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Radical Chain Breaking Bis(*ortho*-organoselenium) Substituted Phenolic Antioxidants

Aditya Upadhyay[+], Bhagat Singh Bhakuni[+], Rahul Meena, and Sangit Kumar*[a]

Abstract: The presence of a chalcogen atom at the *ortho*-position of phenols enhances their radical chain-breaking activity. Here, a copper(I)-catalyzed reaction of 2,6-dibromo- and 2,6-diiodophenols with diorganodiselenides has been studied for the introduction of two organoselenium substituents at both *ortho*-positions of the phenolic radical chain-breaking antioxidants, which afforded 2,6-diorganoseleno-substituted phenols in 80–92% yields having electron-donating CH_3, and electron-withdrawing CN and CHO functionalities. Additionally, 2,6-diiodophenols with electron-withdrawing CHO and CN groups also afforded novel 5,5′-selenobis(4-hydroxy-3-(phenylselanyl)benzaldehyde) and 5,5′-selenobis(4-hydroxy-3-(phenylselanyl)benzonitrile) consisting of three selenium and two phenolic moieties along with 2,6-diorganoseleno-substituted phenols has been synthesized. The electron-withdrawing CHO group has been reduced by sodium borohydride to the electron-donating alcohol CH_2OH group, which is desirable for efficient radical quenching activity of phenols. The developed copper-catalyzed reaction conditions enable the installation of two-arylselenium group *ortho* to phenolic radical chain-breaking antioxidants, which may not be possible by conventional organolithium-bromine exchange methods due to the sluggish reactivity of trianions (dicarba and phenoxide anion), which are generated by the reaction of organolithium with 2,6-dibromophenols, with diorganodiselenides. The antioxidant activities of the synthesized bis and tris selenophenols have been accessed by DPPH, thiol peroxides, and singlet oxygen quenching assay. The radical quenching antioxidant activity has been studied for the synthesized compounds by 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay. The bis-selenophenols show comparable radical deactivating activity, while tris seleno-bisphenols show higher radical deactivating activity than α-tocopherol. Furthermore, the tris seleno-bisphenol shows comparable peroxide decomposing activity with ebselen molecules.

Introduction

Phenol is an important component of the majority of naturally occurring radical chain-breaking antioxidants.[1] The antioxidant activity of these phenolic compounds is due to their radical chain trapping activity (RTA). The phenolic compounds first transfer their phenolic hydrogen to the lipid peroxyl radical before the chain-propagating hydrogen transfer, so it can inhibit the radical chain reaction.[2] It was observed that the incorporation of an electron-donating substituent to the ring enhance the radical chain trapping activity (RTA) of phenolic antioxidant by decreasing the bond dissociation enthalpy (BDE) of the phenolic O–H bond.[3] The best-known example of a naturally occurring phenolic antioxidant is α-tocopherol **1** (Chart 1), also known as vitamin E, which has a fully substituted electron-rich phenol ring, as a result, has lower BDE, 78.3 kcal mol^{-1}. The substitution of oxygen α-tocopherol **1** by sulfur and selenium leading to thio-, and seleno-tocopherols (**2** and **3**)[4a–b] and related selenium analog **4** has also been studied,[5] and it was noticed that the introduction of heavier chalcogen to phenolic ring lower the BDE of O–H bond and consequently enhanced radical deactivating activity. Further, the installation of selenium and tellurium atoms to phenol makes these molecules regenerable at the expense of readily available reductants such thiols and ascorbate. To improve the stability of the antioxidants under oxidative conditions, Valgimigli and Co-workers utilized pyridine and pyrimidine aromatic ring containing antioxidant **5** possessing high ionization potential than benzene, which make them difficult to oxidize under oxidative conditions.[3b,6] Although, pyrimidinol **5** possesses slightly high BDE 89.6 kcal mol^{-1} than vitamin E 78.2 kcal mol^{-1}.[6]

