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Selenium

A One-Pot Access to Benzo[*b*][1,4]selenazines from 2-Aminoaryl Diselenides

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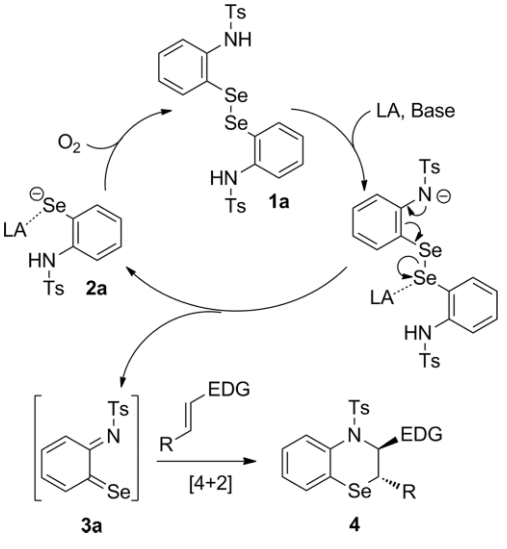
Abstract: Different 2-sulfonylaminoaryl diselenides substituted with electron-withdrawing or -donating groups are transformed in one pot into benzo[*b*][1,4]selenazines. The reaction uses a substoichiometric amount of $Cu(OTf)_2$, and the mechanism involves a base-mediated 1,4-elimination at selenium with the generation of an *o*-iminoselenoquinone and a 2-sulfonylaminoselenolate anion. The former is a dienic species that can react with electron-rich dienophiles to give the target cycloadducts. The latter is oxidised by air back to the starting diselenide, allowing its complete consumption. A preliminary investigation of the GPx-like activity of a selected selenazine is also described.

Introduction

Selenium is a very important element in organic chemistry, and several reviews describe its utility in synthesis.[1] Moreover, it is an essential dietary component for many living organisms, including humans. Recently, selenium-containing compounds have attracted increased attention as a result of their ability to act as glutathione peroxidase (GPx) mimics, catalytic antioxidants, and anticancer compounds.[2]

As part of our research on Diels–Alder reactions and the applications of electron-poor chalcogen-containing heterodienes,[3] we recently reported[4] a simple procedure for the preparation of benzo[*b*][1,4]selenazines from 2-*N*-sulfonylaminoaryl diselenides based on the Cu^{II}-catalysed generation of *o*-iminoselenones, a new class of transient electron-poor heterodienes. The procedure allowed the effective isolation of benzofused selenium-containing heterocycles under quite mild reaction conditions, with complete consumption of both of the selenium-containing subunits of a diselenide. The mechanism showing how this could be achieved is given in Scheme 1.[4] Thus, copper(II) activation of the Se–Se bond of the parent 2-*N*-sulfonylaminoaryl diselenide (i.e., **1a**), followed by base-mediated 1,4-elimination at selenium of selenolate anion **2a**, generates *o*-iminoselenoquinone **3a**. This efficiently participates in inverse-electron-demand hetero-Diels–Alder reactions as a heterodiene with several electron-rich dienophiles to give, regio- and stereoselectively, benzo[*b*][1,4]selenazines **4**. Since selenolate anion **2a**, which acts as a leaving group, is oxidised by molecular oxygen (in air) back to the starting diselenide (i.e., **1a**), the starting diselenide is completely consumed during the process.



Scheme 1. Synthetic one-pot procedure for the preparation of benzo[*b*][1,4]selenazines **4** from the parent 2-*N*-sulfonylaminophenyl diselenide (**1a**). EDG = electron-donating group; LA = Lewis acid.

The above procedure involving aminoaryl diselenides[4] proved to be particularly efficient compared with those of the corresponding aminoaryl disulfides[5] and hydroxy disulfides.[6] Good yields of selenazines **4** were achieved with many different dienophiles, including styrenes, enol ethers, vinyl amides, and

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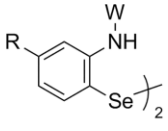
1,3-dienes. Recently, some of us have optimised the preparation of differently substituted 2-aminoaryl diselenides.[7] Thus, in this paper, we report the scope and limitations of the procedure shown in Scheme 1, studying the effect of substitution on the nitrogen atom and on the diselenide ring. Additionally, a benzoselenazine was selected for a preliminary study on the GPx-like activity of these derivatives.

