# Convenient Synthesis, Characterization and GPx-Like Catalytic Activity of Novel Ebselen Derivatives

**Sanjio S. Zade,[a] Snigdha Panda,[a] Santosh K. Tripathi,[a] Harkesh B. Singh,*[a] and Gotthelf Wolmershäuser[b]**

**Keywords:** Ebselen / Nonbonding interactions / Benzisochalcogenazolone / Te−N heterocycles / *ortho*-Lithiation

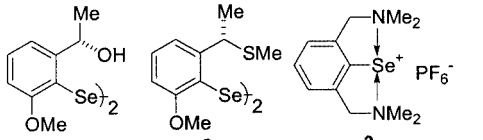
The synthesis and characterization of benzisochalcogenazolones (ebselen derivatives **16**–**21**) is described. The synthesis of **16**–**21** was achieved by treating the bromo precursors **11**–**13** with an appropriate dilithium dichalcogenide. The synthesis of benzisoselenazolones **16** and **18** was also accomplished by an alternative route, that is, by treating the corresponding methoxymethyl selenides **22** and **23** with 1 equiv. of bromine. The synthesis of methoxymethyl selenides **22** and **23** was accomplished by lithiation of the bromo precursors followed by treatment with bis(methoxymethyl) diselenide. The benzisoselenazolones **16** and **17** were characterized by single-crystal X-ray techniques. The GPx-like catalytic activities of compounds **16**–**18** and **21** were determined by using the coupled reductase assay. Compound **16** was found to be less active than ebselen **8** whereas compounds **17** and **18** were more active than ebselen in this assay. Compound **21** showed a 1.5-fold higher activity than its selenium analogue **17**.

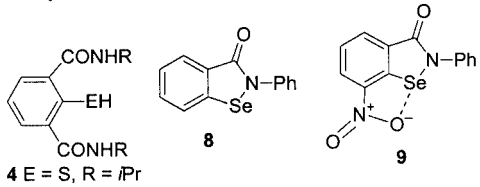

## Introduction

The chemistry of organoselenium derivatives stabilized by intramolecular nonbonding interactions (Se···X; X = N, O, S) has attracted considerable interest because of their applications as (a) chiral reagents in asymmetric synthesis,[1] (b) ligands in the isolations of monomeric MOCVD precursors,[2] (c) ligands for chiral/achiral catalysis[3] and (d) glutathione peroxidase mimics.[4] In recent studies, Tiecco[1g] and Wirth[1h] and their co-workers reported that even better enantioselectivity could be obtained in asymmetric methoxyselenenylation of double bonds by introducing substituents with specific heteroatoms at all the *ortho* positions to selenium in diaryl diselenide (**1** and **2**). Intramolecular nonbonding interactions by two heteroatoms in organoselenium compounds also allow the isolation of rather unstable selenenium cations, for example, the cation **3** is stabilized by chelation with two tertiary amino groups.[5] More recently, Kersting and DeLion reported the synthesis of chalcogenols **4**−**7** by *ortho*-lithiation and selenium insertion, followed by hydrolysis with HCl.[6] The reaction, however, afforded the corresponding benzisochalcogenazolones by air oxidation, followed by disproportionation.

One of our groups reported a series of organochalcogens that are stabilized by an *ortho*-coordinating group.[7] As a continuation of this work, we have started a systematic study of the synthesis, structural characterization and reactions of organochalcogens that have two *ortho*-coordinating groups. Our efforts to synthesize the desired organochalcogen derivatives with two alkyl/arylcarbamoyl groups by treating *N*,*N*′-dialkyl/diphenyl-2-bromo-5-*tert*-butylisophthalamide with $Li_2E_2$ (E = S, Se, Te), interestingly, afforded ebselen derivatives.

Ebselen (**8**) [2-phenylbenzisoselenazol-3(2*H*)-one], its derivatives and analogues[8] are good glutathione peroxidase mimics, antiinflammatory, antiatherosclerotic, anticancer and antimicrobial agents, as well as immunostimulants, cytokine inducers and nitric acid synthase inhibitors.[9]




**4** E = S, R = *i*Pr
**5** E = S, R = *t*Bu
**6** E = Se, R = *i*Pr
**7** E = Te, R = *i*Pr

[a] Department of Chemistry, Indian Institute of Technology, Bombay Powai, Mumbai 400 076, India
Fax: (internat.) + 91-22-2572-3480
E-mail: chhbsia@chem.iitb.ac.in
[b] Fachbereich Chemie, Universität Kaiserslautern, Postfach 3049, Kaiserslautern 67653, Germany
Fax: (internat.) + 49-(0)631-205-2187
E-mail: wolmersh@chemie.unk-kl.de
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

Although ebselen is a major GPx mimic, its synthesis has been a challenge[10] since it was first prepared in 1924.[11] In the earliest and most direct approach, 2,2′-diselenodibenzoic acid was converted into a chloroselenenylbenzoyl chloride which was treated with aniline to give ebselen.[10c] The most expedient method was reported by Engman and Hallberg[10d] and utilized a one-pot procedure in which benzanilide was *ortho*-lithiated, treated with selenium powder and then ring-closed by a cuprous bromide mediated oxidative procedure. A free-radical synthesis of ebselen has been achieved by intramolecular homolytic substitution with amidyl radicals.[10e,10f] It has been further observed that the ebselen derivative **9** with an *ortho*-coordinating nitro group is more active as a GPx mimic than the parent ebselen (**8**).[12] We report here a new general synthetic approach to 2-alkyl/phenyl-5-*tert*-butyl-7-(alkyl/phenylcarbamoyl)benzisochalcogenazol-3(2*H*)-one (substituted ebselen derivatives) using a one-pot procedure.

## Results and Discussion

### Synthesis

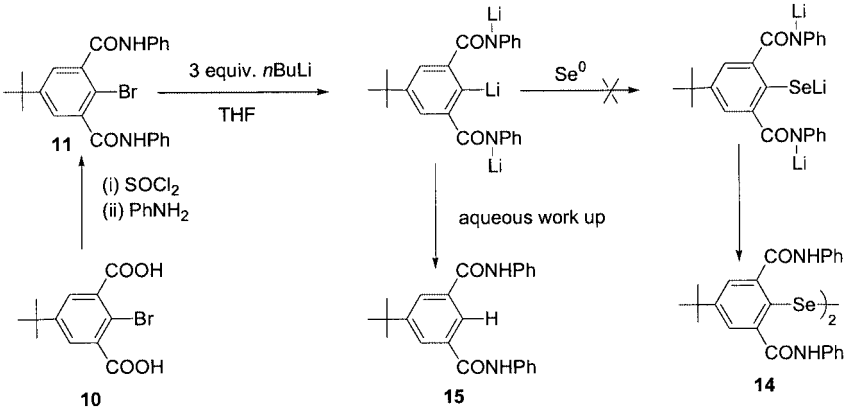
*N*,*N*′-Dialkyl/diphenyl-2-bromo-5-*tert*-butylisophthalamides **11**−**13** were prepared by treating 2-bromo-5-*tert*-butylisophthalic acid (**10**)[13] with thionyl chloride, followed by the reaction with the corresponding amines without isolating the bis(acyl chloride) (Schemes 1 and 2). To prepare diselenide **14**, the well-established route of lithiation, selenium insertion, followed by oxidation, was attempted.[7] The lithiation of **11** with 3 equiv. of *n*BuLi afforded a dark brown slurry; however, insertion of selenium into the C−Li bond was not successful and the final isolated product was the debrominated diamide **15** (Scheme 1).

