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Effects of Methoxy Substituents on the Glutathione Peroxidase-like Activity of Cyclic Seleninate Esters

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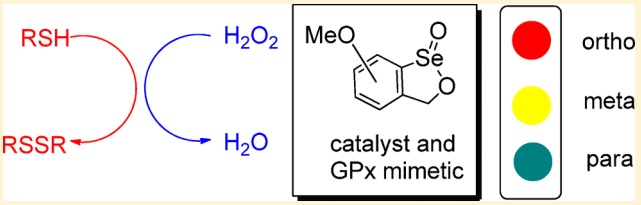
Supporting Information

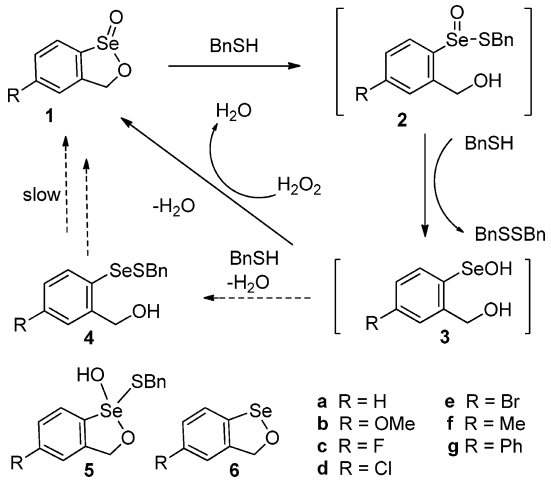
ABSTRACT: Cyclic seleninate esters function as mimetics of the antioxidant enzyme glutathione peroxidase and catalyze the reduction of hydrogen peroxide with a stoichiometric thiol. While a single electron-donating methoxy substituent *para* to the selenium atom enhances the catalytic activity, *m*-methoxy groups have little effect and *o*-methoxy substituents suppress activity. The effects of multiple methoxy groups are not cumulative. This behavior can be rationalized by opposing mesomeric and steric effects. Oxidation of the product disulfide via its thiolsulfinate was also observed.



Glutathione peroxidase (GPx)[1,2] plays a vital antioxidant role in human physiology. It consists of a family of seven isozymes, five of which contain the element selenium in the form of selenocysteine residues.[3] The structure of bovine erythrocyte GPx was first elucidated by Epp, Ladenstein, and Wendel,[4] who established that it consists of a homotetrameric structure, in which each of the four subunits contains a redox-active selenocysteine moiety. GPx functions by catalyzing the reduction of hydrogen peroxide or lipid peroxides with the tripeptide thiol glutathione. This mitigates the contribution of peroxides and related reactive oxygen species (ROS) to the deleterious effects of oxidative stress.[3] The latter has, in turn, been implicated in diverse disorders and disease states, including inflammation, mutagenesis and cancer, neurodegeneration and dementia, cardiovascular disease, and possibly the aging process.[5] Oxidative stress plays an especially detrimental role during ischemic reperfusion of heart attack and stroke patients, where ROS produced by neutrophils result in significant cardiovascular and neurological damage.[6] A catalytic cycle for GPx was first proposed by Ganther and Kraus,[7] where a selenocysteine selenol group serves to reduce the peroxide. The resulting selenenic acid is then recycled back to the selenol through sequential reaction with two molecules of glutathione via the corresponding selenenyl sulfide. Since the protective effect of GPx can be overwhelmed by conditions of exceptionally high oxidative stress, such as during ischemic reperfusion, considerable effort has been expended on the discovery of small molecule mimetics of the selenoenzyme.[5a,8] Two compounds, ebselen[9] and ALT 2074,[6g,10] reached phase III and II clinical trials, respectively, for the treatment of various disorders related to oxidative stress.

We,[11] and Singh et al.,[12] have previously studied cyclic seleninate esters such as **1** as potential GPx mimetics. The catalytic cycle we proposed for this class of compounds, employing benzyl thiol as a surrogate for glutathione and hydrogen peroxide as the oxidant, is shown in Scheme 1 and proceeds via the thiolseleninate **2** and selenenic acid **3**. We also

Scheme 1



observed that the formation of selenenyl sulfides such as **4** (R = H) dominates at high thiol:peroxide ratios and results in a competing deactivation pathway, where the corresponding selenenyl sulfide is relatively inert to further oxidation.[11b,c,e] Computational studies on a simpler aliphatic analogue of **1** by Bayse and Ortwine[13] indicated that a selenurane intermediate analogous to **5** is formed during the initial thiolysis step in Scheme 1, resulting in the formation of **2**. Moreover, they confirmed that the selenenate ester corresponding to **6** is a viable intermediate during the reconversion of the selenenic acid analogous to **3** back to its initial cyclic seleninate ester. During our earlier investigations, we also observed that electron-donating groups *para* to the selenium atom enhanced the catalytic activity of seleninates **1**, whereas electron-

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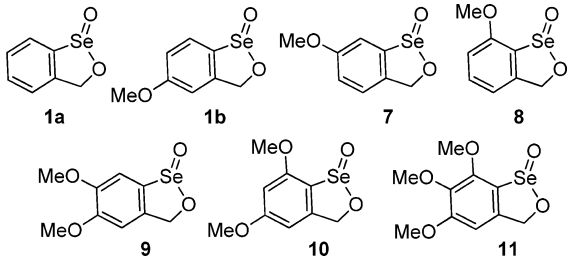
withdrawing groups suppressed it. A Hammett plot of seleninate esters **1** provided the reaction constant $\sigma = -0.45$, consistent with a rate-determining step where the transition state is associated with an increase in positive charge that can be stabilized mesomerically by electron-donating substituents, as in the step where Se(II) in **3** (or **6**) is oxidized to Se(IV) in **1**.[11d]

In view of the salutary effect of the *p*-methoxy substituent of **1b**, we embarked on a more extensive study of the effects of methoxy substituents, including their incorporation at the *ortho* and *meta* positions relative to the selenium center, as well as the possibility of cumulative effects in di- and trimethoxy-substituted analogues. Toward this objective, we prepared the novel cyclic seleninate esters **7**−**11** (Chart 1) and measured their catalytic activity by means of an *in vitro* assay reported previously.[11] The known compounds **1a**[11c,12a] and **1b**[11d] were included for comparison.

