The Role of Methoxy Substituents in Regulating the Activity of Selenides that Serve as Spirodioxyselenurane Precursors and Glutathione Peroxidase Mimetics

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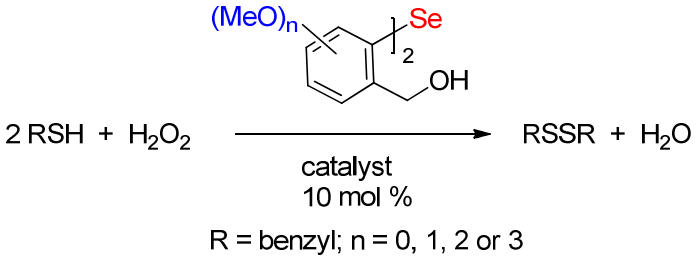
Abstract

A series of *o*-(hydroxymethyl)phenyl selenides containing single or multiple methoxy substituents was synthesized and the rate at which each compound catalyzed the oxidation of benzyl thiol to its disulfide with excess hydrogen peroxide was measured. This assay provided the means for comparing the relative abilities of the selenides to mimic the antioxidant selenoenzyme glutathione peroxidase. The mechanism for catalytic activity involves oxidation of the selenides to their corresponding selenoxides with hydrogen peroxide, cyclization to spirodioxyselenuranes, followed by reduction with two equivalents of thiol to regenerate the original selenide with concomitant disulfide formation. A single *p*-methoxy group on each aryl moiety afforded the highest catalytic activity, while methoxy groups in the *meta* position had little effect compared to the unsubstituted selenide and o-methoxy groups suppressed activity. The installation of multiple methoxy groups on each aryl moiety provided no improvement. These results can be rationalized on the basis of dominating mesomeric and steric effects of the *p*- and *o*-substituents, respectively.

Key Words:

Glutathione peroxidase, organoselenium compounds, antioxidants, selenides

Graphic abstract



R = benzyl; n = 0, 1, 2 or 3

Highest catalytic activity when n = 1 and OMe is in *para* position

Introduction

Glutathione peroxidase [1,2] (GPx) consists of a family of isozymes, several of which contain selenium atoms present as selenol moieties of selenocysteine residues. The redox properties of selenium endow GPx with powerful antioxidant properties that enable it to destroy harmful peroxides in vivo by catalyzing their reduction with the stoichiometric tripeptide thiol glutathione. Hydrogen peroxide and lipid peroxides are produced during the course of normal aerobic metabolism and are harmful to cells and tissues because of their strong oxidizing abilities and their propensity to generate other reactive oxygen species (ROS) such as the superoxide radical anion and the hydroxyl radical. Thus, GPx protects living organisms against oxidative stress by suppressing the formation of ROS.[3] Oxidative stress has in turn been implicated in a variety of disease states and degenerative disorders, including inflammation, mutagenesis and cancer, neurological damage and dementia, cardiovascular disease and possibly the aging process.[4] ROS produced by neutrophils during ischemic reperfusion of heart attack and stroke patients is of special concern, as the high levels of oxidative stress they induce can overwhelm the protective effects of GPx, resulting in serious cardiovascular and neurological injury.[5]

Epp, Ladenstein and Wendel[6] were the first to determine the structure of bovine erythrocyte GPx, which consists of a tetrameric structure wherein each of the four subunits contains a selenocysteine moiety. The catalytic cycle of GPx was first proposed by Ganther and Kraus[7] and is shown in Scheme 1. The selenol moiety of each selenocysteine unit (EnzSeH) functions as a strong reducing agent that converts a peroxide molecule into water or a lipid-derived alcohol, and is itself reduced to the corresponding selenenic acid (EnzSeOH). Step-wise reaction of the latter with two molecules of glutathione (GSH) then regenerates the original selenol via the intermediacy of the selenenyl sulfide (EnzSeSG), while glutathione is oxidized to

its disulfide (GSSG). The disulfide is in turn recycled to GSH by glutathione reductase-mediated reduction with NADPH.

Considering the deleterious effects of peroxides and the limitations of GPx to afford adequate protection under certain physiological conditions associated with exceptionally elevated levels of oxidative stress, there has been significant interest in the design, synthesis and bioassay of novel small-molecule mimetics[4a,8] of GPx that could afford additional protection to such patients. Indeed, ebselen[9,10] and ALT 2074[5a,11] (Figure 1) have undergone clinical trials as therapies for various disorders related to oxidative stress.

Scheme 1. Catalytic cycle of GPx.

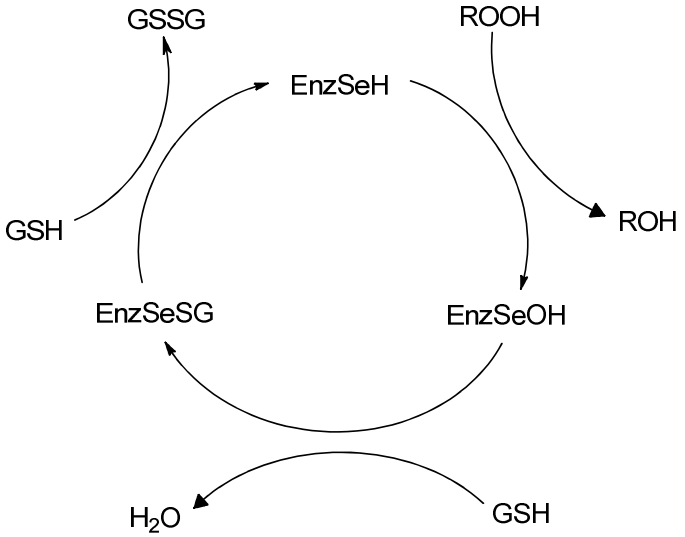
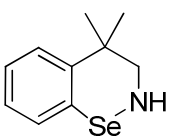
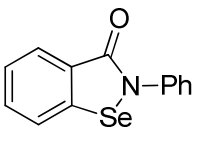


Figure 1. Structures of ALT 2074 and ebselen



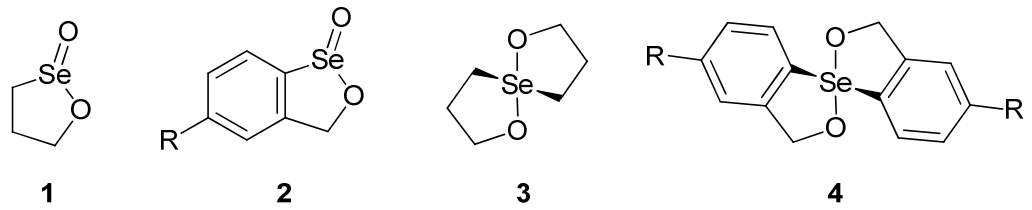
ALT 2074
(Synvista Inc.)



