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Regio- and Stereoselective Methoxyselenenylation of Chiral 2-Vinyl Perhydro-1,3-benzoxazines Promoted by Selenium-Heteroatom Nonbonded Interactions

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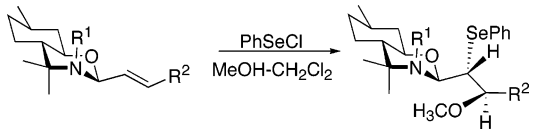

Regio- and diastereoselective methoxyselenenylations of double bonds attached to the N,O-ketalic carbon of chiral perhydrobenzoxazines occur in high yields by reaction with benzeneselenenyl chloride in dichloromethane−methanol. The diastereoselection is dependent on the reaction conditions and the structure of the starting compounds and can be rationalized by accepting the coordination of the selenium to the oxygen atom of the heterocycle.

Introduction

Functionalization of double bonds promoted by an electrophile is versatile and one of the most utilized reactions.[1] In this context, the electrophilic selenenylation of alkenes[2] and cycloseleno functionalization[3] reactions gained increased popularity because the selenium derivatives obtained are useful intermediates in organic synthesis and have interesting biological applications.[4] Transformations of selenoderivatives into carbanions, reductive deselenylation, oxidation to the corresponding selenoxide or selenone and subsequent substitution or elimination, and participation in radical coupling processes make the organoselenium derivatives versatile building blocks in organic synthesis.[5]

The electrophilic selenenylation reaction of alkenes is known to occur by a two-step mechanism that involves the formation of a seleniranium ion intermediate followed by attack of a nucleophile. The reaction exhibits *anti* stereoselectivity and predominantly Markownikoff regioselectivity.

Different strategies can be used for the control of the absolute stereochemistry. The selenylation reaction of alkenes in the presence of enantiomerically pure nucleophiles has been employed in the preparation of 1,4-dioxanes,[6] carbohydrate derivatives,[7] cyclitols,[8] and morpholines[9] but with modest diastereofacial discrimination. Recently chiral organoselenium reagents have been used to effect asymmetric synthesis.[10,11] Several types of chiral selenium electrophiles have been investigated for this purpose, but diastereoselectivity tends to be highly dependent

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upon the reaction conditions and substitution patterns of the alkene. In addition, the mixture of diastereoisomers formed are unseparable,[11c,d] limiting the scope and general effectiveness of this method. However, the use of a chiral auxiliary covalently attached to the alkene has been less studied.

Recently, it has been shown[12−14] that perhydro-1,3-benzoxazines derived from (−)-8-aminomenthol are useful chiral templates in asymmetric synthesis, and we now focus our attention on the preparation of selenenyl perhydro-1,3-benzoxazine derivatives by regio- and stereoselective methoxyselenenylation of 2-vinylperhydro-1,3-benzoxazines.[15]

Results and Discussion

The starting chiral compounds **3a**−**f** were prepared in nearly quantitative yield by condensation of (−)-8-amino menthol[16] **1** with α,β-unsaturated aldehydes in toluene at room temperature, whereas the *N*-benzyl perhydro-1,3-benzoxazines **3g** and **3h** were prepared by condensation of (−)-8-benzylamino menthol[13b] **2** with cinnamaldehyde and 2-methoxycinnamaldeyde in refluxing toluene.

In a typical experiment, PhSeCl (1.1 equiv) was dissolved in methanol, and a solution of the corresponding perhydrobenzoxazine in CH_2Cl_2 was added at the temperature indicated in Table 1. The reaction was quenched with 10% aqueous NaOH, the products were isolated by flash chromatography, and the results are summarized in Scheme 1 and Table 1.

The methoxyselenenylation of alkene **3a** did not take place at −15 °C (entry 1 in the table) but gave a very clean conversion at room temperature for 48 h with excellent yield and total regio- and stereoselectivity (entry 2). Only the formation of diastereoisomer **4a**, of the four possible, resulting from an *anti* addition with attack of methanol at the benzylic position was observed in the reaction mixture.

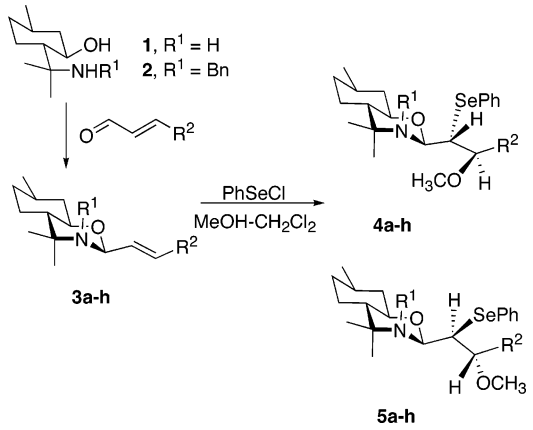
As expected, the methoxyselenenylation of alkenes **3b** and **3c** with an electron-withdrawing nitro group was much slower and the chemical yield decreased, although the excellent levels of regio- and stereoselectivity were maintained (entries 3 and 4).