The other well-known approach to diaryl diselenides involves the treatment of alkali metal diselenides with aryl bromides.[14] Surprisingly, treatment of compound **11** with dilithium diselenide in THF at reflux did not afford the expected diselenide **14**. Instead, the novel substituted ebselen **16** was obtained in high yield (Scheme 2). The reaction was complete at 100 °C in DMF within 1 h, whereas at reflux in THF it took 6 h for the reaction to go to completion.

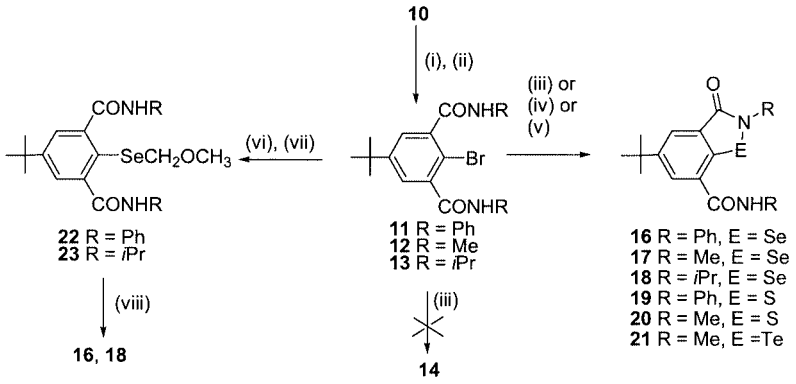
A similar procedure for the synthesis of benzisochalcogenazolone heterocycles by *ortho*-lithiation of dialkylisophthalamide, selenium insertion, followed by oxidation (Scheme 3) has been reported by Kersting and DeLion.[6] The mechanism involves the disproportionation of dichalcogenides to give an equimolar mixture of benzisochalcogenazolones and the corresponding selenol. However, reactions of dimethyl/diethylisophthalamide did not lead to the desired products probably because of the low solubility of the intermediate trilithium salts. The formation of the ebselen framework in this case probably occurs by the disproportionation of diselenide **14** to give benzisoselenazolone **16** as proposed by Kersting and DeLion.[6] The steric bulk may be the extra driving force for this mechanistic pathway.

To examine the general applicability of this synthetic method, the reactions of $Li_2Se_2$ were carried out with **12** and **13**. To our delight, the reactions led to good yields of **17** and **18**. Benzisothiazolones **19** and **20** were similarly synthesized in good yields by the treatment of **11** and **12** with dilithium disulfide. When **11**−**13** were treated with dilithium ditelluride, the expected benzisotellurazolones were obtained in very low yields with the debrominated isophthalamides as the predominant products; only the benzisotellurazolone **21** was isolated and characterized by spectroscopic methods. Only one report on the synthesis and characterization of benzisotellurazolones has appeared in the literature.[6]

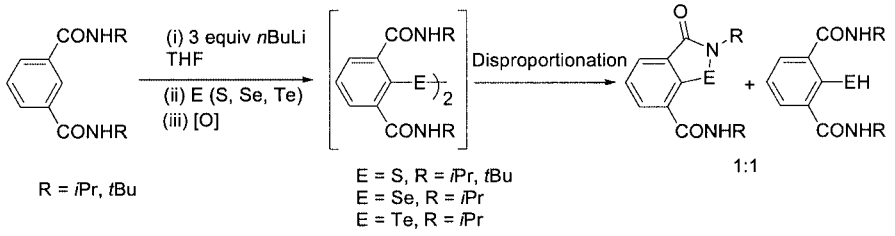
Aryl methoxymethyl selenides are known to afford the corresponding arylselenenyl bromides on treatment with bromine (1 equiv.) solution,[1e] which, in turn, can be converted into diaryl diselenides by reduction with sodium borohydride. With this in mind, the methoxymethyl selenides **22** and **23** were synthesized by lithiation of **11** and **13**, respectively, with 3 equiv. of *n*BuLi, followed by treatment with 1 equiv. of bis(methoxymethyl) diselenide (Scheme 2). The yields of the selenides **22** and **23** were poor. The isolation of pure selenides also proved quite difficult due to contamination of the debrominated products. Interestingly,




Scheme 1




Scheme 2. Reagents and conditions: (i) $SOCl_2$, reflux, 4 h; (ii) $RNH_2$, $CH_2Cl_2$, 0 °C → room temp., 12 h; (iii) $Li_2Se_2$, THF/DMF, reflux, 0.5−1 h; (iv) $Li_2S_2$, THF, reflux, 12−15 h; (v) $Li_2Te_2$, THF/DMF, reflux, 1 h; (vi) 3 equiv. *n*BuLi, THF, −45 °C; (vii) $(CH_3OCH_2)_2Se_2$, THF, 0 °C → room temp.; (viii) $Br_2$, $CHCl_3$, 0 °C → room temp.



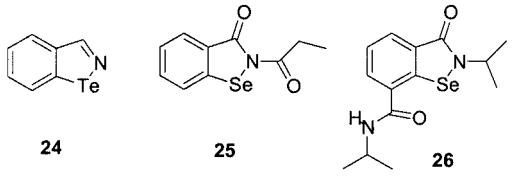

Scheme 3

the treatment of selenides **22** and **23** with 1 equiv. of bromine again afforded the corresponding benzisoselenazolones **16** and **18** instead of the expected selenenyl bromides.

### Spectroscopic Studies

The $^1H$ NMR spectra of diamides **11**−**13** indicate the symmetric nature of these compounds in solution. The aromatic protons of the tetrasubstituted phenyl ring of **11**−**13** appear as a singlet whereas they appear as two different signals in the spectra of benzisoselenazolones **16**−**18**. In the case of **16**, these signals were obtained as two doublets with *meta* coupling ($J$ = 2 Hz). The protons of the two methyl groups in **17** appear as a singlet and doublet, whereas they are present as a doublet in the spectrum of the precursor diamide **12**. In a similar way, the tertiary protons of the isopropyl groups of **18** appear as a septuplet and multiplet whereas the spectrum of diamide **13** exhibits only one septuplet for these two protons. These observations support the formation of the benzisoselenazolone rings. Similar observations were obtained for the sulfur (**19**, **20**) and tellurium analogues (**21**). The aromatic protons of the tetrasubstituted phenyl ring of selenides **22** and **23** appear as a singlet, which indicates the symmetric nature of these two selenides.

$^{77}Se$ NMR spectroscopy serves as an important tool for monitoring these reactions as the chemical shifts of the selenium signal in benzisoselenazolones have a specific range.[10e,10f] The $^{77}Se$ NMR spectra of benzisoselenazolones **16**−**18** exhibit signals at δ = 907, 880 and 822 ppm, respectively, which are well within the range of chemical shifts of related compounds.[10e,10f] The $^{125}Te$ NMR spectrum of benzisotellurazolone **21** exhibits a signal at δ = 1435 ppm, which compares well with the chemical shift of the related Te−N heterocycle benzisotellurazole (**24**) (δ = 1589 ppm).[15]




In the mass spectra (ES-MS and FAB) of the benzisochalcogenazolones, the base peaks correspond to the molecular ion peaks; this indicates the high stability of these compounds under mass spectrometric conditions. Molecular ion peaks were not observed for compounds **22** and **23**. However, the base peaks correspond to $[M - CH_2OCH_3]^+$, which indicates the lability of the methoxymethyl group attached to the selenium atom in **22** and **23**. The IR spectra of compounds **11**−**13** and **16**−**23** exhibit peaks at 1600−1660 and 1520−1560 $cm^{-1}$, which correspond to the amide I and amide II bands, respectively. However, the carbonyl band of the open-chain secondary amide cannot be distinguished from that of the ring amide.