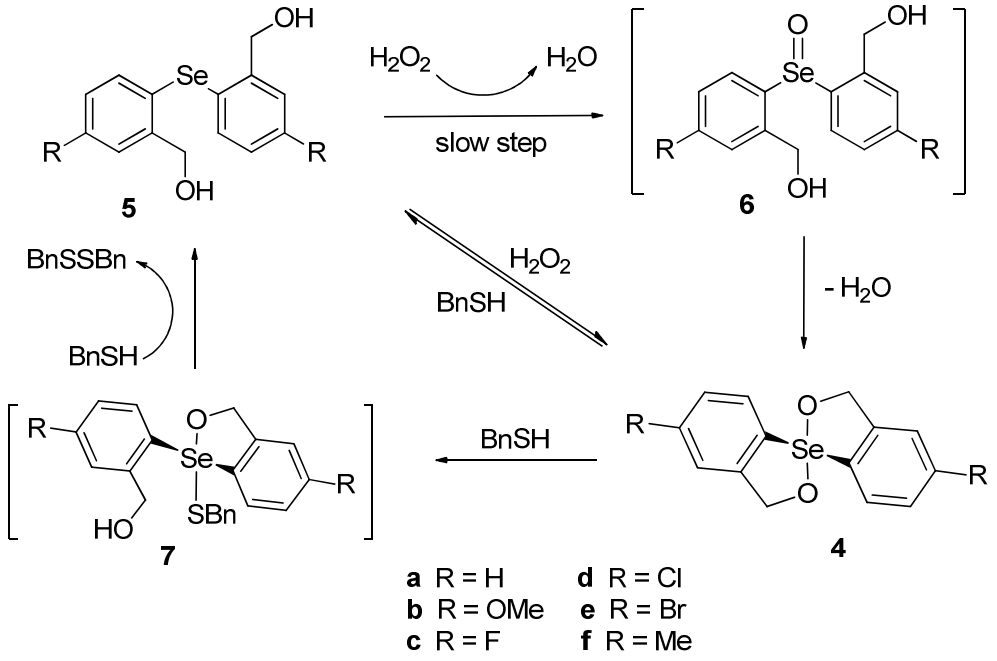
Ebselen
(Daiichi-Sankyo Inc.
and Sound Pharma Inc.)

Two classes of compounds that were first investigated as potential GPx mimetics by our group include the aliphatic and aromatic cyclic seleninate esters **1**[12] and **2**,[12c,13] as well as the corresponding spirodioxyselenuranes **3**[14] and **4**.[12c,13a] Later studies of these types of compounds by Singh et al.[15] and by Bayse and Ortwine[16] have also been reported. Certain members of both classes of compounds display >10-fold greater catalytic activity than that of ebselen.[12b,13a,14] However, the seleninate esters suffer from a competing deactivation pathway which generates selenenyl sulfides that remain relatively inert toward further oxidation or thiolysis.[12,13b] Moreover, we recently observed that the seleninate esters are capable of catalyzing the further oxidation of disulfides produced from sacrificial thiols to the corresponding thiolsulfinates, a process that could unintentionally damage other native disulfide-containing peptides and proteins.[17] On the other hand, the spirodioxyselenuranes display a more robust catalytic cycle (Scheme 2) that does not appear to suffer from similar late-stage side reactions. The catalyst in Scheme 2 can be introduced via either the oxidized selenurane form **4**, or the corresponding reduced selenide analogue **5**, as both are stable and isolable compounds. The catalytic cycle, when starting from selenide **5**, involves oxidation to the corresponding selenoxide **6**, immediately followed by spontaneous cyclization to the selenurane **4**. Substitution at selenium with the thiol generates the postulated intermediate **7**, followed by reductive elimination with a second molecule of thiol to regenerate the selenide catalyst. The choice of benzyl thiol instead of glutathione was made for our in vitro assay of catalytic activity because it has both a chromophore for HPLC analysis and a distinct methylene signal to facilitate NMR investigations.

Figure 2. Structures of representative cyclic seleninate esters **1** and **2**, and spirodioxyselenuranes **3** and **4**.



Scheme 2. Catalytic cycle of spirodioxyselenuranes **2**.



In our earlier investigations, we observed that the aliphatic catalysts **1** and **3** displayed especially high catalytic activities compared with most of the aromatic analogues that were studied.[12c] However, the expected greater metabolic stability and lower toxicity of the aromatic derivatives[8c,18] prompted us to focus attention on the latter compounds. Furthermore, the unsubstituted selenurane **4a** displayed poorer catalytic activity than its derivatives containing

electron-donating groups *para* to the selenium atom (**4b**, **4f**), while electron-withdrawing groups (**4c-4e**) further diminished its activity.[13a] The Hammett plot for compounds **4a-4e** produced a reaction constant σ = -3.1, consistent with a rate-determining step in which the transition state is associated with an increase in positive charge that can be stabilized by electron-donating substituents. This in turn suggests that the oxidation of **5** to **6**, i.e. Se(II) to Se(IV), is rate-limiting in Scheme 2. The corresponding reaction constant for a similar series of substituted cyclic seleninate esters **2** was determined to be σ = -0.45, indicating a significantly lower sensitivity to substituent effects than in the selenurane series.[13a] This proved to be an additional advantage for the use of the selenuranes, as they were more amenable to tuning of their catalytic activity through judicious choice of substituents. Finally, in a recent study of derivatives of cyclic seleninate esters **2** containing single or multiple electron-donating methoxy substituents at various positions, we noted that a single *p*-methoxy group improved activity due to mesomeric effects, while a *m*-methoxy group had little effect upon activity and an *o*-methoxy substituent suppressed activity, presumably because of steric hindrance of the selenium center. The introduction of a second or third methoxy group had little further effect upon catalytic activity.[19]

In view of the undesired complexities associated with cyclic seleninate esters, compared to spirodioxyselenuranes as GPx mimetics, we turned our attention to a similar series of mono-, di- and trimethoxy analogues of selenuranes **4** and selenides **5**.