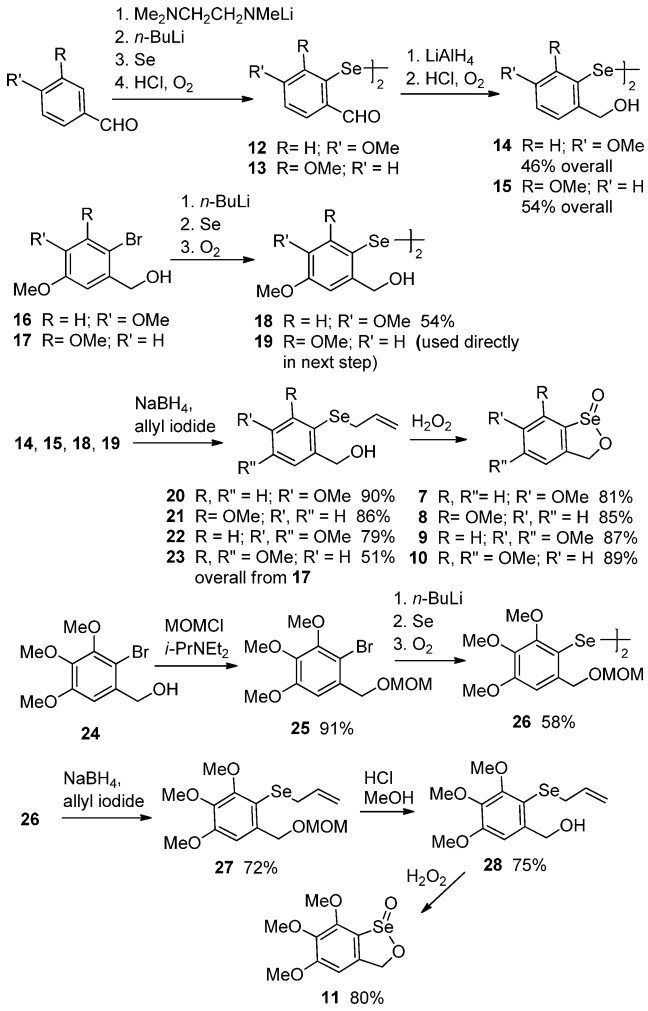
Chart 1



Methoxy groups *ortho* and *para* to the selenium atom might be expected to enhance catalytic activity through mesomeric electron donation, which generally outweighs their electron-withdrawing inductive effects, while *o*-methoxy substituents could also affect rates through steric or coordination effects. On the other hand, *meta*-substituted methoxy groups cannot interact directly with the selenium atom through resonance, but can retain their electron-withdrawing inductive effects, thereby possibly reducing catalytic activity.[14] Compounds **7**−**11** were made to test the relative contributions of these effects. In related work, Mugesh and co-workers studied ebselen,[9n] as well as diaryl diselenides[15] containing methoxy groups present at either the *ortho* or *para* position relative to the selenium atom. In the diselenides, *p*-methoxy groups had little effect on activity when benzenethiol was used as the stoichiometric reductant, whereas *o*-methoxy substituents improved catalytic activity. The latter effect was attributed to steric suppression of unproductive thiol exchange reactions at selenium that compete with thiol attack at the sulfur atom in the corresponding selenenyl sulfides, which were postulated as intermediates. Wirth[16] also reported the GPx activity of a series of diaryl diselenides, where a *p*-methoxy substituent improved GPx-like activity, whereas *o*-hydroxymethyl or *o*-methoxymethyl substituents suppressed it. Coordination effects can also play a promotive role when *O*- or *N*-containing *ortho* substituents are present in various types of organoselenium compounds.[9n,12,17]

The synthesis of *m*- and *o*-monomethoxy seleninate esters **7**−**8** via the corresponding diselenides **14** and **15** is shown in Scheme 2. The introduction of selenium was accomplished by *ortho*-metalation of *p*- or *m*-anisaldehyde via the method of Comins and Brown,[18] followed by reaction with elemental selenium and exposure to air to afford diselenides **12** and **13**, respectively. It proved more expedient to reduce the crude

Scheme 2



products directly with lithium aluminum hydride, again followed by aerial oxidation, to afford the desired hydroxymethyl diselenides **14** and **15**. Diselenides **18** and **19** were prepared more efficiently by transmetalation of the corresponding 2-bromobenzyl alcohols **16** and **17**, respectively, while direct transmetalation and selenization of bromide **24** required prior protection as the methoxymethyl (MOM) ether **25**.

Direct oxidation of diselenides **14**, **15**, **18**, and **19** to the desired cyclic seleninate esters **7**−**10** with hydrogen peroxide afforded relatively low yields of impure products. However, the conversion of the diselenides to the easily purified allyl selenides **20**−**23**, followed by one-pot oxidation with excess hydrogen peroxide, [2,3]sigmatropic rearrangement, and further oxidation,[11] afforded the desired products **7**−**10**, respectively. Diselenide **26** was obtained and treated similarly, except that deprotection of the MOM group was effected prior to oxidation to the cyclic seleninate ester **11**.

It is worth noting that the cyclic seleninate esters all showed nonequivalent methylene proton signals because of the presence of the chiral selenium atom. In contrast, the related spirodioxyselenuranes **29**,[11c,d,19] which are also chiral, displayed the expected AB quartets at low temperature, which coalesced to singlets at ca. room temperature and, unexpectedly, split into new AB quartets upon further heating, as a result of temperature-dependent chemical shifts of the *exo* and *endo* protons.[20,21]

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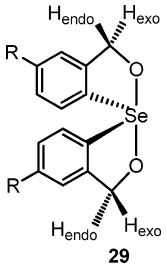

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The catalytic activities of compounds **1a**, **1b**, and **7**−**11** were then measured in our previously described assay,[11,22] in which benzyl thiol was oxidized with excess hydrogen peroxide in the presence of 10 mol % of the catalyst. The formation of dibenzyl disulfide was monitored by HPLC, and the resulting $t_{1/2}$ values are shown in Table 1. Kinetic plots of disulfide formation vs time for catalysts **7**−**11** in the table are provided in the Supporting Information. Similar data for **1a** and **1b** were reported previously.[11d] A control reaction with no catalyst produced a $t_{1/2}$ of >170 h under the same conditions.

