Intramolecular Homolytic Substitution with Amidyl Radicals: A Free-Radical Synthesis of Ebselen and Related Analogues

Mei C. Fong and Carl H. Schiesser*

School of Chemistry, The University of Melbourne, Parkville, Victoria, Australia 3052

Received January 2, 1997[⊗]

Irradiation of a water-cooled benzene solution of pyridine-2-thioneoxycarbonyl (PTOC) imidate esters **9** derived from *N*-butyl-2-(benzylseleno)benzamide (**6**, R = Bu), 2-(benzylseleno)-*N*-hexylbenzamide (**6**, R = Hex), *N*-benzyl-2-(benzylseleno)benzamide (**6**, R = Bn), and 2-(benzylseleno)-*N*-cyclohexylbenzamide (**6**, R = c-Hex) with a 250-W low-pressure mercury lamp affords the corresponding 1,2-benzisoselenazol-3(2*H*)-ones (**1**) in yields of 81−91% (R = primary alkyl) and 45% (R = c-Hex). Presumably, these transformations involve formation of amidyl radicals **2** which undergo subsequent intramolecular homolytic substitution at the selenium atom with expulsion of a benzyl radical. PTOC imidate esters derived from 2-(benzylseleno)benzanilide (**6**, R = Ph) and 2-(benzylseleno)-*N*-*tert*-butylbenzamide (**6**, R = *t*-Bu) were unable to be prepared in this manner. 1,2-Benzisoselenazol-3(2*H*)-ones (**1**, R = Ph, Hex, *i*-Pr, *t*-Bu) could also be prepared in 76−85% yield by reaction of the corresponding 2,2′-diselenobis(benzamide) (**15**) with benzoyl or *tert*-butyl peroxide. The mechanisms of these transformations are discussed.

Introduction

Ebselen (2-phenyl-1,2-benzisoselenazol-3(2*H*)-one) (**1**, R = Ph)) is a nontoxic low molecular weight selenium-containing heterocycle exhibiting antiinflammatory, antiatherosclerotic, and cytoprotective properties.[1] During the last decade several groups have worked toward a better understanding of the pharmacology of **1** (R = Ph) since it was first discovered that ebselen mimics the hydroperoxide reducing ability of glutathione peroxidase (GPx),[2] in particular phospholipid hydroperoxide glutathione peroxidase.[3] The reader is referred to a recent review by Schewe in which the unique antiinflammatory antioxidant molecular actions of ebselen are discussed.[1] Ebselen is remarkable in its catalytic ability and in its ability to inhibit a number of enzymes involved in inflammation; ebselen appears to inhibit lipoxyganases, nitric oxide synthases, NADPH, oxidase, and protein kinase C as well 1,4,5-trisphosphate-induced calcium release.[1,4] Unlike other antioxidants such as α-tocopherol and probucol which act as lipid free-radical scavengers and prevent lipid peroxidation, ebselen appears to be a poor radical scavenger acting instead to reduce hydroperoxy-lipids after their formation. The extraordinarily low toxicity of ebselen has been discussed in terms of the failure of **1** (R = Ph) to release selenium metal during biotransformation.[5] It is not surprising therefore that ebselen is currently undergoing Phase III clinical trials in Japan as an antioxidant.[6]

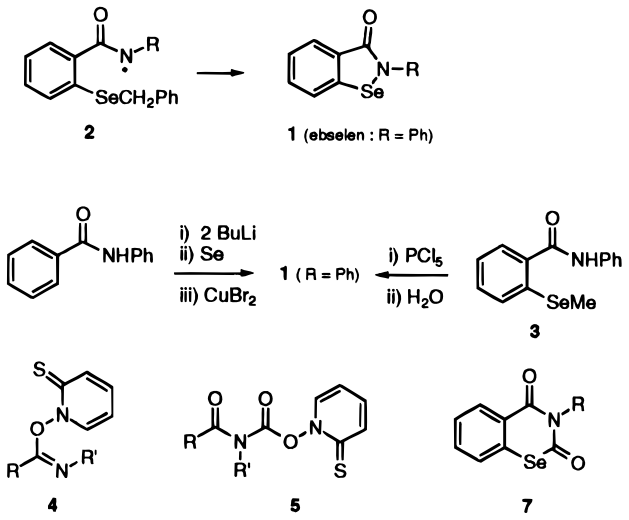
Ebselen (**1**, R = Ph) was first prepared in 1924;[7] since then several syntheses have been reported.[8−12] The highest-yielding of these involves the treatment of 2-(methylseleno)benzanilide (**3**), itself prepared in several steps from anthranilic acid,[9] with phosphorus pentachloride followed by hydrolysis.[10] This procedure affords ebselen in 80−90% yield and appears to be commercially viable.[11] The most expedient method was reported by Engman in 1989 and utlizes a one-pot procedure in which benzanilide is ortho-lithiated and treated with selenium powder followed by cupric bromide oxidative ring closure;[12] ebselen is obtained in 63% yield.

Work in our laboratories has recently focused on the design and application of free-radical homolytic substitution chemistry. Given that homolytic substitution is an effective method for the formation of bonds to higher heteroatoms,[13] and given our recent successes in the application of alkyl, aryl, and iminyl radical substitution at the selenium atom in alkyl selenides during the preparation of a wide variety of selenium-containing heterocycles,[14] it struck us that analogues (**1**) of ebselen and indeed ebselen itself should be amenable to preparation through intramolecular homolytic substitution by amidyl radicals **2** in appropriately substituted benzamides. We now report that photochemical decomposition of pyridine-2-thioneoxycarbonyl (PTOC) imidate esters **9**, or reaction of 2,2′-diselenobis(*N*-alkylbenzamides) **15** with benzoyl or *tert*-butyl peroxides affords ebselen and analogues (**1**) in 56−91% yield.

[⊗] Abstract published in *Advance ACS Abstracts,* April 1, 1997.