Results and Discussion

Since oxidation of the selenium atom had been previously shown to comprise the rate-determining step in the catalytic cycle shown in Scheme 2,[13a] it was expected that electron-donating *o*- or *p*-methoxy groups would enhance catalytic activity through mesomeric effects. In

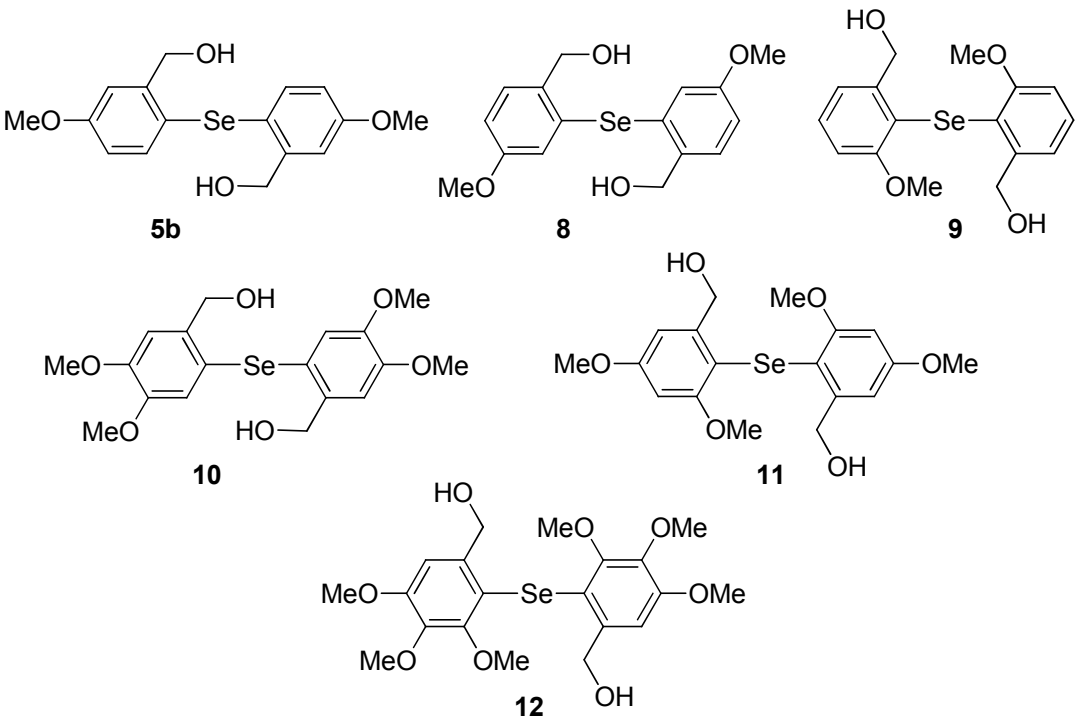
contrast, *meta*-substituted methoxy groups cannot interact with the selenium atom through resonance and were expected to have a less pronounced effect on catalytic activity. In the case of *o*-methoxy substituents, steric effects could retard reaction rates and oppose the expected mesomeric effect. Moreover, substituents that coordinate to selenium in various redox processes can also strongly affect reaction rates.[20] In related work, Mugesh and coworkers[21] reported that *p*-methoxy groups had little effect on the activity of diaryl diselenides, while *o*-methoxy substituents improved catalytic activity by suppressing unproductive thiol exchange reactions at selenium that competed with desired thiol attack at sulfur in postulated selenenyl sulfide intermediates.

Although the selenides and corresponding selenuranes are interconvertible, as shown in Scheme 2, and either can be introduced into an assay for catalytic activity, the selenides were chosen for this purpose instead of the corresponding spirodioxyselenuranes, as the use of the latter can result in abnormally high initial reaction rates due to their very rapid consumption by thiolysis, followed by the slower, rate-determining oxidation of the resulting selenides back to the selenuranes. Furthermore, the concentration of thiols (mainly glutathione) in tissues and cells of living organisms is generally higher than that of peroxides and so the introduction of the catalyst in its oxidized selenurane form would in any case likely result in its rapid reduction to the selenide in vivo.

In view of these considerations, it was of interest to prepare, assay and compare the compounds shown in Figure 3 in order to delineate the effects of various methoxy substituents upon the catalytic activity of the present selenide/selenurane system and to compare the properties of these compounds with those of the corresponding cyclic seleninate series.

The desired novel *o*-hydroxymethyl selenides **8**-**12** shown in Figure 3 were synthesized as indicated in Scheme 3. The selenides **5a** and **5b** were prepared as described previously[12c,13a] and were included for comparison.

Figure 3. Structures of methoxy-substituted diaryl selenides.

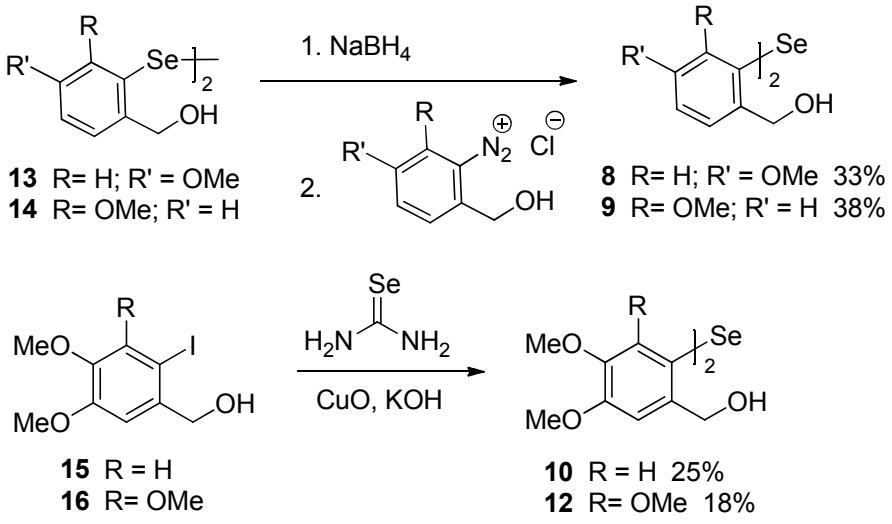


The preparation of the desired selenides **8** and **9** from the corresponding diselenides **13** and **14**, respectively, is shown in Scheme 3. The diselenides had in turn been prepared previously as intermediates for the synthesis of cyclic seleninate esters,[19] while selenide **11** was isolated as a byproduct of its diselenide analogue.[19]