### Crystal Structures of Compounds 16 and 17

An ORTEP view of compound **16** is shown in Figure 1, and selected bond lengths and bond angles are listed in Table 1. The coordination geometry around the Se atom is

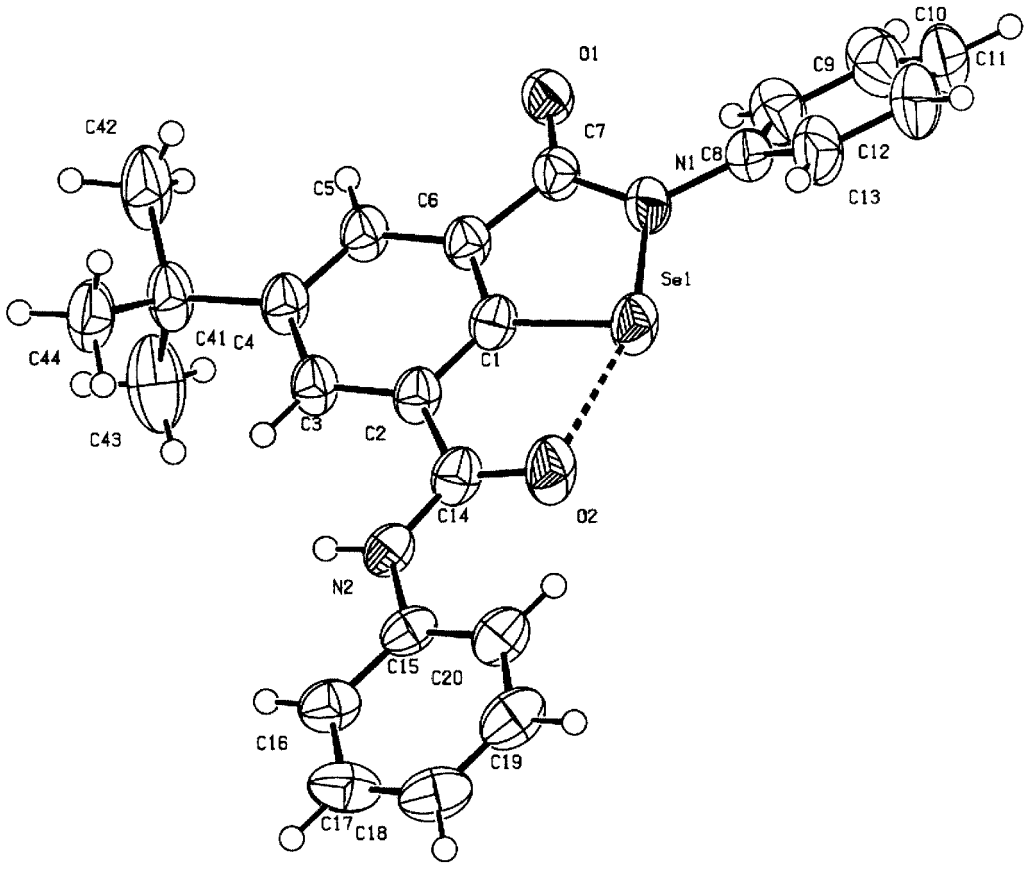



Figure 1. Molecular structure of compound **16**

V-shaped with a bond angle of 84.33(10)°, which is similar to that reported for the parent ebselen [2-phenylbenzisoselenazol-3(2*H*)-one] [85.8(1)°],[16] 7-nitro-2-phenylbenzisoselenazol-3(2*H*)-one (**9**) [85.49(17)°],[17] 2-propionylbenzisoselenazol-3(2*H*)-one (**25**) [85.19(19)°][16] and 7-isopropylcarbamoyl-2-isopropylbenzisoselenazol-3(2*H*)-one (**26**) [84.46(18), 84.74(18)°].[6b] The geometry around the ring nitrogen atom is nearly planar with bond angles of Se(1)−N(1)−C(7) = 115.87(16)°, Se(1)−N(1)−C(8) = 119.98(17)° and C(7)−N(1)−C(8) = 124.1(2)°. These values compare well with the corresponding values for **9**, **25** and **26**. The C(1)−Se(1) [1.856(2) Å] distance is slightly shorter than the sum of the Pauling covalent radii (1.91 Å) and the Se(1)−N(1) [1.916(2) Å] distance is slightly longer than the sum of the Pauling covalent radii (1.87 Å). However, these values are similar to those reported for **9**, **25** and **26**. Of particular interest is the intramolecular interaction between the selenium atom and the oxygen atom of the carboxamide group. Interestingly, the Se(1)···O(2) distance [2.435(2) Å] is significantly shorter than the sum of the van der Waals radii of these two atoms (3.4 Å) and is slightly shorter than that observed in **9** [2.562(4) Å], **25** [2.806(4) Å] and **26** [2.453(3), 2.496(3) Å].

An ORTEP view of compound **17** is shown in Figure 2, and selected bond lengths and bond angles are listed in Table 2. The compound is isostructural with **16**. The coordination geometry around Se is V-shaped with a bond angle of 84.91(14)°. The geometry around the ring nitrogen atom is nearly planar with bond angles of Se(1)−N(1)−C(7) = 116.4(3)°, Se(1)−N(1)−C(8) = 121.1(3)° and C(7)−N(1)−C(8) = 122.4(3)°. The Se(1)···O(2) distance [2.553(3) Å] is significantly shorter than the sum of the van der Waals radii of these two atoms (3.4 Å).

Table 1. Selected bond lengths [Å] and bond angles [°] of compound **16**

| | | | |
|---|---|---|---|
| Se(1)−C(1) | 1.856(2) | C(1)−Se(1)−N(1) | 84.33(10) |
| Se(1)−N(1) | 1.916(2) | C(7)−N(1)−C(8) | 124.1(2) |
| Se(1)···O(2) | 2.435(2) | C(7)−N(1)−Se(1) | 115.87(16) |
| | | C(8)−N(1)−Se(1) | 119.98(17) |

### GPx-Like Catalytic Activity

The catalytic activities were studied by using the coupled reductase assay.[4a] The GPx activities of compounds **16**−**18** and **21** are listed in Table 3. Organoselenium compounds that have intramolecularly coordinating basic amino groups have been studied extensively as Se···N nonbonding interactions are known to enhance the catalytic capacity of these antioxidant agents.[4] The enhancement of the activities of compounds **17** and **18** relative to that of ebselen can be