(1) Schewe, T. *Gen. Pharmacol.* **1995**, *26*, 1153.
(2) Müller, A.; Cadenas, E.; Graf, P.; Sies, H. *Biochem. Pharmacol.* **1984**, *33*, 3235. Wendel, A.; Fausel, M.; Safayhi, H.; Tiegs, G.; Otter, R. *Biochem. Pharmacol.* **1984**, *33*, 3241.
(3) Maiorino, M.; Roveri, A.; Coassin, M.; Ursini, F. *Biochem. Pharmacol.* **1988**, *37*, 2267.
(4) Dimmeler, S.; Brüne, B.; Ullrich, V. *Biochem. Pharmacol.* **1991**, *42*, 1151.
(5) Catineau, R.; Tihange, G.; Plenevaux, A.; Christiaens, L.; Guillaume, M.; Welter, A.; Dereu, N. *J. Labelled Compd. Radiopharm.* **1985**, *23*, 59.
(6) *Drugs Future* **1995**, *20*, 1057.
(7) Lesser, R.; Weiss, R. *Ber. Dtsch. Chem. Ges.* **1924**, *57*, 1077.
(8) Lambert, C.; Hilbert, M.; Christiaens, L.; Dereu, N. *Synth. Commun.* **1991**, *21*, 85.
(9) Ruwet, A.; Renson, M. *Bull. Soc. Chim. Belg.* **1969**, *78*, 571.
(10) Weber, R.; Renson, M. *Bull. Soc. Chim. Fr.* **1976**, 1124.
(11) European Patent EP 44453.
(12) Engman, L.; Hallberg, A. *J. Org. Chem.* **1989**, *54*, 2964.
(13) Schiesser, C. H.; Wild, L. M. *Tetrahedron* **1996**, *52*, 13265 and references cited therein.
(14) Schiesser, C. H.; Sutej, K. *J. Chem. Soc., Chem. Commun.* **1992**, 57. Schiesser, C. H.; Sutej. K. *Tetrahedron Lett.* **1992**, *33*, 5137. Lyons, J. E.; Schiesser, C. H.; Sutej, K. *J. Org. Chem.* **1993**, *58*, 5632. Benjamin, L. J.; Schiesser, C. H.; Sutej, K. *Tetrahedron* **1993**, *49*, 2557. Schiesser, C. H.; Fong, M. C.; Schiesser, C. H. *Tetrahedron Lett.* **1993**, *34*, 4347. Lucas, M. A.; Schiesser, C. H. *J. Org. Chem.* **1996**, *61*, 5754.

S0022-3263(97)00019-4 CCC: $14.00

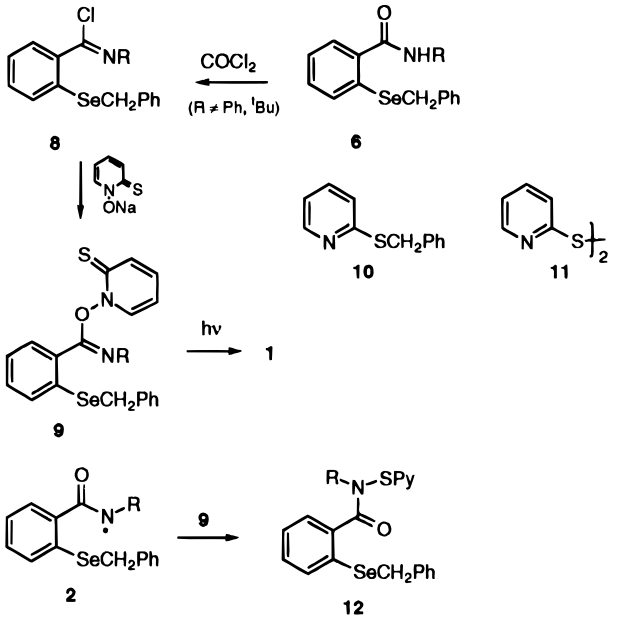


Results and Discussion

Photolysis of PTOC imidate esters (9). Given the sensitivity of alkyl selenides toward oxidation,[15] halogenation,[15] and chain-carrying radicals such as tributylstannyl,[13] some considerable thought was given to the amidyl radical precursor to be used in this study; *N*-haloamides[16] and precursors requiring tributyltin hydride[17] would be clearly unsuitable. Eventually we decided to explore the use of the PTOC imidate esters **4** and *N*-acyl PTOC carbamates **5** recently developed by Newcomb and Esker.[18,19] Unfortunately, attempts to prepare the *N*-acyl PTOC carbamate derivatives of amides **6** by reacting the corresponding trimethylsilyl amides with phosgene as described by Newcomb and Esker[19] were met with little success. We recently reported that amides **6** react with trimethylsilyl triflate followed by phosgene to afford benzoselenazine-2,4-diones **7**.[20]

The 2-(benzylseleno)benzamides **6** required in this study were prepared from 2-benzylselenobenzoic acid following our previously published procedure.[20] Amides **6** bearing primary and secondary alkyl substituents were readily converted into the corresponding iminyl chloride **8** by reaction with 20% phosgene in toluene (Scheme 1). These reactions are normally carried out in benzene but can be carried out in deuteriochloroform and are conveniently followed by ^{1}H NMR spectroscopy. Amides **6** exhibit characteristic singlets corresponding to the benzylic methylenes in the range δ ($CDCl_3$) 4.07−4.12. After the addition of phosgene the formation of primary alkyl-substituted iminyl chlorides (**8**: R = Bu, Hex, Bn) is usually complete within 24 h at room temperature with *N*-cyclohexyl 2-(benzylseleno)benzamide (**6**: R = c-Hex) requiring 4 days. The benzylic methylene is observed to shift upfield by 0.02−0.04 ppm in each case. Unfortunately, 2-(benzylseleno)benzanilide (**6**: R = Ph) and

Scheme 1



N-*tert*-butyl 2-(benzylseleno)benzamide (**6**: R = *tert*-butyl) failed to react under standard conditions. At elevated temperatures (50 °C) the reaction of the phenyl amide (**6**: R = Ph) was only 20% complete after 3 days, while the *tert*-butyl analogue (**6**: R = *t*-Bu) had not reacted. After 5 days at 80 °C substantial decomposition was observed in each case. We attribute the lack of reactivity of the former substrate to the low nucleophilicity of the conjugated amide (**6**: R = Ph), while steric factors may be responsible for the lack of reactivity of the latter.

The iminyl chlorides **8** were not isolated but reacted immediately with the sodium salt of *N*-hydroxypyridine-2-thione to presumably afford PTOC imidate esters **9** *in situ*. To our delight, subsequent irradiation with a 250 W low-pressure mecrury lamp (white light) gave the corresponding benzisoselenazolones (**1**: R ≠ Ph, *t*-Bu) after chromatography (Scheme 1). These reactions are readily followed by ^{77}Se NMR spectroscopy; starting amides **6** exhibit signals in the range δ 367−371, while the ebselen analogues **1** display signals at δ 814−942. Apart from starting amide **6**, byproducts included 2-(benzylthio)pyridine (**10**) (major), 2,2′-dithiobis(pyridine) (**11**) (minor) and bibenzyl (minor) which were conveniently removed by chromatography or, in the case of **11**, treatment of the crude reaction mixture with saturated copper(II) sulfate. Presumably, photochemical decomposition of the PTOC imidate ester **9** affords the amidyl radical **2** which undergoes intramolecular homolytic substitution at the selenium atom in **2** with expulsion of the benzyl radical to afford the ebselen analogues **1**.

