which reagent **4** is employed. In these cases the reaction products are **11a**–**b**, **12a**–**b** and **13c**–**d**.

Using either the diselenide **1** or the diselenide **2** the 6-*endo* cyclizations of the oximes **5c**–**d** gave higher diastereomeric ratios (up to 96:4) than the 5-*exo* and 6-*exo* cyclizations of the oximes **5a**–**b** (up to 82:18). This is in agreement with our previous observations that phenyl substituted alkenes give better

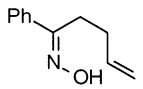
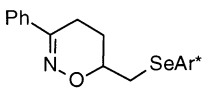
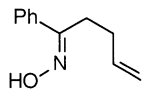
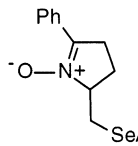
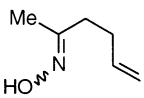
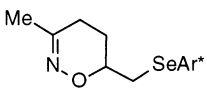
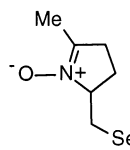
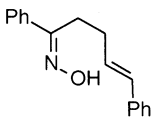
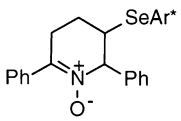
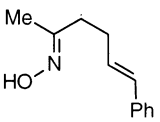
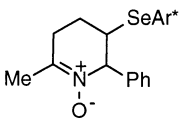
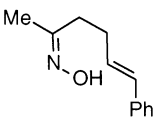
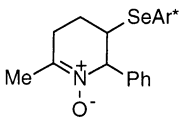


Scheme 2.

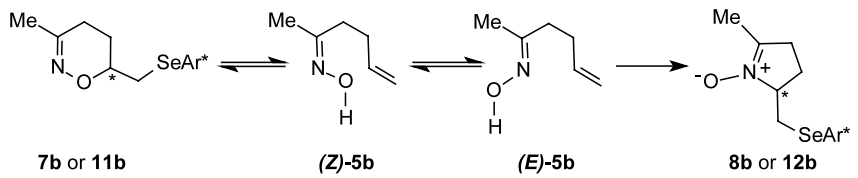
diastereomeric ratios than terminal olefins.[3] As already observed,[2] the diastereomeric ratios obtained in the reactions promoted by **4** in several cases are higher than those observed with the use of the reagent **3**.

The course of the ring closure reaction of the γ-alkenyl oximes is influenced by the nature of the R group. The oxime **5a**, in which R is a phenyl group, is configurationally stable and the structures of the cyclization products depend upon the geometry of the starting oxime. In fact the reactions of the oxime (*E*)-**5a** gave the 1,2-oxazines **7a** or **11a** as the sole reaction product (Table 1, entry 1), and the isomeric (*Z*)-oxime **5a** afforded exclusively the cyclic nitrones **8a** or **12a**. (Table 1, entry 2). In contrast, starting from the oxime **5b**, where R is a methyl group, the ratios of reaction products do not reflect the ratio of the oxime **5b** (*Z*:*E*=1/2) (Table 1, entry 3). Monitoring the progress of the reactions by TLC and GC–MS it was observed that the initially formed 1,2-oxazines **7b** or **11b** were gradually converted into the nitrones **8b** or **12b**. Starting from the diselenide **1**, after 7 h **7b** and **8b** were present in a 1:4 ratio. In another experiment, starting from the diselenide **2**, after 17 h **11b** was completely converted and the nitrone **12b** was the sole reaction product. This can be explained on the basis of the results of some independent experiments. As indicated in Scheme 3, it was, in fact, observed that under these

Table 1. Cyclization of γ-alkenyl oximes **5a–b** and δ-phenyl-γ-alkenyl oximes **5c–d** promoted by the arylselenenyl triflates **3** or **4** in CH_2Cl_2 at −78°C

Entry	Starting Products		Reaction Products[a]		Time (h)	Yields (%)	D.r.[b]
1		(*E*)-**5a**		**7a**	7	82	**82:18**
				11a	*17*	*75*	***80:20***
2		(*Z*)-**5a**		**8a**	12	83	**75:25**
				12a	*17*	*70*	***75:25***
3		(*Z*/*E*)-**5b** 1/2		**7b**	7	18	**78:22**
				**8b**		72	**76:24**
				12b	*17*	*80*	***82:18***
4		(*E*)-**5c**		**9c**	99	51	**90:10**
				13c	*120*	*65*	***96:4***
5		(*E*)-**5d**		**9d**	24	96	**95:5**
				13d	*24*	*89*	***96:4***
6		(*Z*)-**5d**		**9d**	24	96[c]	**94:6**

a) Mixtures of two diastereoisomers which could not be separated. The data in italics refer to the experiments carried out with the Ar*SeOTf **4**. b) Diastereomeric ratios were determined by ^1H NMR spectroscopy. c) Conversion was only 49%.



