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Synthesis of Enantiopure 1,4-Dioxanes, Morpholines, and Piperazines from the Reaction of Chiral 1,2-Diols, Amino Alcohols, and Diamines with Vinyl Selenones

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Abstract: The reactions of readily available vinyl selenones with enantiopure 1,2-diols, N-protected-1,2-amino-alcohols, and diamines gave substituted enantiopure 1,4-dioxanes, morpholines, and piperazines, respectively, in good to excellent yields. The same procedure was extended to the synthesis of thiomorpholine, benzodiazepine, and benzoxazepine. The reactions proceeded in one pot, in the presence of base, through a simple and novel application of the Michael-initiated, ring-closure (MIRC) reactions. The formed heterocycles constitute a framework that is observed in a large number of pharmaceutical compounds.

Keywords: cyclization · enantioselectivity · Michael addition · oxygen heterocycles · selenium

Introduction

1,4-Dioxanes[1] and nitrogen-containing heterocyclic compounds[2] such as morpholines, thiomorpholines, or piperazines are important biologically active compounds. The morpholine skeleton is a chiral core present in many important therapeutic agents.[2a] In particular, *trans*-2,5-disubstituted morpholine derivatives are widely represented among pharmacologically active substances such as $GABA_B$ receptor antagonists, and antitumor and anti-inflammatory agents.[2b–d] Furthermore, piperazines are observed in a large number of compounds of pharmaceutical interest. In 2001 the MDL Drug Data Report listed 2271 piperazines, with 65 structures in phase II clinical trials, expanded in 23 therapeutic areas,[2e] such as antibacterials, antidepressants, antitussives, antifungal, antiviral, anxiolytic, antipsychotics, analgesic, and antiaggregants. Moreover, these six-membered rings contain a heteroatom that can act as an extra coordination site and can be used as a chiral reagent in asymmetric synthesis.[3,2d] A range of multistep procedures are reported in the literature for the synthesis of these heterocycles.[4] The direct alkylation of 1,2-diols and 1,2-amino alcohols or thiols, and of diamines with 1,2-dihalo-derivatives often proceeds in low yields and affords some side products.[5] Aggarwal et al. have recently proposed the preparation of morpholine, thiomorpholine, and piperazine from the reaction of β-heteroatom amino compounds and vinyl sulfonium salts as Michael acceptors.[6] To the best of our knowledge, no use of vinyl selenones as Michael acceptors for the synthesis of these pharmacologically important heterocycles has been reported. The great leaving ability of the selenone group, in both inter-[7] and intramolecular[8] nucleophilic substitutions, is well documented. In contrast, less attention has been devoted to the use of vinyl selenones,[9] in which the $PhSeO_2$ group activates the carbon–carbon double bond towards the addition of several nucleophilic reagents at the β carbon and at the same time acts as a good leaving group in the following cyclization reaction. Whereas a variety of sulfonium ylides[10] have widely been employed in asymmetric Michael-initiated, ring-closure (MIRC) reactions, the corresponding vinyl selenonium salt[11] or the vinyl selenones[12] have rarely been investigated. We have recently reported the reaction of vinyl selenones with di-(−)-bornyl malonate and sodium hydride in the formation of cyclopropanes through an addition–substitution reaction.[13] A mixture of two diastereomeric cyclopropane derivatives was obtained,

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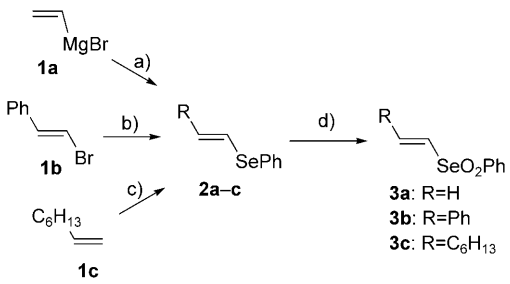
but these could be easily separated by chromatography and led, after removal of the bornyl group, to highly enantiomerically enriched cyclopropanes.[13] Very recently an organocatalytic method for the selective synthesis of highly substituted cyclopropanes starting from β-substituted vinyl selenones has also been reported.[14]

Herein, we describe a simple and novel use of the MIRC reactions to obtain, in one step and in good to excellent yields, six- or seven-membered, enantiopure heterocyclic rings from commercially available enantiopure 1,2-diols, 1,2-amino alcohols, or thiols, and diamines using vinyl selenones as Michael acceptors.