TABLE 1. Methoxyselenenylation of Alkenes 3a−h

entry	compd	R^1	R^2	*T* (°C)	time (h)	yield (%)[a]	products (ratio)[b]
1	**3a**	H	C_6H_5	−15	24		
2	**3a**	H	C_6H_5	22	48	93	**4a** (>96)
3	**3b**	H	2-NO_2-C_6H_4	22	168	70[c]	**4b** (>96)
4	**3c**	H	4-NO_2-C_6H_4	22	168	71[d]	**4c** (>96)
5	**3d**	H	2-CH_3O-C_6H_4	22	24	95	**4d** (58) **5d** (42)
6	**3d**	H	2-CH_3O-C_6H_4	22	72	93	**4d** (35) **5d** (65)
7	**3d**	H	2-CH_3O-C_6H_4	−15	24	98	**4d** (>96)
8	**3e**	H	4-CH_3O-C_6H_4	22	24	96	**4e** (50) **5e** (50)
9	**3e**	H	4-CH_3O-C_6H_4	−15	48	96	**4e** (>96)
10	**3f**	H	CH_3	22	72	89	**4f** (>96)
11	**3g**	Bn	C_6H_5	22	96	76[e]	**4g** (81) **5g** (19)
12	**3g**	Bn	C_6H_5	4	168	42[f]	**4g** (88) **5g** (12)
13	**3h**	Bn	2-CH_3O-C_6H_4	22	108	75[g]	**4h** (50) **5h** (50)
14	**3h**	Bn	2-CH_3O-C_6H_4	−15	168	60[h]	**4h** (>96)

[a] Yield refers to pure compounds after column chromatography. [b] Determined by ^{1}H NMR of the reaction mixtures. [c] 22% of **3b** was recovered. [d] 0% of **3c** was recovered. [e] 16% of **3g** was recovered. [f] 51% of **3g** was recovered. [g] 20% of **3h** was recovered. [h] 31% of **3h** was recovered.

SCHEME 1. Synthesis of Compounds 3a−h and Their Methoxyselenenylation



The effect of temperature has been shown to be very critical in methoxyselenylation of activated alkenes **3d** and **3e**. At room temperature the reaction was completed after 24 h with excellent chemical yield and total regioselectivity (entries 5 and 8), but the reaction showed a very low degree of stereoselection and almost equimolar mixtures of the two possible stereoisomers **4d/5d** and **4e/5e** were obtained. By contrast, the methoxyselenenylation of **3d** and **3e** at −15 °C produces excellent yields and total stereoselection (entries 7 and 9).

The diastereoselectivity of the addition to **3d** was also dependent on the reaction time. Thus, the ratio of diastereoisomers **4d**: **5d** varied when the reaction time increased (compare entry 5 vs 6), changing from 58:42 after 24 h to 35:65 after 72 h at room temperature. These results are a consequence of the reversivility of this reaction,[17] diastereoisomer **4d** was favored under kinetic conditions, whereas **5d** is the major diastereoisomer formed under thermodynamic control.

Interestingly, although it is known that disubstituted alkenes without aryl groups yield mixtures of regioisomers with low diastereoselectivity,[18] methoxyselenenylation of **3f**, with a

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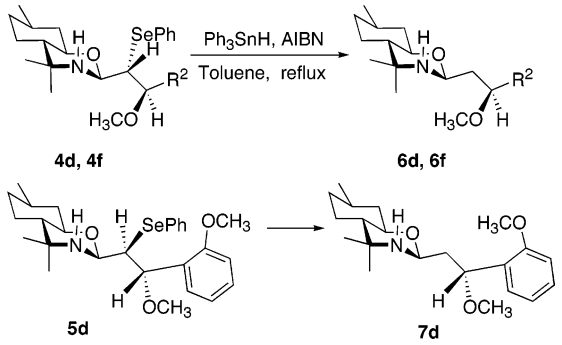
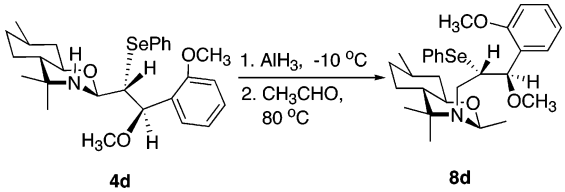
SCHEME 2. Deselenylation of Compounds 4d, 4f, and 5d



SCHEME 3. Stereochemical Correlation of Compound 4d



methyl group at the terminus of the double bond, proceeded with total regio- and stereoselectivity (entry 10).

The influence of a substituent at the nitrogen atom of the perhydro-1,3-benzoxazine was investigated in *N*-benzyl derivatives **3g** and **3h** (entries 11−14). These alkenes were less reactive to electrophilic attack and the addition products are formed with lower yields and diastereoselectivities, but a very good level of diastereoselectivity is retained for methoxyselenenylation of alkene **3h** when the reaction was carried out at −15 °C. This fact demonstrates that the size of the substituent at the nitrogen atom has no influence on the stereochemical outcome of the selenenylation of the double bond.