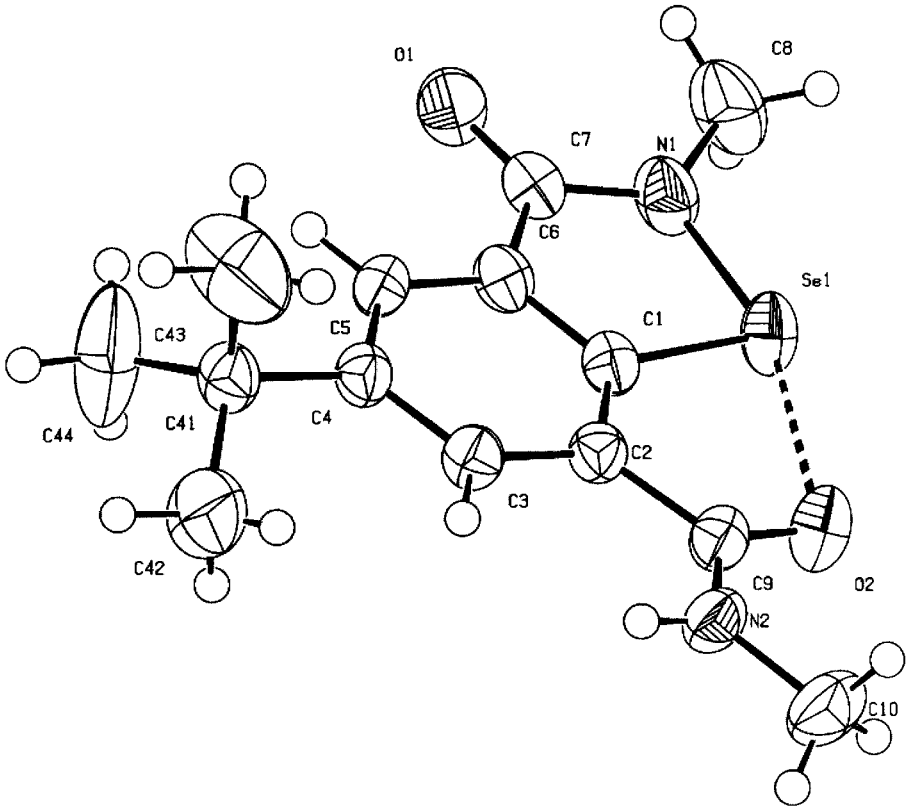



Figure 2. Molecular structure of compound **17**

Table 2. Selected bond lengths [Å] and bond angles [°] of compound **17**

| | | | |
|---|---|---|---|
| Se(1)−C(1) | 1.859(3) | C(1)−Se(1)−N(1) | 84.91(14) |
| Se(1)−N(1) | 1.884(3) | C(7)−N(1)−C(8) | 122.4(3) |
| Se(1)···O(2) | 2.553(3) | C(7)−N(1)−Se(1) | 116.4(3) |
| | | C(8)−N(1)−Se(1) | 121.1(3) |

ascribed to the Se···O intramolecular interaction. However, **16** showed significantly lower activity which could be attributed to its poor solubility. The reactivity toward hydroperoxides usually increases as one descends the chalcogen group. Generally, tellurium compounds are more active than the selenium analogues[18] and in this case the activity of compound **21** was 1.5 times greater than that of its selenium analogue.

Table 3. GPx activities of compounds **16**−**18** and **21**

| Compound | GPx activities[a] |
|---|---|
| Ebselen (**8**) | 4.96 |
| **16** | 1.84 |
| **17** | 15.71 |
| **18** | 7.06 |
| **21** | 23.73 |

[a] 50 μM of Se equiv., 1.2 mM of *t*BuOOH. Measured as the consumption of NADPH [$\mu M \cdot min^{-1}$].

## Conclusion

In conclusion, the reaction of dilithium diselenide/disulfide/ditelluride with *N*,*N*′-dialkyl/diphenyl-2-bromo-5-*tert*-butylisophthalamide affords the novel ebselen derivatives 2-alkyl/phenyl-7-(alkyl/phenylcarbamoyl)-5-*tert*-butylbenzisochalcogenazol-3(2*H*)-one. The yields of the benzisothiazolones and benzisoselenazolones were very good; however, the benzisotellurazolones were obtained in poor yields. Thus, this method provides a convenient alternative strategy to the synthesis of such compounds. Alternatively, benzisoselenazolones can be prepared via methoxymethyl selenides by the reaction with bromine. Benzisoselenazolones **17** and **18** showed higher GPx-like activity than ebselen, whereas compound **16** showed very poor activity. Benzisotellurazolone **21** is 1.5 times more active than the selenium analogue **17**.

## Experimental Section

**General Procedures:** All reactions were carried out under nitrogen or argon using standard vacuum-line techniques. Solvents were purified by standard procedures and were freshly distilled prior to use. Melting points were recorded in capillary tubes and are uncorrected. $^{1}H$ (299.94 MHz), $^{13}C$ (75.42 MHz), $^{77}Se$ (57.22 MHz) and $^{125}Te$ (94.75 MHz) spectra were recorded in $CDCl_3$ with a Varian VXR 300S or Bruker AMX 500 spectrometer at room temperature. Chemical shifts are referenced to TMS ($^{1}H$, $^{13}C$) as internal stand-

ard and to $Me_2Se$ ($^{77}Se$) and $Me_2Te$ ($^{125}Te$) as external standards. Elemental analyses were performed with a Carlo−Erba model 1106 elemental analyzer. IR spectra were recorded as KBr pellets with a Thermo Nicolet Avatar 320 FTIR spectrometer. FAB mass spectra were recorded at room temperature with a JEOL SX 102 DA-6000 mass spectrometer. ESI MS mass spectra were recorded at room temperature with a Q-Tof micro (YA-105) micromass spectrometer. Dilithium dichalcogenides,[14] 2-bromo-5-*tert*-butylisophthalic acid[13] and bis(methoxymethyl) diselenide[1e] were synthesized according to literature methods.

**2-Bromo-5-*tert*-butyl-*N*,*N*′-diphenylisophthalamide (11):** 2-Bromo-5-*tert*-butylisophthalic acid (**10**) (1.51 g, 5 mmol) was refluxed with thionyl chloride (3.6 mL, 50 mmol) for 4 h. Unreacted thionyl chloride was removed by distillation and any remaining traces were removed under vacuum. The liquid obtained was dissolved in $CH_2Cl_2$ (50 mL) and transferred to a dropping funnel mounted on a two-necked 250-mL flask. The flask was charged with aniline (1.2 g, 12 mmol), dissolved in 50 mL of $CH_2Cl_2$. The solution in the dropping funnel was added to the aniline solution at 0 °C. The resulting solution was warmed to room temperature and stirred overnight. The reaction mixture was washed with 10% aqueous NaOH (2 × 50 mL), water (2 × 50 mL) and 10% HCl (2 × 50 mL). The organic layer was washed with water, dried with sodium sulfate and concentrated to give a white solid which was purified by crystallization from dichloromethane. Yield 2.15 g, 98%. M.p. 254−256 °C. $^1$H NMR (300 MHz, [D$_6$]DMSO, 25 °C): δ = 1.34 (s, 9 H), 7.11 (t, *J* = 10.0 Hz, 2 H), 7.35 (t, *J* = 10.0 Hz, 4 H), 7.58 (s, 2 H), 7.73 (d, *J* = 10.0 Hz, 4 H), 10.54 (s, 2 H) ppm. $^{13}$C NMR (400 MHz, $CDCl_3$ + [D$_6$]DMSO, 25 °C): δ = 30.5, 34.2, 112.7, 119.5, 123.5, 125.8, 128.1, 138.1, 139.6, 150.5, 165.9 ppm. IR (KBr): $\tilde{\nu}$ = 3320 $\nu_{N-H}$, 1664, 1522 $\nu_{C=O}$ cm$^{-1}$. MS: *m*/*z* (%) = 451 (100) [M]$^+$, 358 (50). $C_{24}H_{23}BrN_2O_2$ (451.36): calcd. C 63.87, H 5.14, N 6.21; found C 64.11, H 5.13, N 6.07.