In contrast to selenide **5a** and its *p*-monosubstituted derivatives **5b**-**5f**,[13a] the methoxy-substituted selenides **8**-**10** and **12** proved difficult to prepare in pure form. In general, the crude products contained the corresponding diselenides and other unidentified byproducts. In order to

obtain **8-10** and **12** in the high state of purity required for measurement of their catalytic activity, they were typically oxidized to the more easily purified spirodioxyselenuranes, followed by reduction back to their corresponding selenides with benzyl thiol and further purification by chromatography and/or recrystallization. Thus, while crude yields were moderate, the final yields of analytically pure products were low. Among various methods that were attempted for the synthesis of these selenides, the most successful are shown in Scheme 3. Selenides **8** and **9** were obtained by reduction of diselenides **13** and **14**, respectively, with sodium borohydride, followed by treatment of the resulting selenolates with the diazonium salts derived from diazotization of the corresponding 2-aminobenzyl alcohols. On the other hand, the *m,p*-dimethoxy selenide **10** and the trimethoxy derivative **12** were best obtained by the treatment of iodides **15** and **16** with selenourea in the presence of Cu(II)O nanoparticles.[22]

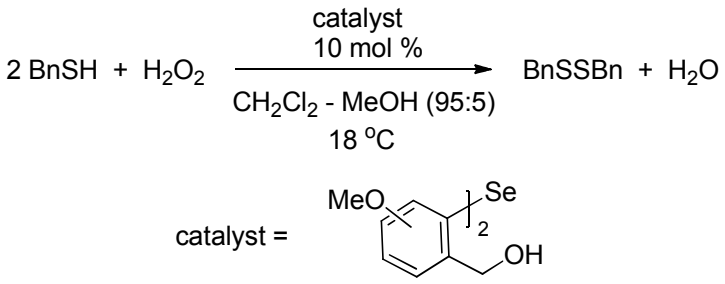
Scheme 3. Synthesis of selenides **8-10** and **12**.



The catalytic activities of compounds **5a**, **5b** and **8-12** were then measured in our previously described assay,[12,13,23] in which benzyl thiol was oxidized with a small excess of

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, representing the time required for the conversion of 50% of the thiol to its disulfide, are shown in Table 1. Kinetic plots of disulfide formation vs. time for selenide catalysts **5a**, **5b** and **8**-**12** are provided in Figures 4-10.

Table 1. Catalytic activity of methoxy-substituted selenides and cyclic seleninate esters



entry	catalyst	MeO substituent(s)[a]	$t_{1/2}$ (h)[b,c]
1	**5a**	none	20 (53)
2	**5b**	*p*	5.5 (38)
3	**8**	*m*	17 (50)
4	**9**	*o*	21 (70)
5	**10**	*m,p*	6.3 (49)
6	**11**	*o,p*	17 (55)
7	**12**	*o,m,p*	15 (45)

[a]*Ortho* and *para* refer to positions relative to the Se substituent; *meta* refers to the position that is *meta* to the Se substituent and *para* to the hydroxymethyl group. [b]Values in parentheses are the $t_{1/2}$ values for the corresponding similarly substituted cyclic seleninate esters,[19] and are included for comparison. All $t_{1/2}$ values are the average of 2-5 runs. [c]A control reaction in the absence of a catalyst afforded a $t_{1/2}$ value of >170 h.

Figure 4. Kinetic plot for selenide **5a**.