The structure of compounds **4a**−**h** and **5d**−**h** was determined on the basis of the ^{1}H and ^{13}C NMR data after chromatographic purification and confirmed by reductive deselenenylation of **4d**, **4f**, and **5d** to **6d**, **6f**, and **7d**, respectively, with triphenyltin hydride in the presence of catalytic amounts of AIBN in refluxing toluene (Scheme 2).[19]

The absolute configuration of the *N*-benzyl derivatives **4g** and **4h** was established by X-ray diffraction analysis,[20] whereas the absolute configuration of the minor diastereoisomers **5g** and **5h** was assigned by assuming an *anti* addition on the basis of the literature precedents.

The absolute configuration of the newly created stereocenters in **4d** was determined by its conversion into perhydrobenzoxazine **8d** by nucleophilic ring opening of the N,O-acetal moiety by aluminum hydride and condensation of the resulting 1,3-amino alcohol derivative with acetaldehyde (Scheme 3). X-ray diffraction analysis allowed for the determination of the stereochemistry of **8d**.[20]

The high regio- and stereoselectivity observed in the methoxyselenylation of alkenes **3a**−**h** could be readily understood by accepting the complexation of the selenium to the nitrogen or oxygen atoms of the perhydro-1,3-benzoxazine ring, so that this nonbonded interaction stabilizes preferably one of the two possible seleniranium ions intermediates.[21] Because the reaction is a reversible process and the electrophilic attack is the rate-determining step, the diastereomeric ratio of the products reflects the stability of the preceding seleniranium intermediates. Alternatively, coordination of the selenium to the heteroatom of the perhydrobenzoxazine could occur prior to the formation of the seleniranium ion intermediate, followed by intramolecular delivery of the electrophilic selenium species to the double bond.[22]

On the other hand, it is well-known that PhSeCl reacts instantaneously with dialkylamines to form selenamides (PhSe−NR^1R^2), which can act as efficient $PhSe^+$ donors to the olefinic double bond.

To determine if a selenium−nitrogen coordination intermediate was responsible for the high stereoselectivity, we envisaged that the transformation of perhydrobenzoxazines into their ammonium salts would prevent the further coordination of the nitrogen atom. To this end, we tested the transformation of **3d** into the corresponding methiodide by reaction with excess of methyl iodide, but no ammonium derivative was isolated. On the contrary, **3d** was transformed into its hydrochloride by bubbling dry hydrogen chloride through a solution of **3d** in ether and filtration of the precipitate. Otherwise, this salt could be formed prior to the methoxyselenenylation by quaternization of the starting perhydrobenzoxazines with hydrogen chloride formed by reaction of PhSeCl with methanol used as solvent. The nitrogen atom of **3d**-HCl is unable to coordinate the selenium reagents, but the reaction of the hydrochloride with PhSeCl at −15 °C yielded **4b** with total regio- and stereoselectivity. This result suggests that chelation with oxygen is preferred over coordination with nitrogen. Moreover, this fact is supported by the observation of intramolecular Se···O nonbonding interactions[23] in **4g** and **4h**. The shorter atomic distances between Se and the O atom of the oxazine ring (r_{Se-O} = 2.765 Å for **4g** and r_{Se-O} = 2.773 Å for **4h**) relative to the sum of van der Waals radii (3.42 Å) and the almost linear O(1)−Se(1)−C(13) angle show the presence of a hypervalent Se−O interaction for these compounds. The coordination geometry around the selenium atom is a distorted T-shape as described for other selenium compounds with nonbonding Se−heteroatom interaction.[24]

The reason for the preferential coordination to the oxygen rather than to the nitrogen atom might be a consequence of the axial position of the substituents at the nitrogen atom in the perhydrobenzoxazine and the assumption that the selenium−heteroatom nonbonded interaction would involve the axial rather than the equatorial lone pair of the heteroatom.

Two possible seleniranium intermediates **A** and **B** with nonbonded Se···O interactions can be envisaged (Figure 1). The intermediate **A** is more stable and responsible for the formation of the single or major diastereoisomers **4a**−**h**. Intermediate **B** is clearly sterically less favorable due to the steric hindrance

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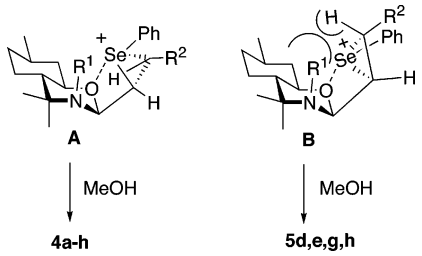

FIGURE 1. Plausible structures for the seleniranium intermediates.

between the olefinic hydrogen and the perhydrobenzoxazine framework; **5d**, **5e**, **5g**, and **5h** are formed as minor diastereomers, or no products were formed from this conformation.