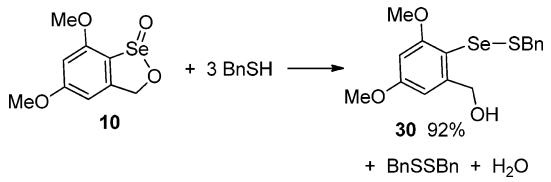
Table 1. Catalytic Activity of Methoxy-Substituted Cyclic Seleninate Esters

entry	compound	MeO substituent(s)[a]	$t_{1/2}$ (h)
1	**1a**	none	53
2	**1b**	*p*	38
3	**7**	*m*	50
4	**8**	*o*	70
5	**9**	*m,p*	49
6	**10**	*o,p*	55
7	**11**	*o,m,p*	45

[a]Indicated position is relative to the Se atom; *m* refers to that *meta* position that is also *para* to the CH_2O substituent.

It can be seen that the introduction of a *p*-methoxy substituent into the unsubstituted seleninate ester **1a** improved the catalytic activity significantly in **1b** (entries 1 and 2), which can be attributed to the electron-donating mesomeric effect of the *p*-methoxy group that stabilizes the developing positive charge on the selenium atom during its oxidation from Se(II) to Se(IV) in the rate-determining step. On the other hand, the *m*-methoxy substituent of **7** in entry 3, where such a mesomeric effect is precluded, had almost no effect upon catalytic activity. Despite the possible resonance interaction between the *o*-methoxy group and the selenium atom in **8** (entry 4), this derivative displayed considerably attenuated activity, suggesting that the mesomeric effect is overwhelmed by steric inhibition of the process. This behavior is in contrast to that observed by Mugesh et al.[15] in the case of substituted diaryl diselenides, where *o*-methoxy substituents enhanced reactivity. In order to determine whether the effect of additional methoxy substituents would be additive to the promotive effect of the *p*-methoxy substituent in **1b**, we also tested the disubstituted seleninates **9** and **10** (entries 5 and 6), as well as the trisubstituted derivate **11** (entry 7). The *m,p*-disubstituted and *o,m,p*-trisubstituted compounds (entries 5 and 7) proved slightly superior to the unsubstituted derivative **1a** (entry 1), whereas the *o,p*-dimethoxy product (entry 6) had essentially the same catalytic activity as **1a**. Surprisingly, however, seleninates **9**−**11** all showed decreased catalytic activity compared to the *p*-monomethoxy compound **1b** (entry 2). Furthermore, in the case of **10**, the formation of the disulfide essentially stopped at ca. 50% completion,[23] followed by a significant decrease in its concentration. This behavior was attributed to the accumulation of the corresponding selenenyl sulfide **30**, which was identified while monitoring the reaction by HPLC.[24] An authentic sample of **30** was prepared by thiolysis of the seleninate **10** in the absence of hydrogen peroxide (Scheme 3)

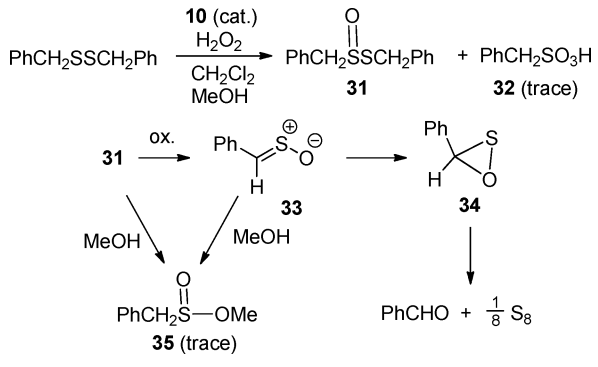
Scheme 3



in order to confirm this assignment. Selenenyl sulfide **30** was then independently subjected to the assay of its catalytic activity under the usual conditions, providing a $t_{1/2}$ value of 69 h, thus confirming that it is a poorer catalyst than **10** itself.[25] The slow rates of disulfide formation with the *o*-substituted catalysts **8** and **10** may, therefore, be due to steric suppression of the normally rate-limiting oxidation of species corresponding to **3** and **6** in Scheme 1. This results in increased formation of the corresponding less reactive selenenyl sulfides, which then slowly re-enter the catalytic cycle by disproportionation to the corresponding diselenides and disulfides, with reoxidation of the former back to the cyclic seleninates, or by oxidation to the corresponding thiolseleninates (analogous to **2** in Scheme 1) and cyclization to regenerate **8** or **10**.[12c]

To our knowledge, the late stages (beyond 50% completion) of the catalytic cycle of cyclic seleninate esters have not yet been explored. When the assay of **10** was conducted at a higher temperature (24 °C instead of 18 °C) and monitored beyond 50% completion, the concentration of disulfide decreased dramatically, as shown in the Supporting Information. This indicated that, in addition to partial deactivation of the catalyst through selenenyl sulfide formation, further oxidation of the disulfide was also taking place. Confirmation of this hypothesis was provided by the identification of substantial new HPLC peaks attributed to the thiolsulfinate **31** and benzaldehyde (Scheme 4). Trace amounts of benzyl sulfonic acid (**32**) and methyl benzylsulfinate (**35**) were also detected. The identification of these compounds was verified by analysis of the late-stage reaction by HPLC−HRMS and comparison with the retention times and mass spectra of authentic samples of the four new products (see the Supporting Information).

Scheme 4



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Since cyclic seleninate esters are known to catalyze the oxidation of sulfides to sulfoxides with hydrogen peroxide,[26] it is reasonable to expect that a similar process produces **31** from dibenzyl disulfide in the later stages of the reaction, where the disulfide is abundant and competes with the more reactive, but now depleted, thiol. Furthermore, thiolsulfinate **31** is known to generate, inter alia, the corresponding sulfinic acid and sulfine **33** upon further oxidation.[27,28] The presence of benzyl sulfinic acid could not be confirmed in the present reaction mixture, but its further oxidation to the observed sulfonic acid **32** is plausible. Sulfines, in turn, are known to hydrolyze,[27,29,30] or rearrange to oxathiiranes, followed by extrusion of sulfur,[29,31] to produce carbonyl compounds, thus providing a rationale for the formation of benzaldehyde. Methanolysis of **31** or **33** affords the sulfinate ester **35** (Scheme 4).