Results and Discussion

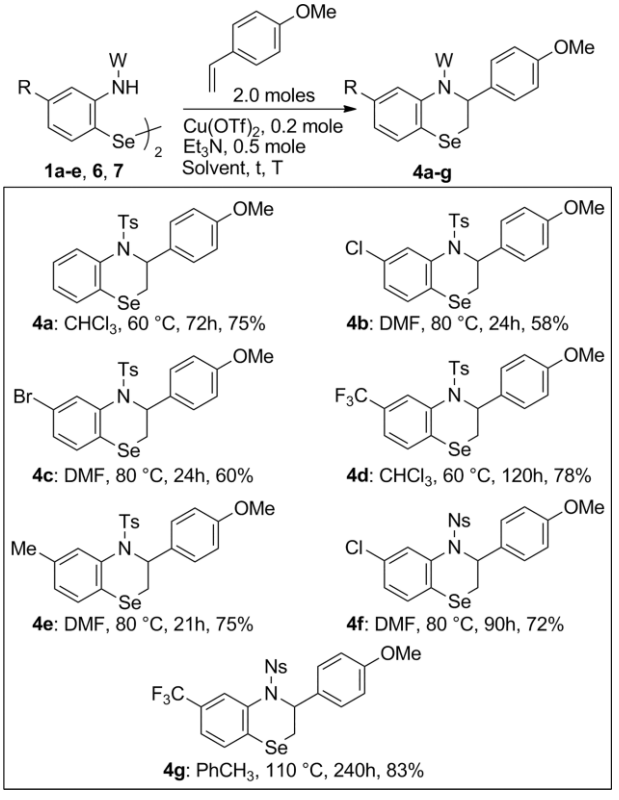
Using the optimised synthetic procedure mentioned above,[7] we were able to prepare the parent unsubstituted 2-aminophenyl diselenide (**5a**), but also diselenides substituted with electrong-withdrawing groups **5b**–**5d** and electron-donating groups **5e** and **5f**. These 2-aminophenyl diselenides **5** were transformed into the corresponding NH-tosyl (NHTs) **1a**–**1e** and NH-*o*-nosyl (NHNs) **6** and **7** sulfonamides, as shown in Figure 1. In fact, we were unable to transform 4-methoxy derivative **5f** into the corresponding 2-NHTs diselenide (i.e., **1f**), since extensive decomposition occurred during attempted sulfonamidation. To verify the generality, scope, and limitations of the procedure shown in Scheme 1 we treated derivatives **1a**–**1e**, **6**, and **7** with $Cu(OTf)_2$ (0.2 mol) as a suitable Lewis acid, Et_3N (0.5 mol), and *p*-methoxystyrene as a dienophile (2.0 mol). The previous optimised conditions[4] used $CHCl_3$ as the solvent at 60 °C; however, some of the new *N*-sulfonylaryl diselenides were only sparingly soluble in chloroform, or needed very long reaction times. Thus we optimised the reaction conditions, choosing the best solvent and reaction time for each of the different diselenides.



5a: R = H, W = H; **1a**: R = H, W = Ts
5b: R = Cl, W = H; **1b**: R = Cl, W = Ts; **6**: R = Cl, W = Ns
5c: R = Br, W = H; **1c**: R = Br, W = Ts
5d: R = CF_3, W = H; **1d**: R = CF_3, W = Ts; **7**: R = CF_3, W = Ns
5e: R = CH_3, W = H; **1e**: R = CH_3, W = Ts
5f: R = OCH_3, W = H

Figure 1. 2-Aminoaryl diselenides **5a**–**5f** and 2-*N*-sulfonylaryl diselenides **1a**–**1e**, **6**, and **7** prepared and used in this study.

Satisfactorily, using nonpolar solvents ($CHCl_3$ and toluene) or polar aprotic solvents (DMSO and DMF),[8] we were able to isolate the expected benzo[*b*]selenazines (i.e., **4a**–**4g**), as shown in Scheme 2. The isolated yields, after a trivial work-up and column chromatography, were acceptable to good, and, in each case, account for the consumption of both subunits of the diselenide residue. Taken together with previous results,[4] the data reported in Scheme 2 definitively show that 2-sulfonylaminoaryl diselenides are suitable starting materials for the synthesis of differently substituted benzoselenazines. The mechanism of this one-pot transformation involves several steps, i.e., secondary sulfonamide deprotonation, Lewis acid/Se interaction with Se–Se bond weakening, 1,4-elimination at selenium, formation and cycloaddition of a dienic *o*-iminoselenone, and oxidation of the selenolate anion to give the diselenide. Thus an explanation of the effect of the substituents on the diselenide aromatic ring is very difficult. Clearly, *o*-iminoselenones **3** retain their ability to act as electron-poor dienes irrespective of the nature of the substituents (H; or electron-withdrawing group: Cl, Br, CF_3; or electron-donating group: CH_3). The best results in terms of the final yield of selenazine (Scheme 2, derivatives **4d** and **4g**), were obtained using 4-CF_3 substituted diselenide **1d** as starting material, i.e., via the more electron-poor iminoselenone **3d**. Thus, it is reasonable to consider the [4+2] process as one of the possible rate-determining steps of the whole procedure.

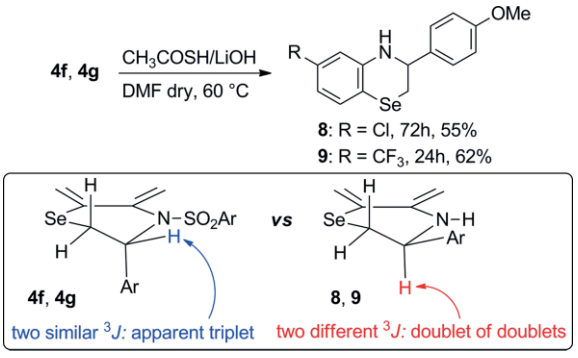


Scheme 2. Benzo[*b*][1,4]selenazines **4a**–**4g** prepared in this study.