Initial photolyses were carried out in benzene at concentrations of approximately 0.1 M and afforded **1** in 27−80% yields. Attempts to optimize the reaction conditions soon revealed a marked concentration dependence. For example, the butyl-substituted precursor **9** (R = Bu) afforded **1** (R = Bu) in yields ranging from 56% (0.2 M) to 90% (0.01 M) with the remaining mass balance comprised predominantly of starting amide (**6**: R = Bu) and sulfides (**10**, **11**); similar results were obtained for the other primary alkyl-substituted precursors in this study. In addition, elevated temperatures (80 °C) resulted in marginal decreases in the yield of **1**. Reactions

(15) *The Chemistry of Organic Selenium and Tellurium Compounds*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1986.

(16) Barton, D. H. R.; Beckwith, A. L. J.; Goosen, A. *J. Chem. Soc.* **1965**, 181. Glover, S. A.; Goosen, A. *J. Chem. Soc. Perkin Trans. 1* **1974**, 2353. Kuehne, M. E.; Horne, D. A. *J. Org. Chem.* **1975**, *40*, 1287. Mackiewicz, P.; Furstoss, R.; Waegell, B.; Cote, R.; Lessard, J. *J. Org. Chem.* **1978**, *43*, 3746. Glover, S. A.; Goosen, A. *J. Chem. Soc., Perkin Trans. 1* **1978**, 653. Chow, Y. L.; Perry, R. A. *Can. J. Chem.* **1985**, *63*, 2203.

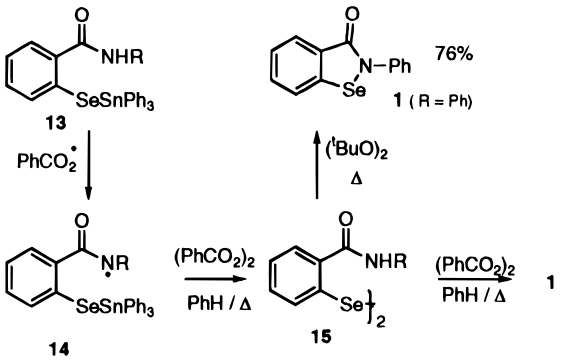
(17) Esker, J. L.; Newcomb, M. *Tetrahedron Lett.* **1993**, *34*, 6877.

(18) Esker, J. L.; Newcomb, M. *J. Org. Chem.* **1993**, *58*, 4933.

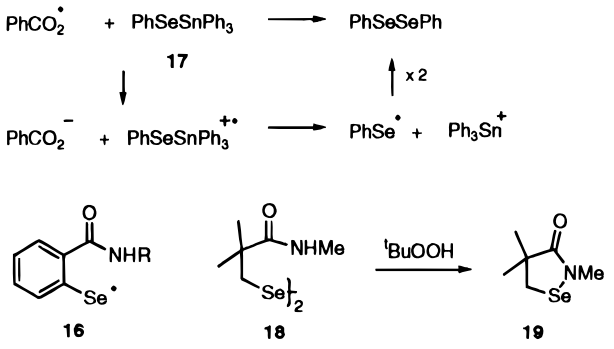
(19) Esker, J. L.; Newcomb, M. *J. Org. Chem.* **1994**, *59*, 2779.

(20) Fong, M. C.; Laws, M. J.; Schiesser, C. H. *Aust. J. Chem.* **1995**, *48*, 1221.

Scheme 2



Scheme 3



carried out in a water-cooled vessel at concentrations of between 0.01 and 0.024 M proved optimum for our requirements. Under these conditions 2-butyl-1,2-benzisoselenazol-3(2*H*)-one (**1**, R = Bu), 2-hexyl-1,2-benzisoselenazol-3(2*H*)-one (**1**, R = Hex), 2-benzyl-1,2-benzisoselenazol-3(2*H*)-one (**1**, R = Bn), and 2-cyclohexyl-1,2-benzisoselenazol-3(2*H*)-one (**1**, R = c-Hex) were obtained in 90, 91, 81, and 45% yield, respectively.

The concentration dependence described above is consistent with ring-closure competing with bimolecular addition of **2** to the precursor **9** to afford the thiopyridyl amide **12**. This competition would be expected to favor cyclization at lower concentrations; **12** then decomposes to give the starting amide **6** on workup (Scheme 1).

Reactions of 2-(Triphenylstannyl)selenobenzamides (12) with Peroxides. Having demonstrated that ebselen analogues (**1**: R ≠ Ph, *t*-Bu) are readily prepared through the use of intramolecular homolytic attack of amidyl radicals at selenium, we next turned our attention to solving the problems associated with the preparation of ebselen itself. We rationalized that if appropriately substituted amides **13** devoid of abstractable alkyl hydrogens could be prepared, then reaction with benzoyloxyl or *tert*-butoxyl radicals should result in abstraction of the amide hydrogen in **13** with formation of the corresponding amidyl radical **14**. The triphenylstannyl group appeared to meet the required criteria of good leaving radical while being devoid of abstractable hydrogens. To that end, *N*-hexyl-2-(triphenylstannyl)selenobenzamide (**13**: R = Hex), *N*-phenyl-2-(triphenylstannyl)selenobenzamide (**13**: R = Ph), *N*-isopropyl-2-(triphenylstannyl)selenobenzamide (**13**: R = *i*-Pr), and *N*-*tert*-butyl-2-(triphenylstannyl)selenobenzamide (**13**: R = *t*-Bu) were prepared in 62−78% yield by the reaction of the corresponding benzylseleno amide **6** with triphenyltin hydride under standard radical conditions. The stannyl selenides **13** exhibit signals at around δ −30 in their ^{77}Se NMR spectra.

To our surprise, treatment of **13** with benzoyl peroxide (0.5 equiv) under reflux did not produce the expected heterocycle **1**. Instead, the 2,2′-diselenobis(benzamide) (**15**: R = Hex, Ph, *i*-Pr, *t*-Bu) was isolated in 54−87% yield (Scheme 2). These transformations appear to be general; indeed (triphenylstannyl)phenyl selenide[25] (**17**) reacts with benzoyl peroxide under the described conditions to afford diphenyl diselenide in quantitative yield. The transformation of stannyl selenides into diselenides by the action of benzoyl peroxide represents a new, albeit unorthodox, method for the preparation of diselenides.