In conclusion, the most effective substitution pattern in the methoxy-substituted series of catalysts for the oxidation of benzyl thiol with hydrogen peroxide is the single *p*-methoxy substituent in **1b** and neither the introduction of lone methoxy groups at the *ortho* or *meta* positions (relative to selenium) nor their introduction in addition to an existing *p*-methoxy group conferred further significant improvements in catalytic activity. The presence of the *o*-methoxy group in compounds **8** and **10** proved especially deleterious, despite the expected enhancement of catalytic activity through electron donation to selenium through resonance. We attribute this behavior to steric suppression of the rate-limiting oxidation of Se(II) intermediates to Se(IV), along with enhanced formation of the less catalytically active selenenyl sulfide **30**. It was also found that, in the case of the *o*,*p*-dimethoxy compound **10**, significant further oxidation of the product dibenzyl disulfide occurred in later stages of the catalytic process, as evidenced by the formation of the corresponding thiolsulfinate **31** and benzaldehyde, along with traces of benzyl sulfonic acid and the methyl sulfinate **35**.

EXPERIMENTAL SECTION

Hydrogen peroxide was titrated prior to use,[32] and benzyl thiol was redistilled. Starting materials **16**, **17**, and **24** are commercially available but were also prepared by bromination of the corresponding benzyl alcohols by standard methods. Authentic samples of thiolsulfinate **31**,[33,34] sulfonic acid **32**,[35] and sulfinate ester **35**[36] were prepared by literature methods.

Spectroscopic Experiments. ^{1}H NMR spectra were recorded at 400 MHz, while ^{13}C and ^{77}Se NMR spectra were obtained at 101 and 76 MHz, respectively. Chemical shifts of ^{77}Se NMR spectra were obtained with diphenyl diselenide in $CDCl_3$ (463.0 ppm)[37] as the standard, relative to dimethyl selenide (0.0 ppm). High-resolution mass spectra were obtained using a time-of-flight (TOF) analyzer with electron impact (EI) ionization or a quadrupole TOF analyzer with electrospray ionization (ESI).

HPLC Assay for Catalytic Activity. Catalytic activity was measured by adding the catalyst (0.031 mmol, 10 mol % relative to thiol) to a mixture of hydrogen peroxide (0.035 M) and redistilled benzyl thiol (0.031 M) in 10.0 mL of dichloromethane−methanol (95:5) while maintaining the temperature at 18 °C. The reactions were monitored by HPLC analysis, using a UV detector at 254 nm and a reversed phase column (Novapak C18; 3.9 × 150 mm). Acetonitrile−water was employed as the solvent (gradient: 60:40 to 80:20 over 15 min with a flow rate of 0.9 mL/min). Naphthalene (0.0080 M) was employed as the internal standard. The values of $t_{1/2}$ were determined by plotting the yield (%) of the product disulfide vs time and represent the time required for conversion of 50% of the thiol into its disulfide. The $t_{1/2}$ values are the average of at least two runs.

HPLC−MS Analysis. The same HPLC column and solvent system as above were employed, except that the gradient was altered as required to better separate individual peaks for exact mass measurement. The mass spectra were obtained by ESI with a quadrupole TOF analyzer.

(2-{[2-(Hydroxymethyl)-5-methoxyphenyl]diselanyl}-4-methoxyphenyl)methanol (14). A solution of *N*,*N*,*N*′-trimethylethylenediamine (0.840 mL, 660 mg, 6.46 mmol) in 20 mL of dry THF was cooled to −20 °C under nitrogen, and *n*-butyllithium (2.6 mL, 2.4 M, 6.2 mmol) was added. After 15 min, 4-methoxybenzaldehyde (0.73 mL, 0.82 g, 6.0 mmol) was added, and the mixture was left at −20 °C for an additional 15 min. A second portion of *n*-butyllithium (2.6 mL, 2.4 M 6.2 mmol) was then added, and the mixture was warmed to 0 °C and left for 1.5 h. Elemental selenium (553 mg, 7.00 mmol) was quickly introduced, and the nitrogen atmosphere was restored. The mixture was warmed to room temperature, stirred for an additional 3 h, and then poured into a mixture of 30 mL of 1 M HCl and 30 mL of ethyl acetate. Air was rapidly bubbled through the mixture for 30 min, and the mixture was extracted with ethyl acetate, washed with brine, dried, and concentrated under reduced pressure to afford crude diselenide **12** (1.27 g) as a red solid.

The above product was suspended in 10 mL of dry THF and added to a suspension of lithium aluminum hydride (750 mg, 19.8 mmol) in 40 mL of THF at 0 °C. The mixture was warmed to room temperature and stirred for an additional 4 h. It was then cooled to 0 °C and carefully quenched with water. Ethyl acetate was added, and the resulting slurry was filtered to remove the solid precipitate. The aqueous layer from the filtrate was extracted with ethyl acetate, and the aqueous layer was stirred in the presence of air for 12 h. During this time, diselenide **14** crystallized as a yellow solid (595 mg, 46% overall); mp 101−102 °C (from ethyl acetate−hexanes); IR (ATR) 3301, 1602, 1468, 1245, 1009 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.27 (d, J = 8.8 Hz, 2 H), 7.26 (d, J = 2.4 Hz, 2 H), 6.80 (dd, J = 8.4, 2.8 Hz, 2 H), 4.70 (s, 4 H), 3.73 (s, 6 H), 1.88 (br s, 2 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 159.7, 134.2, 132.2, 129.9, 119.8, 114.7, 65.1, 55.5; ^{77}Se NMR (76 MHz; $CDCl_3$) δ 437.1; mass spectrum (EI-TOF) m/z (relative intensity) 434 (38, M$^+$), 215 (68), 201 (70), 108 (100); HRMS (EI-TOF) m/z (M$^+$) calcd for $C_{16}H_{18}O_4{}^{80}Se_2$: 433.9536; found: 433.9548. Anal. Calcd for $C_{16}H_{18}O_4Se_2$: C, 44.46; H, 4.20; found: C, 44.50; H, 4.15.

(2-{[2-(Hydroxymethyl)-6-methoxyphenyl]diselanyl}-3-methoxyphenyl)methanol (15). The same procedure was employed as for the preparation of **14**. Yield: 54% (overall). Yellow solid, mp 142−144 °C (from hexanes−ethyl acetate); IR (ATR) 3281, 1571, 1462, 1267, 1033 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.31 (t, J = 8.0 Hz, 2 H), 7.05 (dd, J = 7.6, 1.2 Hz, 2 H), 6.81 (dd, J = 8.4, 0.80 Hz, 2 H), 4.62 (d, J = 6.4 Hz, 4 H), 3.69 (s, 6 H), 2.24 (t, J = 6.6 Hz, 2 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 160.3, 146.3, 131.3, 121.1, 119.6, 110.6, 65.8, 56.3; ^{77}Se NMR (76 MHz; $CDCl_3$) δ 355.5; mass spectrum (EI-TOF) m/z (relative intensity) 434 (48, M$^+$), 216 (46), 200 (100), 108 (98); HRMS (EI-TOF) m/z (M$^+$) calcd for $C_{16}H_{18}O_4{}^{80}Se_2$: 433.9536; found: 433.9532. Anal. Calcd for $C_{16}H_{18}O_4Se_2$: C, 44.46; H, 4.20; found: C, 44.38; H, 4.32.