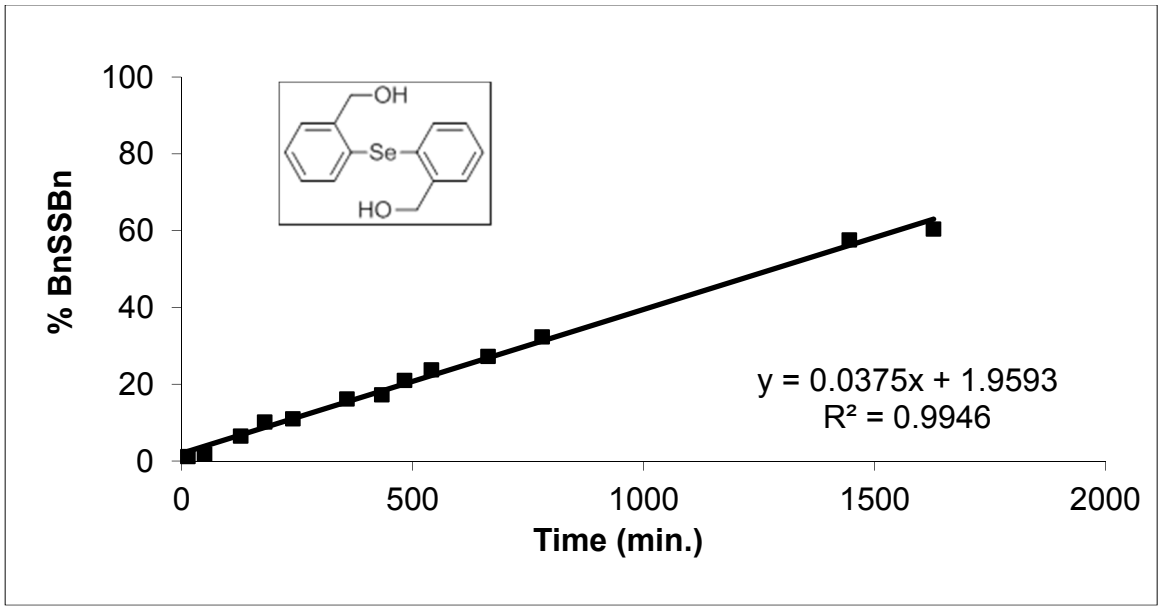


Figure 5. Kinetic plot for selenide **5b.**

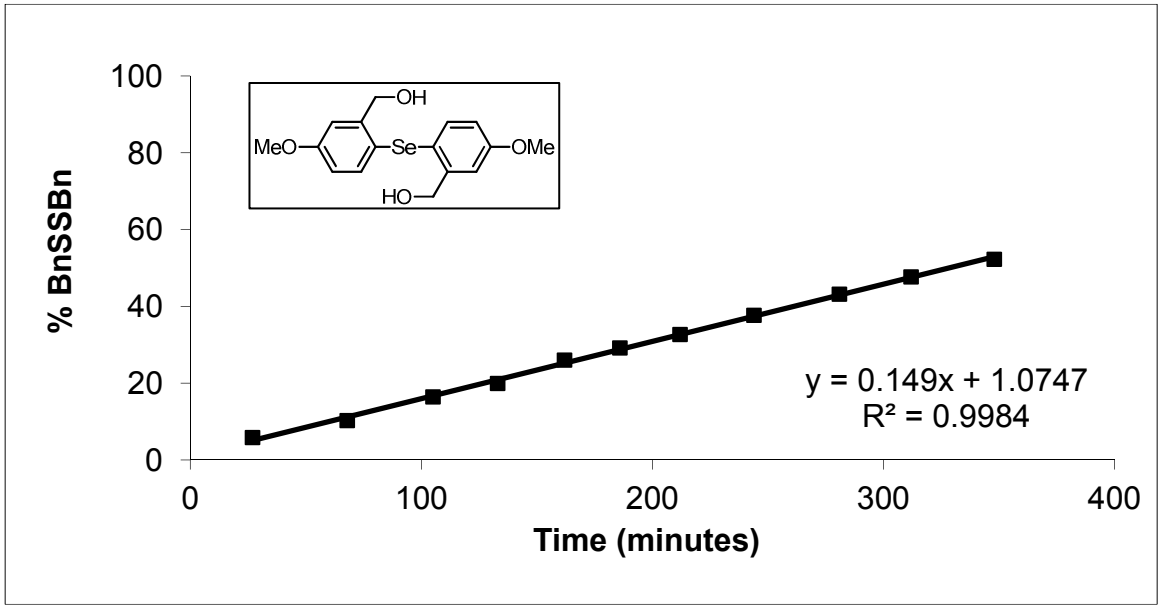


Figure 6. Kinetic plot for selenide **8**.