Scheme 3.

conditions the two isomers of the oxime **5b** interconvert and the formation of the 1,2-oxazines is reversible. Thus, the entire process is shifted towards the formation of the thermodynamically more stable nitrones **8b** or **12b**.

The oxime **5c** was obtained as a single isomer having (*E*)-configuration. In this oxime the substituent R is a phenyl group and therefore it isomerizes only with great difficulty. The intramolecular capture of the seleniranium intermediate **6c** or **10c** by the oxygen atom is difficult since it would lead to the formation of a seven-membered cyclic compound. Moreover, the formation of the 1,2-oxazine would require an anti-Markovnikov addition reaction. Indeed the cyclization of (*E*)-**5c** was a very slow process which afforded the six-membered cyclic nitrones **9c** and **13c** clearly deriving from a preliminary conversion of the starting oxime into the (*Z*)-isomer (Table 1, entry 4).

On the contrary, the cyclization reaction of the oximes **5d** proceeded easily. In this case the (*E*)- and (*Z*)-isomers could be isolated and obtained in a pure form. However, since R is a methyl group, the two isomers can easily interconvert. Their cyclization reactions, in fact, afforded in both cases the thermodynamically more stable six-membered cyclic nitrones (Table 1, entries 5 and 6). Thus, using reagent **3** and starting from either (*E*)-**5d** or (*Z*)-**5d** the same nitrone **9d** was obtained. Similarly, the cyclization of (*E*)-**5d** promoted by reagent **4** afforded the nitrone **13d**.

The arylseleno substituted cyclic nitrones and/or 1,2-oxazines here prepared can find several useful synthetic applications. Thus, the reductive deselenylation of (arylseleno)-1,2-oxazines affords enantiomerically enriched 1,2-oxazines. The cyclic nitrones can be deselenylated or can be employed to effect 1,3-dipolar cycloaddition reactions. Thus, for example, the reaction of the nitrone **12b** (D.r. 82:18) with methyl propiolate at 10°C proceeded smoothly and gave the bicyclic compound **14** in 89% yield (Scheme 4). This was a mixture of two diastereoisomers (D.r. 82:18) which could not be separated.

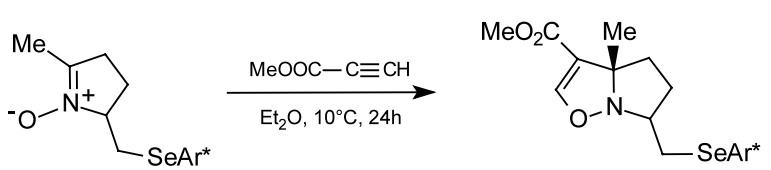
3. Conclusion

In conclusion the results reported in this paper confirm that the triflates of the chiral sulfur containing diselenides **1** and **2** are efficient electrophilic reagents, which promote the ring closure reactions of the γ-alkenyl oximes and δ-phenyl-γ-alkenyl oximes. These reactions proceed with excellent chemical yield, complete regioselectivity and good diastereoselectivity and represent therefore a very convenient method to effect the asymmetric synthesis of cyclic nitrones and 1,2-oxazines.

4. Experimental

New compounds were characterized by MS, ^{1}H and ^{13}C NMR spectroscopy. GLC analyses and MS spectra were carried out with a HP 6890 gas chromatograph (25 m dimethyl silicone capillary column) equipped with an HP 5973 Mass Selective Detector; for the ions containing selenium only the peaks arising from the selenium 80 isotope are given. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100.62 MHz, respectively, on a Bruker DRX 400 instrument; unless otherwise specified, $CDCl_3$ was used as solvent and TMS as standard. Elemental analyses were carried out on a Carlo Erba 1106 Elemental Analyzer.

The oximes **5a** and **5b** were prepared by treating the corresponding ketones with hydroxylamine hydrochloride.[21] The oximes **5c** and **5d** were obtained by treating the dianion of acetophenone or acetone oxime with cinnamyl bromide.[22] Physical and spectral data of **5a–c** are identical to those reported in the literature.[21,22] Physical and spectral data of the oxime **5d** are reported below. The configurations were assigned on the basis of their ^{13}C NMR spectra.[21]



Scheme 4.

4.1. (1*E*,4*E*)-1,5-Diphenylpent-4-en-1-one oxime 5d

(*E*)-Isomer: mp 89–92°C (petroleum ether); ^{1}H NMR: δ 9.30 (brs, 1H), 7.70–7.62 (m, 2H), 7.47–7.20 (m, 8H), 6.43 (d, 1H, J=15.8 Hz), 6.24 (dt, 1H, J=6.4, 15.8 Hz), 3.04–2.97 (m, 2H), 2.54–2.47 (m, 2H); ^{13}C NMR: δ 159.0, 137.5, 135.6, 130.5, 129.3, 129.2, 128.6 (two carbons), 128.4 (two carbons), 126.9, 126.4 (two carbons), 126.0 (two carbons), 29.6, 26.2; MS m/z (rel. int.): 251 (5), 250 (10), 232 (18), 160 (15), 144 (21), 130 (70), 117 (100), 104 (46), 91 (47), 77 (25). Anal. calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.54; H, 6.71; N, 5.45%.