Instead of O–H functionality, N–H bond in ethoxyquin has also been used as an antioxidant in society to preserve food, particularly fish meat.[7] Introduction of chalcogen atom in ethoxyquin corresponding **6–8** precedently enhances radical chain-breaking antioxidant functions.[8] Subsequently, several chalcogen-containing antioxidants **9–16** have been studied.[9–12] Most of the antioxidants contain one chalcogen atom; the role of two selenium atoms has not been studied. However, the installation of more than one chalcogen center in phenolic antioxidant could be more intrigue in search of efficient phenolic antioxidant as recently two alkyl telluro-substituted phenols have been isolated in 10–24% yields by using a large excess tert-butyl lithium with 2,6-dibromophenol, followed by the insertion of tellurium and finally quenching alkyl halides.[13] Moreover, to the best of our knowledge, the installation of two arylseleno groups into phenols has not been reported to date despite the various reports on the synthesis of organoselenides.[14–17] Here, in continuation of our work on the

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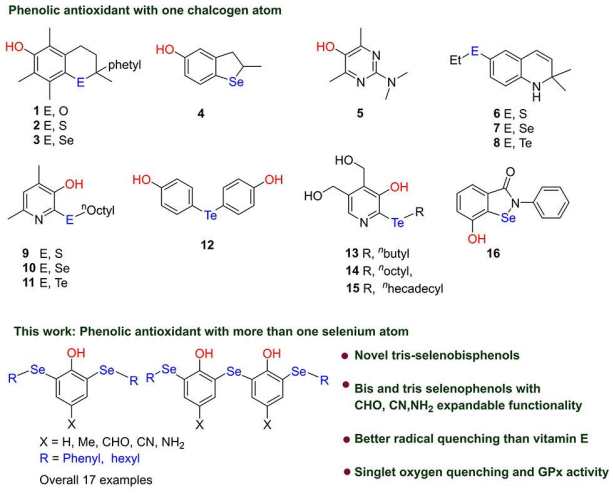


Chart 1. Chalcogen substituted phenolic radical chain-breaking antioxidants.

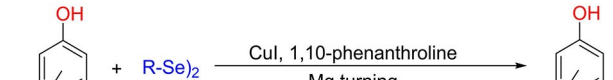
synthesis of organochalcogen compounds,[12,15c,d] we present a copper-catalyzed synthesis of bis-phenylselenide phenols and synthesis and crystal structures of tris selenium substituted phenols have also been presented. The radical quenching, singlet oxygen quenching, and peroxide decomposing antioxidant activity of the synthesized bis and tris selenol-bisphenols have been explored by DPPH assay. In addition, the reactivity of 2,6-bis-bromo/iodo-phenols with diaryl dichalcogenides under copper-catalyzed reaction was also discussed.

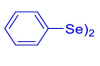
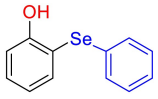
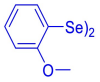
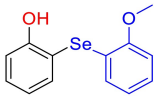
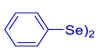
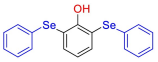
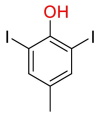
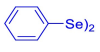
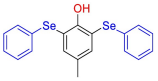
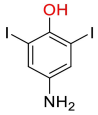
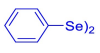
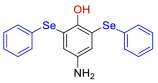
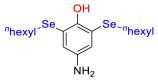
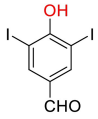
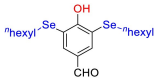
Results and Discussion

Initially, we chose a 2-iodophenol substrate to optimize reaction conditions by applying copper-catalyzed carbon-selenium bond-forming reactions.[14] Diphenyl diselenide reacted smoothly with 2-iodophenol in the presence of 10 mole % of copper iodide and 1,10-phenanthroline catalytic system to afford 2-*ortho*-phenylseleno-substituted phenol (**17**)[15a,c,e] in 90% yield (entry 1, Table 1).