The described regio- and stereochemical results can also be interpreted in terms of simple electrostatic arguments, so that the electrophilic attack occurs preferentially at the α carbon and *syn* to the oxygen, as described for related reactions in acyclic chiral allylic systems with oxygen substituents.[25]

In summary, we have shown that chiral perhydrobenzoxazines serve as excellent templates to promote methoxyselenenylation with total regio- and diastereoselectivity. Depending on the reaction conditions, this methodology yields better face discrimination than when chiral selenyl derivatives are used and offer the advantage of an easier purification of the mixtures of stereoisomers.

Experimental Section

Methoxyselenenylation of Alkenes 3a−h. General Method. To a stirred mixture of benzeneselenenyl chloride (1.1 g, 5.7 mmol) in methanol (20 mL was added a solution of the oxazine **3a**−**h** (5.2 mmol) in CH_2Cl_2 (5 mL). The solution was stirred at the temperature and for the time shown in Table 1 and then diluted with a 10% aqueous solution of NaOH. The CH_2Cl_2 and the methanol were removed under reduced pressure, and the aqueous phase was extracted with chloroform (3 × 30 mL). The combined organic extracts were washed with H_2O and dried over $MgSO_4$, the solvent was removed under reduced pressure, and the residue was chromatographed on silica gel using mixtures of hexane/EtOAc as eluent.

(2*S*,4a*S*,7*R*,8a*R*)-2-[(1*R*,2*R*)-2-Methoxy-2-phenyl-1-phenylselenyl-ethyl]-4,4,7-trimethyl-octahydro-benzo[*e*][1,3]oxazine (4a). Colorless solid. Mp 98−99 °C (from EtOH). $[\alpha]^{25}_D = -62.1$ (*c* 1.3, CH_2Cl_2). ^{1}H NMR (δ): 0.88−1.18 (m, 4H); 0.93 (d, 3H, *J* = 6.4 Hz); 1.13 (s, 3H); 1.17 (s, 3H); 1.46 (m, 1H); 1.53−1.73 (m, 2H); 1.95 (m, 1H); 2.61 (s, broad, 1H); 3.12 (s, 3H); 3.29 (d, 1H, *J* = 10.7 Hz); 3.46 (td, 1H, J_1 = 10.1 Hz, J_2 = 3.9 Hz); 4.41 (d, 1H, *J* = 10.7 Hz); 4.97 (s, 1H); 6.86−6.88 (m, 4H); 6.96−7.14 (m, 6H). ^{13}C NMR (δ): 19.9; 22.1; 25.3; 29.7; 31.1; 34.8; 41.4; 50.9; 51.5; 56.5; 59.8; 74.4; 79.6; 84.3; 126.4; 127.3 (3C); 127.9 (2C); 128.3 (2C); 129.7; 134.1 (2C); 139.6. IR (Nujol): 3270, 3050, 1580, 740, 700, 620 cm^{-1}. Anal. Calcd for $C_{26}H_{35}NO_2Se$: C, 66.09; H, 7.47; N, 2.96. Found: C, 66.22; H, 7.59; N, 3.08.

(2*S*,4a*S*,7*R*,8a*R*)-2-[(1*R*,2*R*)-2-Methoxy-2-(2-nitro-phenyl)-1-phenylselenyl-ethyl]-4,4,7-trimethyl-octahydro-benzo[*e*][1,3]-oxazine (4b). Yellow oil. $[\alpha]^{25}_D = -213.9$ (*c* 1.0, CH_2Cl_2). ^{1}H NMR (δ): 0.80−1.12 (m, 4H); 0.86 (d, 3H, *J* = 6.4 Hz); 1.06 (s, 3H); 1.10 (s, 3H); 1.41 (m, 1H); 1.59−1.61 (m, 2H); 1.85 (m, 1H); 2.45 (s, broad, 1H); 3.21 (s, 3H), 3.22 (d, 1H, *J* = 10.4 Hz); 3.37 (td, 1H, J_1 = 10.5 Hz, J_2 = 4.2 Hz); 4.82 (s, 1H); 5.25 (d, 1H, *J* = 10.4 Hz); 6.81−6.85 (m, 2H); 6.86−6.96 (m, 3H); 7.00−7.11 (m, 2H); 7.19 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.2 Hz); 7.60 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.2 Hz). ^{13}C NMR (δ): 20.0; 22.2; 25.5; 29.8; 31.3; 34.9; 41.4; 51.3; 51.6; 57.5; 59.9; 74.7; 78.1; 79.6; 123.3; 126.6; 128.0; 128.2 (2C); 129.1; 129.9; 131.7; 133.5 (2C); 135.3; 150.7. IR (film): 3285, 3060, 1730, 1690, 785, 740, 695, 670, 620 cm^{-1}. Anal. Calcd for $C_{26}H_{34}N_2O_4Se$: C, 60.34; H, 6.62; N, 5.41. Found: C, 60.49; H, 6.78; N, 5.29.