4.2. Selenocyclization of γ-alkenyl oximes and δ-phenyl γ-alkenyl oximes. General procedure

The diselenide **1** (0.5 mmol), dissolved in dichloromethane (4 mL) was treated under nitrogen with a solution of Br_2 in carbon tetrachloride (1 M, 0.5 mmol) at −78°C. After 15 min silver trifluoromethanesulfonate (1.2 mmol) and methanol (1 mL) were added and the mixture was stirred for 20 min. The oxime (1 mmol) was added at −78°C and the mixture was stirred for the time reported in Table 1. The reaction mixture was allowed to warm gradually to room temperature. The progress of the reaction was monitored by TLC and/or GC–MS. The reaction mixture was poured into a 10% aqueous $NaHCO_3$ solution and extracted with dichloromethane. The organic layer was dried over Na_2SO_4, filtered and evaporated under vacuo. The reaction products were obtained in pure form after column chromatography of the residue on silica gel. The same procedure was applied to the diselenide **2**. Reaction times, yields and diastereomeric ratios of the obtained products are reported in Table 1. Physical and spectral data are reported below. D.r.s were measured by integration of ^{1}H NMR signals. Assignments of ^{13}C NMR signals are tentative because of frequent coincidence between signals from the two stereoisomers and the low intensity of peaks from the minor products.

4.3. 6-[({2-[(1*S*)-1-(Methylthio)ethyl]phenyl}seleno)-methyl]-3-phenyl-5,6-dihydro-4*H*-1,2-oxazine 7a

Major diastereoisomer: ^{1}H NMR: δ 7.71–7.67 (m, 2H), 7.61 (dd, 1H, J=1.5, 7.7 Hz), 7.51 (dd, 1H, J=1.5, 7.7 Hz), 7.42–7.37 (m, 3H), 7.30 (dt, 1H, J=1.5, 7.7 Hz), 7.18 (dt, 1H, J=1.5, 7.7 Hz), 4.62 (quart, 1H, J=6.9 Hz), 3.95 (dddd, 1H, J=2.3, 5.4, 7.6, 10.1 Hz), 3.30 (dd, 1H, J=5.4, 12.4 Hz), 3.05 (dd, 1H, J=7.6, 12.4 Hz), 2.76–2.56 (m, 2H), 2.36–2.28 (m, 1H), 1.99 (s, 3H), 1.93–1.80 (m, 1H), 1.61 (d, 3H, J=6.9 Hz); ^{13}C NMR: δ 154.4, 144.8, 137.3, 135.2, 133.2, 129.2, 128.2 (two carbons), 127.6, 127.4, 126.8, 125.0 (two carbons), 74.0, 43.7, 30.8, 23.8, 21.5, 21.3, 13.9. Anal. calcd for $C_{20}H_{23}NOSSe$: C, 59.41; H, 5.73; N, 3.46. Found: C, 59.14; H, 5.61; N, 3.11%.

Minor diastereoisomer (distinct signals): ^{1}H NMR: δ 7.62 (dd, 1H, J=1.5, 7.7 Hz), 7.52 (dd, 1H, J=1.5, 7.7 Hz), 7.19 (dt, 1H, J=1.5, 7.7 Hz), 4.59 (quart, 1H, J=7.0 Hz), 3.97 (dddd, 1H, J=2.3, 5.3, 7.7, 10.1 Hz), 3.33 (dd, 1H, J=5.3, 12.0 Hz), 3.03 (dd, 1H, J=7.7, 12.0 Hz), 1.98 (s, 3H), 1.60 (d, 3H, J=7.0 Hz); ^{13}C NMR: δ 145.7, 133.1, 29.4.