The magnesium turning is indispensable for the reaction and seems to act as a reductant for the regeneration of copper (III) to copper(I). Similarly, 2-iodophenol smoothly reacted with 2-methoxy-phenyl diselenide to afford unsymmetrical 2-methoxyphenyl 2-hydroxyphenyl selenide **18** in 92% yield (entry 2, Table 1). After the isolation of the mono-*ortho*-phenyselenophenols **17** and **18**, we commence the synthesis of bis-*ortho*-phenylseleno phenols. The reaction of 2,6-diiodophenol with diphenyl diselenide under copper(I)-1,10-phenanthroline (10 mol%) catalytic reaction conditions, afforded mainly mono-*ortho*-substituted phenol (*vide infra*). The use of 15 mole % catalyst under extended reaction hours from 12 to 18 h afforded bis-*ortho*-phenylseleno substituted phenol **19**[15b] as the major product in 81% isolated yield (entry 3, Table 1). Interestingly, electron-donating methyl and amino groups containing phenols also amenable to the copper-catalyzed reaction conditions and resulted in respective bis-*ortho*-phenylseleno substituted phenols **20**–**21** in 81% and 80% yields, respectively (entries 4 and 5, Table 1). In addition to phenyl diselenide, alkyl *n*hexyl diselenide having a relatively weaker selenium-carbon bond, also underwent carbon-selenium bond-forming reaction with phenols to construct bis-alkylseleno substituted phenols **22** and **23** (entries 6 and 7, Table 1).

Table 1. Copper-catalyzed bis-organoselenation of phenols.



Entry	Phenols	Diselenides	Selenophenols	T[°C] & T[h]	Yield [%]
1[a]				110 & 6	90
2[a]				110 & 6	92
3[b]				110 & 18	75
4[b]				110 & 18	81
5[b]				110 & 18	80
6[b]				110 & 12	12
7[b]				110 & 12	32

[a] 10 mole % of CuI and 1,10-phenathroline was used. [b] 15 mole % of CuI and 1,10-phenathroline was used for entries 3–7.

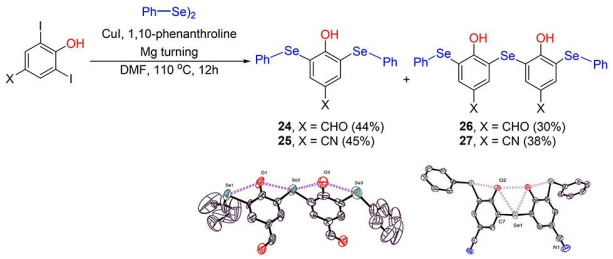
The introduction of organoselenium moiety into phenol has been accomplished by the electrophilic substitution of *in-situ* generated RSe^+ cation.[15] In an alternative approach, the addition of phenylselenium cation ($PhSe^+$) to *in-situ* formed cyclohexenol and subsequently oxidative aromatization afforded *ortho*-phenylselenium substituted phenols.[16] Electrophilic addition of phenylselenenium ion ($PhSe^+$) to phenol has been studied by Henriksen under oxidative conditions in which 2,6-bis(phenyl-seleno)phenol **19** was proposed an intermediate in the reaction for the synthesis of 2,6-bis(phenylseleno)-1,4-benzoquinone.[15a–b] Here, phenols not only with electron-withdrawing or donating group but also CHO and CN sensitive functionalities have been tolerated under the copper-catalyzed reaction conditions. 4-Hydroxy-3,5-diiodobenzonitrile and 4-hydroxy-3,5-diiodobenzaldehyde substrates smoothly reacted with diphenyl diselenide under copper-catalyzed reaction

conditions to afford bis-phenylseleno substituted phenols **24** and **25** (Scheme 1). Unexpectedly, the tris seleno-bisphenols **26** and **27** were also observed in 30% and 38% yields, respectively, along with the expected bis-selenophenols **24** (44%) and **25** (45%).