The transformation of aminoaryl diselenides **5** into *N*-sulfonylaryl diselenides **1** is essential for the success of the procedure, since in this way the deprotonation at nitrogen under mild reaction conditions is possible with a weak base like Et_3N. Indeed, 2-*N*-acylamino- and 2-*N*-carbamoylaminoaryl diselenides were completely unreactive under the same or harsher reaction conditions. On the other hand, restoration of the amino group from NTs cycloadducts **4** is not a trivial process, and several attempts run using Na/naphthalene[9] or SmI_2[10] as detosylating reagents were completely unsuccessful. This prompted us to prepare NHNs derivatives **1f** and **1g**, which were successfully used to synthesise NHNs-selenazines **4f** and **4g** (Scheme 2).

When these derivatives were treated with thioacetic acid and LiOH in dry DMF,[11] we observed a clean denosylation, and *N*-unsubstituted selenazines **8** and **9** were isolated in reasonable yields, as shown in Scheme 3. As reported for related

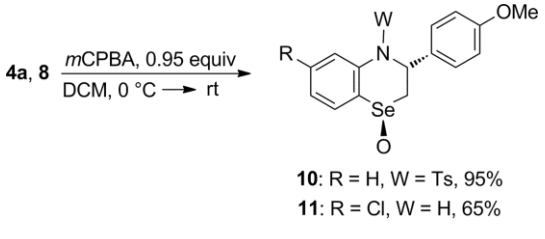
benzo[*b*][1,4]thiazine derivatives,[11b] the removal of the nosyl group causes a remarkable conformational change in these six-membered heterocycles.



Scheme 3. Synthesis of *N*-unsubstituted benzoselenazines **8** and **9** and the conformational consequences of substitution on nitrogen of the selenazines.

In fact, as shown in Scheme 3, the ^{1}H NMR spectra of all derivatives **4**, and in particular of **4f** and **4g** (see the Exp. Section for details), show for the proton on C-3 an apparent triplet, from δ = 5.5 to 6.0 ppm, due to two similar ^3J coupling constants with the two protons on C-2 (J = 7.4 Hz for **4f**, and J = 8.0 Hz for **4g**). This means that the proton on C-3, occupies a pseudoequatorial position, and the *p*-methoxyphenyl group is pseudoaxial. This is only apparently incongruous. In fact, this conformation ensures that there is less steric hindrance between the nosyl group on nitrogen and the aryl group on C-3. After denosylation, the ^{1}H NMR spectra of the secondary amines (i.e., **8** and **9**) show for the proton on C-3 a clean doublet of doublets as the result of two quite different ^3J constants with the protons on C-2 (J = 9.9 and 2.6 Hz for **8**, and J = 9.2 and 2.8 Hz for **9**). In other words, in the secondary amines **8** and **9**, after the removal of the bulky nosyl group on nitrogen, the proton on C-3 is pseudoaxial, and the *p*-methoxyphenyl group on C-3 occupies, as expected, a pseudoequatorial position (Scheme 3 and Exp. Section).

Finally, we transformed selenazines **4a** and **8** into the corresponding selenoxides using a stoichiometric amount of *m*CPBA (*m*-chloroperbenzoic acid) in CH_2Cl_2 at 0 °C. The oxidation occured in quite good yields, and, similarly to the related sulfur-containing heterocyclic systems already reported,[5,11] gave reasonably stable and isolable selenoxides **10** and **11** as single 1,3-*trans* stereoisomer (Scheme 4).



Scheme 4. Synthesis of benzoselenazine selenoxides **10** and **11**.

With these new selenium-containing heterocycles in hand, we decided to preliminarily test their GPx-like catalytic antioxidant activity. We chose *N*-Ts derivative **4b** and the corresponding *N*-unsubstituted derivative (i.e., **8**). Thus, we had a pair of structures that are identical apart from the presence of the protecting group on nitrogen, a feature that could modify the nucleophilic character of the selenium atom. The catalytic activity of these compounds was investigated following a literature procedure[12] for the reaction between hydrogen peroxide (H_2O_2) and reduced dithiothreitol (DTT^{red}). The oxidation of the substrate was monitored by ^{1}H NMR spectroscopy. [D_4]Methanol (CD_3OD) was selected as the solvent[13] for this assay. A control experiment was carried out in the absence of catalyst. As shown in Figure 2, when the reaction was carried out in the presence of **4b**, 96 % of DTT^{red} remained unreacted after 200 min. In contrast, when *N*-unsubstituted benzo[*b*]selenazine **8** was used as the catalyst, 50 % of oxidised dithiothreitol (DTT^{ox}) was formed within 150 min. These results showed that the catalytic function of the heterocycles is strongly influenced by the nucleophilic character of the selenium atom, and by the presence of free amine groups. In this context, it has been reported that free amines behave as good base catalysts for DTT^{red} oxidation.[12a] To compare the activity of our new compounds with a selenium derivative commonly used as a standard,[14,15] we also measured the GPx-like catalytic activity of diphenyldiselenide; as expected, this was appreciably more active (Figure 2 purple line).