4.4. 6-[({2-Methoxy-6-[(1*S*)-1-(methylthio)ethyl]phenyl}-seleno)methyl]-3-phenyl-5,6-dihydro-4*H*-1,2-oxazine 11a

Major diastereoisomer: ^{1}H NMR: δ 7.73–7.68 (m, 2H), 7.42–7.36 (m, 3H), 7.34 (t, 1H, J=8.0 Hz), 7.18 (dd, 1H, J=1.2, 8.0 Hz), 6.80 (dd, 1H, J=1.2, 8.0 Hz), 4.95 (quart, 1H, J=7.0 Hz), 3.92 (s, 3H), 3.91–3.82 (m, 1H), 3.28 (dd, 1H, J=5.2, 12.2 Hz), 2.95 (dd, 1H, J=8.1, 12.2 Hz), 2.75–2.65 (m, 1H), 2.64–2.51 (m, 1H), 2.38–2.28 (m, 1H), 1.99 (s, 3H), 1.88–1.78 (m, 1H), 1.58 (d, 3H, J=7.0 Hz); ^{13}C NMR: δ 159.6, 154.5, 148.4, 135.5, 129.6, 129.4, 128.3 (two carbons), 125.2 (two carbons), 119.3, 118.5, 109.2, 74.8, 56.0, 44.4, 29.9, 23.9, 21.8, 21.7, 14.1. Anal. calcd for $C_{21}H_{25}NO_2SSe$: C, 58.07; H, 5.80; N, 3.22. Found: C, 57.95; H, 5.73; N, 3.11%.

Minor diastereoisomer (distinct signals): ^{1}H NMR: δ 7.20 (dd, 1H, J=1.2, 8.0 Hz), 4.94 (quart, 1H, J=7.0 Hz), 3.27 (dd, 1H, J=5.2, 12.2 Hz), 1.98 (s, 3H), 1.57 (d, 3H, J=7.0 Hz); ^{13}C NMR: δ 73.7, 32.2, 22.7, 21.2.

4.5. 2-[({2-[(1*S*)-1-(Methylthio)ethyl]phenyl}seleno)-methyl]-5-phenyl-3,4-dihydro-2*H*-pyrrole 1-oxide 8a

Oil; major diastereoisomer: ^{1}H NMR: δ 8.33–8.25 (m, 2H), 7.63 (dd, 1H, J=1.5, 7.6 Hz), 7.49–7.42 (m, 4H), 7.26 (dt, 1H, J=1.5, 7.6 Hz), 7.16 (dt, 1H, J=1.5, 7.6 Hz), 4.74–4.60 (m, 1H), 4.50 (quart, 1H, J=7.0 Hz), 3.67 (dd, 1H, J=2.9, 12.6 Hz), 3.37 (dd, 1H, J=8.6, 12.6 Hz), 3.27–3.08 (m, 2H), 2.49–2.35 (m, 1H), 2.20–2.02 (m, 1H), 1.93 (s, 3H), 1.53 (d, 3H, J=7.0 Hz); ^{13}C NMR: δ 145.4, 141.9, 134.1, 131.1, 130.6, 129.3, 128.9 (two carbons), 128.4, 128.1, 128.0 (two carbons), 127.6, 75.0, 44.4, 31.3, 29.3, 23.3, 21.9, 14.5; MS m/z (rel. int.) 374 (M^+−31, 4), 343 (11), 231 (9), 215 (15), 207 (22), 183 (42), 158 (100), 144 (18), 115 (14), 104 (28), 91 (16), 77 (14). Anal. calcd for $C_{20}H_{23}NOSSe$: C, 59.41; H, 5.73; N, 3.96. Found: C, 59.36; H, 5.49; N, 3.86%.

Minor diastereoisomer (distinct signals): ^{1}H NMR: δ 7.14 (dt, 1H, J=1.5, 7.6 Hz), 4.51 (quart, 1H, J=7.0 Hz), 3.71 (dd, 1H, J=3.3, 12.6 Hz), 3.31 (dd, 1H, J=8.0, 12.6 Hz), 1.94 (s, 3H), 1.59 (d, 3H, J=7.0 Hz), ^{13}C NMR: δ 145.3, 133.8, 130.7, 129.4, 128.3, 128.2, 127.9 (two carbons), 127.5, 74.8, 44.3, 31.1, 29.2, 23.4, 14.4.

4.6. 2-[({2-Methoxy-6-[(1*S*)-1-(methylthio)ethyl]phenyl}-seleno)methyl]-5-phenyl-3,4-dihydro-2*H*-pyrrole 1-oxide 12a

Oil; major diastereoisomer: ^{1}H NMR: δ 8.48–8.38 (m, 2H), 7.50–7.40 (m, 3H), 7.31 (t, 1H, J=8.0 Hz), 7.12 (dd, 1H, J=1.2, 8.0 Hz), 6.80 (dd, 1H, J=1.2, 8.0 Hz), 4.79 (quart, 1H, J=7.0 Hz), 4.65–4.55 (m, 1H), 3.94 (s, 3H), 3.66 (dd, 1H, J=3.6, 12.4 Hz), 3.31–3.09 (m, 3H), 2.50–2.35 (m, 1H), 2.15–2.03 (m, 1H), 1.94 (s, 3H), 1.50

(d, 3H, $J=7.0$ Hz); ^{13}C NMR: δ 159.6, 147.9, 140.4, 130.3, 129.5, 129.0, 128.3 (two carbons), 127.3 (two carbons), 119.2, 118.4, 109.3, 75.1, 56.0, 44.3, 30.0, 28.6, 22.8, 21.5, 14.0; MS m/z (rel. int.): 404 (M^+–31, 6), 373 (13), 261 (14), 245 (12), 213 (38), 198 (17), 181 (27), 158 (100), 144 (22), 115 (13), 104 (35), 91 (23), 77 (17), 55 (22). Anal. calcd for $C_{21}H_{25}NO_2SSe$: C, 58.07; H, 5.80; N, 3.22. Found: C, 57.98; H, 5.76; N, 3.09%.