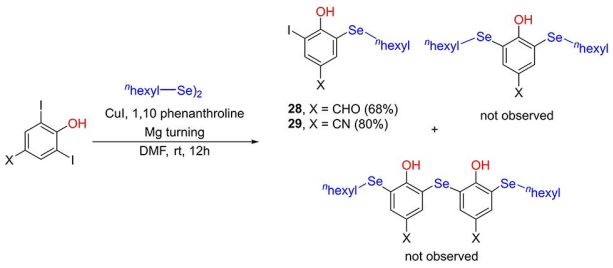
The isolation of tris selen-bisphenols **26** and **27** was only made with 2,6-diiodophenols having para-position substituted with electron-withdrawing CHO and CN groups and diiodophenols having no-substitution or substitution of electron-donating CH_3 and NH_2 group at para-position did not afford any respective tris selenol-bisphenols. Since the formation of tris seleno-bisphenols could occur only by the cleavage of selenium-carbon bond (*vide infra*), therefore, we suspected that alkylseleno substituted phenols **22** and **23** are likely to give tris seleno-bisphenols due to weak aliphatic carbon-selenium bond. Consequently, the reaction of 2,6-diiodophenol and 4-hydroxy-3,5-diiodobenzaldehyde substrates with n-hexyl diselenide (entries 6 and 7, Table 1) were reexamined to obtain respective tris seleno-bisphenols. Unfortunately, the formation of respective tris selen-bisphenols could not be observed (Scheme 2), and instead, a sluggish reaction mixture was noticed. We also performed the reaction of 4-hydroxy-3,5-diiodobenzonitrile and 4-hydroxy-3,5-diiodobenzaldehyde substrates with n-hexyl diselenide at room temperature under a copper-catalyzed condition to obtain desired hexyl tris seleno-bisphenols, nonetheless formation could not be observed. Instead, ortho-hexylseleno-ortho-iodo-substituted phenols **28** (68%) and **29** (80%) were obtained from the reaction mixture.

We also studied the compatibility of dibromo-phenols substrates under copper-catalyzed reaction conditions (Scheme 3). 2,6-Dibromophenol also reacted with diselenide under copper-catalyzed reaction condition; however, it failed to afford the desired bis-selenium substituted phenols. However, para-selenium substituted dibromo-phenol **30** was isolated in 85% yield. When the reaction was conducted with a para-methyl-2,6-dibromo-phenol substrate, debromination was observed, and para-methyl-position was substituted with phenylseleno group to afford benzylselenide **31** in 22% yield. On the other hand, 2,6-dibromo-4-aminophenol reacted smoothly with diphenyl diselenide and afforded bis-phenylselenophenol **21** in 80% yield (entry 5, Table 1, vide supra).

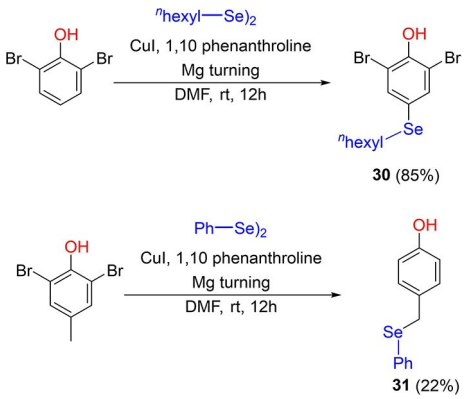
The bis and tris selenophenol **24** and **26** were reduced by using an excess amount of sodium borohydride to get 4-hydroxymethyl substituted bis-selenophenol **32** and tris seleno-bisphenol **33** (Scheme 4). The structure of reduced selenolphenols **32** and **33** was confirmed by ^{77}Se NMR, where the considerable up shielding was observed at 307 ppm and 249 ppm while the single crystal of **32** has been isolated using chloroform solvent (shown in SI).



Scheme 1. Preparation of bis(phenylseleno) substituted phenols and tris seleno-bisphenols. Crystal structures of **26** and **27**.



