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An Efficient Copper-Catalyzed Synthesis of Symmetrical Bis(N-Arylbenzamide) Selenides and Their Conversion to Hypervalent Spirodiazaselenuranes and Hydroxy Congeners

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Abstract

A copper catalyzed efficient synthetic method has been developed to access bis(*N*-arylbenzamide) selenides from 2-halo-N-arylbenzamides substrates and disodium selenide in HMPA at 110°C. The developed protocol tolerates substituents in both *N*-aryl and benzamide rings of the 2-halobenzamide substrates and provide an array of bis(*N*-arylbenzamide) selenides in practical yields. The resulted selenides were transformed into hypervalent spirodiazaselenuranes by the oxidation using aqueous hydrogen peroxide. (*N*-(1-Naphthyl)) spirodiazaselenurane is also structurally characterized by single crystal X-ray study. Hydroxy-substituted spiroselenuranes have been prepared by careful demethylation of methoxy-substituted selenides followed by oxidation by hydrogen peroxide. Antioxidant properties for the decomposition of hydrogen peroxide and for the deactivation of radicals of hydroxy-substituted spiroselenuranes have been studied by thiol assay and 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay. Both hydroxy-substituted spiroselenuranes exhibit dual mimic functions of glutathione peroxidase (GPx) selenoenzyme and α-tocopherol for decomposition of hydrogen peroxide and deactivation of radicals, respectively.

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Introduction

The Studies on hypervalent organochalcogens, particularly, chalcogenuranes have attracted great deal of interest as they seem to open new frontiers in organic synthesis and medicinal chemistry.[1] Several stable hypervalent organochalcogens, mainly sulfurane species have been reported in the begining.[2]

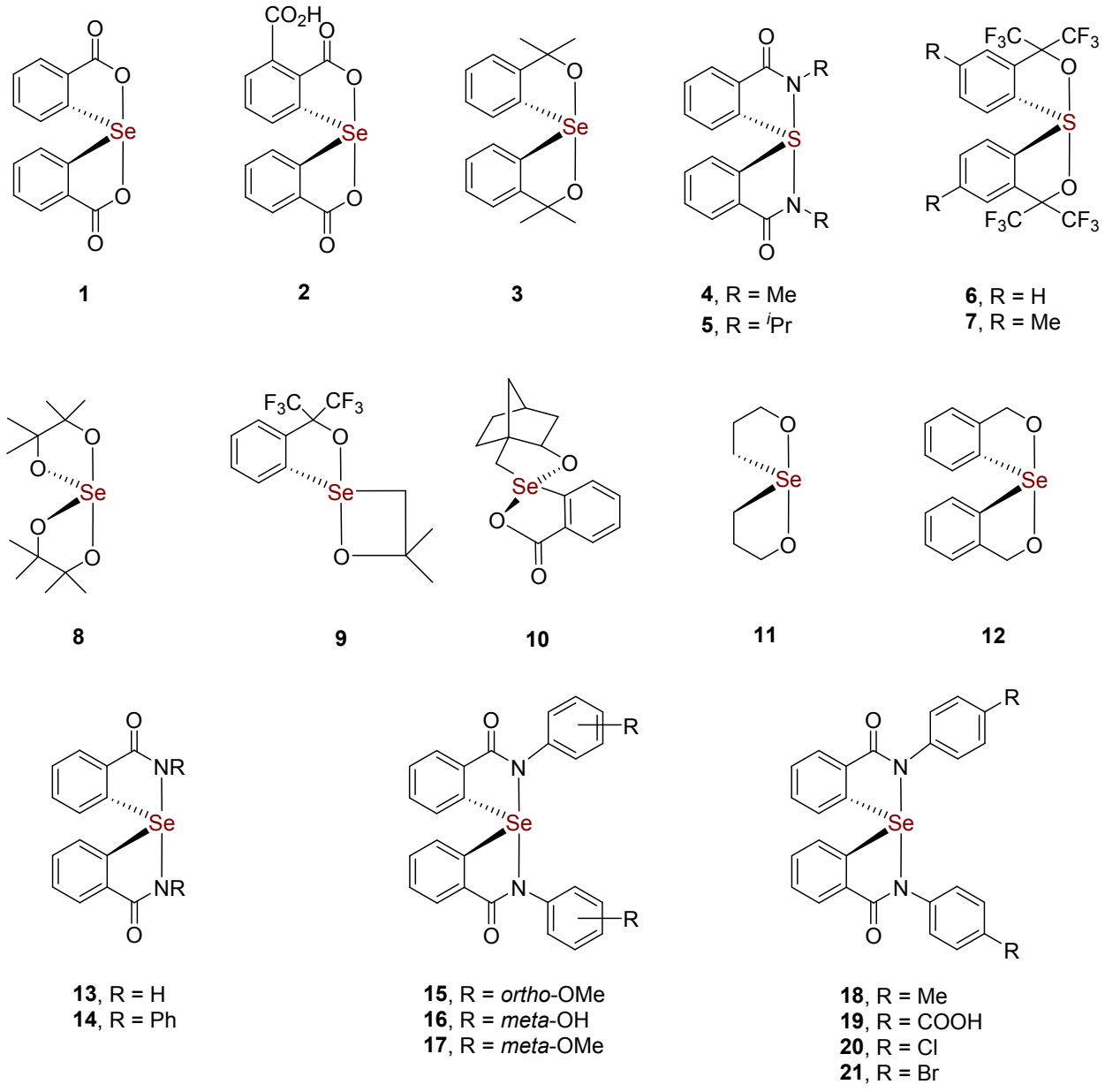

Chart 1. Reported organospirosulfuranes and -selenuranes

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Interestingly, hypervalent spiro chalcogenuranes having trigonal bipyramidal TBP-geometry are chiral molecules due to presence of C_2-symmetry.[3] The first spirodioxyselenurane **1** was synthesized by Lesser and Weiss in 1914 (Chart 1).[4] Subsequently, unsymmetrical carboxy derivative **2** was synthesized and partially resolved by Lindgren,[5] then germinal dimethyl substituted compound **3** was found to possess high configurational stability even at elevated temperature.[6] Spirodiazasulfuranes having two nitrogen atoms at the apical position are rare, the first nitrogen-substituted spirodiazasulfuranes **4** and **5** have been synthesized by Martin and co-workers.[7] The same group in 1979 reported a very facile synthesis of hypervalent spirosulfuranes **6** and **7**.[8] Spirotetraoxyselenurane **8** and various examples have also been reported and their acid catalyzed equilibrium also been studied.[9] The synthesis of oxaselenetane **9** and related analogues have been reported by Okazaki *et al*. in 1993.[10] Camphor-substituted unsymmetrical spirodioxyselenurane **10** was also synthesized as pure diastereomers.[11] In 2004, Back and co-workers have reported the synthesis of spirodioxyselenurane **11** and its homologues and also demonstrated their glutathione peroxide (GPx) mimetic activity.[12] Although the aromatic derivative **12** exhibited much reduced catalytic activity as compared to their aliphatic counterparts,[13] the substituted aromatic analogues have shown improved catalytic activity. Unlike well explored spirodioxyselenuranes,[14,15] spirodiazaselenuranes having apical nitrogen atoms are unique. In 2007, for the first time Back *et al*. reported the relative instability of such spirodiazaselenuranes **13**.[16]

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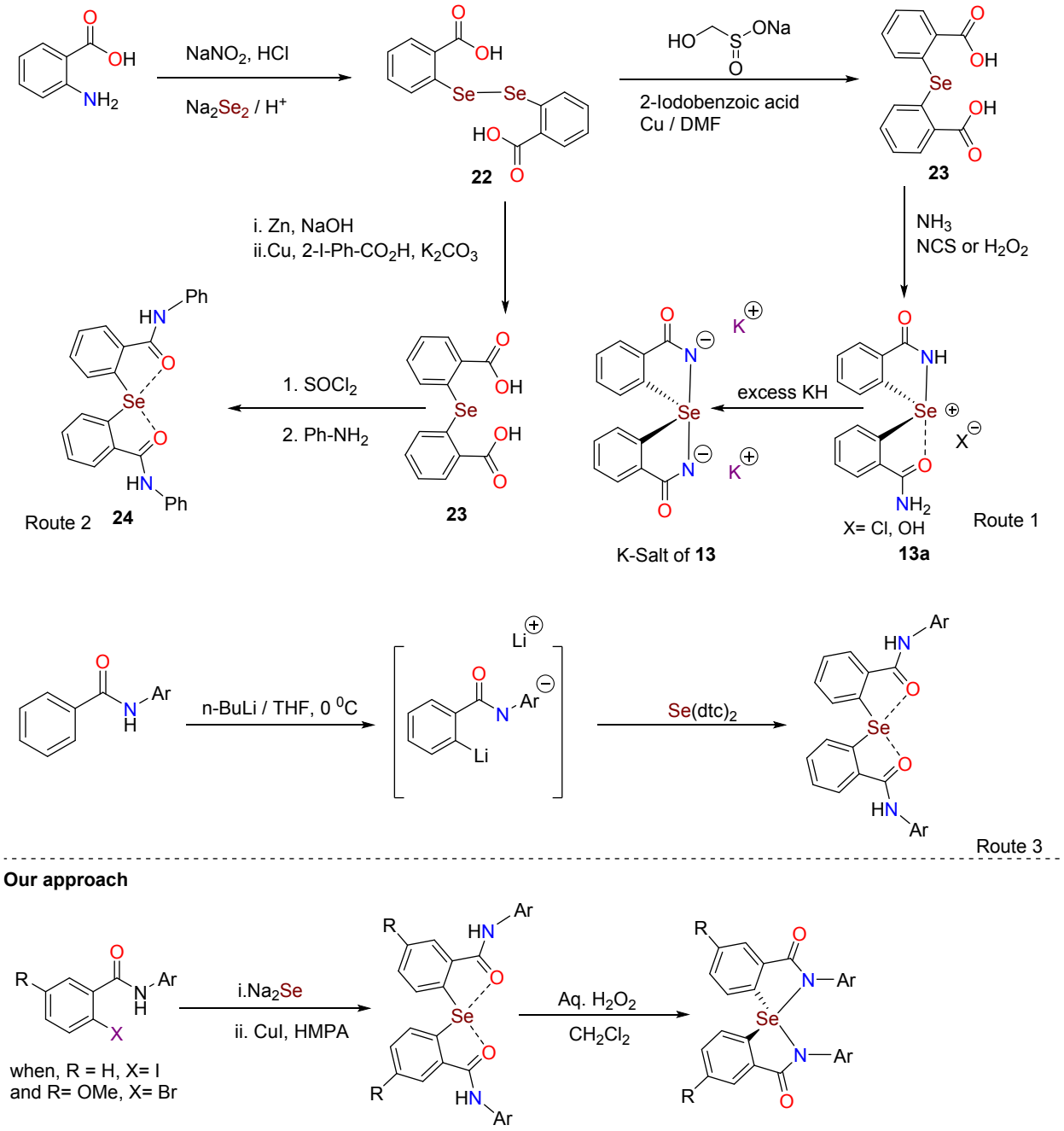