Minor diastereoisomer (distinct signals): ^{1}H NMR: δ 7.33 (t, 1H, $J=8.0$ Hz), 7.16 (dd, 1H, $J=1.2$, 8.0 Hz), 6.78 (dd, 1H, $J=1.2$, 8.0 Hz), 4.82 (quart, 1H, $J=7.0$ Hz), 4.53–4.45 (m, 1H), 3.92 (s, 3H), 3.74 (dd, 1H, $J=3.7$, 12.1 Hz), 1.96 (s, 3H), 1.57 (d, 3H, $J=7.0$ Hz); ^{13}C NMR: δ 148.1, 140.2, 129.6, 75.0, 29.9, 28.5, 22.9.

4.7. 3-Methyl-6-[({2-[(1*S*)-1-(methylthio)ethyl]phenyl}-seleno)methyl-5,6-dihydro-4*H*-1,2-oxazine 7b

Oil; major diastereoisomer: ^{1}H NMR: δ 7.55 (dd, 1H, $J=1.5$, 7.8 Hz), 7.48 (dd, 1H, $J=1.5$, 7.8 Hz), 7.28 (dt, 1H, $J=1.5$, 7.8 Hz), 7.14 (dt, 1H, $J=1.5$, 7.8 Hz), 4.57 (quart, 1H, $J=6.9$ Hz), 3.75 (dddd, 1H, $J=2.2$, 5.2, 7.6, 10.2 Hz), 3.19 (dd, 1H, $J=5.2$, 12.5 Hz), 2.94 (dd, 1H, $J=7.6$, 12.5 Hz), 2.25–2.09 (m, 3H), 1.96 (s, 3H), 1.89 (s, 3H), 1.75–1.60 (m, 1H), 1.57 (d, 3H, $J=6.9$ Hz); ^{13}C NMR: δ 155.7, 145.0, 135.1, 133.3, 127.8, 127.5, 127.0, 73.4, 43.9, 31.2, 24.8, 24.1, 21.5 (two carbons), 14.1; MS m/z (rel. int.): 343 (11), 231 (52), 183 (100), 102 (17), 91 (14), 77 (10), 51 (4). Anal. calcd for $C_{15}H_{21}NOSSe$: C, 52.63; H, 6.18; N, 4.09. Found: C, 52.77; H, 5.99; N, 4.15%.

Minor diastereoisomer (distinct signals): ^{1}H NMR: δ 7.57 (dd, 1H, $J=1.5$, 7.8 Hz), 7.50 (dd, 1H, $J=1.5$, 7.8 Hz), 7.16 (dt, 1H, $J=1.5$, 7.8 Hz), 4.55 (quart, 1H, $J=6.9$ Hz), 3.73 (dddd, 1H, $J=2.2$, 5.2, 7.6, 10.2 Hz), 3.22 (dd, 1H, $J=5.2$, 12.5 Hz), 2.92 (dd, 1H, $J=7.6$, 12.5 Hz), 1.95 (s, 3H), 1.56 (d, 3H, $J=6.9$ Hz); ^{13}C NMR: δ 133.2, 130.7, 127.7, 31.1, 14.2.

4.8. 5-Methyl-2-[({2-[(1*S*)-1-(methylthio)ethyl]phenyl}-seleno)methyl]-3,4-dihydro-2*H*-pyrrole 1-oxide 8b

Oil; major diastereoisomer: ^{1}H NMR: δ 7.61 (dd, 1H, $J=1.5$, 7.8 Hz), 7.48 (dd, 1H, $J=1.5$, 7.8 Hz), 7.27 (dt, 1H, $J=1.5$, 7.8 Hz), 7.14 (dt, 1H, $J=1.5$, 7.8 Hz), 4.55 (quart, 1H, $J=6.9$ Hz), 4.30–4.20 (m, 1H), 3.64 (dd, 1H, $J=3.6$, 12.4 Hz), 3.15 (dd, 1H, $J=8.6$, 12.4 Hz), 2.70–2.55 (m, 2H), 2.35–2.20 (m, 1H), 2.10 (dt, 3H, $J=1.6$, 1.7 Hz), 1.96 (s, 3H), 1.95–1.85 (m, 1H), 1.59 (d, 3H, $J=6.9$ Hz); ^{13}C NMR: δ 144.9, 144.1, 133.5, 130.1, 127.8, 127.5, 127.0, 71.9, 43.8, 30.8, 30.5, 23.1, 21.5, 14.0, 12.7; MS m/z (rel. int.): 327 (M^+–16, 4), 312 (8), 281 (30), 231 (19), 215 (44), 200 (11), 183 (100), 102 (16), 96 (89), 82 (27), 55 (16). Anal. calcd for $C_{15}H_{21}NOSSe$: C, 52.63; H, 6.18; N, 4.09. Found: C, 52.57; H, 6.11; N, 3.99%.