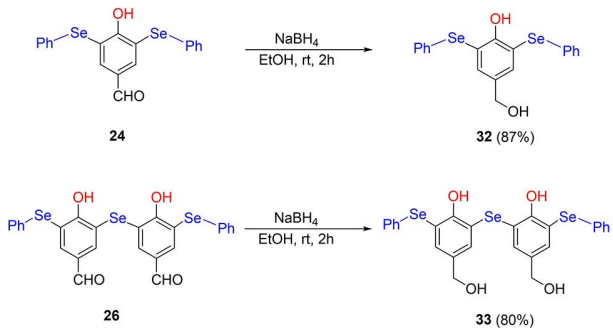
Scheme 2. The reaction of 2,6-diiodophenol and 4-hydroxy-3,5-diiodobenzaldehyde with n-hexyl diselenide under copper-catalyzed reaction.



Scheme 3. The copper-catalyzed reaction of dibromophenols.

Spectral characterization and X-ray crystal structure study

Synthesized bis-selenophenols **17–25**, **32** and tris seleno-bispheonols **26–27**, **33** were characterized by multi-nuclear (^1H, ^{13}C, and ^{77}Se) NMR and mass spectrometry. Bis-selenophenols exhibits ^{77}Se NMR chemical shifts between 196–748 ppm, tris selenol-bisphenols **26**, **27**, and **33** showed two signals in ^{77}Se NMR at 258, 265, and 249 attributed middle selenium and 308, 321 and 307 ppm due to periphery selenium atom, respectively. Although, excellent quality of ^1H, ^{13}C, and variable ^{77}Se NMR,



Scheme 4. Reduction of bis and tris selenol-bisphenols.

mass data on the **26** and **27** were collected. However, structures of tris selenol-bisphenols **26** and **27** could not be established based on solution characterization, presumably due to their unusual formation by the cleavage of phenyl-selenium bond. Next, we sought single X-ray crystal structure studies on tris seleno-bisphenols **26** and **27**. Unfortunately, good quality crystals for X-ray could not be obtained, and poor-quality crystals were collected despite repeated crystallization attempt from various solvents. Nonetheless, single-crystal structure data analysis on tris seleno-bisphenols **26** and **27** helped in elucidating their structures (Figures S1 and S2, SI). Further, signal X-ray crystal structure of 4-hydroxylmethyl bis-selenol-phenol **32** was obtained (Figure 1), which reveals a V-shaped geometry around selenium center resulted from intramolecular selenium and oxygen interactions as observed a significant shorter Se…O [2.83 (3) Å] distances than the sum of their van der Waals radii [Se (1.90) + O (1.52) = 3.42 Å].

Plausible Mechanism

The mechanism for copper-catalyzed carbon-selenium bond-forming reaction is presented in Scheme 5.

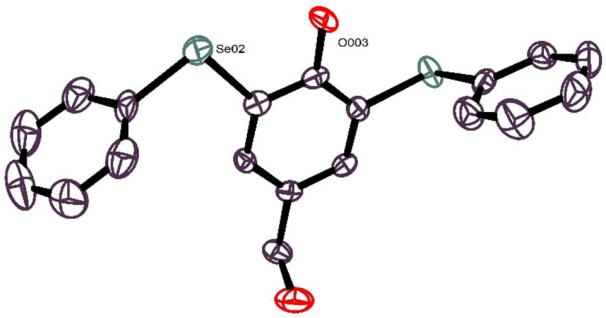
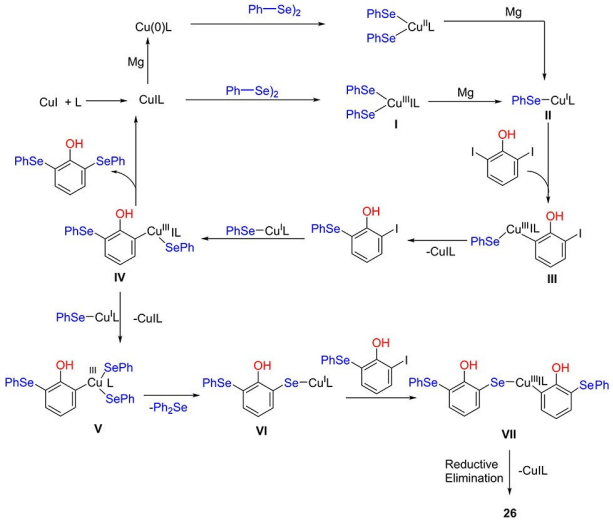


Figure 1. ORTEP view (55%) of 4-hydroxymethyl bis-selenophenol **32**.