Scheme 1. Synthetic routes of spirodiazaselenuranes and their precursors

The synthesis of organodiazaselenuranes involves multi-steps as depicted in Scheme 1. Diazotization of anthranilic acid, subsequent quenching of diazotized intermediate by Na_2Se_2 resulted into 2-benzoic acid diselenide **22**.[17] Back *et al.* have reduced diselenide **23** using sodium hydroxymethyl sulfate and followed by the coupling with 2-iodobenzoic acid mediated by copper in DMF yielded desired monoselenide **23** (route 1). The reaction of **23** with N-chlorosuccinimide

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followed by quenching with ammonia and subsequently attempted oxidation of *in-situ* resulted 2-benzamide selenide failed to provide spirodiazaselenuranes **13** and instead selenium cation **13a** was isolated which was stabilized Se…O intramolecular interaction. Interestingly, when reaction mixture of *in-situ* formed siproselenurane was treated with KH, reaction provided potassium salt of spiroselenurane. In an alternative approach to symmetrical selenide **24**, reduction of diselenide **22** with Zn and NaOH followed by copper-mediated coupling with 2-iodobenzoic acid resulted symmetric bis(2-benzoic acid) selenide **23**. Subsequently, conversion of acid group of **23** into acyl chloride by the reaction of thionyl chloride and followed by the coupling of primary aryl amines resulted into the formation of desired key precursor N-arylphenyl selenide **24** (route 2).[18] However, oxidation of selenide **24** into spirodiselenurane Se(IV) has not been reported by Pietka-Ottlik and Mlochowski.[18]

In 2010, the synthesis of N-phenylbezamide selenide **24** was achieved by o*rtho*-lithiation method in which dianion, resulted from *ortho*-lithiation of N-phenylbenzamide, was treated with selenium dithiacarbamate $Se(dtc)_2$.[19] The resulted N-phenylbezamide selenide **24** was also structurally characterized. Later same group reported the synthesis of N-aryl–substituted benzamide selenides **15-21** by treatment of 2-benzoic acid selenide **23** with thionyl chloride and subsequent quenching with substituted-aryl amines. Interestingly, the selenide precursors **15-21** was successfully transformed into stable spiroselenuranes.[20,21] Also antioxidant activities of spiroselenuranes against peroxynitrite and peroxides have been studied. In 2014 Kawashima and coworkers reported synthesis and structure of tetra-coordinated selenazitidines.[22]

Owing to its high catalytic activity, ebselen having Se-N bond is one of the best candidate which has undergone several clinical trials[23] such as neuro and cardio protective agents, hearing loss treatment. The presence of covalent Se-N and Se-O bonds at various stages of redox cycles have been studied for GP_x mimetics.[24,25] Recently our group along with Engman *et al.* have reported regenerable multifunctional ebselenol antioxidants **25-28** (Chart 2) for radical trapping and H_2O_2 decomposing activities.[26] Mechanistic understanding of ebselenols suggests that the presence of Se-N bond is crucial for peroxyl radical deactivating activity and also their regenerability by ascorbic acid vitamin C.[26] Radical chain breaking antioxidant activity of 2-(hydroxymethyl)-4-hydroxyphenyl 3-hydroxypropyl selenide which is a precursor of its spiroselenurane has also been evaluated.[15a] Our group is continuously working on the development of new and sustainable

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methodologies to construct organochalcogen compounds. We developed a copper-catalyzed Se-N bond forming reaction for the synthesis isoselenazolones and ebselen molecules from 2-halobenzamide substrates.[27] Also benzamide substrates have been successfully exploited for various carbon-carbon and carbon-heteroatom coupling reactions.[28]

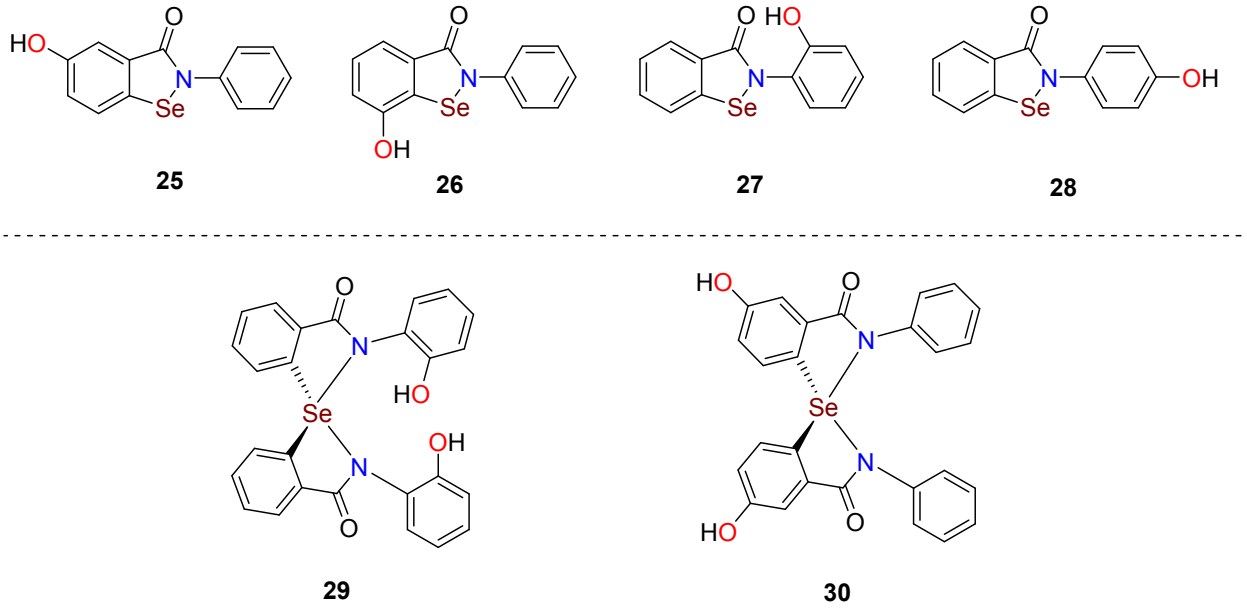

Chart 2: Ebselenols **25-28** and synthesized spiroselenuranols **29-30**

We envisage that the phenolic compounds **29** and **30** having tetravalent selenium and having Se-N bond would serve as potent radical chain breaking antioxidant. Here in continuation of our work on copper catalyzed Se-N bond forming reaction, we present a practical method to access symmetrical bis(N-arylbenzamide) selenide precursors in gram quantity. Also, bis(N-arylbenzamide) selenide precursors was transformed into spiroselenuranes following the reported procedure by Mugesh and coworkers.[19] Hydroxyselenuranes were achieved by de-methylation of methoxysubstituted monoselenides by us using BBr_3 followed by the spirocyclization. Hydrogen peroxide decomposing and radical deactivating antioxidant activities of hydroxy-substituted spiroselenuranes have also been evaluated by vitro assays.