(2*S*,4a*S*,7*R*,8a*R*)-2-[(1*R*,2*R*)-2-Methoxy-2-(4-nitro-phenyl)-1-phenylselenyl-ethyl]-4,4,7-trimethyl-octahydro-benzo[*e*][1,3]-oxazine (4c). Colorless solid. Mp 139−140 °C (from EtOH). $[\alpha]^{25}_D = -93.3$ (*c* 1.1, $CHCl_3$). ^{1}H NMR (δ): 0.93−1.20 (m, 4H); 0.95 (d, 3H, *J* = 6.5 Hz); 1.16 (s, 3H); 1.20 (s, 3H); 1.47 (m, 1H); 1.69−1.72 (m, 2H); 1.95 (m, 1H); 2.55 (s, broad, 1H); 3.16 (s, 3H); 3.29 (d, 1H, *J* = 10.6 Hz); 3.50 (td, 1H, J_1 = 10.3 Hz, J_2 = 4.1 Hz); 4.54 (d, 1H, *J* = 10.6 Hz); 4.97 (s, 1H); 6.85−6.92 (m, 4H); 7.03 (m, 1H); 7.27 (d, 2H, *J* = 8.6 Hz); 7.85 (d, 2H, *J* = 8.6 Hz). ^{13}C NMR (δ): 20.0; 22.2; 25.5; 29.8; 31.3; 34.9; 41.6; 51.3; 51.7; 57.1; 59.0; 74.8; 79.6; 83.8; 122.5 (2C); 126.8; 128.3 (2C); 129.1 (2C); 129.5; 133.6 (2C); 147.3; 147.5. IR (Nujol): 3275, 3050, 1685, 1605, 740, 695 cm^{-1}. Anal. Calcd for $C_{26}H_{34}N_2O_4Se$: C, 60.34; H, 6.62; N, 5.41. Found: C, 60.21; H, 6.79; N, 5.53.

(2*S*,4a*S*,7*R*,8a*R*)-2-[(1*R*,2*R*)-2-Methoxy-2-(2-methoxy-phenyl)-1-phenylselenyl-ethyl]-4,4,7-trimethyl-octahydro-benzo[*e*][1,3]-oxazine (4d). Colorless oil. $[\alpha]^{25}_D = -42.6$ (*c* 0.9, $CHCl_3$). ^{1}H NMR (333 K) (δ): 0.79−1.09 (m, 4H); 0.84 (d, 3H, *J* = 6.5 Hz); 1.03 (s, 3H); 1.05 (s, 3H); 1.38 (m, 1H); 1.57−1.60 (m, 2H); 1.84 (m, 1H); 2.60 (s, broad, 1H); 3.10 (s, 3H); 3.34 (td, 1H, J_1 = 10.2 Hz, J_2 = 4.1 Hz), 3.44 (s, 3H); 3.59 (dd, 1H, J_1 = 10.0 Hz, J_2 = 1.5 Hz); 4.72 (d, 1H, *J* = 10.0 Hz); 4.80 (d, 1H, *J* = 1.5 Hz); 6.53 (dd, 1H, J_1 = 8.1 Hz, J_2 = 1.1 Hz); 6.63 (td, 1H, J_1 = 7.6 Hz, J_2 = 1.1 Hz); 6.84−6.89 (m, 2H); 6.93−7.14 (m, 5H). ^{13}C NMR (333 K) (δ): 20.0; 22.2; 25.6; 29.9; 39.4; 35.2; 41.8; 51.3; 52.0; 55.1; 57.1; 57.6; 74.8; 80.3; 80.6; 110.7; 119.9; 126.5; 128.1 (3C); 128.5; 130.0, 130.6; 134.6 (2C); 158.3. IR (film): 3280, 1600, 1580, 750, 695, 620 cm^{-1}. Anal. Calcd for $C_{27}H_{37}NO_3Se$: C, 64.53; H, 7.42; N, 2.79. Found: C, 64.70; H, 7.56; N, 2.92.

(2*S*,4a*S*,7*R*,8a*R*)-[(1*S*,2*S*)-2-Methoxy-2-(2-methoxy-phenyl)-1-phenylselenyl-ethyl]-4,4,7-trimethyl-octahydro-benzo[*e*][1,3]-oxazine (5d). Colorless oil. ^{1}H NMR (δ): 0.8−1.15 (m, 4H); 0.90 (d, 3H, *J* = 6.5 Hz); 1.06 (s, 3H); 1.10 (s, 3H); 1.38 (m, 1H); 1.62−1.66 (m, 2H); 1.84 (m, 1H); 2.51 (s, broad, 1H); 3.21 (s, 3H); 3.35 (td, 1H, J_1 = 10.5 Hz, J_2 = 4.3 Hz); 3.65 (s, 3H); 3.75 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.8 Hz) 4.75 (d, 1H, *J* = 1.8 Hz); 4.83 (d, 1H, *J* = 8.4 Hz); 6.75 (dd, 1H, J_1 = 8.1 Hz, J_2 = 0.9 Hz); 6.86 (td, 1H, J_1 = 7.4 Hz, J_2 = 0.9 Hz); 7.06−7.38 (m, 5H); 7.39−7.40 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 19.6 (CH_3); 22.3 (CH_3); 25.3 (CH_2); 30.0 (CH_3); 31.3 (CH); 35.0 (CH_2); 41.4 (CH_2); 51.3 (CH + C); 54.5 (CH); 55.0 (CH_3); 57.3 (CH_3); 75.0 (CH); 78.9 (CH); 82.8 (CH); 110.3 (CH); 120.1 (CH); 126.7 (CH); 128.0 (C); 128.3 (2CH); 128.5 (CH); 130.8 (C); 134.0 (CH); 134.5 (2CH); 157.7 (CH). Anal. Calcd for $C_{27}H_{37}NO_3Se$: C, 64.53; H, 7.42; N, 2.79. Found: C, 64.39; H, 7,47; N, 2.64