Minor diastereoisomer (distinct signals): ^{1}H NMR: δ 7.63 (dd, 1H, $J=1.5$, 7.8 Hz), 7.46 (dd, 1H, $J=1.5$, 7.8 Hz), 7.29 (dt, 1H, $J=1.5$, 7.8 Hz), 7.16 (dt, 1H, $J=1.5$, 7.8 Hz), 4.52 (quart, 1H, $J=6.9$ Hz), 3.67 (dd, 1H, $J=3.6$, 12.5 Hz), 3.13 (dd, 1H, $J=8.6$, 12.4 Hz), 2.21 (dt, 3H, $J=1.6$, 1.7 Hz), 1.95 (s, 3H), 1.58 (d, 3H, $J=6.9$ Hz); ^{13}C NMR: δ 144.7, 144.2, 133.4, 130.2, 127.7, 127.6, 126.9, 71.7, 21.4, 13.9.

4.9. 2-[({2-Methoxy-6-[(1*S*)-1-(methylthio)ethyl]phenyl}-seleno)methyl]-5-methyl-3,4-dihydro-2*H*-pyrrole 1-oxide 12b

Major diastereoisomer: ^{1}H NMR: δ 7.29 (t, 1H, $J=7.8$ Hz), 7.14 (dd, 1H, $J=1.2$, 7.8 Hz), 6.76 (dd, 1H, $J=1.2$, 7.8 Hz), 4.84 (quart, 1H, $J=7.0$ Hz), 4.30–4.10 (m, 1H), 3.89 (s, 3H), 3.59 (dd, 1H, $J=3.6$, 12.1 Hz), 3.18 (dd, 1H, $J=9.1$, 12.1 Hz), 2.65–2.55 (m, 2H), 2.33–2.21 (m, 1H), 2.0 (dt, 3H, $J=1.5$, 1.6 Hz), 1.95 (s, 3H), 1.97–1.85 (m, 1H), 1.55 (d, 3H, $J=7.0$ Hz); ^{13}C NMR: δ 159.5, 148.0, 144.2, 130.1, 129.5, 119.2 109.3, 72.5, 55.9, 44.3, 30.7, 29.8, 23.1, 21.7, 14.0, 12.7; MS m/z (rel. int.): 357 (M^+–16, 6), 310 (32), 261 (32), 245 (40), 230 (30), 213 (100), 198 (42), 181 (59), 96 (85), 82 (33), 55 (33). Anal. calcd for $C_{16}H_{23}NO_2SSe$: C, 51.62; H, 6.23; N, 3.76. Found: C, 51.56; H, 6.29; N, 3.59%.

Minor diastereoisomer (distinct signals): ^{1}H NMR: δ 7.12 (dd, 1H, $J=1.2$, 7.8 Hz), 4.83 (quart, 1H, $J=7.0$ Hz), 3.90 (s, 3H), 3.63 (dd, 1H, $J=3.6$, 12.0 Hz), 2.97 (dd, 1H, $J=9.4$, 12.0 Hz), 2.01 (dt, 3H, $J=1.5$, 1.6 Hz), 1.94 (s, 3H); ^{13}C NMR: δ 72.3, 29.5, 21.6.

4.10. 3-({2-[(1*S*)-1-(Methylthio)ethyl]phenyl}seleno)-2,6-diphenyl-2,3,4,5-tetrahydropyridine 1-oxide 9c

Oil; major diastereoisomer: ^{1}H NMR: δ 8.24–8.12 (m, 2H), 7.78 (dd, 1H, $J=1.5$, 7.8 Hz), 7.60–7.10 (m, 11H), 5.25 (d, 1H, $J=2.9$ Hz), 4.62 (quart, 1H, $J=7.0$ Hz), 3.98–3.88 (m, 1H), 3.35–3.15 (m, 1H), 3.10–2.89 (m, 1H), 2.27–2.19 (m, 1H), 2.18–1.90 (m, 1H), 1.95 (s, 3H), 1.61 (d, 3H, $J=7.0$ Hz), ^{13}C NMR: δ 146.5, 142.4, 138.5, 136.3, 136.1, 133.4, 129.7, 129.0, 128.7 (two carbons), 128.0 (four carbons), 127.8, 127.6, 127.3, 126.1 (two carbons), 77.3, 45.1, 44.1, 27.3, 21.1, 20.7, 13.9. Anal. calcd for $C_{26}H_{27}NOSSe$: C, 65.00; H, 5.66; N, 2.92. Found: C, 65.12; H, 6.17; N, 2.99%.