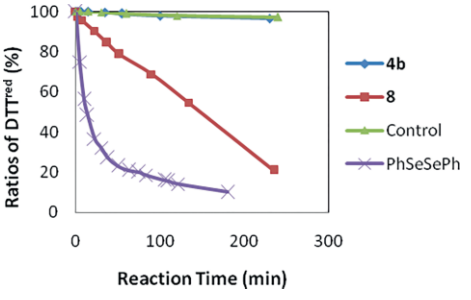


Figure 2. GPx-like activity of compounds **4b**, **8**, and diphenyl diselenide in the formation of DTT^{ox} from DTT^{red} with H_2O_2 in CD_3OD.

Conclusions

In this paper, we report an original yet general approach to the preparation of benzo[*b*][1,4]selenazines from 2-sulfonylamino-aryl diselenides. The procedure takes place in one pot using a substoichiometric amount of $Cu(OTf)_2$ and a weak base. The reaction takes place through a 1,4-elimination at selenium of a selenolate anion, resulting in the generation of an *o*-imino-selenone. The former is oxidised by air to reform the starting diselenide; the latter is trapped as an electron-poor diene in an efficient [4+2] cycloaddition with electron-rich alkenes. Substitution is well tolerated on the dienophile, the nitrogen, and the diselenide aromatic ring. This opens the way to a wide variety of benzo-fused selenazines.

Experimental Section

General Remarks: ^{1}H and ^{13}C NMR spectra were recorded with a Varian Mercury Plus instrument at 400 and 100 MHz, respectively, or with a Varian INOVA instrument at 400 and 100 MHz, respectively, in $CDCl_3$ or $(CD_3)_2CO$. The corresponding residual non-deuterated

solvent was used as a reference. ^{77}Se NMR spectra were recorded in $CDCl_3$ at 76 MHz with a Bruker Ultrashield 400 Plus instrument. PhSeSePh was used as an external reference (δ = 461 ppm). FTIR spectra were recorded with a Perkin–Elmer 1600 FTIR spectrometer in CCl_4 or $CDCl_3$ solutions. Melting points were measured with a Büuchi 510 melting-point apparatus. Elemental analysis was carried out with a Perkin–Elmer 2400 series II elemental analyser. GC mass spectra were recorded with a QMD 100 Carlo–Erba instrument. Reactions were monitored by TLC using commercially available precoated plates (silica gel 60 F 254), and products were visualised with acidic vanillin solution. Silica gel 60, 230–400 mesh, was used for column chromatography. Dry solvents were obtained using a Pure Solv Micro system. $CHCl_3$ and Et_3N were purified following standard procedures. Commercially available reagents and catalysts were used as obtained from freshly opened containers without further purification.

A general procedure for the synthesis of 2-nitroaryl diselenides, 2-aminoaryl diselenides **5**, and 2-*N*-sulfonylaminoaryl diselenides **1**[7] is reported. Spectroscopic data for these compounds is available in the Supporting Information. Derivatives **5a** and **1a** were prepared as already reported.[4]

General Procedure for the Synthesis of 2-Nitroaryl Diselenides: In a round-bottomed flask, a mixture of elemental selenium (158 mg, 2.0 mmol) and KOH (224 mg, 4.0 mmol) was melted with a thermal blower. The resulting mixture was cooled to room temperature, and diluted with distilled water (4 mL). Then the corresponding *o*-halonitrobenzene (1.0 mmol) and THF (1 mL) were added, and the mixture was stirred for 0.5 to 2 h, depending on the substrate. When the reaction was complete, the product was extracted with EtOAc (20 mL), and the organic phase was washed with H_2O (3 × 20 mL). The organic phase was dried with $MgSO_4$, and filtered, and the solvent was removed under reduced pressure. The product was purified by flash column chromatography eluting with an appropriate mixture of hexane/ethyl acetate.

General Procedure for the Synthesis of 2-Aminoaryl Diselenides 5: The appropriate 2-nitroaryl diselenide (1.0 mmol), methanol (20 mL), $FeSO_4$·$7H_2O$ (5.0 mmol, 1.390 g), and distilled water (20 mL) were added to a two-necked round-bottomed flask equipped with a reflux condenser. The reaction mixture was stirred at reflux for 1.5 h. After this time, NH_4OH (10 mL) was added, and the mixture was stirred under reflux for 10 min. A black mixture was formed after the addition of the NH_4OH. Then the mixture was cooled to room temperature, diluted with ethyl acetate (50 mL), filtered, and washed with H_2O (3 × 20 mL). The organic phase was dried with $MgSO_4$, and filtered, and the solvent was removed under reduced pressure. The product was purified by flash column chromatography eluting with an appropriate mixture of hexane/ethyl acetate.

General Procedure for the Synthesis of 2-*N*-Sulfonylaminoaryl Diselenides 1b–1e, 6, 7: A solution of sulfonyl chloride (1.75 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise under a nitrogen flow to a solution of bis(2-aminophenyl) diselenide (0.73· mmol) in dry CH_2Cl_2 (5 mL) and dry pyridine (0.118 mL, 1.46 mmol). The reaction mixture was heated at reflux for 44 h, then it was cooled to room temp. and diluted with CH_2Cl_2 (40 mL). The organic phase was washed with H_2O (3 × 40 mL), and saturated aq. NH_4Cl (2 × 40 mL), and dried with anhydrous Na_2SO_4. The solvents were evaporated under vacuum. Purification by silica gel column chromatography gave derivative **1b**–**1e**, **6**, **7**.