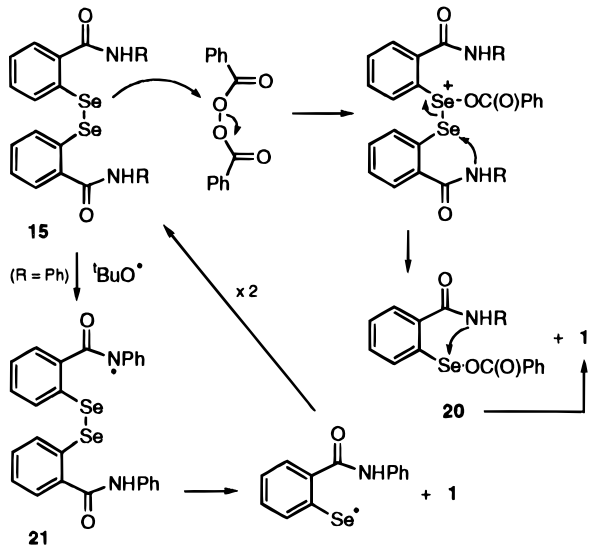
We speculate that this transformation involves either homolytic substitution by benzoyloxyl radical at the tin atom in **13** or **17** with expulsion of selenyl radical (**16** or PhSe•) or electron transfer chemistry[21] in which triphenylstannyl cation is involved (Scheme 3). Subsequent rapid self-combination of radicals **16** presumably leads to the diselenide **15**. Homolytic attack by oxygen-centered radicals at tin is not unprecedented. Scaiano reported that *tert*-butoxyl radicals undergo homolytic substitution at the tin atom in hexabutylditin.[22]

It is well estabilised that diselenides rapidly trap radicals.[13] With this in mind, the diselenides (**15**: R = Hex, *i*-Pr, *t*-Bu, R ≠ Ph) were reacted further with benzoyl peroxide (1.0 equiv) in benzene under reflux. To our delight, the 2-alkyl-1,2-benzisoselenazol-3(2*H*)-ones (**1**: R = Hex, *i*-Pr, *t*-Bu) were isolated in 76−85% yield after chromatography.[23] Once again ^{77}Se NMR spectroscopy serves as a convenient tool for monitoring the reaction outcomes, with starting diselenides **15** exhibiting signals at δ 365−371, significantly further upfield than those observed for **1** (δ 814−942).

Only low yields of ebselen (**1**: R = Ph) were obtained when 2,2′-diselenobis(benzanilide) (**15**: R = Ph) was subjected to this procedure, presumably due to the low solubility of the amide (**15**: R = Ph) in benzene. In order to overcome these difficulties 2,2′-diselenobis(benzanilide) (**15**: R = Ph) was reacted with benzoyl peroxide (1 equiv) in chlorobenzene at 120 °C to afford ebselen in 44% yield (Scheme 2). When benzoyl peroxide was replaced with *tert*-butyl peroxide (1 equiv) and this reaction repeated, ebselen was isolated in 34% yield, the major product being 2-(methylseleno)benzanilide (**3**) which was isolated in 54% yield. Presubably **3** arises by intermolecular homolytic substitution of methyl radicals, generated by fragmentation of *tert*-butoxyl radicals,[24] at the selenium atom in 2,2′-diselenobis(benzanilide) (**15**: R = Ph). Increasing the amount of *tert*-butyl peroxide and ensuring that the reaction was terminated soon after consumption of starting material (**15**: R = Ph)[25,26] resulted in a dramatic increase in the yield of ebselen. Thus, when the reaction of **15** (R = Ph) was carried out at 120 °C in a 1:1 mixture of *tert*-butyl peroxide and chlorobenzene as solvent, ebselen (**1**: R = Ph) was isolated in 76% yield

(21) Rossi, R. A.; de Rossi, R. H. *Aromatic Substitution by the $S_{RN}1$ Mechanism*; American Chemical Society: Washington, DC, 1983.
(22) Scaiano, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 5399.
(23) The transformation of **13** into **1** can be achieved by the reaction of **13** with 1.5 equiv of benzoyl peroxide in benzene under reflux. In our hands, superior yields were always obtained by the stepwise transformation **13** → **15** → **1**, especially in the preparation of ebselen (**1**: R = Ph) where solubility problems are encountered.
(24) Walling, C.; Wagner, P. J. *J. Am. Chem. Soc.* **1964**, *86*, 3368.
(25) A reviewer suggested that *tert*-butyl peroxide may be undergoing induced decomposition at 120 °C, thus acting as a more effective scavenger of methyl radicals at higher concentrations.
(26) TLC analysis indicated that the starting material was consumed after 16 h. Prolonged exposure to *tert*-butyl peroxide at 120 °C resulted in a significantly darker reaction mixture and diminished yields of ebselen (**1**, R = Ph).

Scheme 4



after recrystallization. As this procedure affords ebselen from 2,2′-diselenobis(benzanilide) in yields superior to those reported previously,[8−12] and since 2,2′-diselenobis-(benzanilide) is readily available by ortho-lithiation of benzanilide,[8,12] this method represents an efficient and convenient procedure for the small-scale preparation of ebselen.

Mechanistic considerations. While we are confident that the photochemical transformations of PTOC imidate esters **9** into benzisoselenazol-3(2*H*)-ones (**1**) involve intramolecular homolytic substitution by amidyl radicals **2** at the selenium atom with expulsion of benzyl radical, we are less confident about the mechanism of the reactions of diselenides (**15**) with benzoyl peroxide. Reich and Jasperese reported that diselenides **18** react with *tert*-butyl hydroperoxide to afford selenazolone **19**, a reaction which presumably involves oxidative ring-closure.[27] In addition, Pryor and Bickley reported that benzoyl peroxide undergoes accelerated decomposition in the presence of alkyl sulfides and disulfides, a process consistent with nucleophilic attack of sulfide at the peroxidic oxygen in benzoyl peroxide.[28] In an analogous fashion, **15** may well react with benzoyl peroxide to afford **1** and selenobenzoate **20** which, in turn, undergoes further cyclization to give another 1 equiv of **1** (Scheme 4). The extra steric demand imposed by *tert*-butyl peroxide reduces the likelihood of this peroxide reacting in an analogous fashion to its benzoyl analogue. At this time we feel that *tert*-butyl peroxide is more likely to form *tert*-butoxyl radicals upon thermolysis. Abstraction of the amide hydrogen in **1** then generates the amidyl radical **21**; subsequent cyclization provides ebselen.

We are currently investigating further the mechanistic details of the ring-closures reported in this paper.

Experimental Section

(Phenylseleno)triphenyltin (**17**) was prepared according to the procedure of Macmullin and Peach.[29] Triphenyltin hydride, benzoyl peroxide, and *tert*-butyl peroxide were purchased from Aldrich. The sodium salt of *N*-hydroxypyridine-2-thione (sodium pyrion) was a gift from Harcross Chemicals. Phosgene was purchased from Fluka as a 20% solution in toluene (1.93 M). All melting points and boiling points are uncorrected. NMR spectra were recorded in benzene-d_6 unless otherwise stated. Elemental analyses were carried out by Chemical and Micro Analytical Services Pty. Ltd. Reactions involving *tert*-butyl peroxide at 120 °C were carried out behind a protective (safety) shield.