Minor diastereoisomer (distinct signals): ^{1}H NMR: δ 5.36 (d, 1H, $J=2.9$ Hz), 4.68 (quart, 1H, $J=7.0$ Hz), 1.96 (s, 3H), 1.58 (d, 3H, $J=7.0$ Hz). ^{13}C NMR: δ 128.4, 128.3, 127.4, 43.8.

4.11. 3-({2-Methoxy-6-[(1*S*)-1-(methylthio)ethyl]phenyl}-seleno)-2,6-diphenyl-2,3,4,5-tetrahydropyridine 1-oxide 13c

Oil; major diastereoisomer: ^{1}H NMR: δ 8.23–8.19 (m, 2H), 7.52–7.14 (m, 10H), 6.86 (dd, 1H, $J=1.2$, 8.1 Hz), 5.21 (d, 1H, $J=2.9$ Hz), 4.80 (quart, 1H, $J=6.9$ Hz), 4.22–4.19 (m, 1H), 3.96 (s, 3H), 3.28–3.22 (m, 1H), 3.05–2.90 (m, 1H), 2.20–2.10 (m, 1H), 2.05–1.96 (m, 1H), 1.95 (s, 3H), 1.59 (d, 3H, $J=6.9$ Hz), ^{13}C NMR: δ 160.1, 149.3 (two carbons), 139.3, 133.9, 130.6, 130.3, 129.1 (two carbons), 128.7 (two carbons), 128.6 (two carbons), 128.2, 126.7 (two carbons), 120.3, 117.9,

109.9, 77.9, 56.6, 44.9, 42.9, 27.9, 21.8, 20.7, 14.5. Anal. calcd for $C_{27}H_{29}NO_2SSe$: C, 63.53; H, 5.73; N, 2.74. Found: C, 63.45; H, 5.79; N, 2.65%.

Minor diastereoisomer (distinct signals): ^{1}H NMR: δ 6.74 (dd, 1H, J=1.2, 8.2 Hz), 5.14 (d, 1H, J=2.9 Hz), 4.60 (quart, 1H, J=6.9 Hz), 3.95 (s, 3H), 1.94 (s, 3H), 1.57 (d, 3H, J=6.9 Hz). ^{13}C NMR: δ 128.5, 30.1.

4.12. 6-Methyl-3-({2-[(1*S*)-1-(methylthio)ethyl]phenyl}-seleno)-2-phenyl-2,3,4,5-tetrahydropyridine 1-oxide 9d

Oil; major diastereoisomer: ^{1}H NMR: δ 7.66 (dd, 1H, J=1.5, 7.7 Hz), 7.51 (dd, 1H, J=1.5, 7.7 Hz), 7.40–7.25 (m, 4H), 7.21 (dt, 1H, J=1.5, 7.7 Hz), 7.07–7.05 (m, 2H), 5.09–5.01 (m, 1H), 4.60 (quart, 1H, J=6.9 Hz), 3.85 (quart, 1H, J=3.5 Hz), 2.98–2.80 (m, 1H), 2.70–2.60 (m, 1H), 2.33–2.31 (m, 3H), 2.15–2.05 (m, 1H), 1.97 (s, 3H), 1.94–1.82 (m, 1H), 1.62 (d, 3H, J=6.9 Hz); ^{13}C NMR: δ 146.4, 145.9, 144.1, 138.1, 135.9, 128.9, 128.7 (two carbons), 127.8, 127.6, 127.3, 126.1 (two carbons), 75.1, 45.3, 44.0, 28.7, 21.1, 19.9, 18.6, 13.8; MS m/z (rel. int.): 403 (M^+–16, 1), 357 (3), 231 (14), 183 (32), 172 (100), 104 (19), 91 (20), 77 (6). Anal. calcd for $C_{21}H_{25}NOSSe$: C, 60.29; H, 6.02; N, 3.35. Found: C, 60.12; H, 5.99; N, 3.23%.

Minor diastereoisomer (distinct signals): ^{1}H NMR: δ 5.25–5.24 (m, 1H), 4.65 (quart, 1H, J=6.9 Hz), 1.99 (s, 3H), 1.58 (d, 3H, J=6.9 Hz); ^{13}C NMR: δ 44.1, 22.5.