**2-Bromo-5-*tert*-butyl-*N*,*N*′-dimethylisophthalamide (12):** Compound **12** was prepared from **10** (1.51 g, 5 mmol), thionyl chloride (3.6 mL, 50 mmol) and methylammonium chloride (1.36 g, 20 mmol) according to the procedure described for the preparation of **11**. Yield: 1.28 g, 78%. M.p. 246−248 °C. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.29 (s, 9 H), 3.00 (d, *J* = 4.8 Hz, 6 H), 6.13 (br., 2 H), 7.44 (s, 2 H) ppm. $^{13}$C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 26.8, 31.0, 34.9, 112.7, 127.2, 139.3, 151.5, 168.9 ppm. IR (KBr): $\tilde{\nu}$ = 3231 $\nu_{N-H}$, 1639, 1547 $\nu_{C=O}$ cm$^{-1}$. MS: *m*/*z* (%) = 327 (100) [M]$^+$, 295 (7), 238 (37). $C_{14}H_{19}BrN_2O_2$ (327.22): calcd. C 51.39, H 5.85, N 8.56; found C 51.82, H 5.72, N 8.23.

**2-Bromo-5-*tert*-butyl-*N*,*N*′-diisopropylisophthalamide (13):** Compound **13** was prepared from **10** (1.51 g, 5 mmol), thionyl chloride (3.6 mL, 50 mmol) and isopropylamine (0.89 g, 15 mmol) according to the procedure described for the preparation of **11**. Yield: 1.68 g, 78%. M.p. 248−250 °C. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.28 (d, *J* = 6.4 Hz, 12 H), 1.30 (s, 9 H), 4.28 (m, 2 H), 5.71 (d, *J* = 7.2 Hz, 2 H), 7.43 (s, 2 H) ppm. $^{13}$C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 22.5, 31.0, 34.8, 42.3, 112.5, 126.8, 139.4, 151.5, 167.2 ppm. IR (KBr): $\tilde{\nu}$ = 3244 $\nu_{N-H}$, 1636, 1535 $\nu_{C=O}$ cm$^{-1}$. MS: *m*/*z* (%) = 383 (100) [M]$^+$. $C_{18}H_{27}BrN_2O_2$ (383.33): calcd. C 56.40, H 7.10, N 7.31; found C 56.23, H 6.97, N 7.02.

**5-*tert*-Butyl-2-phenyl-7-(phenylcarbamoyl)benzisoselenazol-3(2*H*)-one (16):** A brown solution of $Li_2Se_2$ (2.5 mmol) was prepared by treating lithium with an equivalent amount of selenium powder in the presence of a catalytic amount of naphthalene in THF. Diamide **11** (0.902 g, 2 mmol) and DMF (10 mL) were added to this stirred solution. The resulting solution was refluxed for 1 h. The brown reaction mixture turned colorless during the reflux period. After cooling to room temperature, the reaction mixture was poured into a solution of brine (100 mL). The resulting pale yellow precipitate was collected by filtration and dried. It was further purified on a silica gel column by using ethyl acetate/petroleum ether (1:9) as eluent. Yield: 0.76 g, 85%. M.p. 304−306 °C. $^1$H NMR (300 MHz, [D$_6$]DMSO, 25 °C): δ = 1.46 (s, 9 H), 7.25 (m, 2 H), 7.45 (t, *J* = 6.0 Hz, 4 H), 7.70 (m, 4 H), 8.15 (d, *J* = 2.0 Hz, 1 H), 8.86 (d, *J* = 2.0 Hz, 1 H), 11.07 (s, 1 H) ppm. $^{13}$C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 31.3, 35.2, 122.0, 124.0, 125.4, 125.6, 125.7, 127.7, 128.1, 128.9, 129.3, 129.4, 137.2, 137.7, 140.1, 151.3, 164.0, 165.2 ppm. $^{77}$Se NMR (500 MHz, $CDCl_3$, 25 °C): δ = 907.2 ppm. IR (KBr): $\tilde{\nu}$ = 3321 $\nu_{N-H}$, 1663, 1526 $\nu_{C=O}$ cm$^{-1}$. MS: *m*/*z* (%) = 451 (100) [M]$^+$, 435 (10), 358 (7). $C_{24}H_{22}N_2O_2Se$ (449.32): calcd. C 64.16, H 4.94, N 6.23; found C 63.80, H 5.13, N 6.52.

**5-*tert*-Butyl-2-methyl-7-(methylcarbamoyl)benzisoselenazol-3(2*H*)-one (17):** Compound **17** was prepared from **12** (0.65 g, 2 mmol) and $Li_2Se_2$ (2.5 mmol) according to the procedure described for the preparation of **16**. The crude solid was recrystallized from a concentrated chloroform solution of the compound. Yield: 0.53 g, 81%. M.p. 240 °C (dec.). $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.27 (s, 9 H), 3.12 (d, *J* = 4.8 Hz, 3 H), 3.41 (s, 3 H), 7.9 (br., 1 H), 8.11 (s, 1 H), 8.20 (s, 1 H) ppm. $^{13}$C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 27.2, 30.8, 31.4, 35.0, 125.0, 125.3, 127.9, 129.5, 138.2, 150.8, 167.0, 167.4 ppm. $^{77}$Se NMR (300 MHz, $CDCl_3$, 25 °C): δ = 880.5 ppm. IR (KBr): $\tilde{\nu}$ = 3276 $\nu_{N-H}$, 1619, 1553 $\nu_{C=O}$ cm$^{-1}$. MS: *m*/*z* (%) = 326 (100) [M]$^+$. $C_{14}H_{18}N_2O_2Se$ (325.18): calcd. C 51.71, H 5.58, N 8.61; found C 51.07, H 5.27, N 8.05.

**5-*tert*-Butyl-2-isopropyl-7-(isopropylcarbamoyl)benzisoselenazol-3(2*H*)-one (18):** Compound **18** was prepared from **13** (0.77 g, 2 mmol) and $Li_2Se_2$ (2.5 mmol) according to the procedure described for the preparation of **16**. The crude solid was recrystallized from a concentrated acetonitrile solution of the compound. Yield: 0.55 g, 71%. M.p. 244−246 °C. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.34 (d, *J* = 6.6 Hz, 6 H), 1.35 (s, 9 H), 1.40 (d, *J* = 6.0 Hz, 6 H), 4.36 (m, 1 H), 3.78 (sept, *J* = 6.0 Hz, 1 H), 6.87 (br. s, 1 H), 7.88 (s, 1 H), 8.24 (s, 1 H) ppm. $^{13}$C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 22.7, 23.5, 31.4, 35.1, 43.0, 46.2, 125.2, 125.9, 127.5, 130.5, 138.2, 150.5, 165.8 ppm. $^{77}$Se NMR (500 MHz, $CDCl_3$, 25 °C): δ = 822.6 ppm. IR (KBr): $\tilde{\nu}$ = 3254 $\nu_{N-H}$, 1599, 1540 $\nu_{C=O}$ cm$^{-1}$. MS: *m*/*z* (%) = 383 (100) [M]$^+$, 341 (37), 299 (17). $C_{18}H_{26}N_2O_2Se$ (381.28): calcd. C 56.70, H 6.87, N 7.35; found C 56.19, H 6.56, N 6.92.