(2*S*,4a*S*,7*R*,8a*R*)-2-[(1*R*,2*R*)-2-Methoxy-2-(4-methoxy-phenyl)-1-phenylselenyl-ethyl]- 4,4,7-trimethyl-octahydro-benzo[*e*][1,3]-oxazine (4e). Colorless oil. $[\alpha]^{25}_D = -58.3$ (*c* 1.1, $CHCl_3$). ^{1}H NMR (δ): 0.86−1.18 (m, 4H); 0.94 (d, 3H, *J* = 6.5 Hz); 1.15 (s, 3H); 1.18 (s, 3H); 1.46 (m, 1H); 1.68−1.71 (m, 2H); 1.95 (m, 1H); 2.52 (s, broad, 1H); 3.13 (s, 3H); 3.29 (d, 1H, *J* = 10.6 Hz); 3.48 (td, 1H, J_1 = 10.3 Hz, J_2 = 4.1 Hz); 3.73 (s, 3H); 4.36 (d, 1H, *J* = 10.6 Hz); 4.95 (s, 1H); 6.59 (d, 2H, *J* = 8.6 Hz); 6.89−6.96 (m, 4H); 7.03 (m, 1H); 7.04 (d, 2H, *J* = 8.6 Hz). ^{13}C NMR (δ): 20.1; 22.3; 25.5; 29.9; 31.4; 35.0; 41.7; 51.3; 51.7; 55.2; 56.6; 60.2; 74.7; 79.9; 84.0; 112.9 (2C); 126.6; 128.1 (2C); 129.5 (2C); 130.0; 132.0; 134.4 (2C); 159.0. IR (film): 3325, 1610, 1510, 830, 745, 735, 690 cm^{-1}. Anal. Calcd for $C_{27}H_{37}NO_3Se$: C, 64.53; H, 7.42; N, 2.79. Found: C, 64.63; H, 7.56; N, 2.68.

(2*S*,4a*S*,7*R*,8a*R*)-2-[(1*S*,2*S*)-2-Methoxy-2-(4-methoxy-phenyl)-1-phenylselenyl-ethyl]- 4,4,7-trimethyl-octahydro-benzo[*e*][1,3]-oxazine (5e). Colorless oil. $[\alpha]^{25}_D = +34.5$ (*c* 1.0, $CHCl_3$). ^{1}H NMR

(25) (a) Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 666. (b) Kahn, S. D.; Pau, C. F.; Chamberlin, A. R.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 650. Chamberlin, A. R.; Mulholland, R. L., Jr.; Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 672.

(δ): 0.81−1.12 (m, 4H); 0.93 (d, 3H, J = 6.5 Hz); 1.03 (s, 3H); 1.09 (s, 3H); 1.45 (m, 1H); 1.63−1.67 (m, 2H); 1.93 (m, 1H); 2.51 (s, broad, 1H); 3.15 (s, 3H); 3.38 (td, 1H, J_1 = 10.5 Hz, J_2 = 4.1 Hz); 3.47 (dd, 1H, J_1 = 9.7 Hz, J_2 = 2.2 Hz); 3.77 (s, 3H); 4.47 (d, 1H, J = 9.7 Hz); 4.79 (d, 1H, J = 2.2 Hz); 6.73 (d, 2H, J = 8.6 Hz); 7.02−7.27 (m, 7H). ^{13}C NMR (δ): 19.4; 22.3; 25.4; 30.0; 31.3; 35.0; 41.6; 51.2; 51.7; 55.1; 55.8; 56.3; 75.1; 83.3; 83.8; 113.1 (2C); 126.9; 128.3 (2C); 129.2 (2C); 130.3; 132.0; 134.5 (2C); 159.1. IR (film): 3325, 3060, 1610, 1580, 830, 740, 690, 670, 640 cm^{-1}. Anal. Calcd for $C_{27}H_{37}NO_3Se$: C, 64.53; H, 7.42; N, 2.79. Found: C, 64.61; H, 7.50; N, 2.89.