2-(Benzylseleno)-N-*tert*-butylbenzamide (6: R = *t*-Bu) was prepared according to our previously published procedure[20] using 2-(benzylseleno)benzoic acid,[20] and *t*-butylamine and isolated as a white crystalline solid (61%): mp = 153 °C (sharp); ^{1}H NMR ($CDCl_3$) δ 1.43 (9H, s), 4.11 (2H, s), 5.85 (1H, s(br)), 7.23−7.26 (7H, m), 7.45−7.48 (2H, m); ^{13}C NMR ($CDCl_3$) δ 28.8, 31.9, 51.9, 126.6, 126.9, 127.2, 128.4, 128.9, 130.2, 130.4, 132.7, 137.9, 139.2, 168.0; ^{77}Se NMR (C_6H_6) δ 367; IR (KBr) ν 1626, 3287 cm^{-1}; MS *m*/*z* (relative intensity) 347 (M^+, 4.9), 256 (68), 200 (100), 91 (82). Anal. Calcd for $C_{18}H_{21}NOSe$: C, 62.4; H, 6.1; N, 4.0. Found: C, 62.3; H, 6.0; N, 3.9.

2-(Benzylseleno)-N-cyclohexylbenzamide (6: R = *c*-Hex) was prepared according to our previously published procedure[20] using 2-(benzylseleno)benzoic acid[20] and cyclohexylamine and isolated as a white crystalline solid (91%): mp = 171−172 °C; ^{1}H NMR ($CDCl_3$) δ 1.12−1.25 (3H, m), 1.32−1.47 (2H, m), 1.60−1.76 (3H, m), 1.98−2.04 (2H, m), 3.88−3.98 (1H, m), 4.10 (2H, s), 5.90 (1H, s(br)), 7.16−7.32 (7H, m), 7.48−7.52 (2H, s); ^{13}C NMR ($CDCl_3$) δ 24.9, 25.6, 31.9, 33.0, 48.8, 126.6, 126.9, 127.8, 128.4, 128.9, 130.4, 130.8, 132.8, 137.9, 138.1, 167.6; ^{77}Se NMR (C_6H_6) δ 369; IR (KBr) ν 1617, 3237 cm^{-1}; MS *m*/*z* (relative intensity) 372 ($M - H^+$, 4.9), 281 (48), 228 (19), 200 (38), 91 (100), 83 (41). Anal. Calcd for $C_{20}H_{23}NOSe$: C, 64.5; H, 6.2; N, 3.8. Found: C, 64.5; H, 6.2; N, 3.7.

Standard Protocol A for the Preparation of 1,2-Benzisoselenazol-3(2*H*)-ones (1) by the PTOC Imidate Ester Method. *N*-Butyl-1,2-benzisoselenazol-3(2*H*)-one (1: R = Bu). 20% Phosgene in toluene (1.93 M, 2.40 mL, 4.64 mmol) was added via syringe to a cooled (0−5 °C) solution of 2-(benzylseleno)-*N*-butylbenzamide (**6**: R = Bu) (400 mg, 1.16 mmol) and DMF (9.0 μL, 120 μmol) in benzene (20 mL). The solution was stirred at rt overnight. The solvent was removed *in vacuo* and replaced with dry ether (20 mL), the sodium salt of *N*-hydroxypyridine-2-thione (210 mg, 2.31 mmol) added, and the mixture stirred overnight while shielded from background light. The precipitate was filtered off and washed with cold CH_2Cl_2 (5 mL), the combined organic phases were dried ($MgSO_4$), and the solvent was removed *in vacuo*. The yellow-green residue was dissolved in benzene (50 mL) and the solution transferred to a water-cooled reaction vessel and irradiated with a 250 W low-pressure mercury lamp (white light) at a distance of 20 cm for 3 h. The solvent was removed *in vacuo*, the residue separated by flash chromatography (CH_2Cl_2), and the title compound isolated as a white solid (240 mg, 90%): mp = 92 °C (sharp) (lit.[10] 92 °C); ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, *J* = 7.3 Hz), 1.33−1.46 (2H, m), 1.59−1.73 (2H, m), 3.84 (2H, t, *J* = 7.2 Hz), 7.38 (1H, t, *J* = 7.4 Hz), 7.51−7.60 (2H, m), 8.01 (1H, d, *J* = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 13.7, 19.8, 32.6, 44.5, 123.9, 126.1, 127.6, 128.8, 131.8, 137.6, 167.1; ^{77}Se (C_6H_6) NMR δ 872; IR (KBr) ν 1554, 1588 cm^{-1}; MS *m*/*z* (relative intensity) 255 (M^+, 39.8), 220 (55), 199 (71), 184 (100), 156 (43), 78 (56). HRMS Calcd for $C_{11}H_{13}NO^{80}Se$: 255.0162, found: 255.0166.

***N*-Hexyl-1,2-benzisoselenazol-3(2*H*)-one (1: R = Hex)** was prepared according to standard protocol A using 2-(benzylseleno)-*N*-hexylbenzamide (**6**: R = Hex). Flash chromatography (CH_2Cl_2) afforded **1** (R = Hex) as a white crystalline solid (91%): mp = 84−85 °C; ^{1}H NMR ($CDCl_3$) δ 0.89 (3H, t, *J* = 7.2 Hz), 1.30−1.42 (6H, m), 1.68−1.75 (2H, m), 3.86 (2H, t, *J* = 7.2 Hz), 7.42 (1H, t, *J* = 7.5 Hz), 7.58−7.64 (2H, m), 8.05 (1H, d, *J* = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 13.9, 22.4, 26.2, 30.5, 31.4, 44.8, 124.0, 126.0, 127.6, 128.6, 131.7, 137.7, 167.0; ^{77}Se (C_6H_6) NMR δ 872; IR (KBr) ν 1554, 1585 cm^{-1}; MS *m*/*z* (relative intensity) 283 (M^+, 26.9), 220 (48), 199 (66), 184 (100), 156 (27), 78 (30). Anal. Calcd for $C_{13}H_{17}NOSe$: C, 55.3; H, 6.0; N, 5.0. Found: C, 55.2; H, 6.1; N, 4.7.

N-Benzyl-1,2-benzisoselenazol-3(2*H*)-one (1: R = Bn) was prepared according to standard protocol A using *N*-benzyl-

(27) Reich, H. J.; Jasperese, C. P. *J. Am. Chem. Soc.* **1987**, *109*, 5549.
(28) Pryor, W. A.; Bickley, H. T. *J. Org. Chem.* **1972**, *37*, 2885.
(29) Macmullin, E. C. ; Peach, M. E. *J. Organomet. Chem.* **1973**, *52*, 355.