Results and Discussion

Synthesis and Characterization: 2-Iodo/bromo-*N*-phenylbenzamide substrates **31-36** were prepared by following literature procedure.[29-30]

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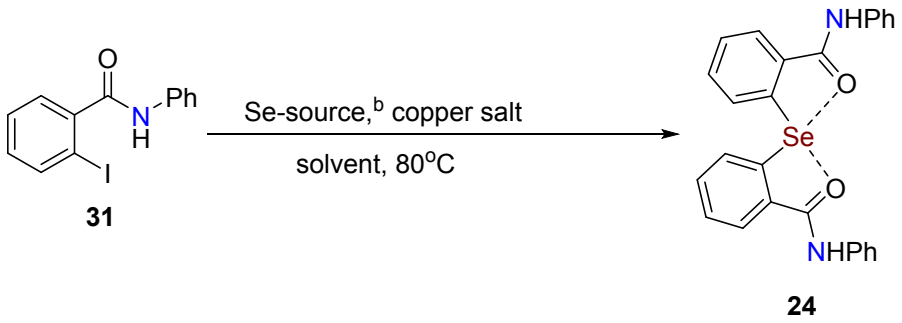
Table 1. Optimization of reaction conditions for the synthesis of selenide **24**[a]



31 **24**

Entry	Cu-Source	Base/Additive	Solvent	Yield of 24
1	CuI (10 mol%)[c]	1,10-Phen., Mg (one equiv)	DMF	trace[d]
2	CuOTf (10 mol%)[c]	1,10-Phen., Mg (one equiv)	DMF	trace[d]
3	CuI (100 mol%)	1,10-Phen., Mg (one equiv)	DMF	trace[d]
4	CuI (10 mol %)	1,10-Phen.	THF	trace
5	CuI (10 mol %)	1,10-Phen.	DMF	50%
6	CuI (10 mol %)	1,10-Phen.	DMSO	65%
7	CuI (10 mol %)	1,10-Phen.	HMPA	75%
8	**CuI** (10 mol %)	—	**HMPA**	**86%**
9	—	—	HMPA	25%
10	CuI (10 mol%)	Mg (one equiv)	HMPA	45%
11	CuI (5 mol%)	Mg (one equiv)	HMPA	30%
12	—	$NaBH_4$ (two equiv)[e]	PEG-400	15%

[a,b] Selenium powder was used in entries 1-3 and disodium selenide Na_2Se was used a source of selenium in entries 4-11. Na_2Se was in-situ generated by the reaction of selenium (4.15 g, 52.5 mmol) with sodium (2.53 g, 110 mmol) in the presence of catalytic amount of naphthalene (1.28 g, 10 mmol) in THF (30 mL). After formation of Na_2Se, THF solvent was distilled, 2-iodo-N-phenyl benzamide **24** (3.23 g, 100 mmol) and HMPA (5 mL) were added. The resulted reaction mixture was heated at 80°C. [c] Selenium powder was used instead of Na_2Se. [d] Observed by TLC. [e] Na_2Se was prepared by the reaction of $NaBH_4$ (101 mg, 2.7 mmol) with selenium (128 mg, 1.6 mmol).

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Our initial trial for the synthesis of selenide **24** was unsuccessful by using selenium powder in the presence of copper iodide and 1,10-phenanthroline catalyst and magnesium as a reductant[31] in the absence of a base (entry 1, Table 1). Further, the use of different copper source and even 100 mole % CuI and 1,10-phenanthroline afforded only traces of selenide **24** (entries 2 and 3, Table 1). Next, we envisage that the substitution of iodide by selenide dianion Se^{2-} in 2-iodobenzamide would provide smooth access to symmetric selenide **24**. For this purpose, selenium dianion was *in-situ* generated by the reaction of selenium powder and sodium metal in the presence of naphthalene catalyst in THF. The subsequent reaction of in-situ generated selenide anion with 2-iodophenyl benzamide **31** in same solvent THF was unsuccessful (entry 4). The change in solvent from THF to DMF led to 50% yield of the desired selenide **24** (entry 5). Further, DMSO afforded slightly better yield 65% (entry 6). Nonetheless, selenide **24** was difficult to purify due to difficulty in column chromatography of benzamide substrates. Next, we sought for a practical method which devoid further purification to access selenide **24**. The use of HMPA solvent together with copper catalyst enabled substantial improvement in the yield of **24** by 10% (entry 7 *vs* entry 6, Table 1). Interestingly, reaction noticed to be clean and better yield (86%) of selenide **24** was realized in the absence of 1,10-phenanthroline ligand (entry 8).

The reaction in the absence of copper catalyst was ineffective and afforded only 25% yield of the product **24** (entry 9, Table 1). Further, catalyst loading from 20 to 10 or 5 mole % was not successful in the presence of magnesium additive and seems 20 mole % is essential for complete conversion (entries 10-11, Table 1). We also attempted to substitute HMPA with benign and greener solvent PEG-400. For this purpose, Na_2Se was generated by the reaction of $NaBH_4$ with selenium in PEG-400. Subsequent reaction of 2-iodobenzamide **31** with Na_2Se afforded only 15% yield of **24** (entry 12, Table 1).

Next, substrate scope was explored under the optimized conditions (Scheme 2). Methoxy-substituted-N-aryl-iodo-benzamides smoothly reacted to afford respective selenides **37-39** in 91-94% yields. Similarly, N-naphthyl substituted substrate **35** underwent C-Se bond forming reaction to give respective naphthyl selenide **40** quantitatively. Although, synthetic methods are available

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to prepare N-phenyl-benzamide selenides, synthesis of benzamide ring substituted selenides have not been accomplished. Interestingly, methoxy-substituted benzamide ring containing bromo substrate **36** also coupled smoothly to yield **41**. Next, oxidation of divalent selenides **24** and **37-41** into tetravalent spirodizaselenuranes **14**, **15**, **17**, **42-44** was studied. Oxidation occurred smoothly by aqueous hydrogen peroxide and afforded spirodiazaselenuranes **14**,[19] **15**, and **17**,[20] and **42-44** quantitatively.

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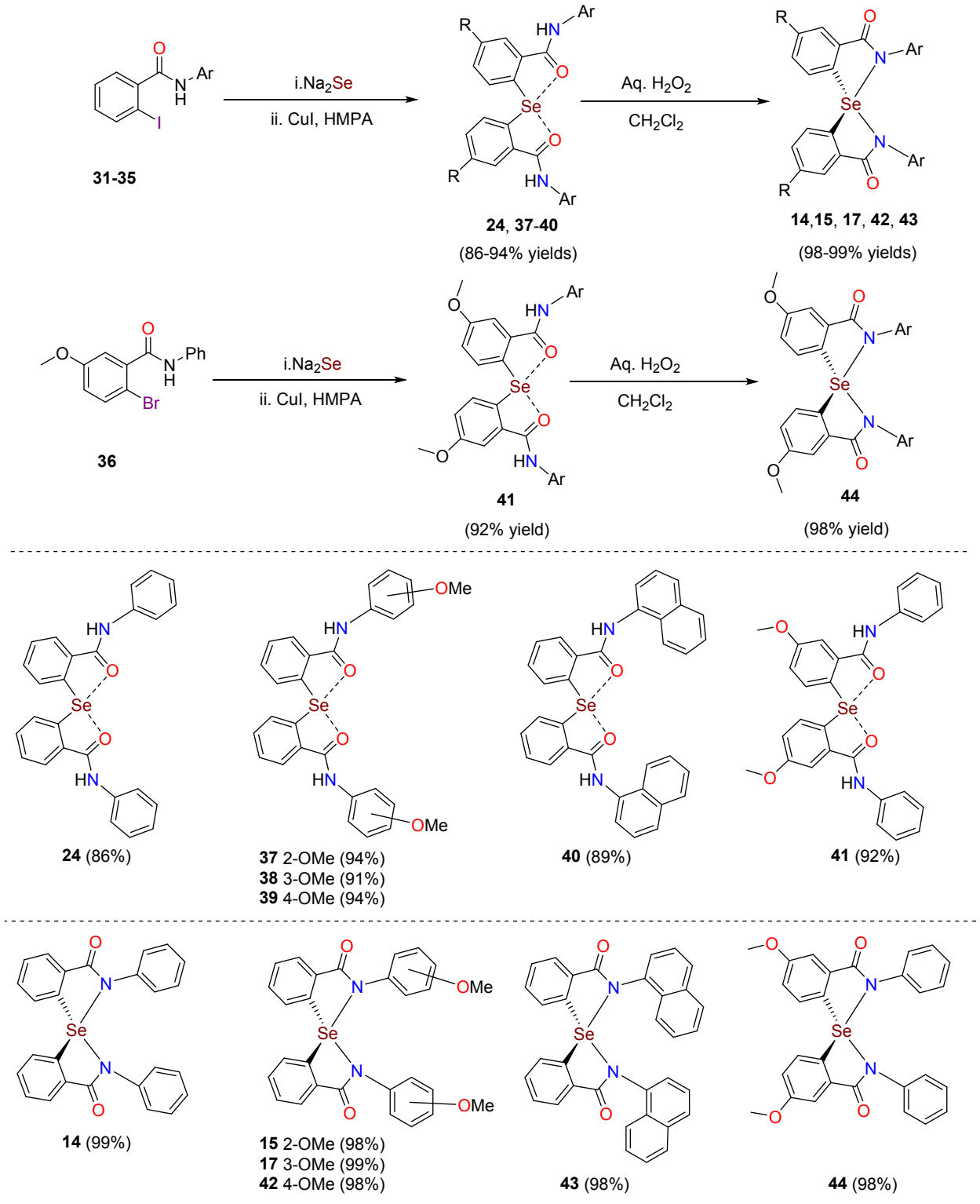