**5-*tert*-Butyl-2-phenyl-7-(phenylcarbamoyl)benzisothiazol-3(2*H*)-one (19):** Compound **11** (0.9 g, 2 mmol) in THF (25 mL) was added to a stirred solution of $Li_2S_2$ [2.5 mmol, prepared by adding 1 M superhydride solution in THF (2.5 mL) to sulfur powder (0.08 g, 2.5 mmol) at room temperature] in THF. The reaction mixture was refluxed for 12 h, cooled to room temperature, washed with water (20 mL) and extracted with $CHCl_3$ (3 × 25 mL). The combined organic layers were dried with $Na_2SO_4$ and concentrated to give a white solid which was purified on a silica gel column by using ethyl acetate/petroleum ether (1:9) as eluent. Yield: 0.6 g, 67%. M.p. 260 °C (dec.). $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.46 (s, 9 H), 7.23 (t, *J* = 7.2 Hz, 1 H), 7.31 (t, *J* = 7.6 Hz, 1 H), 7.44 (m, 4 H), 7.71 (d, *J* = 7.2 Hz, 2 H), 7.76 (d, *J* = 7.6 Hz, 2 H), 8.08 (s, 1 H), 8.36 (s, 1 H), 8.47 (br., 1 H) ppm. $^{13}$C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 31.2, 35.2, 121.7, 124.2, 124.5, 125.0, 125.8, 126.2, 126.7, 128.4, 128.9, 129.5, 137.4, 137.6, 138.6, 150.2, 162.7, 164.3 ppm. IR (KBr): $\tilde{\nu}$ = 3260 $\nu_{N-H}$, 1656, 1541 $\nu_{C=O}$ cm$^{-1}$. MS: *m*/*z* (%) = 403 (100) [M]$^+$. $C_{24}H_{22}N_2O_2S$ (402.52): calcd. C 71.62, H 5.51, N 6.96; found C 71.89, H 5.62, N 7.03.

**5-*tert*-Butyl-2-methyl-7-(methylcarbamoyl)benzisothiazol-3(2*H*)-one (20):** Compound **20** was prepared from **12** (0.65 g, 2 mmol) and $Li_2S_2$ (2.5 mmol) according to the procedure described for the preparation of **19**, but with a reflux time of 10 h. The crude solid was recrystallized from a concentrated acetonitrile solution of the compound. Yield: 0.34 g, 61%. M.p. 208−210 °C. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.37 (s, 9 H), 3.10 (d, *J* = 4.4 Hz, 3 H), 3.44 (s, 3 H), 7.0 (br., 1 H), 7.89 (s, 1 H), 8.22 (s, 1 H) ppm. $^{13}$C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 27.1, 30.3, 31.6, 35.2, 124.1, 125.6, 126.4, 126.7, 139.4, 149.8, 165.3, 166.8 ppm. IR (KBr): $\tilde{\nu}$ = 3239 $\nu_{N-H}$, 1630, 1538 $\nu_{C=O}$ cm$^{-1}$. MS: *m*/*z* (%) = 279 (100) [M]$^+$. $C_{14}H_{18}N_2O_2S$ (278.37): calcd. C 60.41, H 6.52, N 10.06; found C 60.72, H 6.58, N 10.41.

**5-*tert*-Butyl-2-methyl-7-(methylcarbamoyl)benzisotellurazol-3(2*H*)-one (21):** Compound **21** was prepared from **12** (0.65 g, 2 mmol) and $Li_2Te_2$ (2.5 mmol) according to the procedure described for the preparation of **16**. The crude solid was purified on a silica gel column using petroleum ether (boiling range 60−80 °C)/$CHCl_3$ (4:1) as eluent. Yield: 0.03 g, 4%. $^1$H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.18 (s, 9 H, *t*Bu), 3.16 (d, *J* = 4.0 Hz, 3 H), 3.25 (s, 3 H), 8.12 (s, 1 H), 8.22 (s, 1 H), 8.42 (br., 1 H) ppm. $^{13}$C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 27.5, 31.5, 31.9, 35.0, 125.1, 127.3, 128.3, 129.5, 134.6, 152.1, 168.2, 169.7 ppm. $^{125}$Te NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1535.3 ppm. IR (KBr): $\tilde{\nu}$ = 3295 $\nu_{N-H}$, 1646, 1553 $\nu_{C=O}$ cm$^{-1}$. MS: *m*/*z* (%) = 376 (100) [M$^+$]. $C_{14}H_{18}N_2O_2Te$ (373.90): calcd. C 44.99, H 4.48, N 7.48; found C 45.47, H 4.87, N 7.24.

**4-*tert*-Butyl-2,6-bis(phenylcarbamoyl)phenyl Methoxymethyl Selenide (22):** A 1.6 M solution of *n*BuLi (1.9 mL, 3 mmol) was added to a solution of 2-bromo-5-*tert*-butyl-*N*,*N*′-diphenylisophthalamide (**11**) (0.45 g, 1 mmol) under nitrogen at −45 °C and warmed to room temperature. Bis(methoxymethyl) diselenide (0.248 g, 1 mmol) was added to the reaction mixture at 0 °C, which was then warmed to room temperature and stirred for an additional 0.5 h. The reaction mixture was washed with water and extracted with ethyl acetate (2 × 25 mL). The combined organic layers were dried with sodium sulfate and concentrated under vacuum to give a colorless solid which was purified on neutral alumina (chloroform/petroleum ether, 1:3) and recrystallized from a saturated solution of acetonitrile. Yield: 0.2 g, 45%. M.p. 218−220 °C. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.34 (s, 9 H), 3.22 (s, 3 H), 5.16 (s, 2 H), 7.16 (t, *J* = 7.3 Hz, 2 H), 7.16 (t, *J* = 7.9 Hz, 4 H), 7.64 (d, *J* = 8.4 Hz, 4 H), 7.67 (s, 2 H), 8.13 (s, 2 H) ppm. $^{13}$C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 31.2, 35.2, 59.0, 117.5, 120.1, 124.7, 126.7, 129.0, 137.9, 144.5, 153.5, 167.5 ppm. $^{77}$Se NMR (300 MHz, $CDCl_3$, 25 °C): δ = 295.0 ppm. IR (KBr): $\tilde{\nu}$ = 3288 $\nu_{N-H}$, 1625, 1549 $\nu_{C=O}$ cm$^{-1}$. MS: *m*/*z* (%) = 451 (100) [M − $CH_2OCH_3$]$^+$, 435 (25), 358 (10). $C_{26}H_{28}N_2O_3Se$ (495.39): calcd. C 63.04, H 5.70, N 5.65; found C 62.76, H 5.58, N 5.63.

**4-*tert*-Butyl-2,6-bis(isopropylcarbamoyl)phenyl Methoxymethyl Selenide (23):** Compound **23** was prepared from **13** (0.383 g, 1 mmol), a 1.6 M solution of *n*BuLi (1.9 mL, 3 mmol) and bis(methoxymethyl) diselenide (0.248 g, 1 mmol) according to the procedure described for the preparation of **22**. The crude product was purified on a silica gel column using dichloromethane/ethyl acetate (1:5) as eluent and recrystallized from a saturated solution of acetonitrile. Yield: 0.08 g, 21%. M.p. 196−198 °C. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.27 (d, *J* = 6.8 Hz, 12 H), 1.32 (s, 9 H), 3.33 (s, 3 H), 4.25 (m, 1 H), 5.13 (s, 2 H), 5.05 (d, *J* = 7.6 Hz, 2 H), 7.48 (s, 2 H) ppm. $^{13}$C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 22.7, 31.2, 35.0, 42.4, 58.7, 76.7, 118.3, 126.2, 144.7, 152.9, 169.1 ppm. IR (KBr): $\tilde{\nu}$ = 3293 $\nu_{N-H}$, 1622, 1544 $\nu_{C=O}$ cm$^{-1}$. MS: *m*/*z* (%) = 413 (16) [M − Me]$^+$, 383 (100) [M − $CH_2OMe$]$^+$, 356 (8), 341 (43), 299 (19).