(2-{[2-(Hydroxymethyl)-4,5-dimethoxyphenyl]diselanyl}-4,5-dimethoxyphenyl)methanol (18). 2-Bromo-4,5-dimethoxybenzyl alcohol (3.13 g, 12.7 mmol) was dissolved in 130 mL of dry THF and cooled to −78 °C under nitrogen. *n*-Butyllithium (14.3 mL, 2.00 M, 28.6 mmol) was added, and the mixture was warmed to 0 °C over 45 min. Elemental selenium (2.25 g, 28.5 mmol) was added, and the nitrogen atmosphere was restored. The mixture was stirred for 3 h at room temperature and was then quenched with 80 mL of saturated ammonium chloride solution. Air was rapidly bubbled through the mixture for 30 min, and the mixture was washed with brine, dried, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (gradient of hexanes−ethyl acetate, 2:1 to 100% ethyl acetate) to afford 1.67 g (54%) of diselenide **18** as a yellow solid, mp 148−150 °C (from ethyl acetate); IR (ATR) 3349, 1584, 1494, 1259, 1213, 1150, 1032 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.01 (s, 2 H), 6.98 (s, 2 H), 4.60 (s, 4 H), 3.89 (s, 6 H), 3.76 (s, 6 H), 2.08 (br s, 2 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 150.6, 148.4, 137.2, 120.7, 120.0, 111.6, 65.3, 56.2, 56.1; ^{77}Se NMR (76 MHz; $CDCl_3$) δ 467.6; mass spectrum (EI-TOF) m/z (relative intensity) 494 (9, M$^+$), 245

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(20), 230 (24), 138 (100); HRMS (EI-TOF) m/z (M^+) calcd for $C_{18}H_{22}O_6{}^{80}Se_2Na$ (ESI, M + Na^+): 516.9639; found: 516.9642.

(2-{[2-(Hydroxymethyl)-4,6-dimethoxyphenyl]diselanyl}-3,5-dimethoxyphenyl)methanol (19). 2-Bromo-3,5-dimethoxybenzyl alcohol (1.00 g, 4.05 mmol) was dissolved in 50 mL of dry THF and cooled to −78 °C under a nitrogen atmosphere. *n*-Butyllithium (3.7 mL, 2.4 M, 8.9 mmol) was added, and the mixture was warmed to room temperature over 1 h. Elemental selenium (355 mg, 4.50 mmol) was added, and the nitrogen atmosphere was restored. The mixture was stirred at room temperature for an additional 3 h and was then quenched with 30 mL of saturated ammonium chloride solution. Air was rapidly bubbled through the mixture for 30 min, and the mixture was washed with brine, dried, and concentrated under reduced pressure. Flash chromatography (100% ethyl acetate) provided an inseparable mixture of diselenide **19** and the corresponding selenide in the ratio of ca. 3:1. This mixture was used in subsequent steps without further purification, as it was easier to separate the selenide at a later stage.

Typical Procedure for the Preparation of Allyl Aryl Selenides: [4-Methoxy-2-(prop-2-en-1-ylselanyl)phenyl]-methanol (20). Diselenide **14** (200 mg, 0.463 mmol) was dissolved in 18 mL of THF−ethanol (5:1) and cooled to 0 °C. Sodium borohydride (122 mg, 3.22 mmol) was added, followed after 5 min by allyl iodide (0.145 mL, 266 mg, 1.58 mmol). The mixture was stirred at room temperature for an additional 3 h and was then quenched with 15 mL of water. The mixture was extracted with ethyl acetate, washed with brine, dried, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (hexanes−ethyl acetate, 2:1) to afford 215 mg (90%) of the product **20** as a colorless oil; IR (neat) 3438, 1600, 1476, 1233, 1038 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.26 (d, J = 8.4 Hz, 1 H), 7.06 (d, J = 2.8 Hz, 1 H), 6.76 (dd, J = 8.4, 2.8 Hz, 1 H), 5.97−5.87 (m, 1 H), 4.99 (ddt, J = 16.9, 2.6, 1.3 Hz, 1 H), 4.96−4.93 (m, 1 H), 4.65 (d, J = 6.0 Hz, 2 H), 3.77 (s, 3 H), 3.49 (br d, J = 7.6 Hz, 2 H), 2.54 (t, J = 6.2 Hz, 1 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 159.1, 135.0, 134.2, 131.1, 129.6, 119.7, 117.3, 112.9, 64.8, 55.4, 30.8; ^{77}Se NMR (76 MHz; $CDCl_3$) δ 269.0; mass spectrum (EI-TOF) m/z (relative intensity) 258 (64, M^+), 217 (96), 159 (30), 135 (36), 108 (100); HRMS (EI-TOF) m/z (M^+) calcd for $C_{11}H_{14}O_2{}^{80}Se$: 258.0159; found: 258.0160. Anal. Calcd for $C_{11}H_{14}O_2Se$: C, 51.37; H, 5.49; found: C, 51.33; H, 5.63.

[3-Methoxy-2-(prop-2-en-1-ylselanyl)phenyl]methanol (21). Prepared from diselenide **15** by the same procedure as for **20**. Yield: 86%. Colorless oil; IR (neat) 3462, 1633, 1567, 1471, 1248, 1176 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.30 (t, J = 8.0 Hz, 1 H), 7.03 (dd, J = 7.6, 0.8 Hz, 1 H), 6.84 (dd, J = 8.2, 1.0 Hz, 1 H), 5.90−5.79 (m, 1 H), 4.84−4.82 (m, 1 H), 4.79 (br s, 1 H), 4.77 (d, J = 6.8 Hz, 2 H), 3.90 (s, 3 H), 3.48 (d, J = 7.6 Hz, 2 H), 2.50 (t, J = 6.6 Hz, 1 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 160.1, 146.1, 134.9, 130.0, 121.1, 117.0, 116.5, 110.4, 66.1, 56.2, 30.0; ^{77}Se NMR (76 MHz; $CDCl_3$) δ 178.4; mass spectrum (EI-TOF) m/z (relative intensity) 258 (100, M^+), 217 (72), 199 (32), 108 (90); HRMS (EI-TOF) m/z (M^+) calcd for $C_{11}H_{14}O_2{}^{80}Se$: 258.0159; found: 258.0157. Anal. Calcd for $C_{11}H_{14}O_2Se$: C, 51.37; H, 5.49; found: C, 51.39; H, 5.50.