Scheme 2: Synthetic routes of monoselenenides and spirodiazaselenuranes

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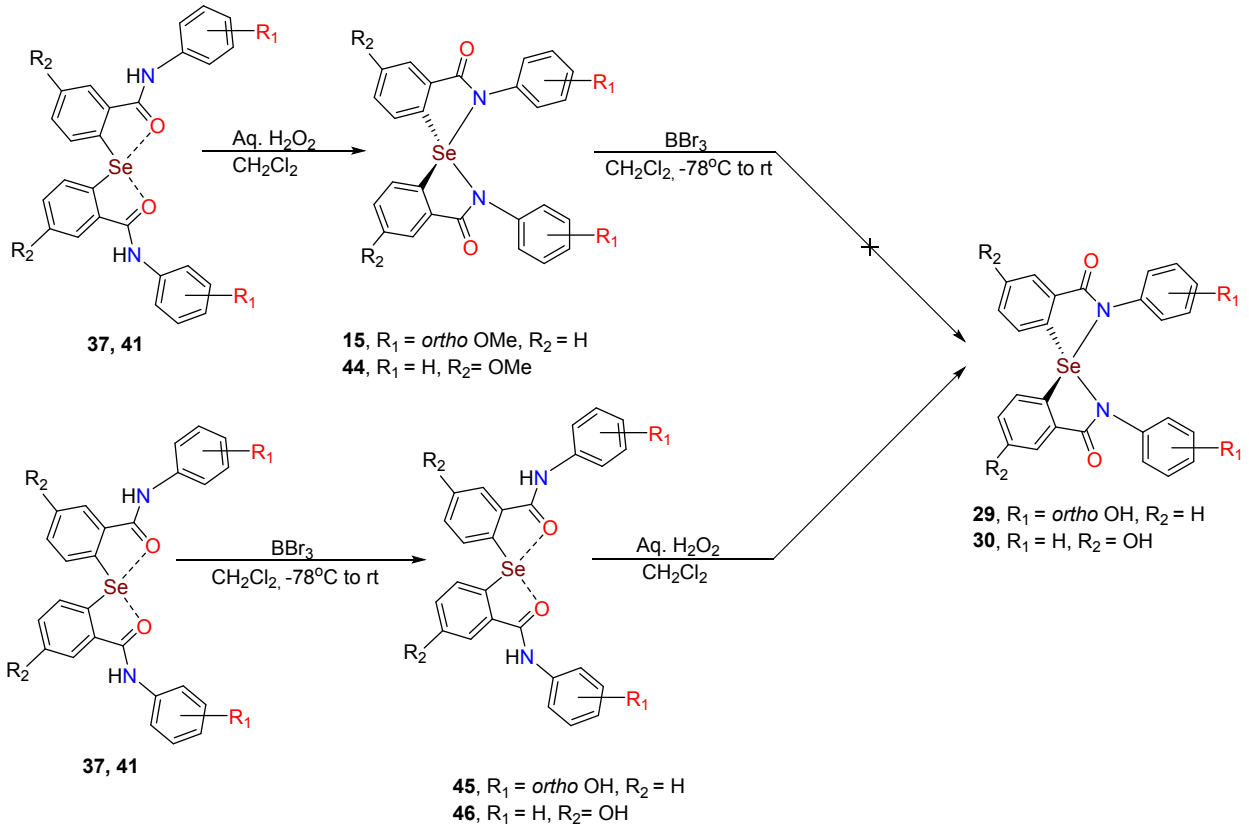
Finally, demethylation reaction on methoxy-substituted spirodiazaselenuranes **15**, **17, 42**, and **44** were explored to access phenolic radical chain breaking antioxidants having tetravalent selenium (Scheme 3).



Scheme 3: Synthesis of hydroxy-monoselenides and respective spirodiazaselenuranes

Demethylation of methoxy-substituted spirodiazaselenuranes **15**, **17, 42**, and **44** using BBr_3 noticed to be sluggish procedure and the cleavage of Se-N bond of **15**, **17, 42**, and **44** was realized. In the presence of an excess of BBr_3, resulted in the demethylation of spirodiazaselenuranes **15**, **17, 42**, and **44** as the reaction was monitored by ^1H NMR. However, cleavage of Se-N bond was also realized which led to complex reaction mixture. Next demethylation was attempted using sodium ethane thiolate, which also resulted in the cleavage of Se-N bond instead of demethylation.

In an alternative approach, methoxy-substituted selenides **37** and **41**were treated with an excess of BBr_3 which provided hydroxy-substituted selenides **45-46.** Careful variation in the stoichiometry of BBr_3 led to complete demethylation of methoxy substituent smoothly afforded 93 and 95% yields respectively.

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Synthesized selenides **24**, **37-41** and spirodiazaselenuranes **14**, **15**, **17**, **42-44** were characterized by multinuclear (^{1}H, ^{13}C and ^{77}Se) NMR and mass spectrometry. Spirodiazaselenuranes exhibited signals of ^{77}Se NMR (571-596 ppm) which are significantly downfield shifted, due to tetravalency of selenium, as compare to selenides which resonate in the range of 376-430 ppm. Structure of naphthyl spirodiazaselenurane (rectangular, colorless white crystal) **43** is also studied by single crystal X-ray diffractometer. (Bruker APEX2) Spirodiazaselenurane **43** crystallized in distorted trigonal bipyramidal (TBP) with the electronegative nitrogen atoms occupying the apical positions and two carbon atoms projecting lone pair at the equatorial position (Figure 1). Both enantiomers are crystallized in single unit cell. Consequently, averages of both (bond distances and angles) are presented. Se─C and Se─N distances are 1.93(1) and 2.0355(7)Å and ∠ N─Se─N is nearly linear 174.15(3)° whereas ∠ C─Se─C is bent at 98.05(4)°.

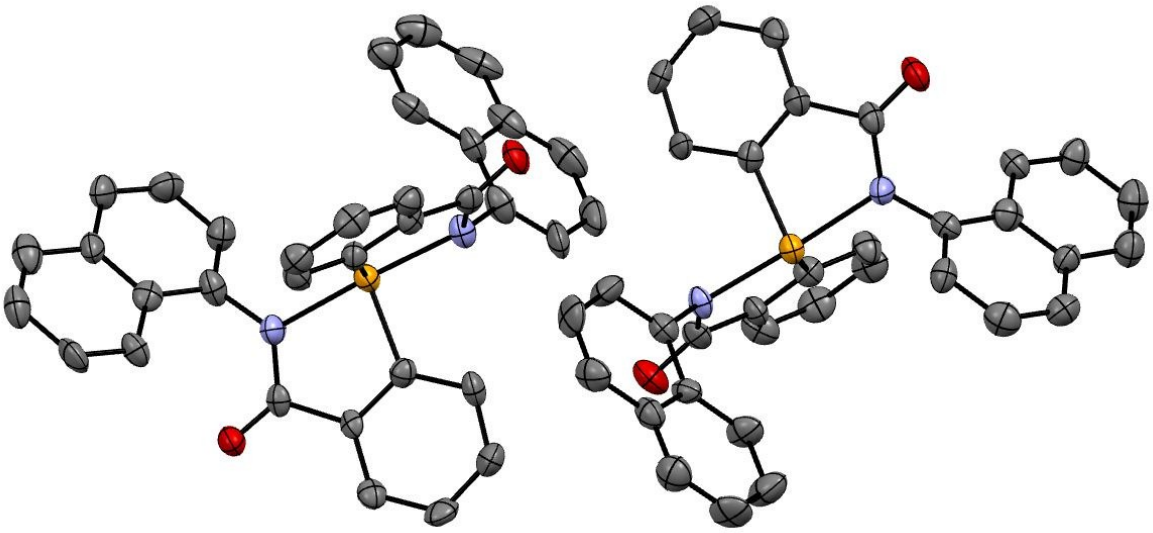

Figure 1. *ORTEP* view of **43** (both enantiomers) with 40% probability of thermal ellipsoids

Proposed mechanism: The tentative mechanism of the copper-catalyzed selenation reaction is shown in the Scheme 4. Although, mechanism for copper-catalyzed carbon-selenium bond formation has been proposed from carbon-halogen bond.[27a,31,32] However, these reports utilized bases namely sodium carbonate, potassium carbonate or potassium hydroxide. The presence of a

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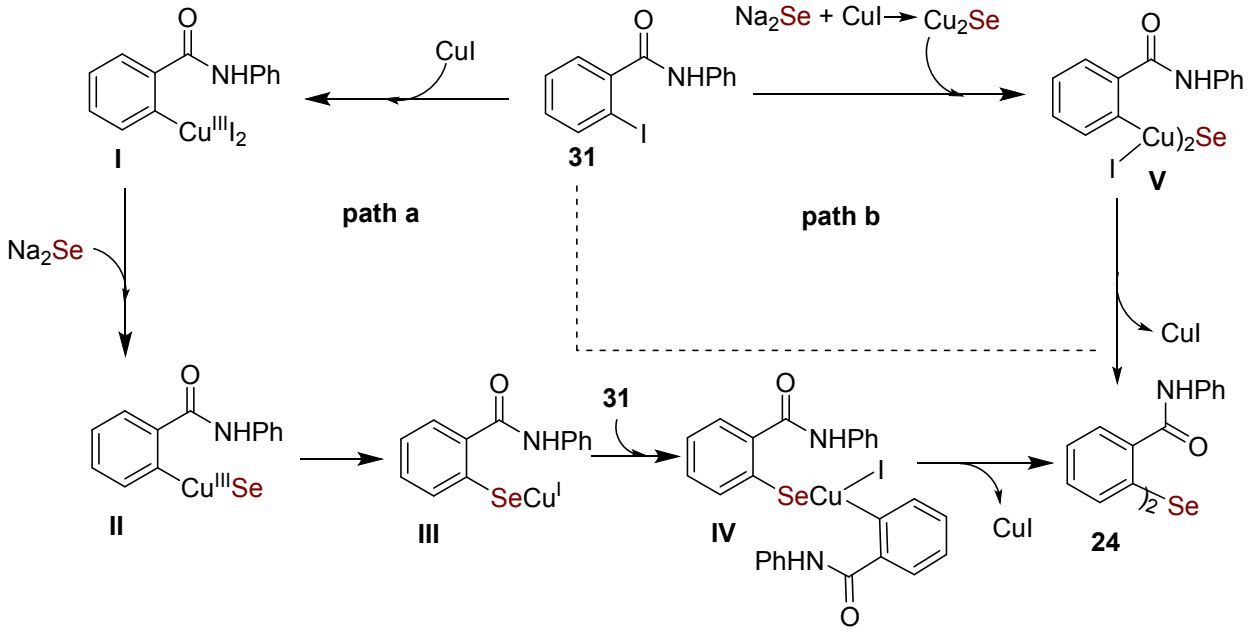
base in the reaction of 2-iodoN-arylbenzamides resulted in the formation of Se-N heterocycles instead of respective symmetric monoselenides.[27a] Also, addition of elemental selenium powder instead of selenium dianion does not provide satisfactory result under the reaction conditions. This suggests that the insertion of selenium powder into copper-carbon bond in the amidate intermediate **I** is not a viable path under base free conditions.