**Determination of GPx-Like Activity:** The catalytic activities were determined by the coupled reductase assay.[4a] The reaction was carried out at 25 °C in a solution (1 mL) containing 0.1 M potassium phosphate buffer (pH = 7.3), 1 mM DTPA, 1 mM GSH, 0.1 mM NADPH, 0.6 U of GSH reductase and 50 μM of the test compound. The reaction was initiated by the addition of 1.2 mM *tert*-butyl hydroperoxide. As soon as the glutathione was oxidized to the corresponding disulfide, the hydroperoxide was enzymatically reduced. The activity was determined by UV/Vis spectrophotometry by monitoring the decrease of NADPH absorption at λ = 340 nm . Appropriate controls were run in the absence of enzyme and were subtracted from the test samples. The activity is expressed in terms of the consumption of NADPH (μM·min$^{-1}$).

**X-ray Crystallography:** The diffraction measurements for compounds **16** and **17** were performed at room temperature using graphite-monochromated Mo-$K_\alpha$ radiation (λ = 0.7107 Å). The structures were solved by direct methods and full-matrix least-squares refinement on $F^2$ (program SHELXL-97).[19] Hydrogen atoms were localized by geometrical means. A riding model was chosen for refinement. The isotropic thermal parameters of the H atoms were fixed at 1.5 times ($CH_3$ groups) or 1.2 times *U*(eq) (Ar−H) of the corresponding C atom. Some details of the refinement are given in Table 4. Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC-237094 and -237095. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

Table 4. Crystal data and structure refinement for **16** and **17**

| | **16** | **17** |
|---|---|---|
| Empirical formula | $C_{24}H_{22}N_2O_2Se$ | $C_{14}H_{18}N_2O_2Se$ |
| Formula mass | 449.40 | 325.26 |
| Crystal system | monoclinic | monoclinic |
| Space group | *I*2/*a* | *P*21/*n* |
| *a* [Å] | 18.5372(11) | 6.3549(9) |
| *b* [Å] | 12.5770(10) | 11.0351(10) |
| *c* [Å] | 19.9907(12) | 19.982(3) |
| β [°] | 115.284(6) | 92.497(16) |
| *V* [Å$^3$] | 4214.2(5) | 1399.9(3) |
| *Z* | 8 | 4 |
| $D_{calcd.}$ [Mg·m$^{-3}$] | 1.417 | 1.543 |
| Abs. coeff. [mm$^{-1}$] | 1.804 | 2.682 |
| Obsd. reflns. [$I > 2\sigma$] | 30780 | 1717 |
| Final $R(F)$ [$I > 2\sigma(I)$][a] | 0.0349 | 0.0409 |
| $wR(F^2)$ indices [$I > 2\sigma(I)$] | 0.0803 | 0.0904 |
| Data/restraints/parameters | 4444/0/265 | 14740/0.106/2919 |
| Goodness of fit on $F^2$ | 0.900 | 0.86 |

[a] Definitions: $R(F_o) = ||F_o| - |F_c||/|F_o|$ and $wR(F_o^2) = \{[w(F_o^2 - F_c^2)^2]/[w(F_c^2)^2\}^{1/2}$.

**Supporting Information:** $^1$H and $^{13}$C NMR spectra of all newly synthesized compounds, $^{77}$Se NMR spectra for **16**−**18** and **22**, $^{125}$Te NMR spectrum of **21** and tables for GPx-like activity of **16**−**18** and **21**.

## Acknowledgments

We are grateful to the Department of Science and Technology (DST), New Delhi, for funding this work. Additional help from the Regional Sophisticated Instrumentation Center (RSIC), Indian Institute of Technology (IIT), Bombay, and the Tata Fundamental

Research Institute (TIFR), Bombay, for performing 300 MHz and 500 MHz NMR spectroscopic analyses, respectively, is gratefully acknowledged. Thanks are also due to the RSIC, Central Drug Research Institute (CDRI), Lucknow, for providing mass spectra. S. S. Z. wishes to thank the CSIR, New Delhi, for a fellowship.

[1] [1a] T. Wirth, *Tetrahedron* **1999**, *55*, 1−28. [1b] T. Wirth, *Angew. Chem. Int. Ed.* **2000**, *39*, 3740−3749. [1c] M. Tiecco, L. Testaferri, C. Santi, C. Tomassini, F. Marini, L. Bagnoli, A. Temperini, *Tetrahedron: Asymmetry* **2000**, *11*, 4645−4650. [1d] M. Uchiyama, M. Oka, S. Harai, A. Ohta, *Tetrahedron Lett.* **2001**, *42*, 1931−1934. [1e] L. Uehlin, T. Wirth, *Org. Lett.* **2001**, *3*, 2931−2933. [1f] T. G. Back, Z. Moussa, M. Parvez, *J. Org. Chem.* **2002**, *67*, 499−509. [1g] M. Tiecco, L. Testaferri, C. Santi, C. Tomassini, F. Marini, L. Bagnoli, A. Temperini, *Chem. Eur. J.* **2002**, *8*, 1118−1124. [1h] L. Uehlin, G. Fragale, T. Wirth, *Chem. Eur. J.* **2002**, *8*, 1125−1133.

[2] [2a] P. J. Bonasia, J. Arnold, *J. Organomet. Chem.* **1993**, *449*, 147−157. [2b] Y. Cheng, T. J. Emge, G. Brennan, *Inorg. Chem.* **1994**, *33*, 3711−3714. [2c] Y. Cheng, T. J. Emge, G. Brennan, *Inorg. Chem.* **1996**, *35*, 342−346. [2d] Y. Cheng, T. J. Emge, G. Brennan, *Inorg. Chem.* **1996**, *35*, 7339−7344. [2e] G. Mugesh, H. B. Singh, R. J. Butcher, *Inorg. Chem.* **1998**, *37*, 2663−2669. [2f] G. Mugesh, H. B. Singh, R. J. Butcher, *J. Organomet. Chem.* **1999**, *577*, 243−248.

[3] [3a] M. Iwaoka, S. Tomoda, *J. Chem. Soc., Chem. Commun.* **1992**, 1165−1167. [3b] K. Fujita, M. Iwaoka, S. Tomoda, *Chem. Lett.* **1994**, 923−926. [3c] T. Wirth, *Tetrahedron Lett.* **1995**, *36*, 7849−7852. [3d] R. Kaur, H. B. Singh, R. P. Patel, *J. Chem. Soc., Dalton Trans.* **1996**, 2719−2726. [3e] S. Fukuzawa, K. Takahashi, H. Kato, H. Yamazaki, *J. Org. Chem.* **1997**, *62*, 7711−7716. [3f] T. Wirth, H. Hauptli, M. Leuenberger, *Tetrahedron: Asymmetry* **1998**, *9*, 547−550. [3g] K. Hiroi, Y. Suzuki, I. Abe, *Tetrahedron: Asymmetry* **1999**, *10*, 1173−1188. [3h] H. Ehara, M. Noguchi, S. Sayama, T. Onami, *J. Chem. Soc., Perkin Trans. 1* **2000**, 1429−1431. [3i] C. Bolm, M. Kesselgraber, A. Grehz, N. Hermanns, J. P. Hilderbrand, *New J. Chem.* **2001**, 13−15.