(2*S*,4a*S*,7*R*,8a*R*)-2-[(1*R*,2*R*)-2-Methoxy-1-phenylselenyl-propyl]- 4,4,7-trimethyl-octahydro-benzo[*e*][1,3]oxazine (4f). Colorless oil. $[\alpha]^{25}_D$ = +16.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (δ): 0.83−1.11 (m, 4H); 0.91 (d, 3H, J = 6.5 Hz); 1.12 (s, 3H); 1.13 (s, 3H); 1.24 (d, 3H, J = 6.2 Hz); 1.42 (m, 1H); 1.66−1.68 (m, 2H); 1.86 (m, 1H); 2.43 (s, broad, 1H); 3.13 (d, 1H, J = 9.0 Hz); 3.29 (s, 3H); 3.41 (td, 1H, J_1 = 10.4 Hz, J_2 = 4.2 Hz); 3.63 (dq, 1H, J_1 = 9.0 Hz, J_2 = 6.2 Hz); 4.71 (s, 1H); 7.18−7.27 (m, 3H); 7.59−7.62 (m, 2H). ^{13}C NMR (δ): 18.2; 19.8; 22.1; 25.3; 29.6; 31.1; 34.7; 41.3; 50.9; 51.4; 56.6; 58.9; 74.3; 78.4; 80.1; 126.7; 128.6 (2C); 130.6; 133.4 (2C). IR (film): 3280, 3060, 1580, 785, 740, 690 cm^{-1}. Anal. Calcd for $C_{21}H_{33}NO_2Se$: C, 61.45; H, 8.10; N, 3.41. Found: C, 61.54; H, 8.22; N, 3.56.

(2*S*,4a*S*,7*R*,8a*R*)-3-Benzyl-2-[(1*R*,2*R*)-2-methoxy-2-phenyl-1-phenylselenyl-ethyl]-4,4,7-trimethyl-octahydro-benzo[*e*][1,3]-oxazine (4g). Colorless solid. Mp 124−125 °C (from EtOH). $[\alpha]^{25}_D$ = +39.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR (δ): 0.82−1.18 (m, 3H); 0.92 (d, 3H, J = 6.5 Hz);; 1.00 (s, 3H); 1.09 (s, 3H); 1.40−1.49 (m, 2H); 1.56 (m, 1H); 1.64 (m, 1H); 1.97 (m, 1H); 3.13 (s, 3H); 3.42 (dd, 1H, J_1 = 4.1 Hz, J_2 = 3.8 Hz); 3.47 (td, 1H, J_1 = 10.4 Hz, J_2 = 3.9 Hz); 3.68 (d, 1H, J = 18.3 Hz); 4.18 (d, 1H, J = 4.1 Hz); 4.35 (d, 1H, J = 18.3 Hz); 4.92 (d, 1H, J = 3.8 Hz); 6.76−6.84 (m, 2H); 6.88−6.95 (m, 2H); 7.02−7.07 (m, 3H); 7.17−7.28 (m, 8H). ^{13}C NMR (δ): 19.4; 22.2; 24.9; 26.9; 31.2; 34.9; 40.9; 46.3; 46.7; 54.7; 57.4; 57.8; 76.1; 83.0; 84.8; 125.9; 126.5; 126.9 (2C); 127.3 (3C); 127.7 (2C); 128.0 (2C); 128.3 (2C); 130.6; 134.2 (2C); 139.3; 143.4. IR (Nujol): 3060, 3040, 1600, 1580, 770, 745, 710, 700, 640 cm^{-1}. Anal. Calcd for $C_{33}H_{41}NO_2Se$: C, 70.44; H, 7.34; N, 2.49. Found: C, 70.60; H, 7.45; N, 2.58.

(2*S*,4a*S*,7*R*,8a*R*)-3-Benzyl-2-[(1*S*,2*S*)-2-methoxy-2-phenyl-1-phenylselenyl-ethyl]-4,4,7-trimethyl-octahydro-benzo[*e*][1,3]-oxazine (5g). Colorless oil. $[\alpha]^{25}_D$ = −17.5 (*c* 1.2, $CHCl_3$). ^{1}H NMR (δ): 0.88−1.03 (m, 3H); 0.93 (d, 3H, J = 6.5 Hz); 0.94 (s, 3H); 1.06 (s, 3H); 1.31 (m, 1H); 1.48−1.56 (m, 2H); 1.67 (m, 1H); 1.79 (m, 1H); 3.07 (s, 3H); 3.37 (td, 1H, J_1 = 10.4 Hz, J_2 = 4.0 Hz); 3.72 (dd, 1H, J_1 = 8.3 Hz, J_2 = 3.7 Hz); 3.80 (d, 1H, J = 17.9 Hz); 4.11 (d, 1H, J = 17.9 Hz); 4.56 (d, 1H, J = 3.7 Hz); 4,69 (d, 1H, J = 8.3 Hz); 7.06−7.13 (m, 4H); 7.18−7.33 (m, 9H); 7.43−7.51 (m, 2H). ^{13}C NMR (δ): 21.0; 22.3; 24.9; 27.5; 31.3; 35.1; 40.9; 44.8; 47.5; 54.1; 56.7; 58.1; 76.5; 81.9; 87.6; 125.7; 126.6; 127.2; 127.3 (2C); 127.5 (4C); 128.1 (2C); 128.4 (2C); 131.3; 133.8 (2C); 139.8; 143.0. IR (film): 3060, 3030, 1600, 1580, 740, 760, 670, 650, 615 cm^{-1}. Anal. Calcd for $C_{33}H_{41}NO_2Se$: C, 70.44; H, 7.34; N, 2.49. Found: C, 70,56; H, 7.21; N, 2.61.