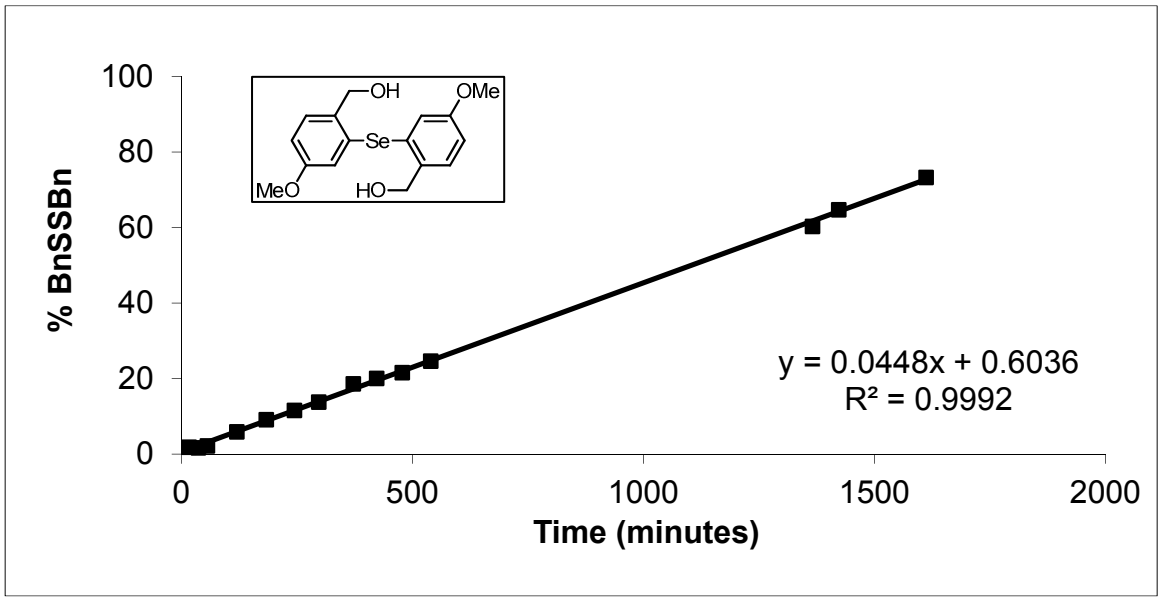


Figure 7. Kinetic plot for selenide **9.**

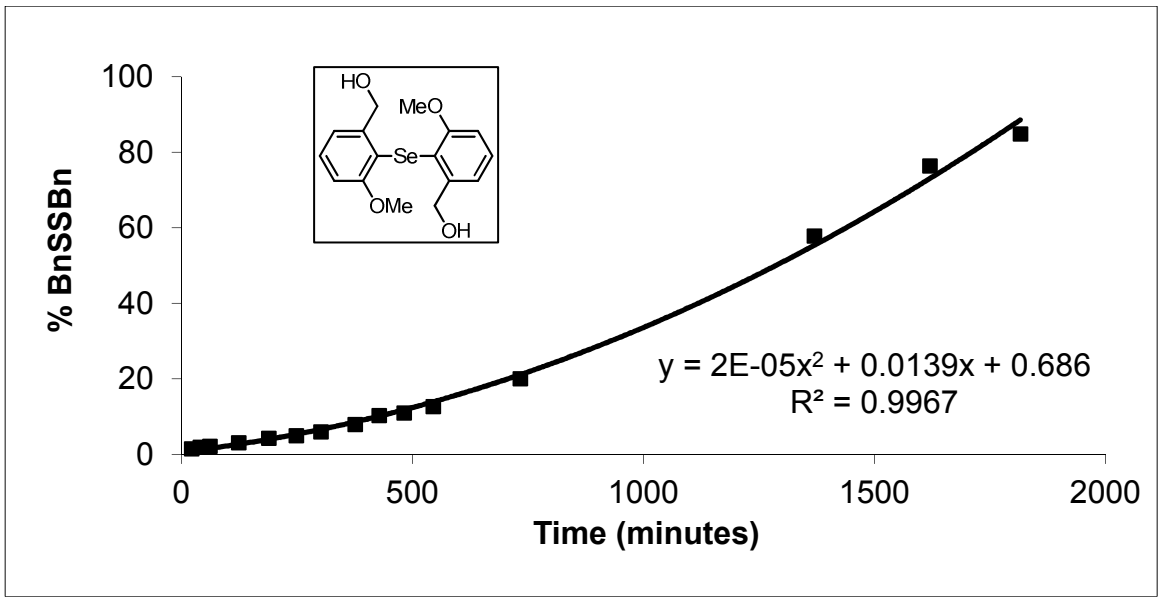


Figure 8. Kinetic plot for selenide **10.**

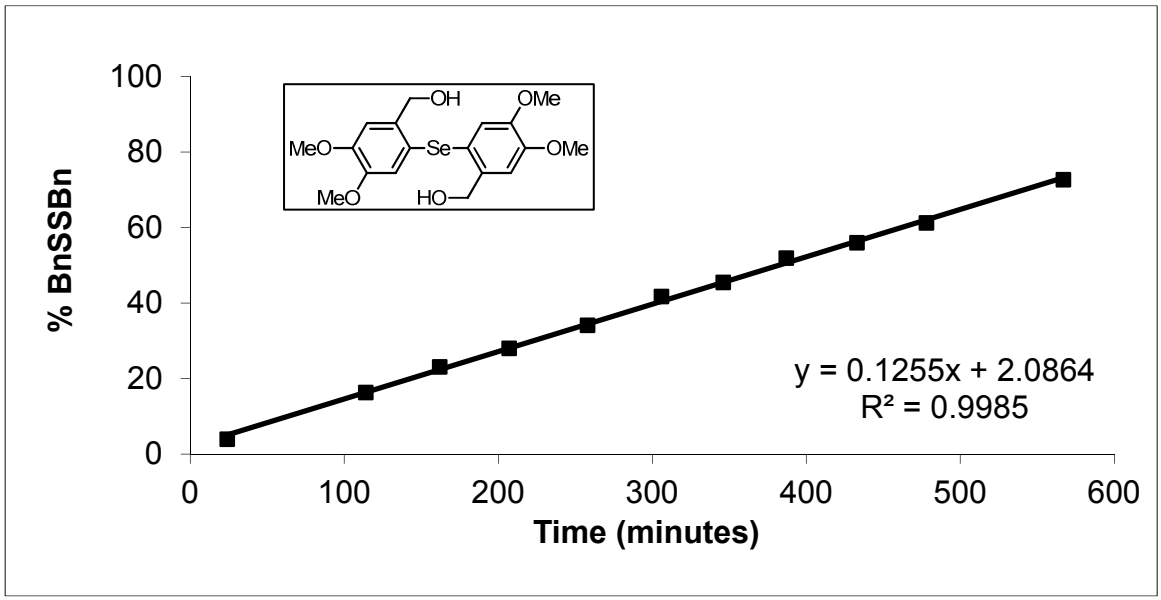


Figure 9. Kinetic plot for selenide **11.**

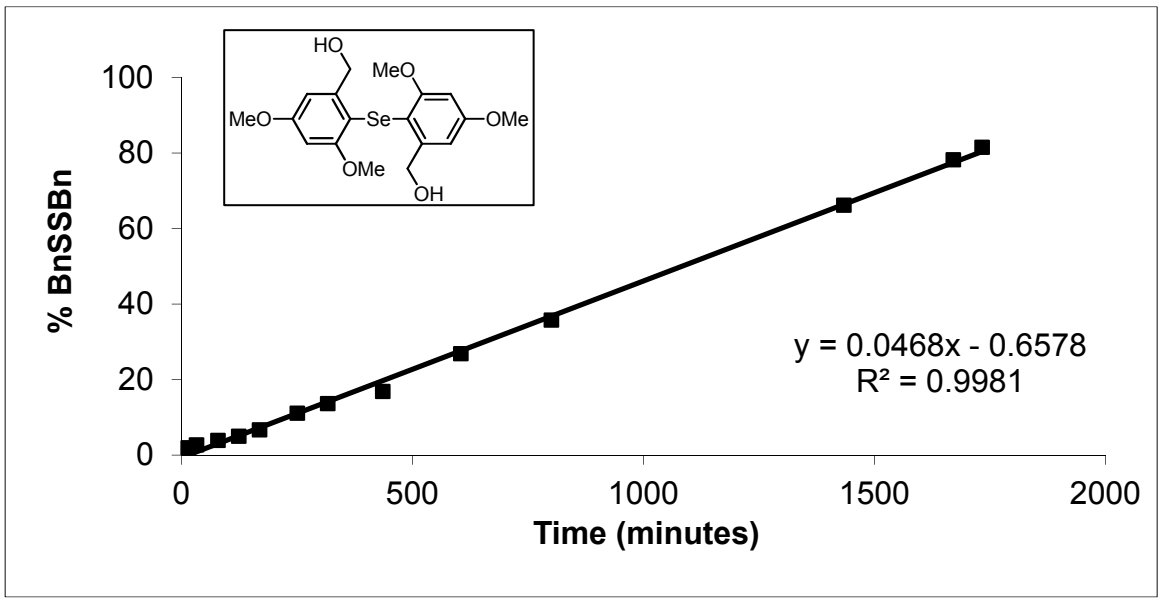
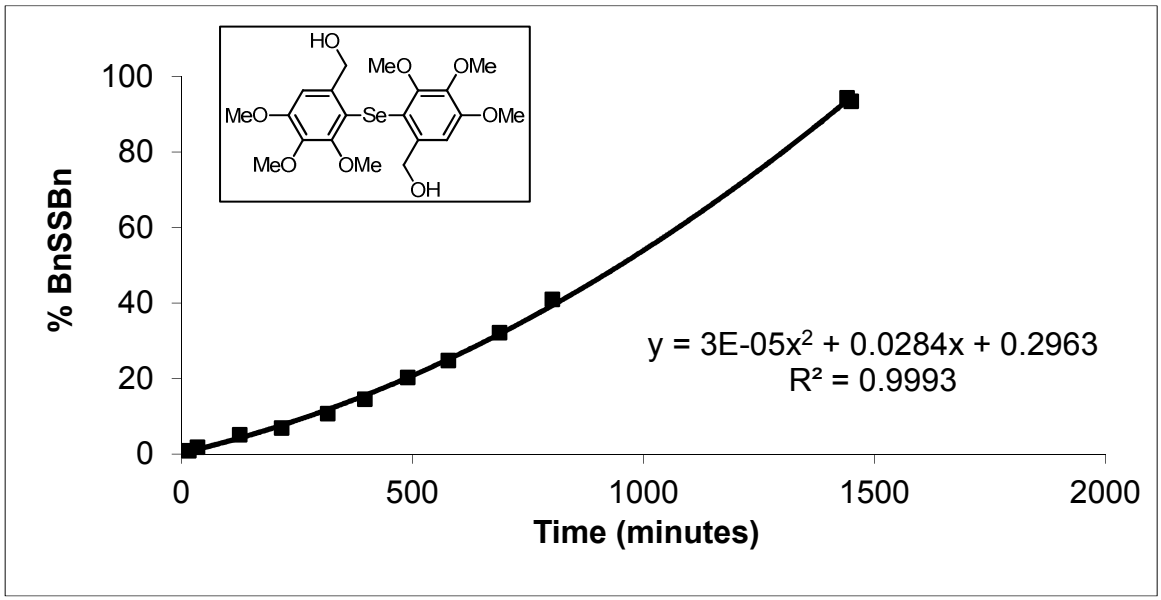