Scheme 4: Mechanism for Cu-catalyzed selenide formation

It seems that under base-free conditions, copper undergo oxidative addition of C─I bond of substrate **31** and form Cu^{III} intermediate **I** (path a). Subsequent iodide ligands of copper might be substituted by selenide ion to furnish copper^{III}selenolate **II**. Migration of selenium into copper-carbon bond might afford Cu^{I}selenolate intermediate **III**. Oxidative addition of another C-I bond to Cu-complex **III** could provide copper^{III}selenolate intermediate **IV**. Reductive elimination would afford desired selenides **24** along with concomitant regeneration of Cu^{I} catalyst. In an alternative path (b, see right side of the Scheme 2), CuI would undergo substitution with selenide dianion to provide Cu^{I}_2Se which might undergo oxidative addition with C-I bond of **31** to furnish intermediate **V**. This intermediate having C─Cu─Se bonds could undergo reductive elimination reaction to enable selenide **24** and release of Cu^{I} catalyst.

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Peroxide decomposing GPx-like antioxidant property: Peroxide decomposing antioxidant activity as a mimic for glutathione peroxidase (GPx) selenoenzyme was evaluated by thiol assay[33] using benzenethiol (PhSH) co-reductant and hydrogen peroxide as an oxidant in the presence of synthesized spiroselenuranes **29** and **30**. The oxidation of PhSH to diphenyl disulfide (PhSSPh) by H_2O_2 was monitored by UV-visible spectrophotometry at 305 nm (eq. 1)

$$PhSH + H_2O_2 \xrightarrow[305\ nm]{Catalyst} PhSSPh + H_2O \qquad (1)$$

The H_2O_2 decomposing antioxidant activity of **29** was found to be higher than the standard diphenyl diselenide (Table 2). However, spiroselenurane **30** having hydroxyl group in anilinic ring shows lower hydrogen peroxide decomposing antioxidant activity as compared to Ph_2Se_2.

Table 2. Thiol peroxidase assay of **29** and **30**

entry	catalyst	reduction rate (v_0 = μM min^{-1})[a]
1	Ph_2Se_2	25.57 ± 5.2[33b]
2	**29**	27.92 ± 4.5
3	**30**	13.06± 4.5

[a]Assay condition: The reactions were carried out in methanol at 25 °C. Catalyst: 0.1 mM; PhSH: 1.0 mM; hydrogen peroxide: 3.75 mM. The control experiments were performed under identical conditions in the absence of selenium catalysts. The initial rates were corrected for the back ground reaction between thiol and peroxide.

Radical chain breaking antioxidant property by DPPH assay: Radical chain breaking antioxidant activity of the synthesized hydroxy-spiroselenuranes **29** and **30** has been evaluated by their hydrogen transfer capacity to 2,2-diphenyl-1-picrylhydrazyl (DPPH•) radical (eq. 2) in 80% methanol: water (v/v) at 25 °C.

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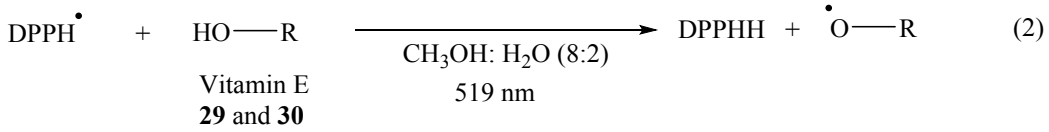

The formation of DPPHH by the reaction phenolic antioxidants **29** and **30** and DPPH• was monitored by UV-visible spectrophotometer at 519 nm.[35] The quenching of DPPH• (64 μM) by Vitamin E (100 μM) is studied and compared with synthesized hydroxy-spiroselenuranes **29** and **30** (Figure 2).

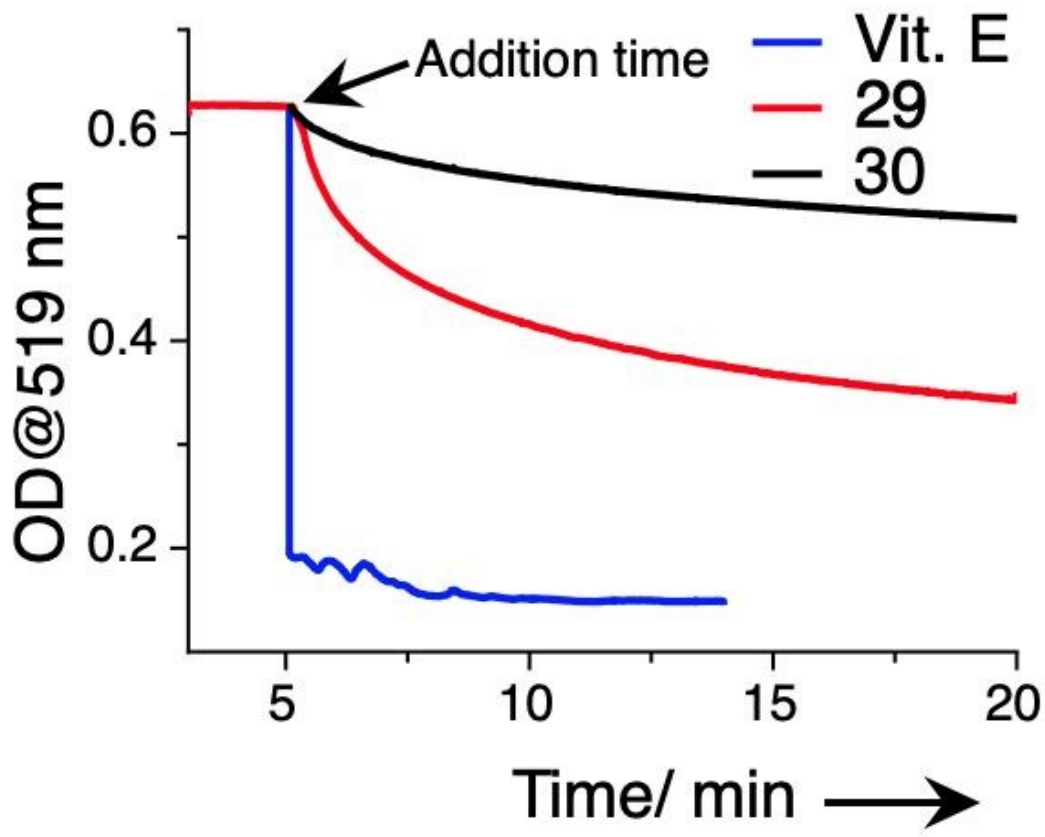

Figure 2. Hydrogen transfer capacity of vitamin E, **29** and **30** to DPPH•

The H-atom abstraction rate constants were obtained from the plot of log of optical density of DPPH• (64 μM) vs time (min)/ for vitamin E (6.25 μM), vitamin C (6.25 μM), **29** (6.25 μM), and **30** (6.25 μM) Figure 4.