2-(benzylseleno)benzamide (**6**: R = Bn). Flash chromatography (CH_2Cl_2) afforded **1** (R = Bn) as a white crystalline solid (81%): mp = 139−140 °C (lit.[30] 141−144 °C); ^{1}H NMR ($CDCl_3$) δ 5.02 (2H, s), 7.35−7.58 (8H, m), 8.08 (1H, d, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 48.6, 123.9, 126.2, 127.4, 128.0, 128.3, 128.5, 128.8, 128.9, 132.0, 137.2, 167.1; ^{77}Se NMR (C_6H_6) δ 878; IR (KBr) ν 1556, 1590 cm^{-1}; MS m/z (relative intensity) 289 (M^+, 18.0), 220 (82), 184 (41), 156 (57), 91 (100), 78 (69). HRMS Calcd for $C_{14}H_{11}NO^{80}Se$: 289.0005, found: 289.0011.

N-Cyclohexyl-1,2-benzisoselenazol-3(2*H*)-one (1: R = *c*-Hex) was prepared according to standard protocol A using 2-(benzylseleno)-*N*-cyclohexylbenzamide (**6**: R = c-Hex). Flash chromatography (CH_2Cl_2) afforded **1** (R = c-Hex) as a white crystalline solid (45%): mp = 159−160 °C; ^{1}H NMR ($CDCl_3$) δ 1.15−1.54 (5H, m), 1.69−1.74 (1H, m), 1.83−1.87 (2H, m), 2.04−2.11 (2H, m), 4.44−4.52 (1H, m), 7.40 (1H, t, J = 7.6 Hz), 7.55 (1H, t, J = 7.6 Hz), 7.58−7.64 (1H, m), 8.04 (1H, d, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 25.2, 25.5, 34.1, 53.6, 123.8, 125.9, 128.5, 131.4, 137.3, 137.8, 166.4; ^{77}Se (C_6H_6) NMR δ 825; IR (KBr) ν 1554, 1584 cm^{-1}; MS m/z (relative intensity) 281 (M^+, 15.3), 220 (43), 199 (100), 184 (21), 156 (32), 78 (41). Anal. Calcd for $C_{13}H_{15}NOSe$: C, 55.7; H, 5.3; N, 5.0. Found: C, 55.6; H, 5.3; N, 5.0.

Standard Protocol B for the Preparation of 2-[(Triphenylstannyl)seleno]benzamides (13). *N*-Phenyl-2-[(triphenylstannyl)seleno]benzamide (13: R = Ph). Triphenyltin hydride (530 mg, 1.51 mmol) was added to a solution of 2-(benzylseleno)-*N*-phenylbenzamide (**6**: R = Ph) (500 mg, 1.37 mmol) and azobis(isobutryonitrile) (AIBN) (10 mg, 60 μmol) in dry benzene (20 mL) and the solution heated overnight at reflux under nitrogen. The white precipitate was removed by filtration and the solvent removed *in vacuo*. The residue was separated by flash chromatography (23% ethyl acetate/petroleum ether) to afford the title stannyl selenide (**13**: R = Ph) as a white crystalline solid after recrystallization (ethanol) (585 mg, 68%): mp = 144−145 °C; ^{1}H NMR (acetone-d_6) δ 6.93 (1H, dt, J = 1.7, 7.2 Hz), 7.07 (1H, t, J = 6.9 Hz), 7.15 (1H, t, J = 7.2 Hz), 7.23−7.26 (11H, m), 7.39−7.51 (10H, m), 7.80 (1H, s(br); ^{13}C NMR (acetone-d_6) δ 120.0, 121.7, 124.1, 127.3, 128.66, 128.70, 128.8, 129.7, 129.9, 136.5, 136.9, 137.7, 139.3, 141.9, 166.4; ^{77}Se (acetone) NMR δ −32; IR (KBr) ν 1647, 3275 cm^{-1}; MS m/z (relative intensity) 547 (M^+ − Se, 20), 469 (2), 350 (11), 274 (45), 195 (100), 156 (21), 77 (29). The structure of **13** (R = Ph) was confirmed by X-ray analysis.[31]

***N*-Hexyl-2-[(triphenylstannyl)seleno]benzamide (13: R = Hex)** was prepared according to standard protocol B using 2-(benzylseleno)-*N*-hexylbenzamide (**6**: R = Hex). Flash chromatography afforded **13** (R = Hex) as a white crystalline solid after recrystallization (ethanol) (78%): mp = 143−144 °C; ^{1}H NMR (acetone-d_6) δ 0.87 (3H, t, J = 6.6 Hz), 1.26−1.41 (6H, m), 1.48−1.58 (2H, m), 3.24 (2H, q(apparent), J = 6.6 Hz), 6.96 (1H, dt, J = 1.5, 7.8 Hz), 7.03 (1H, s(br)), 7.14 (1H, t, J = 7.5 Hz), 7.25 (1H, d, J = 7.8 Hz), 7.34−7.41 (9H, m), 7.49 (1H, d, J = 7.8 Hz), 7.57−7.62 (6H, m) ; ^{13}C NMR (acetone-d_6) δ 14.3, 23.3, 27.4, 30.2, 32.3, 40.2, 124.2, 127.5, 128.5, 129.4, 130.0, 130.2, 137.5, 138.9, 139.8, 143.5, 169.7; IR (KBr) ν 1641, 3296 cm^{-1}; MS m/z (relative intensity) 555 (M^+ − Se, 100), 350 (27), 284 (29), 197 (63), 105 (42), 77 (44). Anal. Calcd for $C_{31}H_{33}NOSeSn$: C, 58.8; H, 5.2; N, 2.2. Found: C, 58.6; H, 5.3; N, 2.1.

N-Isopropyl-2-[(triphenylstannyl)seleno]benzamide (13: R = *i*-Pr) was prepared according to standard protocol B using 2-(benzylseleno)-*N*-isopropylbenzamide (**6**: R = *i*-Pr). Flash chromatography afforded **13** (R = *i*-Pr) as a white semisolid (78%): ^{1}H NMR (acetone-d_6) δ 1.15 (6H, d, J = 6.6 Hz), 4.08 (1H, sept, J = 6.6 Hz), 6.93 (1H, dt, J = 1.5, 7.5 Hz), 7.13 (1H, t, J = 7.8 Hz), 7.25 (1H, dd, J = 1.5, 7.5 Hz), 7.37−7.39 (9H, m), 7.47 (2H, d, J = 7.8 Hz), 7.58−7.60 (6H, m); ^{13}C NMR (acetone-d_6) δ 22.6, 42.0, 123.8, 127.5, 128.4, 129.4, 129.9, 130.2, 137.3, 138.8, 139.5, 143.5, 168.9; MS m/z (relative intensity) 513 (M^+ − Se, 100), 350 (33), 257 (33), 242 (78), 197 (74), 91 (54), 77 (34). HRMS Calcd for $C_{28}H_{27}NO^{120}Sn$: 513.1115, found: 513.1098.