Results and Discussion

The vinyl phenyl selenones **3a–c** necessary for the present investigation were synthesized starting from the corresponding vinyl phenyl selenides **2a–c** using *m*-chloroperbenzoic acid (MCPBA) as oxidant in dichloromethane at room temperature (Scheme 1).[13] Selenide **2a** was synthesized starting



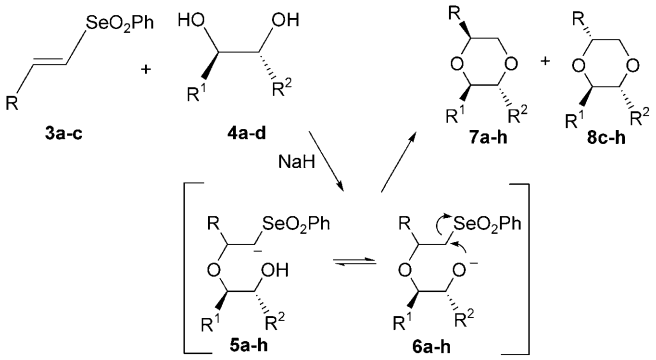
Scheme 1. Synthesis of vinyl phenyl selenones. a) $(PhSe)_2$, THF, 0°C; b) $(PhSe)_2$, $NaBH_4$, DMF, 120°C; c) 1) PhSeBr, $CHCl_2$, RT; 2) lithium diisopropylamide (LDA), Et_2O, 0°C; d) MCPBA, CH_2Cl_2, RT.

from vinyl magnesium bromide (**1a**) and diphenyl diselenide according to the procedure described in the literature.[15] Selenide **2b** was obtained according to the previously described vinylic substitution starting from the corresponding commercially available bromide **1b**,[16] whereas selenide **2c** was synthesized by the one-pot Markovnikov addition of phenylselenyl bromide to the corresponding alkene **1c** followed by dehydrobromination with LDA (Scheme 1 and Table 1).[17]

Table 1. Yields of selenides and selenones.

R	Selenide **2**	Yield [%]	Selenone **3**	Yield [%]
H	**2a**	92	**3a**	86
Ph	**2b**	94	**3b**	90
C_6H_{13}	**2c**	78	**3c**	77

The first experiments conducted concerned the synthesis of 1,4-dioxanes by the reaction of commercially available, enantiopure 1,2-diols **4a–d** with the vinyl selenones **3a–c** (Scheme 2). The reaction conditions, the reaction products, and the yields are reported in Table 2. A single dioxane was obtained starting from the selenone **3a**, whereas two reac-



Scheme 2. Reaction of vinyl selenones with enantiopure 1,2-diols.

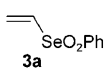
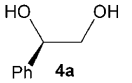
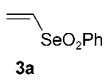
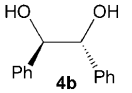
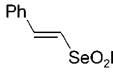
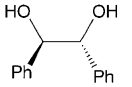
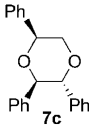
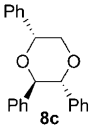
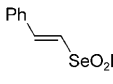
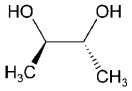
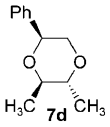
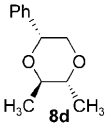
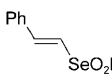
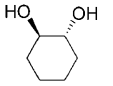
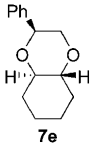
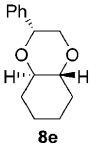
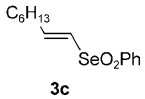
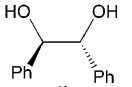
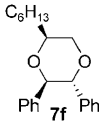
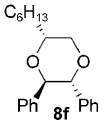
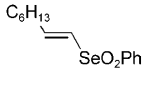
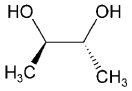
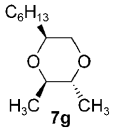
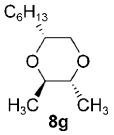
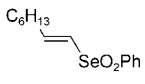
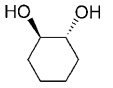
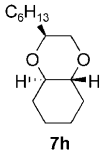
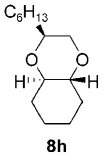
tion products were isolated from the reactions of substituted selenones **3b** and **3c**. In the last case, the products were easily separated by column chromatography and were identified as dioxanes **7c–h** and **8c–h**.