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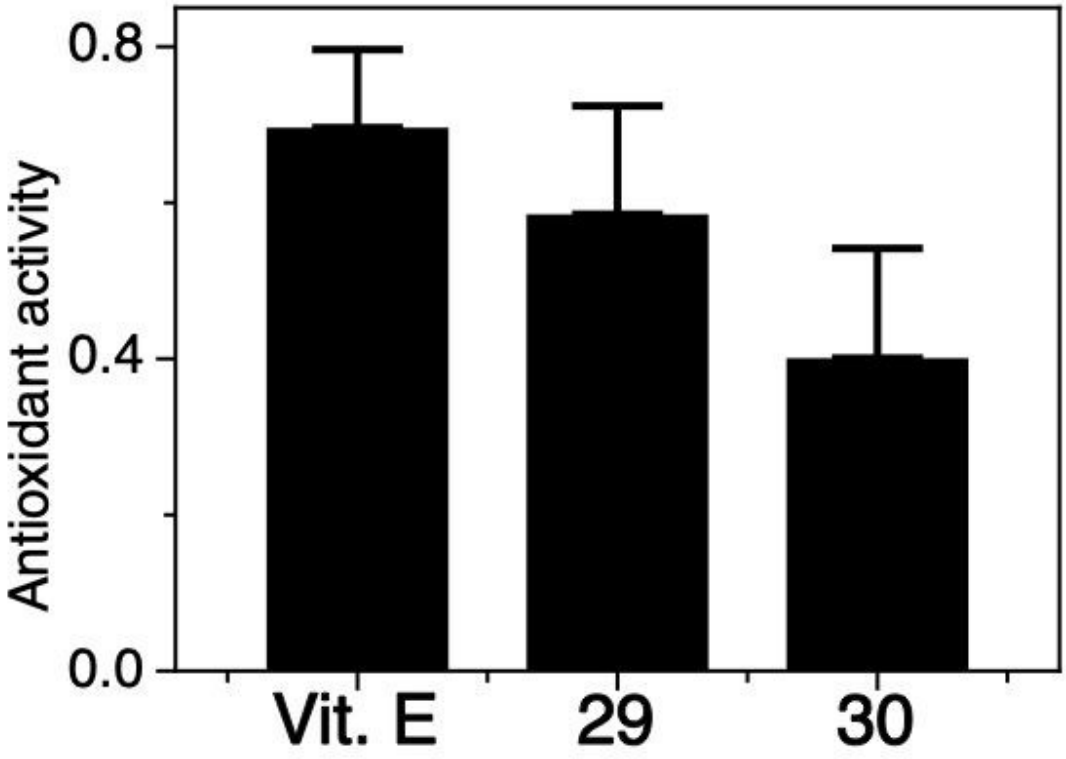

Figure 3. Rate constants for hydrogen transfer capacity of vitamin E, **29** and **30** to DPPH•

Although, DPPH-assay has some limitations to evaluate antioxidant activity due to reverse electron transfer from $DPPH^-$ to $[Ph{-}OH]^{\bullet+}$.[35c] Nonetheless, some insights were gained about the antioxidants **29** and **30** in comparison with benchmark antioxidant vitamin E. It is evident from Figure 2 that vitamin E quenches maximum concentration of DPPH•, **29** medium and **30** is the lowest at 0.64:1 concentration ratio of DPPH• and antioxidants [DPPH• (64 μM) and antioxidant (100 μM)]. The lower rate constants for hydrogen transfer of spiroselenuranes **29** and **30** could be due to the presence of tetravalent selenium which would increase the –O─H bond dissociation energy. Further, hydroxyl group attached to electron withdrawing benzamide ring of **30** whereas in **29**, hydroxyl group is present in electron donating aniline ring. *ortho*-Hydroxy substituted spiroselenurane **29** exhibit a rate constant of 0.583±0.138 min^{-1} which is comparable with vitamin E (0.696±0.100 min^{-1}). Similarly, *para*-substituted spiroselenurane **30** transfer hydrogen atom to DPPH following the rate constant of 0.400±0.141 min^{-1}. When spiroselenurane **29** was used along with vitamin C co-reductant, the slightly higher rate constant (0.724 min^{-1}) was realized.

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Conclusion: In summary, a copper-catalyzed practical method has been established for the synthesis of symmetrical bis(*N*-arylbenzamide) selenides from iodo-*N*-phenylbenzamides and di-sodium selenide without using any base. The developed protocol is practical and competitive to earlier established *ortho*-lithiation and diazotization routes in which dianion (carbanion and amidate ion) is an intermediate which shows sluggish reactivity towards selenation reactions. Also, synthesis of hydroxy-spiroselenuranes containing tetravalent selenium has been achieved. Our preliminary investigation of radical quenching activity on hydroxy-spiroselenuranes by DPPH vitro assay suggests that hydroxy-spiroselenuranes could deactivates radicals. Further, hydroxy-spiroselenuranes show some regeneration by co-reductant such as vitamin C, although, further validation is required. Crystal structure study on naphthyl-spirodiazaselenurane shows racemic mixture of both enantiomers. Currently, efforts are being made to develop an enantioselective synthesis of hypervalent spirodiazaselenuranes molecules.

Experimental Section

General Experimental Details.

All reactions were carried out in oven-dried glassware with magnetic stirring. Elemental selenium (60 mesh size), sodium, copper iodide, copper triflate, 1,10-pheananthroline, 2-iodobenzoic acid and amines used in this study were purchased from commercial sources (Aldrich/Fluka) and used without further purification. All the solvents were purified by a standard procedure and freshly distilled prior to use. Anhydrous DMF and DMSO solvents with sure seal septa were purchased from Sigma Aldrich and used without further drying. All NMR experiments were carried out on Bruker 400/500 MHz spectrometer in $CDCl_3$/DMSO-d_6 solvents. NMR chemical shifts are reported in ppm referenced to the solvent peaks of $CDCl_3$ (7.26 ppm for ^1H and 77 (± 0.07) ppm for ^{13}C) or DMSO-d_6 (3.31 ppm for H_2O, 2.47 ppm for ^1H and 39.50 (±0.07) ppm for ^{13}C), respectively. The ^{77}Se NMR spectra were obtained at 76.31 MHz in CDCl3 or DMSO-d_6. Chemical shifts are reported relative to dimethyl selenide (^{77}Se) (0 ppm). The following abbreviations were used to indicate multiplicity: s (singlet), brs (broad singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), ddd (doublet of a doublet of a doublet) and m (multiplet). High resolution mass (HRMS) analysis is performed on quadrupole-time of flight Bruker MicroTOF-Q II mass spectrometer equipped with an ESI and APCI source, ^{80}Se isotope is

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used in exact mass calculation; LR-GC mass analysis is performed on Agilent Technologies MS-S975C inert XLEI/CIMSD with triple axis detector. X-ray single crystal structure data for compound **43** (CCDC no. 1882307) were collected on a Bruker D8 VENTURE diffractometer equipped with CMOS Photon 100 detector and MoKα (λ = 0.71073 Å) radiation was used. Room temperature corresponds to 25°C (computing data collection: Bruker APEX2). Low temperature reaction performed over EYELA PSL-1810. Column chromatography was performed on glass columns loaded with silica gel (60-120 mesh size) purchased from RANKEM Pvt. Ltd. India. TLC analysis of reaction mixtures was performed using Merck silica gel (60 F254) plates and spots were visualized by UV irradiation. Melting points were recorded in capillary tubes and are uncorrected. Substituted benzamides were prepared by reported procedure.[28-29] ^{1}H and ^{13}C NMR of 2-halobenzamides (**24**, **37-39**, **40-41**) are presented in supporting information (SI).

Peroxide decomposing GPx-like antioxidant property (**thiol assay**): The thiol-peroxidase like activity was performed spectrophotometrically (eq. 1). The test mixture contained benzenethiol (1.0 mM), organoselenium catalyst (0.1 mM) and hydrogen peroxide (3.75 mM). Reaction of model compound with PhSH and H_2O_2 were studied in dried HPLC grade MeOH by following the appearance of diphenyl disulfide absorption at 305 nm at 25 °C using molar extinction coefficient as 1.24 $mM^{-1}cm^{-1}$ for PhSSPh.[26,33]

Radical Chain Breaking Antioxidant Property by DPPH Assay:

Purification of DPPH (DPPH•): The crude solid was crystallized from benzene-petroleum ether (1:1). The melting point was taken carefully after drying it well and it was found 132-133 ^{0}C (literature 135 ^{0}C).[36]

Kinetic study: Radical chain breaking antioxidant activity of the synthesized hydroxy-spiroselenuranes **29** and **30** has been evaluated by their hydrogen transfer capacity to 2,2-diphenyl-1-picrylhydrazyl (DPPH$^{\bullet}$) radical in 80% methanol: water (v/v) at 25 °C at 519 nm.[35] The quenching of DPPH$^{\bullet}$ by antioxidants were monitored by using UV-visible spectrophotometry. Each experiments conducted thrice. Rate constant was calculated by plotting natural log of absorbance (OD) of DPPH$^{\bullet}$ vs time (min). The slope which is equal to rate constant was obtained by liner fit.

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A typical synthetic procedure. 2,2'-selenobis(*N*-arylbenzamides): Under inert atmosphere, 4.15 g (52.5 mmol, 1.0 equiv) of grinded selenium powder and dry THF (30 mL) were taken in single neck round bottom flask. To this suspension, 2.53 g (2.1 equiv, 110 mmol) of fresh Na-pieces was added cautiously with stirring and followed by 1.28 g (2 equiv, 10 mmol) of naphthalene was added. Further, reaction mixture was allowed to stir at room temperature for 12 h. During this period, colour changes from reddish brown to off-white. THF solvent was evaporated under vacuum. To this, 2 equivalents (100 mmols) of corresponding 2-iodo-*N*-arylbenzamides and 4-metoxy-2-bromo-N-arylbenzamide (**31-35**, and **36**) and 5 mL of HMPA was added to the reaction mixture. 1.90 g (10 mmol, 0.2 equiv) of CuI was added and allowed to stir at 80 °C for 60 h. Reaction mixture was added to 300-400 mL of brine and stirred vigorously for 3-4 h. Residue was filtered out and washed with distilled water. Crude product was dried under vacuum. Selenides **24**, **37-39**, **40**, **41** were purified by washing of crude product with diethyl ether (20 mL x 2) to remove trace amount of unreacted starting material and dried under high vacuum.