Scheme 5. Plausible mechanism for the synthesis of bis and tris seleno-bisphenols.

CuI form complex with 1,10-phenanthroline (L) to form CuIL. Oxidative addition of diphenyl diselenide to CuIL would provide copper(III) selenolate intermediate **I**, which upon reduction by magnesium would provide Cu(I) selenolate intermediate **II**.[14a–f] Alternatively, formation of copper(II) selenolate intermediate is also possible by the oxidative addition of diphenyl diselenide to Cu(0) which is formed from by the reduction of CuI by magnesium. Copper(II) selenolate complex further reduced to copper(I) selenolate **II** by magnesium. Oxidative addition of carbon-iodine bond of 2,6-diiodophenol to **II** would furnish copper(III)-phenolate intermediate **III**. Reductive elimination could lead to 2-iodo-6-(phenylselanyl) phenol. In the next step, a carbon-iodine bond of 2-iodo-6-(phenylselanyl)phenol would undergo oxidative addition to Copper(I) selenolate intermediate to form copper-phenolate **IV**. Second reductive elimination would afford desired 2,6-bis-phenylselenophenol and concomitant release of CuIL catalyst.

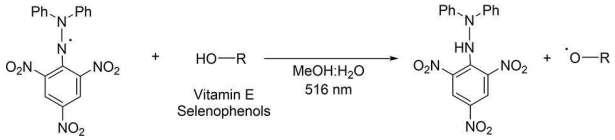
The formation tris seleno-bisphenols **26** and **27** from 2,6-diiodophenol could proceed *via* an iodide ligand exchange of **IV** with copper selenolate **II** leading to a copper diselenolate **V**. The removal of the diphenyl selenide (Ph_2Se) followed by the selenium insertion between carbon and copper bond form the copper(I) intermediate **VI**. The formation of Ph_2Se is also confirmed by ^{77}Se NMR in the reaction mixture which shows a signal at 416 ppm correspond to Ph_2Se (416 ppm)[14b,c,15e] along with the signal 462 ppm attributed to starting material Ph_2Se_2 (SI, S67-S68). Copper selenolate **VI** would undergo the oxidative addition with monoselenylphenol iodide, form **VII**, followed by the reduction elimination afforded the tris selenol-bisphenols.

Further to notice that the 2,6-diiodophenol substrates underwent carbon-selenium bond formation in a shorter time (18 h) in comparison to another iodo-arenes (36 h) and could be due to -OH coordination of phenols. 2,6-Dibromophenols were poorly reactive for carbon-selenium bond-forming reaction; however, *para*-amino-substituted 2,6-dibromophenols having three acidic protons showed good reactivity for carbon-selenium bond formation.

Radical quenching antioxidant activity

The radical quenching antioxidant activity of the synthesized bis and tris selenol-bisphenols has been evaluated for their hydrogen transfer activity to the 2,2-diphenyl1-picrylhydrazyl (DPPH) radical in 80% methanol: water (v/v) at 25 °C (Scheme 6).

The formation of DPPHH by the reaction of phenolic antioxidants and DPPH$^{\bullet}$ was monitored by using a UV-visible spectrophotometer at 517 nm.[18]



Scheme 6. Hydrogen atom transfer capacity from phenolic antioxidant to the 2,2-diphenyl1-picrylhydrazyl (DPPH$^{\bullet}$) radical.