General Procedure for the Synthesis of Selenazines 4: $Cu(OTf)_2$ (0.016 mmol, 20 mol-%), *p*-methoxystyrene (21 mg, 0.16 mmol, 1 equiv.) and Et_3N (8 mg, 0.08 mmol, 0.5 equiv.) were added in sequence to a solution of 2-*N*-sulfonyl diselenide **1a**–**1e**, **6**, **7** (0.08 mmol, 1 equiv.) in dry solvent (0.03 M) in a reaction vial. The mixture was heated at the right temperature until TLC showed complete disappearance of the diselenide. Then, the reaction mixture was diluted with dichloromethane (40 mL), washed with saturated NH_4Cl (40 mL), and dried with anhydrous Na_2SO_4, and the solvents were evaporated to dryness. Purification by silica gel column chromatography gave derivative **4a**–**4g**.

4-Tosyl-3,4-dihydro-2*H*-benzo[*b*][1,4]selenazine (4a): The reaction mixture was heated in dry $CHCl_3$ at 60 °C for 72 h. Purification by silica gel column chromatography (dichloromethane/petroleum ether, 3:1, R_f = 0.70) gave derivative **4a** (55 mg, 75 %) as a white solid, m.p. 50–51 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.47–7.43 (m, 2 H), 7.34–7.30 (m, 2 H), 7.21 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.20–7.15 (m, 3 H), 7.04 (td, *J* = 7.6, 1.6 Hz, 1 H), 6.81–6.77 (m, 2 H), 5.74 (at, *J* = 6.6 Hz, 1 H), 3.75 (s, 3 H), 3.36 (dd, *J* = 12.2, 6.6 Hz, 1 H), 3.04 (dd, *J* = 12.2, 6.6 Hz, 1 H), 2.40 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 143.5, 136.7, 135.5, 132.1, 131.3, 130.4, 129.3 (2 C), 128.8, 127.8, 127.5, 126.8, 126.6, 113.9, 59.7, 55.2, 27.0, 21.6 ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 212 ppm. $C_{22}H_{21}NOSSe$ (426.43): calcd. C 57.64, H 4.62, N 3.06; found C 58.01, H 4.95, N 3.02.

6-Chloro-3-(4-methoxyphenyl)-4-tosyl-3,4-dihydro-2*H*-benzo[*b*][1,4]selenazine (4b): The reaction mixture was heated in DMF at 80 °C for 24 h. Purification by silica gel column chromatography (dichloromethane/petroleum ether, 5:1, R_f = 0.70) gave derivative **4b** (46 mg, 58 %) as a glassy solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 2.2 Hz, 1 H), 7.50–7.48 (m, 2 H), 7.31–7.27 (m, 2 H), 7.21–7.19 (m, 2 H), 7.13 (d, *J* = 8.3 Hz, 1 H), 7.01 (dd, *J* = 8.3, 2.2 Hz, 1 H), 6.82–6.78 (m, 2 H), 5.75 (at, *J* = 6.3 Hz, 1 H), 3.76 (s, 3 H), 3.37 (dd, *J* = 12.2, 6.3 Hz, 1 H), 3.07 (dd, *J* = 12.2, 6.3 Hz, 1 H), 2.40 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2, 144.1, 136.7, 136.6, 131.9, 131.4, 131.0, 130.9, 129.6, 128.0, 127.6, 127.2, 126.6, 114.1, 59.1, 55.3, 26.4, 21.8 ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 213 ppm. IR: $\tilde{\nu}$ = 2935, 2260, 1611, 1513, 1461, 1352, 1251, 1165 cm^{-1}. $C_{22}H_{20}ClNO_3SSe$ (492.88): calcd. C 53.61, H 4.09, N 2.84; found C 53.65, H 4.05, N 2.84.

6-Bromo-3-(4-methoxyphenyl)-4-tosyl-3,4-dihydro-2*H*-benzo[*b*][1,4]selenazine (4c): The reaction mixture was heated in DMF 80 °C for 24 h. Purification by silica gel column chromatography (dichloromethane/petroleum ether, 3:1, R_f = 0.65) gave derivative **4c** (52 mg, 60 %) as a glassy solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 2.1 Hz, 1 H), 7.50–7.48 (m, 2 H), 7.30–7.28 (m, 2 H), 7.21–7.19 (m, 2 H), 7.15 (dd, *J* = 8.3, 2.1 Hz, 1 H), 7.06 (d, *J* = 8.3 Hz, 1 H), 6.82–6.78 (m, 2 H), 5.75 (at, *J* = 6.3 Hz, 1 H), 3.76 (s, 3 H), 3.36 (dd, *J* = 12.2, 6.3 Hz, 1 H), 3.07 (dd, *J* = 12.2, 6.3 Hz, 1 H), 2.41 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2, 144.1, 136.8, 136.7, 133.6, 131.4, 131.3, 130.0, 129.7, 128.0, 127.6, 127.3, 119.4, 114.2, 59.1, 55.4, 26.4, 21.8 ppm. IR: $\tilde{\nu}$ = 2959, 2840, 2259, 1610, 1513, 1460, 1353, 1252, 1165, 1090 cm^{-1}. $C_{22}H_{20}BrNO_3SSe$ (537.33): calcd. C 49.18, H 3.75, N 2.61; found C 49.27, H 3.79, N 2.67.