***N*-*tert*-Butyl-2-[(triphenylstannyl)seleno]benzamide (13: R = *t*-Bu)** was prepared according to standard protocol B using 2-(benzylseleno)-*N*-*tert*-butylbenzamide (**6**: R = *t*-Bu). Flash chromatography afforded **13** (R = *t*-Bu) as a pale oil (62%): ^{1}H NMR (acetone-d_6) δ 1.41 (9H, s), 6.53 (1H, s(br)), 6.90 (1H, dt, J = 1.5, 7.8 Hz), 7.13 (1H, t, J = 7.2 Hz), 7.27 (1H, dt, J = 1.5, 7.5 Hz), 7.23−7.41 (9H, m), 7.48 (1H, d, J = 7.8 Hz), 7.58−7.63 (6H, m); ^{13}C NMR (acetone-d_6) δ 28.9, 51.8, 123.0, 127.4, 128.3, 129.4, 129.6, 130.2, 137.3, 138.9, 139.0, 144.3, 169.1; MS m/z (relative intensity) 527 (M^+ − Se, 100), 471 (34), 351 (32), 197 (75), 105 (42), 77 (45). HRMS Calcd for $C_{29}H_{29}NO^{120}Sn$: 527.1271, found: 527.1255.

Standard Protocol C for the Preparation of 2,2′-Diselenobis(benzamides) (15) from 2-[(triphenylstannyl)seleno]benzamides (13). *N*,*N*′-Diphenyl-2,2′-diselenobis(benzamide) (15: R = Ph). Benzoyl peroxide (100 mg, 0.4 mmol) was added to a stirred solution of *N*-phenyl-2-[(triphenylstannyl)seleno]benzamide (**13**) (R = Ph) (610 mg, 0.98 mmol) in dry benzene (40 mL). The solution was heated at reflux under nitrogen overnight. *N*,*N*′-Diphenyl-2,2′-diselenobis(benzamide) (**15**: R = Ph) was collected by filtration as a white crystalline solid (213 mg, 79%): mp = 260−263 °C (lit.[31] 263−265 °C); ^{1}H NMR (DMSO-d_6) δ 7.15 (2H, t, J = 7.2 Hz), 7.39−7.48 (8H, m), 7.75−7.80 (6H, m), 7.95 (2H, d, J = 7.2 Hz), 10.56 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 120.6, 124.2, 126.5, 128.7, 128.8, 130.2, 132.0, 132.1, 133.8, 138.7, 166.4; ^{77}Se (DMSO) NMR δ 451; IR (KBr) ν 1634, 3288 cm^{-1}; MS m/z (relative intensity) 471 (M^+ − SeH, 5.5), 261 (31), 195 (93), 167 (57), 156 (68), 91 (63), 77 (100).

***N*,*N*′-Dihexyl-2,2′-diselenobis(benzamide) (15: R = Hex)** was prepared according to standard protocol C using *N*-hexyl-2-[(triphenylstannyl)seleno]benzamide (**13**: R = Hex) and isolated as a white crystalline solid after recrystallization (ethanol) (87%): mp = 164−165 °C; ^{1}H NMR (DMSO-d_6) δ 0.88 (6H, t, J = 6.8 Hz), 1.26−1.37 (12H, M), 1.51−1.59 (4H, m), 3.29 (4H, q(apparent), J = 6.9 Hz) 7.30−7.40 (4H, m), 7.69 (2H, d, J = 7.5 Hz), 7.78 (2H, dd, J = 1.5, 7.5 Hz), 8.74 (2H, t, J = 5.7 Hz); ^{13}C NMR (DMSO-d_6) δ 14.0, 22.1, 26.2, 29.0, 31.1, 39.4, 126.2, 127.8, 129.9, 131.5, 131.9, 133.3, 167.3; ^{77}Se (DMSO) NMR δ 442; IR (KBr) ν 1610, 3329 cm^{-1}; MS m/z (relative intensity) 487 (M^+ − SeH, 0.6), 282 (24), 212 (34), 199 (46), 184 (100), 156 (21). Anal. Calcd for $C_{26}H_{36}N_2O_2Se_2$: C, 55.1; H, 6.4; N, 5.0. Found: C, 55.2; H, 6.7; N, 4.8.

***N*,*N*′-Diisopropyl-2,2′-diselenobis(benzamide) (15: R = *i*-Pr)** was prepared according to standard protocol C using *N*-isopropyl-2-[(triphenylstannyl)seleno]benzamide (**13**: R = *i*-Pr) and isolated as a white crystalline solid after recrystallization (ethanol) (56%): mp = 259−260 °C; ^{1}H NMR (DMSO-d_6) δ 1.21 (12H, d, J = 6.6 Hz), 4.11 (2H, sept, J = 6.6 Hz), 7.29−7.41 (4H, m), 7.69 (2H, d, J = 7.8 Hz), 7.80 (2H, d, J = 7.5 Hz), 8.54 (2H, d, J = 7.8 Hz); ^{13}C NMR (DMSO-d_6) δ 22.3, 41.4, 126.1, 128.0, 130.0, 131.5, 131.9, 133.5, 166.5; ^{77}Se (DMSO) NMR δ 451; IR (KBr) ν 1609, 3292 cm^{-1}; MS m/z (relative intensity) 483 (M^+ − H, 2.6), 404 (3), 242 (92), 199 (92), 184 (100), 156 (56), 77 (30). HRMS Calcd for $C_{20}H_{23}N_2O_2{}^{80}Se_2$: 483.0089, found: 483.0109.

***N*,*N*′-Di-*tert*-butyl-2,2′-diselenobis(benzamide) (15: R = *t*-Bu)** was prepared according to standard protocol C using *N*-*tert*-butyl-2-[(triphenylstannyl)seleno]benzamide (**13**: R = *t*-Bu) and isolated as a white crystalline solid after recrystallization (ethanol) (54%): mp = 215−216 °C; ^{1}H NMR (acetone-d_6) δ 1.50 (18H, s), 7.22 (2H, t, J = 7.2 Hz), 7.29 (2H, t, J = 7.5 Hz), 7.38 (2H, s(br)), 7.67 (2H, d, J = 7.5 Hz), 7.79 (2H, d, J = 7.8 Hz); ^{13}C NMR (acetone-d_6) δ 29.0, 52.4, 126.7, 128.3, 131.2, 131.8, 133.1, 136.0, 168.6; ^{77}Se (acetone) NMR δ 445; IR (KBr) ν 1622, 3441 cm^{-1}; MS m/z (relative intensity) 431 (M^+ − SeH, 3.3), 255 (65), 200 (100), 184 (50), 156 (19), 77 (21). Anal. Calcd for $C_{22}H_{28}N_2O_2Se_2$: C, 51.8; H, 5.5; N, 5.5. Found: C, 51.9; H, 5.7; N, 5.3.