On the basis of the accepted mechanism for the MIRC reactions,[10,12,13] it can be suggested that the reaction of selenones **3a–c** with the commercially available, enantiopure 1,2-diols in the presence of sodium hydride initially give the carbanions **5a–h**, which then can undergo a proton transfer to give **6a–h**. Finally, intramolecular displacement of the $PhSeO_2$ group by the heteroatom anions afford the 1,4-dioxanes **7a–h** and **8c–h**.

The configurations of the carbon atoms with R^1 and R^2 in compounds **7a–h** and **8c–h** were clearly unchanged with respect to those of the starting 1,2-diols **4a–d** (Table 2). With the exception of compound **7b**, which presented a symmetric NMR spectrum, the ^1H NMR spectra of 1,4-dioxanes **7a**, **7c–h**, and **8c–h** revealed the presence of large axial–axial coupling constants between the protons H-2 and H-3, which clearly suggests that R^1 and R^2 occupy equatorial positions, assuming a chair conformation as indicated in Figure 1. In compounds **7c–h** and **8c–h** the absolute configurations of the newly generated stereogenic centers (carbon atom C-5), reported in Figure 1, are suggested on the basis of the values of the vicinal coupling constants between the proton H-5 and the two protons in position 6. These coupling constants clearly suggest that the R groups occupy an equatorial position in compounds **7c–h** and an axial position in compounds **8c–h**.

As reported in Table 2, the enantiomerically pure 1,4-dioxanes **7a–h** and **8c–h** were obtained in very good yields after column chromatography. The enantiomeric purities of the 1,4-dioxanes **7a–f**, **8c**, **8e**, and **8f** were confirmed by HPLC analysis using the chiral column Chiralpak AD-H. In the case of compound **8d**, the enantiomeric purity was instead determined by ^1H NMR spectroscopic analysis using (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol.

Table 2. Synthesis of enantiopure 1,4-dioxanes.

Entry	Selenone	Substrate	Conditions	Product	Yield [%]	Product	Yield [%]
1	 **3a**	 **4a**	CH_2Cl_2, 0 °C to RT, 1 d	 **7a**	82		
2	 **3a**	 **4b**	CH_2Cl_2, 0 °C to RT, 5 h	 **7b**	80		
3	 **3b**	 **4b**	CH_2Cl_2, 0 °C to RT, 2 d	 **7c**	49	 **8c**	29
4	 **3b**	 **4c**	CH_2Cl_2, 0 °C to RT, 1 d	 **7d**	34	 **8d**	21
5	 **3b**	 **4d**	Toluene, RT, 2 d[a]	 **7e**	26	 **8e**	47
6	 **3c**	 **4b**	CH_2Cl_2, 0 °C to RT, 3 d	 **7f**	18	 **8f**	60
7	 **3c**	 **4c**	CH_2Cl_2, 0 °C to RT, 4 d	 **7g**	14	 **8g**	42
8	 **3c**	 **4d**	CH_2Cl_2, 0 °C to RT, 4 d	 **7h**	16	 **8h**	47

[a] 2 equivalents of diol **4d** and 2 equivalents of NaH were used.

disubstituted morpholines, which are the chiral cores of a wide variety of pharmacologically highly active substances.[2a–d]

Enantiopure morpholines were prepared by employing commercially available chiral amino alcohols, such as (*R*)-phenylglycinol and methyl L-serinate hydrochloride (Scheme 4 and Table 3). These β-amino alcohols were protected as the corresponding N-tosyl derivatives **11a** and **11c** by treatment with tosyl chloride, 4-(*N*,*N*-dimethylamino)pyridine (DMAP), and triethylamine,[18] and as *N*-benzyl derivative **11b** by condensation with benzaldeyde followed by reduction of the obtained oxazolidine in situ.[19] As indicated in Scheme 4, the MIRC reaction of selenones **3a–c** with **11a–c**, in the presence of sodium hydride, is suggested to initially give the carbanions **12a–e** by attack of the oxygen atoms of the aminoalcohols at the β-carbon atoms of the selenones. The subsequent proton transfer gives the nitrogen anions **13a–e**, which effected the intramolecular displacement of the $PhSeO_2$ group. The morpho-