3-(4-Methoxyphenyl)-4-tosyl-6-(trifluoromethyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]selenazine (4d): The reaction mixture was heated in $CHCl_3$ at 60 °C for 120 h. Purification by silica gel column chromatography (dichloromethane/petroleum ether, 1:1, R_f = 0.34) gave derivative **4d** (66 mg, 78 %) as a white solid, m.p. 192–198 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 1.2 Hz, 1 H), 7.51–7.48 (m, 2 H), 7.32–7.28 (m, 3 H), 7.24–7.20 (m, 3 H), 6.81–6.77 (m, 2 H), 5.82 (at, *J* = 5.8 Hz, 1 H), 3.74 (s, 3 H), 3.45 (dd, *J* = 12.1, 5.8 Hz, 1 H), 3.18 (dd, *J* = 12.1, 5.8 Hz, 1 H), 2.41 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 144.1, 136.5, 135.6, 132.5, 130.4, 130.3, 129.6, 128.6 (q, $^2J_{C,F}$ = 32 Hz), 127.8, 127.4, 127.3 (q, $^3J_{C,F}$ = 10 Hz), 123.7

(q, $^1J_{C,F}$ = 270 Hz), 123.0 (q, $^3J_{C,F}$ = 10 Hz), 114.0, 57.7, 55.2, 25.4, 21.6 ppm. IR: $\tilde{\nu}$ = 2926, 2257, 1606, 1512, 1343, 1325, 1254, 1166, 1133 cm^{-1}. MS (EI): *m/z* = 526 $[M]^+$. $C_{23}H_{20}F_3NO_3SSe$ (526.43): calcd. C 52.48, H 3.83, N 2.66; found C 52.51, H 3.79, N 2.60.

3-(4-Methoxyphenyl)-6-methyl-4-tosyl-3,4-dihydro-2*H*-benzo[*b*][1,4]selenazine (4e): The reaction mixture was heated in DMF 80 °C for 21 h. Purification by silica gel column chromatography (dichloromethane/petroleum ether, 5:1, R_f = 0.50) gave derivative **4e** (57 mg, 75 %) as a pale yellow glassy solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (d, *J* = 8.2 Hz, 1 H), 7.46–7.44 (m, 2 H), 7.32–7.29 (m, 2 H), 7.18–7.16 (m, 2 H), 7.03 (d, *J* = 1.3 Hz, 1 H), 6.97 (dd, *J* = 8.2, 1.3 Hz, 1 H), 6.81–6.77 (m, 2 H), 5.70 (at, *J* = 6.7 Hz, 1 H), 3.75 (s, 3 H), 3.32 (dd, *J* = 12.2, 6.7 Hz, 1 H), 3.01 (dd, *J* = 12.2, 6.7 Hz, 1 H), 2.40 (s, 3 H), 2.25 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 143.6, 137.0, 132.9, 132.4, 131.1, 130.9, 129.4, 128.4, 127.9, 127.8, 127.6, 114.0, 59.7, 55.3, 29.8, 26.9, 21.7 ppm. IR: $\tilde{\nu}$ = 2962, 2928, 2852, 1610, 1512, 1348, 1251, 1165 cm^{-1}. $C_{23}H_{23}NO_3SSe$ (472.46): calcd. C 58.47, H 4.91, N 2.96; found C 58.54, H 5.01, N 3.02.

6-Chloro-3-(4-methoxyphenyl)-4-[(2-nitrophenyl)sulfonyl]-3,4-dihydro-2*H*-benzo[*b*][1,4]selenazine (4f): The reaction mixture was heated in DMF 80 °C for 90 h. Purification by silica gel column chromatography (dichloromethane/petroleum ether, 3:1, R_f = 0.70) gave derivative **4f** (60 mg, 72 %) as a brown glassy solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.66 (m, 1 H), 7.60 (d, *J* = 2.2 Hz, 1 H), 7.57–7.54 (m, 1 H), 7.49–7.45 (m, 1 H), 7.39–7.37 (m, 1 H), 7.30–7.25 (m, 3 H), 7.15 (dd, *J* = 8.3, 2.2 Hz, 1 H), 6.83–6.80 (m, 2 H), 5.94 (at, *J* = 7.4 Hz, 1 H), 3.77 (s, 3 H), 3.53 (dd, *J* = 16.0, 7.4 Hz, 1 H), 3.11 (dd, *J* = 16.0, 7.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4, 136.5, 134.1, 132.8, 132.0, 131.9, 131.8, 131.6, 131.2, 130.9, 129.0, 128.1, 123.9, 114.3, 61.2, 55.4, 28.6 ppm. IR: $\tilde{\nu}$ = 2931, 1544, 1514, 1374, 1251, 1177 cm^{-1}. $C_{21}H_{17}ClN_2O_5SSe$ (523.85): calcd. C 48.15, H 3.27, N 5.35; found C 48.24, H 3.15, N 5.41.