Figure 10. Kinetic plot for selenide **12.**



The presence of a *p*-methoxy group in each of the aryl moieties in **5b** increased the catalytic activity almost four-fold relative to the unsubstituted compound **5a** (entries 1 and 2). Single methoxy groups in the *meta* or *ortho* positions had little effect, with the former providing a slightly enhanced rate and the latter a very slightly suppressed one (entries 3 and 4) compared to **5a**. Inclusion of an additional methoxy substituent into the *meta* positions of the monomethoxy derivative **5b** to give **10** decreased its activity slightly (entry 5), while the additional *ortho* substituent in **11** strongly suppressed it (entry 6). The trimethoxyaryl derivative **12** (entry 7) was also nearly three times less active than the *p*-methoxy derivative **5b**. These results indicate that the presence of an *o*-methoxy substituent is slightly (entry 4 vs. 1) or considerably (entry 6 vs. 2, entry 7 vs. 5) detrimental to catalytic activity, while *m*-methoxy groups can be either activating (entry 3 vs. 1, entry 7 vs. 6) or deactivating (entry 5 vs. 2)

Furthermore, a comparison of the present selenides **5b** and **8**-**12** with the analogous cyclic seleninate esters reported previously[19] reveals that the selenides are all considerably more active, with shorter $t_{1/2}$, than their similarly substituted seleninate counterparts.

It is also noteworthy that *o*-methoxy-substituted compounds **9** and **12** (but not **11**) displayed nonlinear kinetic behaviour, characterized by a slower reaction rate in the early stages of the reaction. While the reason for this behaviour is uncertain, we note that all of the present catalysts, including **9** and **12**, persist in their selenide form throughout the reaction, as long as unreacted thiol is present. Thus, the significant accumulation of an unexpected and more active catalytic species that could accelerate the reaction in its later stages does not appear to be responsible for the nonlinear kinetics of these two catalysts (for HPLC analyses of **9** and **12**, see the Supporting Information). Furthermore, the persistence of the catalysts in their reduced selenide form is consistent with the oxidation of selenium as the rate-determining step, followed by a considerably more rapid thiolysis of the resulting spirodioxyselenurane. It is interesting to note that the anomalous behaviour of **9** and **12** contrasts with the abnormally fast initial reaction rates observed when similar catalysts are introduced in their oxidized spirodioxyselenurane form.[13a] The accelerated rates of the latter can be attributed to the rapid thiolysis of the catalyst (Scheme 2) to produce the disulfide in the early stages of the reaction, followed by the slower reoxidation of the reduced selenide catalyst.

In conclusion, the most effective substitution pattern in the selenide/selenurane series of catalysts is a single *p*-methoxy substituent (on each aryl moiety), while single *ortho* and *meta* methoxy groups had relatively little effect on activity. There is little or no advantage to the incorporation of additional *m*-methoxy groups to the *p*-substituted compound **5b** and the addition of an *o*-methoxy group to **5b** or **10** resulted in significant loss of activity. This suggests that

detrimental steric effects outweigh performance-enhancing mesomeric or coordination effects in the case of the *o*-methoxy substituents in the present series of compounds, as well as in the cyclic seleninate esters. Finally, the hydroxymethyl selenides in Table 1 proved in each case superior catalysts to the corresponding cyclic seleninate esters under the conditions of this assay.

Experimental Section

General Experimental.

Diselenides **13-16** and selenide **11** were prepared as described previously.[19] 2-Amino-4-methoxybenzyl alcohol and 2-amino-3-methoxybenzyl alcohol are known compounds[24] that were prepared by the reduction of the corresponding carboxylic acids with lithium aluminum hydride. Iodo alcohols **15** and **16** were obtained by the method of Lete and coworkers.[25]

^{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 measured with diphenyl diselenide in $CDCl_3$ (463.0 ppm)[26] 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).

The HPLC-based *in vitro* assay was carried out in the following manner. Catalytic activity was measured by adding the catalyst (0.031 mmol; 10 mol % relative to benzyl thiol) to a mixture of 33% hydrogen peroxide (0.035 M) and benzyl thiol (0.031 M) in 10.0 mL of dichloromethane-methanol (95:5) while maintaining the temperature at 18 ºC. The reactions were monitored by HPLC analysis, using a UV detector at 254 nm and a reversed phase column (Novapak C18; 3.9 x 150 mm). The eluant was acetonitrile-water (90:10) at a flow rate of 0.9

mL/min. Naphthalene (0.0080 M) was employed as an internal standard. Benzyl thiol was redistilled and hydrogen peroxide was titrated[27] prior to use. The assay is sensitive to acidic and other contaminants. Each replicate assay was performed in a clean new vial.[28]

Preparation of 2,2'-selenobis(4-methoxybenzyl alcohol) (8).

2-Amino-4-methoxybenzyl alcohol (492 mg, 3.22 mmol) was suspended in 12 mL of water, cooled to 0 °C and treated with 1.8 mL of concentrated HCl, followed by the dropwise addition of $NaNO_2$ (260 mg, 3.77 mmol) in 1.8 mL of water. In a separate round bottom flask, the diselenide **13** (460 mg, 1.06 mmol) was dissolved in 34 mL of THF:water (1:1), cooled to 0 °C and treated with $NaBH_4$ (283 mg, 7.48 mmol). The pH of the diazonium salt solution was then adjusted to ~5.5 with saturated aqueous sodium acetate. This mixture was subsequently transferred in a dropwise manner to the clear selenolate solution. The reaction mixture was warmed to room temperature, left for 2 h and quenched with 15 mL of saturated aqueous NH_4Cl solution. The mixture was extracted with ethyl acetate, washed with brine, dried ($MgSO_4$) and concentrated. The resulting oil was purified by flash chromatography (hexanes-ethyl acetate, 1:1) to afford 301 mg of a mixture of desired selenide and the diselenide starting material. In order to separate them, the mixture and 29% hydrogen peroxide (0.51 mL) were dissolved in 10 mL of dichloromethane and left for 12 h. The resulting mixture of the corresponding spirodioxyselenurane and cyclic seleninate ester was concentrated under reduced pressure and separated by flash chromatography (ethyl acetate-methanol, 9:1). The selenurane was reduced to the desired selenide by treating it with 2 equivalents of benzyl thiol in 5 mL of dichloromethane for 1 h. Concentration of the mixture and purification by chromatography (ethyl acetate-hexanes, 1:1) afforded 123 mg (33%) of selenide **8** as a white solid, mp 115-116 °C; IR (film) 3319, 2919, 1590, 1471, 1224, 1038 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.35 (d, J = 8.4 Hz, 2 H), 6.89 (d, J