2,2'-Selenobis(*N*-phenylbenzamide) (24):[19,20] White solids, yield: 86%, 4.29 g. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.44 (s, 2H), 7.71 (t, J = 6.2 Hz, 6H), 7.36 – 7.32 (m, 10H), 7.10 (t, J = 7.3 Hz, 2H). ^{13}C NMR (DMSO-d_6, 126 MHz) δ 167.22, 139.56, 139.45, 134.54, 132.31, 131.33, 129.14, 128.57, 127.66, 124.21, 120.40. ^{13}C NMR DEPT-135 (DMSO-d_6, 126 MHz) δ 134.54, 131.33, 129.14, 128.57, 127.66, 124.21, 120.40 (all CH). ^{77}Se NMR (DMSO-d_6, 76 MHz) δ 419.33.

2,2'-Selenobis(*N*-(2-methoxyphenyl)benzamide) (37):[20] White solid, yield: 94%, 4.81 g. ^{1}H NMR ($CDCl_3$, 76.31 MHz) δ 8.52 (s, 2H), 8.36 (d, J = 7.7 Hz, 2H), 7.67 (dd, J = 7.2, 1.7 Hz, 2H), 7.48 (dd, J = 7.2, 1.7 Hz, 2H), 7.36-7.30 (m, 4H), 6.99 (td, J = 7.9, 1.5 Hz, 2H), 6.91 (t, J = 7.3 Hz, 2H), 6.75 (dd, J = 8.0, 0.9 Hz, 2H), 3.71 (s, 6H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 165.88, 148.18, 137.87, 134.80, 131.98, 131.41, 128.59, 127.71, 127.55, 123.88, 120.86, 119.67, 109.84, 55.63. ^{13}C NMR DEPT-135 ($CDCl_3$, 101 MHz) δ 134.80, 131.40, 128.60, 127.70, 123.85, 120.87, 119.67, 109.81 (all CH), 55.62 (CH_3). ^{77}Se NMR ($CDCl_3$, 76 MHz) δ 427.11.

2,2'-Selenobis(*N*-(3-methoxyphenyl)benzamide) (38):[20] White solid, yield: 91%, 4.65 g. ^{1}H NMR ($CDCl_3$, 76.31 MHz) δ 8.03 (s, 2H), 7.60 (dd, J = 5.9, 3.2 Hz, 2H), 7.50 – 7.43 (m, 2H), 7.34

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– 7.26 (m, 4H), 7.15 – 7.09 (m, 3H), 6.84 (d, *J* = 7.9 Hz, 2H), 6.63 (dd, *J* = 8.2, 2.0 Hz, 2H), 3.71 (s, 6H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 166.39, 160.04, 138.85, 137.84, 134.81, 131.47, 130.79, 129.52, 128.98, 128.08, 112.19, 110.55, 105.50, 55.28. ^{13}C NMR DEPT-135 ($CDCl_3$, 101 MHz) δ 134.81, 131.47, 129.52, 128.98, 128.08, 112.18, 110.55, 105.50 (all CH), 55.28 (CH_3). ^{77}Se NMR ($CDCl_3$, 76 MHz) δ 416.64.

2,2'-Selenobis(*N*-(4-methoxyphenyl)benzamide) (39): White solid, yield: 94%, m.p.: 165-167 ^{0}C, 4.81 g. ^{1}H NMR (DMSO-d_6, 76.31 MHz) δ 10.27 (s, 2H), 7.66 (d, *J* = 7.0 Hz, 2H), 7.58 (d, *J* = 8.9 Hz, 4H), 7.39 – 7.27 (m, 6H), 6.86 (d, *J* = 8.9 Hz, 4H), 3.70 (s, 6H). ^{13}C NMR (DMSO-d_6, 101 MHz) δ 166.80, 156.03, 139.63, 134.50, 132.62, 132.42, 131.16, 128.50, 127.56, 121.94, 114.25, 55.66. ^{13}C NMR DEPT-135 (DMSO-d_6, 101 MHz) δ 134.50, 131.17, 128.49, 127.56, 121.94, 114.25 (all CH), 55.66(CH_3). ^{77}Se NMR (DMSO-d_6, 76 MHz) δ 419.40.

2,2'-selenobis(*N*-(1-naphthyl)benzamide) (40): Yellow solid, yield: 89%, m.p.: 198-200 ^{0}C, 5.08 g. ^{1}H NMR (DMSO-d_6, 76.31 MHz) δ 10.47 (s, 2H), 8.01 (d, *J* = 8.3 Hz, 2H), 7.90 (t, *J* = 11.2 Hz, 4H), 7.80 (d, *J* = 8.0 Hz, 2H), 7.61 – 7.33 (m, 14H). ^{13}C NMR (DMSO-d_6, 101 MHz) δ 168.18, 139.04, 134.65, 134.21, 133.92, 132.46, 131.42, 129.23, 128.96, 128.80, 128.47, 128.19, 127.78, 126.65, 126.52, 126.42, 126.38, 125.96, 123.79, 123.71(all CH). ^{13}C NMR DEPT-135 (DMSO-d_6, 101 MHz) δ 134.65, 131.42, 128.80, 128.47, 127.78, 126.65, 126.52, 126.38, 125.96, 123.79, 123.71. ^{77}Se NMR (DMSO-d_6, 76 MHz) δ 423.46; HRMS (ESI) m/z calculated for $C_{34}H_{24}N_2O_2Se$ $[M+H]^+$ 573.1078, found 573.1079.

6,6'-Selenobis(3-methoxy-N-phenylbenzamide) (41): Yellowish white solid, yield: 92%, m.p.: 140-142 ^{0}C, 5.12 g. ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.83 (s, 3H), 7.00 (dd, *J* = 8.7, 2.8 Hz, 1H), 7.05 – 7.13 (m, 1H), 7.21 – 7.27 (m, 2H), 7.33 (dd, *J* = 8.5, 7.4 Hz, 2H), 7.63 – 7.75 (m, 2H), 10.38 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 56.01, 113.79, 117.48, 120.40, 122.40, 124.16, 129.10, 136.03, 139.43, 140.86, 158.80, 166.96. ^{77}Se NMR (95 MHz, DMSO-d_6) δ 384.67. HRMS (ESI) m/z calculated for $C_{28}H_{24}N_2O_4Se$ $[M-H]^+$ 531.0819, found 531.0801.

Spirodiazaselenuranes (14, 15,17, 42, 43, 44): Hydrogen peroxide (aqueous, 30%) was added to a stirred CH_2Cl_2 solution containing of respective 2,2'-selenobis(*N*-arylbenzamide) **27**, **35-39**, **43**, and **44** (0.1 mmol, 1 equiv). The reaction mixture was allowed to stir for 20-24 h at 25 °C and then solvent was evaporated to dryness. Resultant solids were pass through column of silica gel using

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petroleum ether/ethyl acetate as eluent to give the pure spirodiazaselenuranes **14**, **15**, **17**, and **42-44** in 96-99% yields.

(*N*-phenyl) spirodiazaselenuranes (14):[19,20] White solid. Yield: 99%, 46.47 mg ^{1}H NMR ($CDCl_3$, 76.31 MHz) δ 8.27 (dd, *J* = 7.5, 1.2 Hz, 2H), 7.86 (d, *J* = 8.1 Hz, 2H), 7.72 – 7.67 (m, 6H), 7.62 – 7.57 (m, 2H), 7.40 (t, *J* = 7.9 Hz, 4H), 7.18 (t, *J* = 7.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 164.60, 140.51, 135.62, 135.37, 133.91, 133.07, 129.87, 129.64, 126.44, 125.23, 123.35. ^{13}C NMR DEPT-135 ($CDCl_3$, 101 MHz) δ 133.91, 133.07, 129.87, 129.64, 126.44, 125.24, 123.35 (all CH). ^{77}Se NMR ($CDCl_3$, 76 MHz) δ 571.79.

(*N*-(2-Methoxy)phenyl) spirodiazaselenuranes (15):[20] White solid, yield: 98%, 52 mg. ^{1}H NMR ($CDCl_3$, 76.31 MHz) δ 8.20 (dd, *J* = 7.5, 1.2 Hz, 2H), 8.11 (d, *J* = 8.0 Hz, 2H), 7.75 (dd, *J* = 7.8, 1.3 Hz, 2H), 7.64 – 7.60 (m, 3H), 7.55 – 7.51 (m, 2H), 7.25 – 7.19 (m, 2H), 7.06 – 6.98 (m, 4H), 6.85 (t, *J* = 8.5 Hz, 2H), 3.76 (s, 6H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 166.13, 153.40, 136.45, 134.78, 132.25, 131.58, 129.48, 128.18, 127.56, 126.96, 126.27, 121.44, 120.84, 112.23, 110.02, 55.80, 55.64. ^{13}C NMR DEPT-135 ($CDCl_3$, 101 MHz) δ 133.12, 132.25, 129.40, 128.18, 127.56, 126.96, 126.27, 121.44, 112.23, 110.02 (all CH), 55.80, 55.64 (CH_3). ^{77}Se NMR ($CDCl_3$, 76 MHz) δ 592.33.