3-(4-Methoxyphenyl)-4-[(2-nitrophenyl)sulfonyl]-6-(trifluoromethyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]selenazine (4g): The reaction mixture was heated in toluene at 110 °C for 240 h. Purification by silica gel column chromatography (dichloromethane/petroleum ether, 3:1, R_f = 0.70) gave derivative **4g** (74 mg, 83 %) as a white solid, m.p. 157–160 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74–7.68 (m, 2 H), 7.60–7.58 (m, 1 H), 7.53–7.49 (m, 1 H), 7.46–7.42 (m, 2 H), 7.37–7.35 (m, 1 H), 7.30–7.27 (m, 2 H), 6.80 (d, *J* = 8.0 Hz, 2 H), 5.97 (at, *J* = 8.0 Hz, 1 H), 3.75 (s, 3 H), 3.63 (dd, *J* = 12.0, 8.0 Hz, 1 H), 3.23 (dd, *J* = 12.0, 8.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2, 148.0, 135.5, 134.8, 134.2, 132.0, 131.3, 131.1, 130.9, 130.6, 129.2 (q, $^2J_{C,F}$ = 30 Hz), 127.9, 127.8 (q, $^3J_{C,F}$ = 10 Hz), 123.9, (q, $^2J_{C,F}$ = 30 Hz), 123.5 (q, $^1J_{C,F}$ = 270 Hz), 114.1, 59.6, 55.2, 27.3 ppm. IR: $\tilde{\nu}$ = 3650, 2932, 1545, 1513, 1326, 1176, 1136 cm^{-1}. $C_{22}H_{17}F_3N_2O_5SSe$ (557.40): calcd. C 47.40, H 3.07, N 5.03; found C 47.72, H 3.22, N 5.21.

6-Chloro-3-(4-methoxyphenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]-selenazine (8): Thioacetic acid (17 µL, 0.24 mmol, 4.0 equiv.) and lithium hydroxide (14 mg, 0.48 mmol, 8.0 equiv.) were added to a solution of **4f** (30 mg, 0.06 mmol) in dry DMF (3.0 mL) under nitrogen. The mixture was stirred at 60 °C for 72 h, then it was diluted with EtOAc (20 mL), and washed with saturated aq. $NaHCO_3$ (15 mL). The organic phase was dried with anhydrous Na_2SO_4, and the solvents were evaporated to dryness. Purification by silica gel column chromatography (dichloromethane/petroleum ether, 3:1, R_f = 0.80) gave derivative **8** (11 mg, 55 %) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.26 (m, 2 H), 7.08 (d, *J* = 8.0 Hz, 1 H), 6.94–6.90 (m, 2 H), 6.62 (dd, *J* = 8.0, 2.0 Hz, 1 H), 6.49 (d, *J* = 2.0 Hz, 1 H), 4.63 (dd, *J* = 9.9, 2.6 Hz, 1 H), 4.08 (br. s, 1 H), 3.82 (s, 3 H), 3.27 (dd, *J* = 11.3, 9.9 Hz, 1 H), 2.94 (dd, *J* = 11.3, 2.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.8, 145.5, 135.3, 131.6, 130.8, 127.9, 119.0, 115.8, 114.5, 108.5, 56.3, 55.5, 25.9 ppm. IR: $\tilde{\nu}$ = 3365, 2939, 1583, 1512, 1465, 1251 cm^{-1}. $C_{15}H_{14}ClNOSe$ (338.69): calcd. C 53.19, H 4.17, N 4.14; found C 53.12, H 4.20, N 4.10.

3-(4-Methoxyphenyl)-6-(trifluoromethyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]selenazine (9): Thioacetic acid (4 µL, 0.06 mmol, 2.0 equiv.) and lithium hydroxide (3 mg, 0.12 mmol, 4.0 equiv.) were added to a solution of **4g** (17 mg, 0.03 mmol) in dry DMF (1.0 mL) under nitrogen. The mixture was stirred at 60 °C for 24 h, then it was diluted with EtOAc (20 mL), and washed with saturated aq. $NaHCO_3$ (15 mL). The organic phase was dried with anhydrous Na_2SO_4, and the solvents were evaporated to dryness. Purification by silica gel column chromatography (dichloromethane/petroleum ether, 8:1, R_f = 0.67) gave derivative **9** (7 mg, 62 %) as a colourless oil. ^{1}H NMR [400 MHz,$(CD_3)_2CO$]: δ = 7.37–7.30 (m, 3 H), 7.06 (s, 1 H), 6.96–6.93 (m, 2 H), 6.82 (d, *J* = 8.0 Hz, 1 H), 5.76 (br. s, 1 H), 4.70 (dd, *J* = 9.2, 2.8 Hz, 1 H), 3.80 (s, 3 H), 3.30 (dd, *J* = 11.2, 9.2 Hz, 1 H), 3.07 (dd, *J* = 11.2, 2.8 Hz, 1 H) ppm. ^{13}C NMR [100 MHz,$(CD_3)_2CO$]: δ = 161.5, 147.5, 137.3, 135.8, 131.8, 129.8, 129.4 (q, $^2J_{C,F}$ = 30 Hz), 126.5 (q, $^1J_{C,F}$ = 270 Hz), 115.9, 115.4 (q, $^3J_{C,F}$ = 10 Hz), 113.9 (q, $^3J_{C,F}$ = 10 Hz), 57.3, 56.6, 27.3 ppm. IR: $\tilde{\nu}$ = 2928, 1601, 1512, 1464, 1325, 1250, 1173, 1127, 1079 cm^{-1}. $C_{16}H_{14}F_3NOSe$ (372.25): calcd. C 51.63, H 3.79, N 3.76; found C 51.37, H 3.35, N 3.83.