[4,5-Dimethoxy-2-(prop-2-en-1-ylselanyl)phenyl]methanol (22). Prepared from diselenide **18** by the same procedure as for **20**. Yield: 79%. Brown oil; IR (neat) 3490, 1602, 1498, 1267, 1148, 1036 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.04 (s, 1 H), 6.94 (s, 1 H), 5.92−5.81 (m, 1 H), 4.87−4.79 (m, 2 H), 4.69 (s, 2 H), 3.83 (s, 3 H), 3.82 (s, 3 H), 3.36 (d, J = 7.2 Hz, 2 H), 2.54 (br s, 1 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 149.3, 148.1, 137.0, 134.6, 119.5, 118.9, 116.8, 111.6, 65.3, 56.1, 55.9, 31.9; ^{77}Se NMR (76 MHz; $CDCl_3$) δ 273.1; mass spectrum (EI-TOF) m/z (relative intensity) 288 (27, M^+), 247 (24), 138 (100); HRMS (EI-TOF) m/z (M^+) calcd for $C_{12}H_{16}O_3{}^{80}Se$: 288.0265; found: 288.0275.

[3,5-Dimethoxy-2-(prop-2-en-1-ylselanyl)phenyl]methanol (23). Prepared from diselenide **19** by the same procedure as for **20**. Yield: 51% overall from benzyl alcohol **17**. Colorless oil; IR (neat) 3452, 1590, 1462, 1152, 1067 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 6.63 (d, J = 3.6 Hz, 1 H), 6.42 (d, J = 3.2 Hz, 1 H), 5.92−5.78 (m, 1 H), 4.83−4.75 (m, 4 H), 3.88 (s, 3 H), 3.83 (s, 3 H), 3.40 (d, J = 10.4 Hz, 2 H), 2.38 (t, J = 9.2 Hz, 1 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 161.5, 161.1, 147.2, 134.9, 116.3, 107.4, 105.0, 98.0, 66.1, 56.1, 55.4, 30.1; ^{77}Se NMR (76 MHz; $CDCl_3$) δ 162.6; mass spectrum (EI-TOF) m/z (relative intensity) 288 (52, M^+), 247 (22), 166 (100), 138 (78); HRMS (EI-TOF) m/z (M^+) calcd for $C_{12}H_{16}O_3{}^{80}Se$: 288.0265; found: 288.0262.

During chromatography of allyl selenide **23**, 50 mg of the corresponding symmetrical aryl selenide analogue of **19** was also isolated as a byproduct from the preparation of **19**. Colorless solid, mp 159−161 °C (from ethyl acetate); IR (ATR) 3252, 1586, 1462, 1310, 1157 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 6.62 (d, J = 2.4 Hz, 2 H), 6.33 (d, J = 2.4 Hz, 2 H), 4.84 (d, J = 6.4 Hz, 4 H), 3.80 (s, 6 H), 3.63 (s, 6 H), 3.31 (t, J = 6.6 Hz, 2 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 161.2, 160.5, 146.2, 110.0, 106.4, 98.8, 66.4, 56.2, 55.5; ^{77}Se NMR (76 MHz; $CDCl_3$) δ 122.8; mass spectrum (EI-TOF) m/z (relative intensity) 414 (46, M^+), 246 (44), 230 (30), 165 (100), 139 (64); HRMS (EI-TOF) m/z (M^+) calcd for $C_{18}H_{22}O_6{}^{80}Se$: 414.0582; found: 414.0598.

Typical Procedure for the Preparation of Cyclic Seleninate Esters: 6-Methoxy-3*H*-benzo[*c*]-1,2-oxaselenole-1-oxide (7). Allyl selenide **20** (186 mg, 0.723 mmol) and 29% H_2O_2 (0.260 mL, 2.2 mmol) were stirred in 10 mL of dichloromethane for 16 h. The solution was concentrated, and the resulting mixture was purified by flash chromatography (ethyl acetate-methanol, 9:1) to afford 137 mg (81%) of the cyclic seleninate ester **7** as a colorless solid, mp 148−149 °C (from ethyl acetate-methanol); IR (ATR) 1598, 1472, 1257, 1230, 1023 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.35 (d, J = 8.8 Hz, 1 H), 7.25 (d, J = 2.4 Hz, 1 H), 7.10 (dd, J = 8.4, 2.4 Hz, 1 H), 5.90 (d, J = 12.8 Hz, 1 H), 5.56 (d, J = 13.2 Hz, 1 H), 3.81 (s, 3 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 160.5, 149.3, 135.2, 123.4, 119.9, 108.9, 78.4, 55.9; ^{77}Se NMR (76 MHz; $CDCl_3$) δ 1348.5; mass spectrum (EI-TOF) m/z (relative intensity) 232 (38, M^+), 215 (24), 136 (100), 108 (46); HRMS (EI-TOF) m/z (M^+) calcd for $C_8H_8O_3{}^{80}Se$: 231.9639; found: 231.9642. Anal. Calcd for $C_8H_8O_3Se$: C, 41.58; H, 3.49; found: C, 41.40; H, 3.35.

7-Methoxy-3*H*-benzo[*c*]-1,2-oxaselenole-1-oxide (8). Prepared from allyl selenide **21** by the same procedure as for **7**. Yield: 85%. Colorless solid; mp 156−157 °C (from ethyl acetate−methanol); IR (ATR) 1567, 1468, 1275, 1068, 964 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.50 (t, J = 8.0 Hz, 1 H), 6.99 (dd, J = 7.6 Hz, 0.8 Hz, 1 H), 6.89 (d, J = 8.0 Hz, 1 H), 5.95 (d, J = 14.0 Hz, 1 H), 5.58 (d, J = 13.6 Hz, 1 H), 3.91 (s, 3 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 157.4, 146.3, 136.3, 134.7, 114.5, 110.4, 79.2, 56.2; ^{77}Se NMR (76 MHz; $CDCl_3$) δ 1341.7; HRMS (ESI-TOF) m/z (M + H)$^+$ calcd for $C_8H_9O_3{}^{80}Se$: 232.9717; found: 232.9712. Anal. Calcd for $C_8H_8O_3Se$: C, 41.58; H, 3.49; found: C, 41.66; H, 3.38.