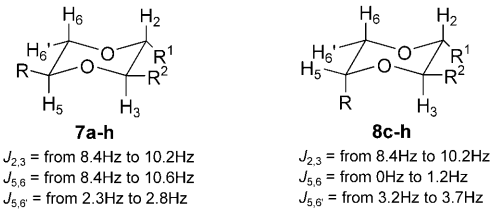
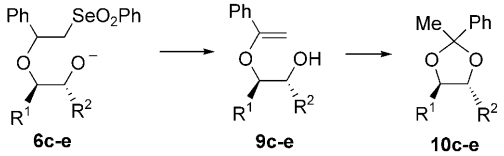


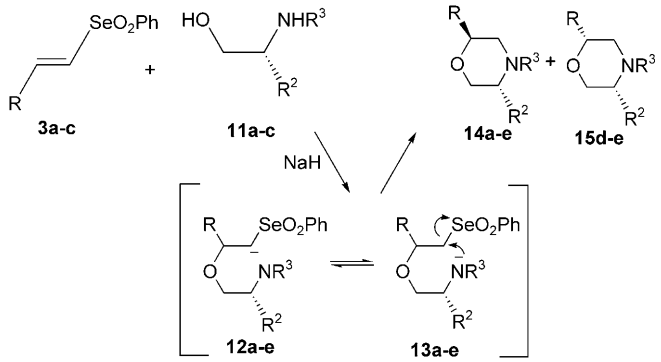
Figure 1. Coupling constants of the 1,4-dioxanes.



Scheme 3. Synthesis of acetals **10c–e**.

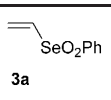
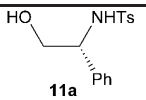
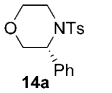
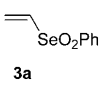
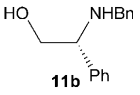
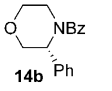
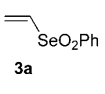
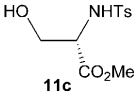
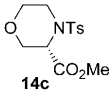
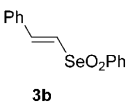
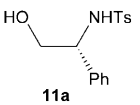
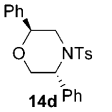
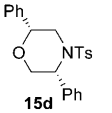
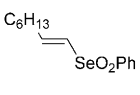
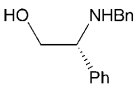
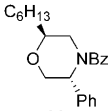
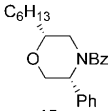
In the syntheses of 1,4-dioxanes **7c–e** and **8c–e** (Table 2, entries 3–5), the alkoxide ions **6c–e** also behave as bases[12d] and give the alkenes **9c–e**, which, on attempted purification by column chromatography on silica gel, were partially converted into the acetals **10c** (8% yield), **10d** (18% yield), and **10e** (19% yield), as shown in Scheme 3

These results encouraged us to examine the feasibility of using a similar procedure for the preparation of mono- and disubstituted morpholines **14a–e** and **15d–e** obtained, the reaction conditions, and the reaction yields, are reported in Table 3. The proposed reaction sequence could not be demonstrated unambiguously. However, the complexity of the NMR spectra of compounds **14d** and **15d** (see the Supporting Information) seems to give some support to the proposed reaction pathway. In fact, in these cases, if the initial attack was by the nitrogen atom, symmetrical compounds would be expected to form, which would generate simpler NMR spectra.



Scheme 4. Reaction of vinyl selenones with enantiopure 1,2-amino alcohols.