4.13. 3-({2-Methoxy-6-[(1*S*)-1-(methylthio)ethyl]phenyl}-seleno)-6-methyl-2-phenyl-2,3,4,5-tetrahydropyridine 1-oxide 13d

Oil; major diastereoisomer: ^{1}H NMR: δ 7.40–7.25 (m, 4H), 7.19 (dd, 1H, J=1.2, 7.9 Hz), 7.08–7.02 (m, 2H), 6.84 (dd, 1H, J=1.2, 7.9 Hz), 5.08–5.01 (m, 1H), 4.78 (quart, 1H, J=7.0 Hz), 4.08 (quart, 1H, J=3.5 Hz), 3.93 (s, 3H), 3.01–2.92 (m, 1H), 2.63–2.57 (m, 1H), 2.32–2.29 (m, 3H), 2.02–1.93 (m, 1H), 1.97 (s, 3H), 1.83–1.76 (m, 1H), 1.59 (d, 3H, J=7.0 Hz); ^{13}C NMR: δ 160.0, 149.3, 147.0, 139.0, 130.6, 129.1 (two carbons), 128.1, 126.6 (two carbons), 120.3, 118.0, 109.9, 75.8, 56.6, 45.0, 43.5, 29.2, 21.8, 20.2, 19.2, 14.4; MS m/z (rel. int.) 433 (M^+–16, 1), 261 (20), 213 (29), 172 (100), 104 (15), 91 (22), 77 (6). Anal. calcd for $C_{22}H_{27}NO_2SSe$: C, 58.93; H, 6.07; N, 3.12. Found: C, 58.85; H, 6.18; N, 2.99%.

Minor diastereoisomer (distinct signals): ^{1}H NMR: δ 6.77 (dd, 1H, J=1.2, 7.9 Hz), 4.63 (quart, 1H, J=7.0 Hz), 3.92 (s, 3H), 1.58 (d, 3H, J=7.0 Hz); ^{13}C NMR: δ 109.8, 44.8, 19.0, 14.3.

4.14. Reaction of the cyclic nitrone 12b with methyl propiolate

The cycloaddition of compound **12b** with methyl propiolate was effected in ethyl ether at 10°C according to the procedure reported in the literature.[20] The progress of the reaction was monitored by TLC and GC–MS. The reaction mixture was worked-up in the usual way and the reaction product was purified by column chromatography on silica gel. Compound **14** was obtained in 89% yield as a mixture of two diastereoisomers (D.r. 82:18) which could not be separated. Physical and spectral data are reported below.

4.15. Methyl 6-[({2-methoxy-6-[(1*S*)-1-(methylthio)-ethyl]phenyl}seleno)methyl]-3a-methyl-3a,4,5,6-tetrahydropyrrolo[1,2-*b*]isoxazolo-3-carboxylate 14

Oil; major diastereoisomer: ^{1}H NMR: δ 7.33 (t, 1H, J=7.8 Hz), 7.21 (s, 1H), 7.19 (dd, 1H, J=1.2, 7.8 Hz), 6.79 (dd, 1H, J=1.2, 7.8 Hz), 4.92 (quart, 1H, J=7.0 Hz), 3.90 (s, 3H), 3.73 (s, 3H), 3.45–3.30 (m, 1H), 3.19 (dd, 1H, J=4.7, 12.0 Hz), 2.98 (dd, 1H, J=8.8, 12.0 Hz), 2.25–2.15 (m, 1H), 2.0–1.90 (m, 2H), 1.97 (s, 3H), 1.70–1.58 (m, 1H), 1.56 (d, 3H, J=7.0 Hz), 1.49 (s, 3H); ^{13}C NMR: δ 164.1, 159.6, 152.2, 148.3, 142.2, 129.4, 119.3, 113.3, 109.1, 74.3, 71.5, 55.9, 51.0, 44.5, 36.0, 30.6, 27.6, 27.5, 21.8, 14.1; MS m/z (rel. int.): 457 (1), 439 (28), 261 (100), 213 (86), 198 (23), 178 (34), 146 (31), 118 (27), 91 (14). Anal. calcd for $C_{20}H_{27}NO_4SSe$: C, 52.63; H, 5.96; N, 3.07. Found: C, 52.51; H, 5.89; N, 3.19%.

Minor diastereoisomer (distinct signals): ^{1}H NMR: δ 7.22 (s, 1H), 6.78 (dd, 1H, J=1.2, 7.8 Hz), 3.91 (s, 3H), 3.74 (s, 3H), 3.23 (dd, 1H, J=4.7, 12.0 Hz), 2.94 (dd, 1H, J=8.9, 12.0 Hz), 1.54 (d, 3H, J=7.0 Hz), 1.48 (s, 3H); ^{13}C NMR: δ 129.3, 119.1, 35.9; MS m/z (rel. int.): 457 (1), 439 (27), 263 (23), 261 (100), 213 (87), 198 (24), 178 (35), 146 (32), 118 (28), 91 (15).

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