3-(4-Methoxyphenyl)-4-tosyl-6-(trifluoromethyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]selenazine 1-Oxide (10): A solution of *m*CPBA (9 mg, 0.054 mmol, 0.95 equiv.) in dry CH_2Cl_2 (1 mL) was added to a solution of **4a** (26 mg, 0.057 mmol) in dry CH_2Cl_2 (1 mL) at 0 °C. The mixture was stirred at 0 °C for 20 min, then it was diluted with CH_2Cl_2 (20 mL), washed with Na_2SO_3 (20 mL) and with saturated aq. $NaHCO_3$ (20 mL), and dried with anhydrous Na_2SO_4. The solvents were evaporated to dryness to give derivative **10** (31 mg, 95 %) without further purification, m.p. 55–57 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.79–7.76 (m, 1 H), 7.56–7.52 (m, 3 H), 7.42–7.39 (m, 2 H), 7.26–7.23 (m, 2 H), 7.16–7.14 (m, 2 H), 6.82–6.79 (m, 2 H), 5.59 (dd, *J* = 9.8, 7.8 Hz, 1 H), 3.94 (dd, *J* = 11.8, 7.8 Hz, 1 H), 3.76 (s, 3 H), 2.99 (dd, *J* = 11.8, 9.8 Hz, 1 H), 2.42 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4, 144.9, 135.2, 133.4, 131.8, 131.6, 131.2, 130.1, 129.0, 128.1, 127.1, 126.3, 114.3, 55.8, 55.3, 54.5, 21.6 ppm. MS: *m/z* (%) = 459 (28), 304 (80), 223 (60), 134 (64), 91 (100). $C_{22}H_{21}NO_4SSe$ (474.43): calcd. C 55.70, H 4.46, N 2.95; found C 55.83, H 4.57, N 2.99.

6-Chloro-3-(4-methoxyphenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]-selenazine 1-Oxide (11): A solution of *m*CPBA (4 mg, 0.022 mmol, 0.95 equiv.) in dry CH_2Cl_2 (0.5 mL) was added to a solution of **8** (8 mg, 0.024 mmol) in dry CH_2Cl_2 (0.5 mL) at 0 °C. The mixture was stirred at 0 °C for 2 h. Purification by silica gel column chromatography (EtOAc/MeOH, 10:1, R_f = 0.45) gave derivative **11** (4 mg, 50 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 8.3 Hz, 1 H), 7.43–7.40 (m, 2 H), 6.97–6.93 (m, 2 H), 6.76 (dd, *J* = 8.3, 1.9 Hz, 1 H), 6.72 (d, *J* = 1.9 Hz, 1 H), 5.12–5.08 (m, 1 H), 4.63 (s, 1 H), 3.84 (s, 3 H), 3.04–2.93 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3, 146.3, 139.5, 134.2, 132.1, 128.6, 127.9, 118.6, 116.9, 114.9, 55.6, 47.2, 29.9 ppm. IR: $\tilde{\nu}$ = 3689, 2928, 2852, 2359, 2253, 1591, 1512, 1466, 1251, 1092 cm^{-1}. $C_{15}H_{14}ClNO_2Se$ (354.69): calcd. C 50.79, H 3.98, N 3.95; found C 50.91, H 3.87, N 3.91.

GPx-Like Catalytic Activity:[12b] In the NMR assay, DTT^{red} (0.15 mmol) and Se catalyst (0.015 mmol) were dissolved in CD_3OD (1.1 mL), and the solution was added to H_2O_2 (35 % aq.; 15 µL, 0.15 mmol) to start the reaction. ^{1}H NMR spectra were measured at variable reaction times at 25 °C. The relative populations of DTT^{red}

and DTT^{ox} were determined by integration of the signals in the ^1H NMR spectra.

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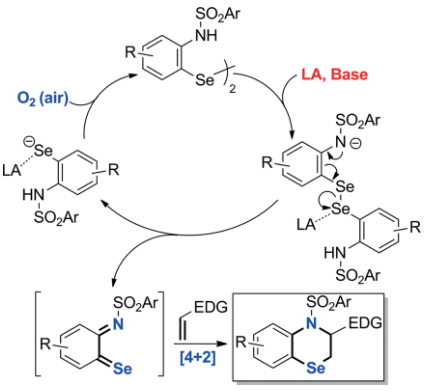

2-Sulfonylaminoaryl diselenides are transformed in one pot into benzo[*b*][1,4]selenazines using a sub-stoichiometric amount of $Cu(OTf)_2$, through a base-mediated 1,4-elimination at selenium, and generation of a dienic *o*-iminoselenoquinone

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