Table 3. Synthesis of enantiopure morpholines.[a]

Entry	Selenone	Substrate	Conditions	Product	Yield [%]	Product	Yield [%]
1	 **3a**	 **11a**	THF, 0 °C, 5 h	 **14a**	88		
2	 **3a**	 **11b**	THF, 0 °C, 4 h	 **14b**	78		
3	 **3a**	 **11c**	THF, RT, 1 d	 **14c**	87		
4	 **3b**	 **11a**	THF, reflux, 1 d	 **14d**	31	 **15d**	44
5	 **3c**	 **11b**	THF, 0 °C, 7 h	 **14e**	27	 **15e**	44

[a] Ts = tosyl, Bn = benzyl.

Starting from selenone **3a**, the enantiomerically pure morpholines **14a–c** (Table 3, entries 1–3) were obtained in excellent yields. The absolute configurations of the carbon atoms in the 3-positions were clearly unchanged with respect to those of the starting aminoalcohols **11a–c**.

As shown in Figure 2, the vicinal coupling constants indicate that the substituents at C-3 occupy axial positions in the N-tosyl morpholines **14a** and **14c**,[6a] and equatorial position in the N-benzyl morpholine **14b**.

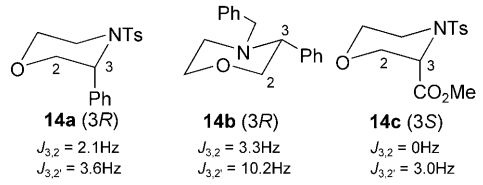


Figure 2. Coupling constants of morpholines **14a–c**.

The possibility of removing the protecting group increases the importance of the present method for the synthesis of optically active morpholines.[6a,20]

Starting from the selenones **3b** and **3c**, a mixture of two diastereoisomeric N-tosyl-morpholines **14d** and **15d**, and N-benzyl morpholines **14e** and **15e**, respectively, were formed in very good yields (Table 3, entries 4 and 5). These were separated and isolated in enantiomerically pure form after column chromatography. All of the protons of compounds **14d**, **14e**, **15d**, and **15e** could be assigned by analysis of the NMR ^{1}H–^{1}H-COSY and HMQC spectra. The absolute configurations at the carbon atoms in the 5-positions of these morpholines were clearly unchanged with respect to those of the starting aminoalcohols **11a** and **11b** (Table 3, entries 4 and 5). As indicated in Figure 3, the vicinal coupling constants suggest that the phenyl group at C-5 occupies an equatorial position in compounds **14d**,[21] **14e**, and **15e** and an axial position in compound **15d**. Assuming a chair conformation, the indicated absolute configurations of the newly generated stereogenic centers at the C-2 carbon atoms can be suggested on the basis of the values of the vicinal coupling constants between the proton H-2 and the two protons in the 3-positions. The enantiomeric purities of all the 1,4-morpholines **14a–e** and **15d–e** were confirmed by HPLC analysis using the chiral column Chiralpak AD-H.

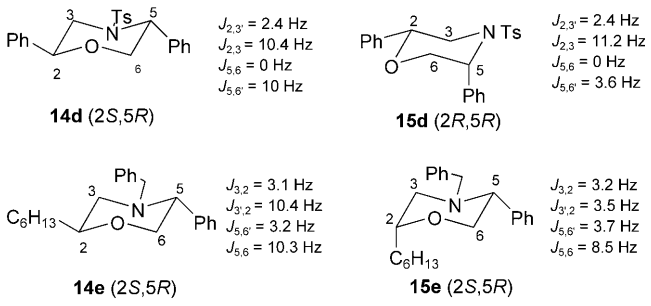
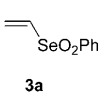
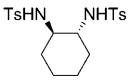
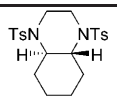
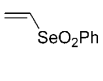
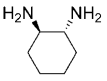
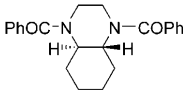
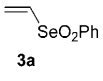
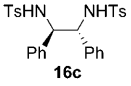
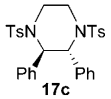
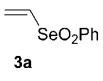
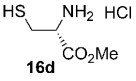
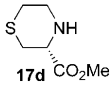
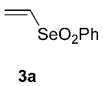
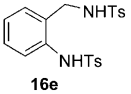
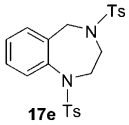
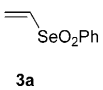
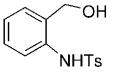
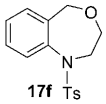


Figure 3. Coupling constants of morpholines **14d**, **14e** and **15d**, **15e**.