(2*S*,4a*S*,7*R*,8a*R*)-3-Benzyl-2-[(1*R*,2*R*)-2-methoxy-2-(2-methoxy-phenyl)-1-phenylselenyl-ethyl]-4,4,7-trimethyl-octahydro-benzo-[*e*][1,3]oxazine (4h). Colorless solid. Mp 159−160 °C (from EtOH). $[\alpha]^{25}_D$ = +37.7 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 0.87 (s, 3H); 0.901.11 (m, 2H); 0.99 (d, 3H, J = 6.4 Hz); 1.03 (s, 3H); 1.19 (m, 1H); 1.45−1.59 (m, 3H); 1.73 (m, 1H); 2.13 (m, 1H); 3.20 (s, 3H); 3.39 (s, 3H); 3.53 (t, 1H, J = 1.9 Hz); 3.65 (td, 1H, J_1 = 10.5 Hz, J_2 = 3.9 Hz); 3.72 (d, 1H, J = 18.6 Hz); 4.50 (d, 1H, J = 1.9 Hz); 4,57 (d, 1H, J = 18.6 Hz); 5.09 (d, 1H, J = 1.9 Hz); 6.74 (d, 1H, J = 8.1 Hz); 6.97−7.32 (m, 12H); 7.50 (d, 1H, J = 7.2 Hz). ^{13}C NMR (δ): 20.3; 22.1; 24.7; 26.3; 31,1; 34.9; 40.8; 45.4; 46.0; 51.5; 53.7; 57.2; 58.0; 76.3; 78.7; 82.8; 109.4; 119.5: 125.2; 126.3; 126.5; 126.8; 127.0; 127.5 (2C); 127.9 (2C); 128.0; 130.0; 135.0 (2C); 144.0; 156.3. IR (Nujol): 3060, 3040, 1600, 1590, 740, 720, 690, 635 cm^{-1}. Anal. Calcd for $C_{34}H_{43}NO_3Se$: C, 68.90; H, 7.31; N, 2.36. Found: C, 69.01; H, 7.22; N, 2.50.

(2*S*,4a*S*,7*R*,8a*R*)-3-Benzyl-2-[(1*S*,2*S*)-2-methoxy-2-(2-methoxy-phenyl)-1-phenylselenyl-ethyl]-4,4,7-trimethyl-octahydro-benzo-[*e*][1,3]oxazine (5h). Colorless oil. $[\alpha]^{25}_D$ = −37.7 (*c* 0.5, $CHCl_3$). ^{1}H NMR (δ): 0.71−1.05 (m, 3H); 0.84 (s, 3H); 0.85 (d, 3H, J = 6.3 Hz); 1.25−1.67 (m, 5H); 1.32 (s, 3H); 3,24 (s, 3H); 3.31 (td, 1H, J_1 = 10.4 Hz, J_2 = 4.0 Hz); 3.56 (s, 3H); 3.86 (d, 1H, J = 17.4 Hz); 3.90 (dd, 1H, J_1 = 8.7 Hz, J_2 = 3.0 Hz); 4.10 (d, 1H, J = 17.4 Hz); 4.55 (d, 1H, J = 3.0 Hz); 5,17 (d, 1H, J = 8.7 Hz); 6.71 (d, 1H, J = 8.2 Hz); 6.86 (t, 1H, J = 7.0 Hz); 7.11−7.34 (m, 8H); 7.41 (dd, 2H, J_1 = 7.4 Hz, J_2 = 1.5 Hz); 7.52 (d, 2H, J = 7.2 Hz). ^{13}C NMR (δ): 22.3; 22.9; 24.8; 27.8; 31.4; 35.2; 40.4; 43.5; 47.4; 50.9; 54.6; 58.0; 58.5; 77.0; 78.1; 86.4; 109.7; 119.5; 125.4; 127.0; 127.3 (2C); 127.4; 127.5; 127.7 (2C); 128.2 (2C); 128.8; 130.5; 135.2 (2C); 143.7; 156.5. IR (film): 3065, 3040, 1600, 1585, 750, 740, 720, 690 cm^{-1}. Anal. Calcd for $C_{34}H_{43}NO_3Se$: C, 68.90; H, 7.31; N, 2.36. Found: C, 68.79; H, 7.38; N, 2.49.

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Supporting Information Available: General experimental methods and physical and spectral characteristics for compounds **3g,h**, **6d**, **6f**, **7d**, and **8d**. Copies of ^{1}H NMR and ^{13}C NMR spectra for all of the described compounds. ORTEP representations of X-ray structures for compounds **4g**, **4h**, and **8d** including CIF files. Table of selected bond lengths and bond angles for **4g** and **4h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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