5,6-Dimethoxy-3*H*-benzo[*c*]-1,2-oxaselenole-1-oxide (9). Prepared from allyl selenide **22** by the same procedure as for **7**. Yield: 87%. Colorless solid; mp 168−169 °C (from ethyl acetate−methanol); IR (film) 1576, 1497, 1280, 1215, 1030 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.23 (s, 1 H), 6.86 (s, 1 H), 5.89 (d, J = 13.2 Hz, 1 H), 5.52 (d, J = 13.6 Hz, 1 H), 3.91 (s, 3 H), 3.86 (s, 3 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 152.8, 150.1, 139.0, 137.0, 107.0, 104.2, 78.7, 56.37, 56.35; ^{77}Se NMR (76 MHz; $CDCl_3$) δ 1355.9; mass spectrum (EI-TOF) m/z (relative intensity) 262 (6, M^+), 166 (100), 138 (26); HRMS (ESI-TOF) m/z (M + H)$^+$ calcd for $C_9H_{11}O_4{}^{80}Se$: 262.9818; found: 262.9819. Anal. Calcd for $C_9H_{10}O_4Se$: C, 41.40; H, 3.86; found: C, 41.22; H, 4.10.

5,7-Dimethoxy-3*H*-benzo[*c*]-1,2-oxaselenole-1-oxide (10). Prepared from allyl selenide **23** by the same procedure as for **7**. Yield: 89%. Colorless solid; mp 149−151 °C (from ethyl acetate−methanol); IR (ATR) 1590, 1467, 1352, 1224, 1157 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 6.46 (d, J = 2.0 Hz, 1 H), 6.41 (d, J = 1.6 Hz, 1 H), 5.90 (d, J = 13.6 Hz, 1 H), 5.50 (d, J = 14.0 Hz, 1 H), 3.88 (s, 3 H), 3.84 (s, 3 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 165.6, 158.5, 148.1, 128.6, 98.7, 98.2, 78.9, 56.2, 56.1; ^{77}Se NMR (76 MHz; $CDCl_3$) δ 1355.1; HRMS (ESI-TOF) m/z (M + H)$^+$ calcd for $C_9H_{11}O_4{}^{80}Se$: 262.9818; found: 262.9814. Anal. Calcd for $C_9H_{10}O_4Se$: C, 41.40; H, 3.86; found: C, 41.57; H, 3.81.

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2-Bromo-3,4,5-trimethoxy-1-[(methoxymethoxy)methyl]-benzene (25). 2-Bromo-3,4,5-trimethoxybenzyl alcohol (800 mg, 2.89 mmol) was dissolved in 10 mL of dichloromethane. Diisopropylethylamine (0.610 mL, 453 mg, 3.50 mmol) was added, followed by chloromethyl methyl ether (0.265 mL, 281 mg, 3.47 mmol). After 14 h of stirring at room temperature, the mixture was poured into 20 mL of water. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (hexanes−ethyl acetate, 1:1) to afford 845 mg (91%) of the MOM-protected alcohol **25** as a colorless oil; IR (neat) 1576, 1481, 1324, 1152 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 6.87 (s, 1 H), 4.75 (s, 2 H), 4.61 (s, 2 H), 3.88 (s, 3 H), 3.864 (s, 3 H), 3.861 (s, 3 H), 3.43 (s, 3 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 152.9, 151.0, 142.6, 133.0, 109.1, 108.2, 96.3, 69.1, 61.2, 61.1, 56.3, 55.7; mass spectrum (EI-TOF) m/z (relative intensity) 320 (68, M^+), 259 (84), 181 (100); HRMS (EI-TOF) m/z (M^+) calcd for $C_{12}H_{17}{}^{79}BrO_5$: 320.0259; found: 320.0261. Anal. Calcd for $C_{12}H_{17}BrO_5$: C, 44.88; H, 5.34; found: C, 44.60; H, 5.15.

1,2,3-Trimethoxy-5-[(methoxymethoxy)methyl]-4-({2,3,4-trimethoxy-6-[(methoxymethoxy)methyl]phenyl}diselanyl)-benzene (26). Aryl bromide **25** (1.30 g, 4.69 mmol) was dissolved in 40 mL of dry THF and cooled to −78 °C under a nitrogen atmosphere. *n*-Butyllithium (3.0 mL, 1.9 M, 5.7 mmol) was added, and the mixture was warmed to 0 °C over 1.5 h. Elemental selenium (450 mg, 5.70 mmol) was quickly introduced, and the nitrogen atmosphere was restored. The mixture was warmed to room temperature, left for an additional 3 h, and then quenched with 40 mL of saturated ammonium chloride solution. Air was rapidly bubbled through the mixture for 30 min, and the mixture was washed with brine, dried, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (hexanes−ethyl acetate, 1:2) to afford 850 mg (58%) of the product **26** as a yellow oil, which was used in subsequent steps immediately.

1,2,3-Trimethoxy-5-[(methoxymethoxy)methyl]-4-(prop-2-en-1-ylselanyl)benzene (27). Prepared from diselenide **26** by the same procedure as for **20**. Yield: 72%. Colorless oil; IR (neat) 1586, 1476, 1324, 1095 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 6.87 (s, 1 H), 5.92−5.81 (m, 1 H), 4.84 (d, J = 16.8 Hz, 1 H), 4.80 (d, J = 10.4 Hz, 1 H), 4.742 (s, 2 H), 4.736 (s, 2 H), 3.93 (s, 3 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.46−3.44 (m, 2 H), 3.44 (s, 3 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 155.3, 154.1, 142.0, 137.8, 135.0, 116.3, 115.3, 108.1, 96.3, 70.4, 61.1, 61.0, 56.2, 55.7, 31.0; ^{77}Se NMR (76 MHz; $CDCl_3$) δ 197.7; mass spectrum (EI-TOF) m/z (relative intensity) 362 (80, M^+), 289 (100), 259 (25); HRMS (EI-TOF) m/z (M^+) calcd for $C_{15}H_{22}O_5{}^{80}Se$: 362.0632; found: 362.0623.