In the light of the satisfactory results described above, we extended this method to the synthesis of other pharmacologically important heterocyclic compounds. Experiments were therefore carried out to effect the preparation of piperazines, which are a framework observed in a large number of compounds,[2e] starting from 1,2-diamine **16b** or from the

corresponding tosylamides **16a** and **16c** and employing the vinyl selenone **3a** (Table 4, entries 1–3). In the case of cyclohexanediamine **16b**, the piperazine **17b** was isolated after benzoylation.[6a]

Table 4. Synthesis of enantiopure piperazines, thiomorpholine, benzodiazepine, and benzoxazepine.

Entry	Selenone	Substrate	Conditions	Product	Yield [%]
1	 **3a**	 **16a**	NaH, CH_2Cl_2, 0 °C to RT, 15 h	 **17a**	99
2	 **3a**	 **16b**	NaH,CH_2Cl_2, 0 °C to RT, 15 h[a]	 **17b**	45
3	 **3a**	 **16c**	DBU, toluene, 0 °C to RT, 15 h[b]	 **17c**	57
4	 **3a**	 **16d**	Et_3N, CH_2Cl_2, 0 °C to RT, 15 h[c]	 **17d**	92
5	 **3a**	 **16e**	NaH, CH_2Cl_2, 0 °C to RT, 24 h[d]	 **17e**	80
6	 **3a**	 **16f**	NaH, CH_2Cl_2, 0 °C to RT, 2 d[e]	 **17f**	80

[a] Isolated after benzoylation.[6a] [b] A second equivalent of selenone was added and 3 equiv of DBU were used. [c] 2.8 equiv of Et_3N were used. [d] 3.5 equiv of NaH were used. [e] 5.5 equiv of NaH were used.

By using a similar procedure, reactions were also carried out starting from β-aminothiol **16d** and vinyl selenone **3a**. The expected thiomorpholine **17d** was obtained in excellent yield using triethylamine as base (Table 4, entry 4).

Finally, we applied this procedure to the synthesis of seven-membered 1,4-heterocycles fused to an aromatic group, such as 1,4-benzodiazepine. These compounds present interesting therapeutic activities,[22] including dampening of the central nervous system, and can act as a muscle relaxant. Employing the *N*-tosyl-1,3-diamine **16e** and the *N*-tosyl-1,3-amino alcohol **16f**, the 1,4-benzodiazepine **17e** and 1,4-benzoxazepine **17f**, respectively, were obtained in excellent yields (Table 4, entries 5 and 6).

Conclusion

A novel and concise synthetic route to enantiomerically pure substituted 1,4-dioxanes, morpholines, and piperazines starting from vinyl selenones and commercially available enantiopure 1,2-diols, amino alcohols, and diamines is described. This simple one-step procedure can also be extended to the preparation of enantiomerically pure thiomorpholines, 1,4-benzoxazepine, and 1,4-benzodiazepine. All of these compounds have very important applications in medicinal chemistry.[2] Owing to the ready availability of the starting material and to the extremely simple operational procedure, the present method compares favorably with other methods reported in the literature. Moreover, the present investigation represents the first example of the use of vinyl selenones in the synthesis of six- or seven-membered heterocyclic rings through a MIRC reaction.

Experiments in which more substituted vinyl selenones are used as starting products are under investigation in our laboratory

Experimental Section

General: All new compounds were characterized by GC-MS and ^1H and ^{13}C NMR spectroscopic analyses. ^1H and ^{13}C NMR spectra were recorded at 400 and 100.62 MHz, respectively, with a Bruker DRX 400 instrument. Unless otherwise specified, $CDCl_3$ was used as the solvent; *J* values are given in Hertz. GC analyses and MS spectra were recorded with an HP 6890 gas chromatograph (25 m dimethyl silicone capillary column) equipped with an HP 5973 Mass-Selective Detector at an ionizing voltage of 70 eV. For the ions containing selenium, only the peaks arising from the selenium-80 isotope are given. Optical rotations were measured in a 50 mm cell with a Jasco DIP-1000 digital polarimeter. Enantiomeric purity was determined by HPLC performed with a HP 1100 instrument equipped with a chiral column (Chiralpack AD-H column) and a UV detector. Elemental analyses were carried out with a Carlo Erba 1106 Elemental Analyzer. Flash column chromatography was performed using Merk silica gel 60 (230–400 mesh).