Standard Protocol D for the Preparation of 1,2-Benzisoselenazol-3(2*H*)-ones (1) by the Benzoyl Peroxide Method. *N*-Hexyl-1,2-benzisoselenazol-3(2*H*)-one (1: R = Hex). Benzoyl peroxide (70 mg, 0.29 mmol) was added to a stirred suspension of *N*,*N*′-dihexyl-2,2′-diseleno-

(30) Fischer, H.; Dereu, N. *Bull. Soc. Chim. Belg.* **1987**, *96*, 757.
(31) Fong, M. C.; Gable, R. W.; Schiesser, C. H. *Acta. Crystallogr.* **1996**, *C52*, 1886.

bis(benzamide) (**15**: R = Hex) (150 mg, 0.26 mmol) in benzene (12 mL). The mixture was heated to reflux at which point a clear solution was obtained which was heated at reflux under nitrogen overnight. The solvent was removed *in vacuo*, the residue dissolved in CH_2Cl_2 and washed with saturated sodium bicarbonate (2 × 15 mL) and dried ($MgSO_4$). Removal of the solvent afforded **1** (R = Hex) as a crystalline solid after recrystallization (125 mg, 83%) exhibiting physical data identical to those reported above (protocol A).

N-Isopropyl-1,2-benzisoselenazol-3(2*H*)-one (1: R = *i*-Pr) was prepared according to standard protocol D using *N*,*N*′-diisopropyl-2,2′-diselenobis(benzamide) (**15**: R = *i*-Pr) in chlorobenzene as solvent and isolated as a white crystalline solid after recrystallization (ethanol) (85%): mp = 105−106 °C; ^{1}H NMR ($CDCl_3$) δ 1.36 (6H, d, J = 6.6 Hz), 4.87 (1H, sept, J = 6.6 Hz), 7.41 (1H, t, J = 6.9 Hz), 7.56 (1H, t, J = 8.1 Hz), 7.65 (1H, d, J = 8.1 Hz), 8.03 (1H, d, J = 7.8 Hz); ^{13}C NMR δ 23.3, 46.5, 123.9, 126.0, 128.5, 129.5, 131.6, 137.5, 166.5; ^{77}Se (C_6H_6) NMR δ 814; IR (KBr) ν 1596, 1562 cm^{-1}; MS m/z (relative intensity) 241 (M^+, 36.6), 226 (33), 199 (100), 184 (44), 156 (58), 77 (37). Anal. Calcd for $C_{10}H_{11}NOSe$: C, 50.0; H, 4.6; N, 5.8. Found: C, 50.0; H, 4.6; N, 5.9.

N-*tert*-Butyl-1,2-benzisoselenazol-3(2*H*)-one (1: R = *t*-Bu) was prepared according to standard protocol D using *N*,*N*′-di-*tert*-butyl-2,2′-diselenobis(benzamide) (**15**: R = *t*-Bu) and isolated as a white crystalline solid after recrystallization (ethanol) (76%): mp = 230−231 °C; ^{1}H NMR ($CDCl_3$) δ 1.68 (9H, s), 7.36−7.41 (1H, m), 7.52−7.59 (2H, m), 7.96 (1H, d, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 29.0, 58.7, 123.2, 125.9, 128.3, 130.0, 131.5, 136.8, 166.9; ^{77}Se (acetone) NMR δ 847; IR (KBr) ν 1588, 1558 cm^{-1}; MS m/z (relative intensity) 255 (M^+, 12.5), 199 (100), 156 (21), 105 (18). Anal. Calcd for $C_{11}H_{13}NOSe$: C, 52.0; H, 5.1; N, 5.5. Found: C, 52.0; H, 5.3; N, 5.2.

N-Phenyl-1,2-benzisoselenazol-3(2*H*)-one (1: R = Ph) (Ebselen, 1: R = Ph). *tert*-Butyl peroxide (500 μL) was added to a stirred solution of 2,2′-diselenobis(benzanilide) (**15**: R = Ph) (50 mg, 90 μmol) in chlorobenzene (700 μL) and the solution stirred under nitrogen at 120 °C for 16 h.[26,32] The white solid was filtered off and the filtrate washed with water (2 × 10 mL) and dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was recrystallized (ethanol) to afford **1** (R = Ph) as a white solid (38 mg, 76%): mp = 182−183 °C (lit.[7] 182−183 °C); ^{1}H NMR (DMSO-d_6) δ 7.28 (1H, t, J = 7.0 Hz), 7.44−7.52 (3H, m), 7.64−7.73 (3H, m), 7.93 (1H, d, J = 7.8 Hz), 8.10 (1H, d, J = 7.8 Hz); ^{13}C NMR (DMSO-d_6) δ 124.7, 125.8, 126.3, 128.0, 128.5, 129.2, 132.3, 138.9, 139.7, 165.0; ^{77}Se (DMSO) NMR δ 942; IR (KBr) ν 1593, 1560 cm^{-1}; MS m/z (relative intensity) 275 (M^+, 100), 195 (73), 184 (9), 167 (22), 156 (14), 91 (6). HRMS Calcd for $C_{13}H_9NO^{80}Se$: 274.9849, found: 274.9850.

2-(Methylseleno)benzanilide (3). *tert*-Butyl peroxide (39 μL, 0.21 mmol) was added to a stirred solution of 2,2′-diselenobis(benzanilide) (**15**: R = Ph) (115 mg, 0.21 mmol) in chlorobenzene (30 mL) and the solution stirred at 120 °C under nitrogen for 36 h. After washing with water (2 × 10 mL) and drying ($MgSO_4$), the solvent was removed *in vacuo* and the residue separated by preparative TLC (1:9 petroleum ether: CH_2Cl_2). The fraction of lower R_f proved to be **3** which was isolated as a white solid (65 mg, 54%): mp = 173−174 °C (lit.[10] 176 °C); ^{1}H NMR ($CDCl_3$) δ 2.31 (3H, s), 7.16 (1H, t, J = 7.2 Hz), 7.29−7.51 (5H, m), 7.65 (3H, m), 7.93 (1H, s(br)); ^{13}C NMR ($CDCl_3$) δ 7.5, 120.1, 124.6, 125.8, 128.0, 129.1, 130.2, 131.2, 133.2, 135.9, 137.8, 166.4; MS m/z (relative intensity) 291 (M^+, 24), 276 (21), 199 (100), 184 (13), 156 (19), 91 (94). The structure of **3** was confirmed by X-ray analysis.[30]

The fraction of higher R_f proved to be *N*-phenyl-1,2-benzisoselenazol-3(2*H*)-one (**1**: R = Ph) (39 mg, 34%).

Acknowledgment. We thank Ms. Melissa Laws for providing spectral data on **3** and the Australian Research Council for financial support.

JO970019T

(32) Heating concentrated *tert*-butyl peroxide at 120 °C is potentially hazardous and should never be attempted on a large scale. This experiment was carried our behind a protective (safety) shield.