= 2.8 Hz, 2 H), 6.82 (dd, *J* = 8.4, 2.8 Hz, 2 H), 4.68 (s, 4 H), 3.71 (s, 6 H), 2.11 (br s, 2 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 159.7, 134.5, 131.8, 130.4, 120.1, 113.6, 65.0, 55.5; ^{77}Se NMR (76 MHz; $CDCl_3$) δ 335.8; mass spectrum, *m/z* (EI, relative intensity) 354 (10, M^+), 199 (20), 135 (82), 121 (68), 108 (75), 77 (100); exact mass calcd. for $C_{16}H_{18}O_4{}^{80}Se$: 354.0370; found: 354.0357. Anal. calcd. for $C_{16}H_{18}O_4Se$: C, 54.40; H, 5.14; found: C, 54.38; H, 5.49.

Preparation of 2,2'-selenobis(5-methoxybenzyl alcohol) (9).

Selenide **9** was prepared similarly to **8** from 2-amino-3-methoxybenzyl alcohol and diselenide **14** in 38% yield; white solid, mp 182-183 °C; IR (film) 3214, 2929, 1557, 1462, 1267, 1000 cm^{-1}; ^{1}H NMR (400 MHz; DMSO-d_6) δ 7.25 (t, *J* = 8.0 Hz, 2 H), 7.09 (d, *J* = 8.4 Hz, 2 H), 6.82 (d, *J* = 8.0 Hz, 2 H), 5.13 (t, *J* = 5.6 Hz, 2 H), 4.54 (d, *J* = 5.2 Hz, 4 H), 3.56 (s, 6 H); ^{13}C NMR (101 MHz; DMSO-d_6) δ 158.6, 146.2, 128.5, 119.1, 118.0, 109.9, 62.9, 55.8; ^{77}Se NMR (76 MHz; DMSO-d_6) δ 144.2; mass spectrum, *m/z* (EI, relative intensity) 354 (50, M^+) 200 (65), 121 (100), 77 (60); exact mass calcd. for $C_{16}H_{18}O_4{}^{80}Se$: 354.0370; found: 354.0371. Anal. calcd. for $C_{16}H_{18}O_4Se$: C, 54.40; H, 5.14; found: C, 54.20; H, 5.18.

Preparation of 2,2'-selenobis(4,5-dimethoxybenzyl alcohol) (10).

Selenide **10** was prepared according to a modification of the general procedure of Reddy, Kumar and Rao[22] for the synthesis of symmetrical aryl selenides. 2-Iodo-4,5-dimethoxybenzyl alcohol (1.09 g, 3.70 mmol) and selenourea (151 mg, 1.23 mmol) were dissolved in 5 mL of DMSO. Commercially available nanopowder (<50 nm particle size) copper(II) oxide (59 mg, 0.74 mmol) was added and the mixture was degassed with a stream of argon for 20 min. Potassium hydroxide (138 mg, 2.46 mmol) was added and the mixture was heated at 85 °C for 18 h. The mixture was poured onto 15 mL of water, extracted with ethyl acetate, washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The product was subjected to

flash chromatography (ethyl acetate-hexanes, 1:1) to afford a mixture of the desired selenide **10** and the corresponding diselenide, which were separated as in the case of selenide **8** and diselenide **13**. The crude selenide was purified by chromatography (ethyl acetate-hexanes, 1:1) to afford 128 mg (25%) of selenide **10** as a white solid, mp 112-113 °C; IR (film) 3533, 3419, 2924, 1500, 1252, 1195, 1148 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 6.96 (s, 2 H), 6.83 (s, 2 H), 4.64 (s, 4 H), 3.83 (s, 6 H), 3.68 (s, 6 H), 2.67 (br s, 2 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 149.2, 148.8, 135.1, 120.9, 117.3, 112.1, 64.9, 56.1, 56.0; ^{77}Se NMR (76 MHz; $CDCl_3$) δ 310.8; mass spectrum, *m/z* (EI, relative intensity) 414 (38, M^+), 316 (32), 151 (100) 138 (46); exact mass calcd. for $C_{18}H_{22}O_6{}^{80}Se$: 414.0582; found: 414.0583. Anal. calcd. for $C_{18}H_{22}O_6Se$: C, 52.31; H, 5.36; found: C, 52.38; H, 5.51.

Preparation of 2,2'-selenobis(3,4,5-trimethoxybenzyl alcohol) (12).

Selenide **12** was prepared similarly to **10** from 2-iodo-3,4,5-trimethoxybenzyl and selenourea. in 18% yield as a colourless oil; IR (neat) 3457, 2929, 2848, 1581, 1481, 1314, 1152, 1105, 1010 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 6.85 (s, 2 H), 4.87 (br s, 4 H), 3.88 (s, 6 H), 3.77 (s, 6 H), 3.46 (s, 6 H), 3.36 (s, 2 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 154.3, 154.2, 142.1, 139.4, 116.4, 108.9, 66.4, 60.9 (x 2), 56.2; ^{77}Se NMR (76 MHz; $CDCl_3$) δ 156.0; mass spectrum, *m/z* (EI, relative intensity) 474 (40, M^+), 276 (18), 198 (36), 181 (100), 168 (38); exact mass calcd. for $C_{20}H_{26}O_8{}^{80}Se$: 474.0793; found: 474.0792.

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Supporting Information

Copies of NMR spectra of selenides **8**, **9**, **10** and **12**, as well as HPLC analyses of reactions conducted with catalysts **9** and **12** are available in the Supporting Information.

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