[3,4,5-Trimethoxy-2-(prop-2-en-1-ylselanyl)phenyl]-methanol (28). Allyl selenide **27** (147 mg, 0.408 mmol) was dissolved in 5 mL of methanol. Concentrated HCl (6 drops) was added, and the mixture was heated at 60 °C. After 5 h, the methanol solution was poured into 5 mL of saturated sodium bicarbonate solution. The mixture was extracted with ethyl acetate, washed with brine, dried, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (hexanes−ethyl acetate, 1:2) to afford 97 mg (75%) of the free alcohol **28** as a slightly yellow oil; IR (neat) 3424, 2929, 1590, 1481, 1319, 1100 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 6.80 (s, 1 H), 5.91−5.80 (m, 1 H), 4.85−4.82 (m, 1 H), 4.80 (m, 1 H), 4.72 (br s, 2 H), 3.92 (s, 3 H), 3.87 (s, 3 H), 3.85 (s, 3 H), 3.45 (br d, J = 7.6 Hz, 2 H), 2.48 (br s, 1 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 155.3, 154.2, 141.8, 140.7, 134.9, 116.7, 113.9, 107.9, 66.1, 61.2, 61.0, 56.1, 30.9; ^{77}Se NMR (76 MHz; $CDCl_3$) δ 194.4; mass spectrum (EI-TOF) m/z (relative intensity) 318 (54, M^+), 277 (44), 196 (30), 168 (100), 153 (34); HRMS (EI-TOF) m/z (M^+) calcd for $C_{13}H_{18}O_4{}^{80}Se$: 318.0370; found: 318.0364.

5,6,7-Trimethoxy-3*H*-benzo[*c*]-1,2-oxaselenole-1-oxide (11). Allyl selenide **28** (88 mg, 0.28 mmol) and 33% H_2O_2 (0.057 mL, 0.56 mmol) were stirred in 5 mL of dichloromethane at room temperature for 6 h. The mixture was concentrated, and the resulting solid was purified by flash chromatography (ethyl acetate−methanol, 9:1) to afford 64 mg (80%) of the cyclic seleninate ester **11**, mp 160−161 °C (from ethyl acetate−methanol); IR (ATR) 1576, 1460, 1340, 1104 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 6.62 (s, 1 H), 5.91 (d, J = 13.6 Hz, 1 H), 5.53 (d, J = 13.6 Hz, 1 H), 4.08 (s, 3 H), 3.90 (s, 3 H), 3.86 (s, 3 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 158.6, 150.6, 140.8, 140.4, 133.0, 99.8, 79.3, 61.9, 61.3, 56.6; ^{77}Se NMR (76 MHz; $CDCl_3$) δ 1360.5; mass spectrum (EI-TOF) m/z (relative intensity) 292 (20, M^+), 276 (12), 196 (100); HRMS (EI-TOF) m/z (M^+) calcd for $C_{10}H_{12}O_5{}^{80}Se$: 291.9850; found: 291.9855. Anal. Calcd for $C_{10}H_{12}O_5Se$: C, 41.25; H, 4.15; found: C, 41.31; H, 4.07.

{2-[(Benzylsulfanyl)selanyl]-3,5-dimethoxyphenyl}methanol (30). Seleninate ester **10** (131 mg, 0.502 mmol) was dissolved in dichloromethane (0.03 M) and cooled to 0 °C. Benzyl thiol (0.18 mL, 1.5 mmol) was added, and the solution was stirred for 1 h, concentrated in vacuo, and immediately chromatographed (hexanes−ethyl acetate, 6:1) to give 171 mg (92%) of **30** as a yellow solid: mp 81−83 °C; IR (film) 3385, 1569, 1449, 1379, 1260, 1110 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.29−7.21 (m, 5 H), 6.69 (d, J = 2.4 Hz, 1 H), 6.42 (d, J = 2.5 Hz, 1 H), 4.86 (s, 2 H), 4.11 (s, 2 H), 3.87 (s, 3 H), 3.84 (s, 3 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 162.7, 161.6, 147.6, 138.7, 129.2, 128.7, 127.5, 105.5, 98.2, 66.3, 56.3, 55.7, 42.7; ^{77}Se NMR (76 MHz; $CDCl_3$) δ 341.1; HRMS (ESI-TOF) m/z ($M + H$)$^+$ calcd for $C_{16}H_{19}O_3S^{80}Se$: 371.0215; found; 371.0208. Anal. Calcd for $C_{16}H_{18}O_3SSe$: C, 52.03; H, 4.91; found: C, 52.00; H, 4.73.

{[Benzylsulfanyl)sulfinyl]methyl}benzene (31).[33] The product was obtained by the method of Pratt et al.[33a] in 55% yield: white solid; mp 79−81 °C (from ether) (lit.[33c,e] mp 130 °C; lit.[33d] mp 86 °C;); IR (film); 3019, 1448, 1081, 1052 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.36−7.23 (m, 10 H), 4.32 (d, J = 12.9 Hz, 1 H), 4.28 (d, J = 13.5 Hz, 1 H), 4.26 (d, J = 12.9 Hz, 1 H); 4.24 (d, J = 13.5 Hz, 1 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 136.8, 130.6, 130.2, 129.3, 129.0, 128.9, 128.0, 62.4, 36.4; HRMS (ESI-TOF) m/z ($M + H$)$^+$ calcd for $C_{14}H_{15}OS_2$: 263.0559; found: 263.0560. Anal. Calcd for $C_{14}H_{14}OS_2$: C, 64.08; H, 5.38; found: C, 64.10; H, 5.42.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H, ^{13}C, and ^{77}Se NMR spectra for new compounds and for thiolsulfinate **31**; kinetic plots for assays of compounds **7**−**11** and **30**; and HPLC and HRMS data for the assay of compound **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(24) HPLC measurements indicated that conversion of the catalyst **10** to the selenenyl sulfide **30** was 39% complete after 0.5 h and 89% complete after 27 h.
(25) Most of the cyclic seleninate esters that we have investigated to date have produced linear kinetic plots to at least the 50% completion point, whereas **1a** showed linear behavior to at least 70% completion. However, in some cases, we have noticed that the increase in disulfide concentration slowed considerably, well before completion (e.g., see ref 11e). This can be attributed to the accumulation of the corresponding selenenyl sulfides, which are generally poorer catalysts than the seleninate esters (refs 11b and 11c).
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