Starting materials: Vinylselenones **3a–c** were prepared according to the procedure reported by us previously (Scheme 1).[13–17] Enantiopure monosubstituted 1,2-diol **4a** and disubstituted 1,2-diols **4b–d** are commercially available. The *N*-tosyl derivatives of β-amino alcohols **11a** and **11c** were prepared by treatment of (*R*)-phenylglycinol and methyl L-serinate hydrochloride, which are both commercially available, with tosyl chloride, DMAP, and triethylamine in dichloromethane, according to the procedure described in the literature.[18] The *N*-benzyl derivative of β-amino alcohol **11b** was prepared by condensation of (*R*)-phenylglycinol with benzaldeyde followed by reduction of the obtained oxazolidine in situ.[19]

General procedure for the synthesis of dioxanes 7a–h and 8c–h: A stirred solution of enantiopure diol **4a–d** (1 mmol) in CH_2Cl_2 (6 mL) was treated with NaH (1.2 mmol) at 0 °C under argon (see differences in Table 2, entry 5). After 10 min, a solution of vinyl selenone **3a–c** (1.2 mmol) in CH_2Cl_2 (3 mL) was added and the reaction was allowed to warm to RT and stirred for the times indicated in the Table 2. The reaction mixture was poured into aqueous ammonium chloride and extracted with CH_2Cl_2, washed with water and brine, dried over Na_2SO_4, filtered, and evaporated under vacuum. Reaction products were obtained in pure form after flash column chromatography of the residue on silica gel. The reaction products **7a–h** and **8c–h** and the reaction yields are reported in Table 2. Starting from selenone **3b**, the acetals **10c–e** were also obtained

(Scheme 3). Physical and spectral data for 1,4-dioxane **7a–h**, **8c–h**, and the acetal **10e** are reported in the Supporting Information, for acetals **10c**[23] and **10d**,[24] see the literature.

General procedure for the synthesis of morpholines 14a–e and 15d–e: A stirred solution of enantiopure N-protected amino alcohols **11a–c**[18,19] (1 mmol) in THF (7 mL) was treated with NaH (1.2 mmol) at 0°C under argon. After 10 min, a solution of vinyl selenone **3a–c** (1.7 mmol) in THF (3 mL) was added and the reaction was stirred for the times and at the temperatures indicated in Table 3. The reaction mixture was poured into aqueous ammonium chloride and extracted with diethyl ether, washed with water and brine, dried over Na_2SO_4, filtered, and evaporated under vacuum. Reaction products were obtained in pure form after column chromatography of the residue on silica gel The reaction products and the reaction yields are reported in Table 3. Physical and spectral data for compounds **14a–e** and **15d–e** are reported in the Supporting Information.

General procedure for the synthesis of 17a–d, 17e, and 17f: A stirred solution of enantiopure 1,2-diammine **16b** or the corresponding tosylamides **16a** and **16c** (1 mmol) was treated with NaH (1.2 mmol) in CH_2Cl_2 (10 mL) at 0°C under argon (for the reaction of compound **16c** see Table 4). After 10 min, a solution of vinyl selenone **3a** (1.2 mmol) was added and the reaction was stirred and allowed to warm to RT for 15 h. The reaction mixture was poured into aqueous ammonium chloride and extracted with CH_2Cl_2, washed with water and brine, dried over Na_2SO_4, filtered, and evaporated under vacuum. The piperazine **17b** was isolated after benzoylation.[6a] The thiomorpholine **17d**, 1,4-benzodiazepine **17e**, and 1,4-benzoxazepine **17f** were synthesized by the same conditions reported in the literature.[6] Reaction products were obtained in pure form after flash column chromatography of the residue on silica gel. The reaction products and the reaction yields are reported in Table 4. Physical and spectral data are reported in the Supporting Information.

Acknowledgements

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