The quenching of DPPH$^{\bullet}$ radical (64.0 μM) by vitamin E (6.4 μM) is studied and compared with synthesized selenophenols (Figure 2). The H-atom abstraction rate constants were obtained from the plot of the natural log of the optical density of DPPH (64 μM) *vs.* time (min) for vitamin E (6.4 μM) and synthesized selenophenols (6.4 μM). It is evident from Figure 3 that the synthesized selenophenols **20**, **32**, and **33** show considerable activity for radical quenching in comparison with vitamin E (1.16 ± 0.13 min^{-1}) while 2,5-bis-phenylselenophenol **19** shows less activity (0.294 ± 0.061 min^{-1}). The high hydrogen atom transfer capacity of **20** and **32** could be due to electron donor methyl and hydroxylmethyl groups at the para position, while the presence of two selenium centers at both ortho positions of phenol lowers down the bond dissociation energy of phenolic OH group. Furthermore, the presence of three selenium centers at the ortho position of phenol **33** increases the hydrogen transfer capacity of the phenolic antioxidant. *Para*-substituted bis selenophenol **20** and **32** exhibits the rate constant of 0.706 ± 0.269 min^{-1} and 0.78 ± 0.08 min^{-1}, respectively, compared to vitamin E (1.16 ± 0.13 min^{-1}). The tris selenol-bisphenol **33** shows the maximum rate constant 1.31 ± 0.06 min^{-1} among the tested selenophenols and vitamin E.

Hydrogen peroxide quenching activity by thiol assay

A considerable number of organoseleniums exhibit the ability to mimic the activity of selenoenzyme glutathione peroxidase (GPx).[19] Thus, the GPx like activity, which is characterized by the rate of peroxide reduction with thiol cofactor, has attracted interest in this class of compounds. The synthesized bis and tris seleno-bisphenol have been tested for hydrogen peroxide reduction by taking benzene thiol cofactor, and the initial reduction rate was calculated by the appearance of disulfides absorption at 305 nm, at 25 °C.[20]

The H_2O_2 decomposing activity of the synthesized bis and tris selenophenols was evaluated compared with the well-known ebselen molecule (entry 1, Table 2). Un-substituted and methyl-substituted selenophenols **19** and **20** were noticed to be inactive in the thiol peroxidase assay (entries 2 and 3, Table 2). Biselenophenols and tris selenobisphenols **32** and **33** having an electron-donating CH_3OH group show reduction rates of 4.62 ± 0.62 and 13.67 ± 1.17 μM min^{-1}, respectively. Although **32** and **33** exhibits a low rate for the decomposition of H_2O_2 nonetheless (Figure S4–S9, SI), these compounds decomposed H_2O_2 for considerably more extended periods (Figure S3, SI).

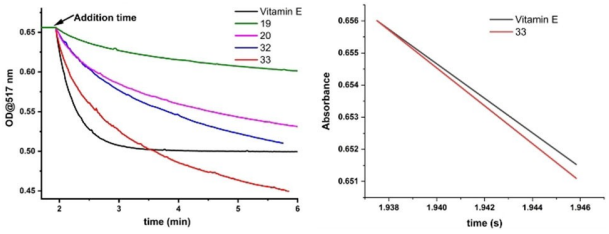


Figure 2. Hydrogen transfer capacity of vitamin E and synthesized selenophenols (right), a comparison of the initial slope of radical deactivation has shown between vitamin **E** and **33**.

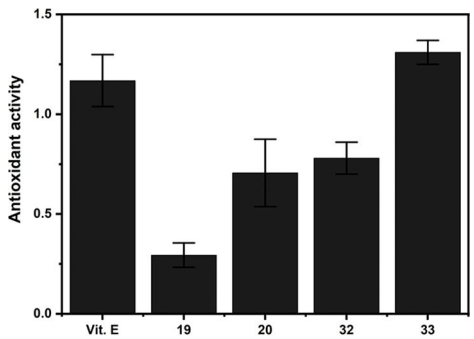


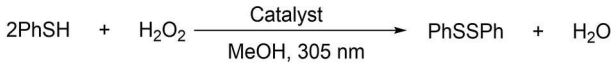
Figure 3. Rate constant for hydrogen transfer capacity of Vitamin E and synthesized selenophenols.