(*N*-(3-Methoxy)phenyl) spirodiazaselenuranes (17):[20] White solid, yield: 99%, 52 mg. ^{1}H NMR ($CDCl_3$, 76.31 MHz) δ 8.26 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.69 (t, *J* = 7.3 Hz, 1H), 7.65 – 7.53 (m, 1H), 7.42 (t, *J* = 2.1 Hz, 1H), 7.32 – 7.22 (m, 1H), 7.15 (dd, *J* = 8.0, 1.1 Hz, 1H), 6.73 (dd, *J* = 8.2, 2.1 Hz, 1H), 3.81 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 164.61, 160.52, 141.74, 135.66, 135.37, 133.95, 133.07, 130.20, 129.80, 126.47, 115.41, 110.71, 109.26, 77.35, 77.03, 76.71, 55.40. ^{13}C NMR DEPT-135 ($CDCl_3$, 101 MHz) δ 133.95, 133.07, 130.20, 129.80, 126.47, 115.41, 110.71, 109.25 (all CH), 55.40 (CH_3). ^{77}Se NMR ($CDCl_3$, 76 MHz) δ 574.75.

(*N*-(4-Methoxy)phenyl) spirodiazaselenuranes (42): White solid, yield: 98%, m.p.: 230-232 ^{0}C, 52 mg. ^{1}H NMR (DMSO-d_6, 76.31 MHz) δ 8.03 (d, *J* = 6.3 Hz, 2H), 7.78 – 7.64 (m, 10H), 6.93 (d, *J* = 8.9 Hz, 4H), 3.71 (s, 6H). ^{13}C NMR (DMSO-d_6, 101 MHz) δ 164.58, 156.63, 136.73, 136.07, 134.46, 134.02, 133.07, 129.05, 126.46, 125.94, 114.59, 55.70. ^{13}C NMR DEPT-135 (DMSO-d_6, 101 MHz) δ 134.02, 133.07, 129.05, 126.46, 125.94, 114.59, 55.69. ^{77}Se NMR

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(DMSO-d_6, 76 MHz) δ 584.24; HRMS (ESI) m/z calculated for $C_{28}H_{22}N_2O_4Se$ $[M+H]^+$ 531.0819, found 531.0801.

(*N*-(1-Naphthyl)) spirodiazaselenuranes (43): Off white solid, yield: 98%, m.p.: 232-234 ^{0}C, 60 mg. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.31 (dd, *J* = 7.5, 1.2 Hz, 2H), 8.28 (d, *J* = 7.6 Hz, 2H), 7.95 (d, *J* = 8.5 Hz, 4H), 7.85 (d, *J* = 8.2 Hz, 2H), 7.72 (t, *J* = 7.3 Hz, 2H), 7.60 – 7.52 (m, 10H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ 164.91, 136.24, 135.55, 135.16, 133.51, 133.02, 130.08, 129.88, 128.93, 127.56, 126.66, 126.48, 126.41, 125.78, 123.91. ^{13}C NMR DEPT-135 ($CDCl_3$, 126 MHz) δ 133.51, 133.02, 130.08, 128.93, 127.56, 126.66, 126.48, 126.41, 125.78, 123.91. ^{77}Se NMR ($CDCl_3$, 76 MHz) δ 578.27; HRMS (ESI) m/z calculated for $C_{34}H_{22}N_2O_2Se$ $[M+H]^+$ 570.0922, found 571.0902. X-ray quality crystal were obtained from CH_2Cl_2 solvent.

5,5'-Dimethoxy-2,2'-diphenyl-1l4-1,1'-spirobi[benzo[d][1,2]selenazole]-3,3'(2H,2'H)-dione (44): m.p.: 160-163 ^{0}C Yellowish white solid, yield: 98%, 52 mg. ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.85 (s, 3H), 7.16 (tt, *J* = 7.4, 1.2 Hz, 1H), 7.26 (dd, *J* = 9.0, 2.9 Hz, 1H), 7.35 – 7.43 (m, 2H), 7.55 (d, *J* = 2.9 Hz, 1H), 7.62 (d, *J* = 8.9 Hz, 1H), 7.79 – 7.94 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 56.46, 113.36, 120.27, 120.54, 124.13, 124.76, 126.97, 128.02, 129.43, 129.75, 137.95, 141.82, 163.25, 164.38. ^{77}Se NMR (95 MHz, DMSO-d_6) δ 580.02.

Hydroxy-substituted selenides (**45**, **46**)**:** In a long neck, 10 mL round bottom flask monoselenides (**37** and **41**) (0.1 mmol) were dissolved in CH_2Cl_2 (10 mL) under nitrogen atmosphere and cooled to -78 ^{o}C. After that, BBr_3 (0.4 mL, 0.38 mmol, 1M solution in CH_2Cl_2) was added via a syringe and the resulted solution was stirred at -78 ^{o}C for 30 min. After this, reaction temperature was raised to room temperature and the resulted reaction mixture was stirrer for 12 hours. CH_2Cl_2 was evaporated under vacuum, the resulted residue was washed with distilled water and resulted sold dried under vacuum. Crystallization from dichloromethane resulted in white crystalline solid.

2,2'-Selenobis(*N*-(2-hydroxyphenyl)benzamide) 45: White solid, yield: 92%, m.p.: 138-140 ^{0}C, 46 mg. ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.82 (t, J = 7.7 Hz, 1H), 6.92 (dd, J = 8.1, 1.4 Hz, 1H), 7.03 (td, J = 7.7, 1.7 Hz, 1H), 7.43 (dd, J = 7.4, 1.9 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 7.4 Hz, 1H), 9.59 (s, 1H), 9.71 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 116.41, 119.44, 124.04, 126.07, 126.23, 127.63, 128.56, 131.42, 132.83, 134.58, 138.77, 149.40, 167.23. ^{77}Se NMR (95

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MHz, DMSO-d_6) δ 424.91. HRMS (ESI) m/z calculated for $C_{26}H_{20}N_2O_4Se$ $[M+H]^+$ 505.0661, found 505.0681.

6,6'-selenobis(3-hydroxy-N-phenylbenzamide) 46: White solid, yield: 91%, m.p.: 98-100 ^{0}C, 45 mg. ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.80 (dd, J = 8.5, 2.7 Hz, 1H), 7.02 (d, J = 2.7 Hz, 1H), 7.08 (tt, J = 7.3, 1.2 Hz, 1H), 7.14 (d, J = 8.6 Hz, 1H), 7.29 – 7.35 (m, 2H), 7.69 (d, J = 8.0 Hz, 2H), 9.88 (s, 1H), 10.32 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 115.15, 118.62, 120.21, 120.27, 124.05, 129.09, 136.17, 139.55, 141.09, 157.01, 167.24. ^{77}Se NMR (95 MHz, DMSO-d_6) δ 376.39. HRMS (ESI) m/z calculated for $C_{26}H_{20}N_2O_4Se$ $[M-H]^+$ 503.0510, found 503.0428.

Hydroxy substituted spirodiazaselenuranes (29, 30): Hydrogen peroxide (aqueous, 30% w/w) was added to a stirred CH_2Cl_2 solution containing of respective hydroxy substituted selenides (**45, 46**) (0.1 mmol, 1 equiv). The reaction mixture was allowed to stir for 20-24 h at 25 °C, progress of the reaction was monitored by TLC, after complete conversion of selenides (**45** and **46**), solvent was evaporated to dryness. The resulted white colored compounds were purified by crystallization using CH_2Cl_2.

(*N*-(2-Hydroxy)phenyl) Spirodiazaselenuranes (29): White solid, yield: 98%, m.p.: 205-207 ^{0}C, 51 mg. ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.90 (td, J = 7.6, 1.4 Hz, 1H), 6.98 (dd, J = 8.1, 1.4 Hz, 1H), 7.12 (td, J = 7.8, 1.7 Hz, 1H), 7.68 (td, J = 8.0, 1.6 Hz, 1H), 7.72 (dd, J = 7.8, 1.7 Hz, 1H), 7.76 (td, J = 7.4, 1.2 Hz, 1H), 8.07 (ddd, J = 17.8, 7.7, 1.4 Hz, 2H), 9.85 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 14.56, 29.46, 31.17, 60.22, 116.39, 117.65, 119.42, 120.06, 126.52, 127.22, 128.07, 128.78, 129.05, 133.01, 133.95, 134.92, 137.62, 152.11, 165.29. ^{77}Se NMR (95 MHz, DMSO-d_6) δ 596.04. HRMS (ESI) m/z calculated for $C_{26}H_{18}N_2O_4Se$ $[M+Na]^+$ 525.0326, found 525.0347

5,5'-Dihydroxy-2,2'-diphenyl-1l4-1,1'-spirobi[benzo[d][1,2]selenazole]-3,3'(2H,2'H)-dione (30): Off white solid, yield: 98%, m.p.: 130-132 ^{0}C, 51 mg**.** ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.81 (dd, J = 8.5, 2.7 Hz, 1H), 7.03 (d, J = 2.7 Hz, 1H), 7.08 (t, J = 7.4 Hz, 1H), 7.15 (d, J = 8.6 Hz, 1H), 7.32 (t, J = 7.8 Hz, 3H), 7.70 (d, J = 8.1 Hz, 3H), 10.34 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$ with DMSO-d_6) δ 165.53, 153.45, 138.64, 138.15, 128.54, 127.26, 123.80, 119.89, 119.09, 117.45, 117.40. ^{77}Se NMR (95 MHz, DMSO-d_6) δ 579.99. HRMS (ESI) m/z calculated for $C_{26}H_{18}N_2O_4Se$ $[M+Na]^+$ 525.0326, found 525.0506

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Supporting Information. ^{1}H, ^{13}C, ^{77}Se NMR and mass spectra of synthesized compounds and crystallographic details of spiroselenurane **43** (CCDC no. 1882307). These materials are available from the website.

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