[4] [4a] S. R. Wilson, P. A. Zucker, R.-R. C. Huang, A. Spector, *J. Am. Chem. Soc.* **1989**, *111*, 5936−5939. [4b] A. Spector, S. R. Wilson, P. A. Zucker, USP 5321138 (C1, 546−224; C07C37/02), **1994** [*Chem. Abstr.* **1994**, *121*, P256039r]. [4c] L. Engman, D. Stern, I. A. Cotgreave, C. M. Andersson, *J. Am. Chem. Soc.* **1992**, *114*, 9737−9743. [4d] V. Galet, J.-L. Bernier, J.-P. Henichart, D. Lesieur, C. Abadie, L. Rochette, A. Lindenbaum, J. Chalas, J.-F. R. Faverie, B. Pfeiffer, P. Renard, *J. Med. Chem.* **1994**, *37*, 2903−2911. [4e] M. Iwaoka, S. Tomoda, *J. Am. Chem. Soc.* **1994**, *116*, 2557−2561. [4f] T. Saiki, K. Goto, R. Okazaki, *Angew. Chem.* **1997**, *109*, 2320−2322; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2223−2224. [4g] G. Mugesh, W.-W. du Mont, H. Sies, *Chem. Rev.* **2001**, *101*, 2125−2179. [4h] G. Mugesh, A. Panda, H. B. Singh, N. S. Punekar, R. J. Butcher, *J. Am. Chem. Soc.* **2001**, *123*, 839−850. [4i] G. Mugesh, W.-W. du Mont, *Chem. Eur. J.* **2001**, *7*, 1365−1370.

[5] H. Fujihara, H. Mima, N. Furukawa, *J. Am. Chem. Soc.* **1995**, *117*, 10153−10154.

[6] [6a] B. Kersting, M. DeLion, *Z. Naturforsch., Teil B* **1999**, *54*, 1042−1047. [6b] B. Kersting, *Z. Naturforsch., Teil B* **2002**, *57*, 1115−1119.

[7] G. Mugesh, H. B. Singh, *Acc. Chem. Res.* **2002**, *35*, 226−236.

[8] For reviews of bioactive organoselenium compounds, see: [8a] H. Sies, *Free Radical Biol. Med.* **1993**, *14*, 313−323. [8b] T. Schewe, *Gen. Pharmacol.* **1995**, *26*, 1153−1169. [8c] G. Mugesh, H. B. Singh, *Chem. Soc. Rev.* **2000**, *29*, 347−357. [8d] See also: C. Jacob, G. I. Giles, N. M. Giles, H. Sies, *Angew. Chem.* **2003**, *115*, 4890−4907; *Angew. Chem. Int. Ed.* **2003**, *39*, 4742−4758.

[9] [9a] A. Muller, E. Cadenas, P. Graf, H. Sies, *Biochem. Pharmacol.* **1984**, *33*, 3235−3240. [9b] A. Wendel, M. Fausel, H. Safayachi, G. Tiegs, R. Otter, *Biochem. Pharmacol.* **1984**, *33*, 3241−3245. [9c] H. J. Reich, C. P. Jasperse, *J. Am. Chem. Soc.* **1987**, *109*, 5549−5551. [9d] A. D. Inglot, J. Zielinska-Jenczylik, E. Piasecki, L. Syper, J. Mlochowski, *Experientia* **1990**, *46*, 308−311. [9e] P. V. Jaquemin, L. E. Christiaens, M. J. Renson, M. J. Evers, N. Dereu, *Tetrahedron Lett.* **1992**, *33*, 3863−3866. [9f] J. Mlochowski, K. Kloc, L. Syper, A. D. Inglot, E. Piasecki, *Liebigs Ann. Chem.* **1993**, 1239−1244. [9g] J. Mlochowski, R. J. Gryglewski, A. D. Inglot, L. Juchniewicz, K. Kloc, *Liebigs Ann.* **1996**, 1751−1755. [9h] T. G. Back, B. P. Dyck, *J. Am. Chem. Soc.* **1997**, *119*, 2079−2083. [9i] J. Chandiere, I. Erdelmeier, M. Montet, J. C. Yadan, *Phosphorus, Sulfur Silicon* **1998**, *136−138*, 467−470. [9j] M. Bien, B. Blaszczyk, K. Kalinowska, A. D. Inglot, *Arch. Immun. Ther. Exp.* **1999**, *47*, 185−193. [9k] M. Osajda, K. Kloc, J. Mlochowski, E. Piasecki, K. Rybka, *Pol. J. Chem.* **2001**, *75*, 823−830.

[10] [10a] R. Weber, M. Renson, *Bull. Soc. Chim. Fr.* **1976**, 1124−1126. [10b] C. Lambert, A. Welter, L. E. Christiaens, N. Dereu, *Synth. Commun.* **1991**, *21*, 85−98. [10c] L. E. Christiaens, P. Wirtz, Eur. Pat. Appl. EP 44453, **1982** [*Chem. Abstr.* **1982**, *96*, 199699v]. [10d] L. Engman, A. Hallberg, *J. Org. Chem.* **1989**, *54*, 2964−2965. [10e] M. C. Fong, C. H. Schiesser, *Tetrahedron Lett.* **1995**, *36*, 7329−7332. [10f] M. C. Fong, C. H. Schiesser, *J. Org. Chem.* **1997**, *62*, 3103−3108. [10g] K. Kloc, J. Mlochowski, M. Osajda, L. Syper, H. Wojtowicz, *Tetrahedron Lett.* **2002**, *43*, 4071−4074.

[11] R. Lesser, R. Weiss, *Ber. Dtsch. Chem. Ges.* **1924**, *57*, 1077−1082.

[12] M. J. Parnham, J. Biederman, C. Bittner, N. Dereu, S. Leyck, H. Wetzig, *Agents Actions* **1989**, *27*, 306−308.

[13] V. A. Benin, J. C. Martin, M. R. Willcott, *Tetrahedron* **1997**, *53*, 10133−10154.

[14] [14a] D. P. Thompson, P. Boudjouk, *J. Org. Chem.* **1988**, *53*, 2109−2112. [14b] L. Syper, J. Mlochowski, *Tetrahedron* **1988**, *44*, 6119−6130.

[15] A. G. Maslakov, W. R. McWhinnie, M. C. Perry, N. Shaikh, S. L. W. McWhinnie, T. A. Hamor, *J. Chem. Soc., Dalton Trans.* **1993**, 619−624.

[16] L. Dupont, O. Dideberg, M. Sbit, N. Dereu, *Acta Crystallogr., Sect. C* **1988**, *44*, 2159−2161.

[17] Y. S. Peng, H. S. Xu, P. Naumov, S. S. S. Raj, H.-K. Fun, I. A. Razak, S. W. Ng, *Acta Crystallogr., Sect. C* **2000**, *56*, 1386−1388.

[18] G. Mugesh, A. Panda, S. Kumar, S. D. Apte, H. B. Singh, R. J. Butcher, *Organometallics* **2002**, *21*, 884−892.

[19] G. M. Sheldrick, *SHELXL-97, Program for Crystal Structure Determination*, University of Göttingen, Germany, **1974**.

Received May 10, 2004