Singlet oxygen quenching activity

Next, we performed a qualitative experiment for the singlet oxygen quenching activity of vitamin E, **32**, and **33**. For this, the 9,10-diphenylanthracene was treated with methylene blue as a singlet oxygen generator, which led to the formation of 9,10-diphenylanthracene peroxide (Scheme 7). Thus, change in the absorption of the 9,10-diphenylanthracene is a measure of the singlet oxygen quenching activity of the antioxidant.[21]

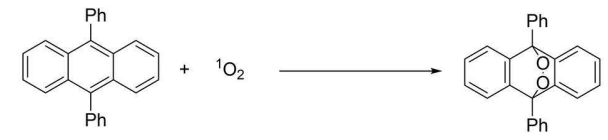
A smaller decrease in the absorbance of 9,10-diphenylanthracene was observed in the presence of the tris selenophenol **33** than the vitamin E (Figure 4), which suggests that selenophenol **33** can quench singlet oxygen. On the other hand, biselenophenol **32** showed poor singlet oxygen quenching in comparison to the vitamin E.

Table 2. Thiol peroxidase assay of the synthesized catalysts.



S. No.	Catalyst	Reduction rate v_0 [μM min^{-1}]
1	Ebselen	22.3 ± 2.3
2	**19**	Not Active
3	**20**	Not Active
4	**32**	4.62 ± 0.62
5	**33**	13.67 ± 1.17

[a] PhSH (1 mM), catalyst (0.1 mM), and H_2O_2 (3.75 mM) in methanol was used to calculate peroxide reduction rate.



9,10-diphenylanthracene — 9,10-diphenylanthracene peroxide

Scheme 7. Quenching of 9,10-diphenylanthracene by singlet oxygen.

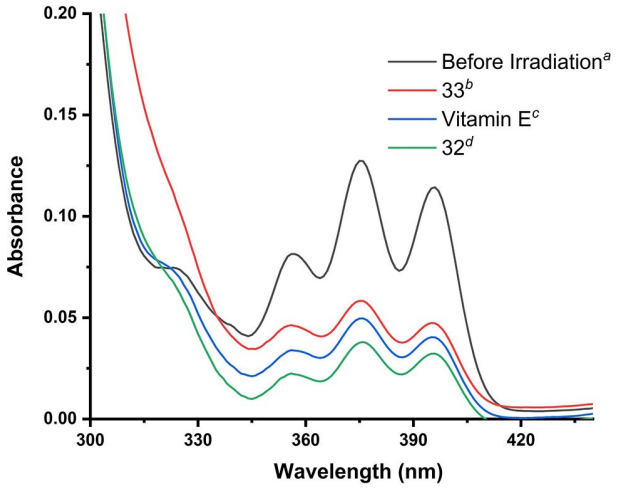


Figure 4. *a* Absorption spectrum of 9,10-diphenylanthracene (10 μM) in $CHCl_3$ solvent before irradiation. *b* Absorption spectrum of 9,10-diphenylanthracene (10 μM), methylene blue (10 μM), and **33** (10 μM) after 15 min of irradiation under UV light in a photoreactor in $CHCl_3$ solvent. *c,d* Absorption spectrum of 9,10-diphenylanthracene (10 μM), methylene blue (10 μM), and **32** and Vitamin E (10 μM) after 15 min of irradiation under UV light in a photoreactor in $CHCl_3$ solvent.

Conclusion

Here we have developed an accessible method from diiodophenols/dibromophenols and diorgano diselenides to construct two carbon-selenium bonds exploiting copper catalysis for the first time. The developed method allows the installation of two stable arylseleno group at the orthopostion of phenol leading novel pincer-type of molecules having one OH functionality and two ortho-selenium donor atoms.[22] The influence of intramolecular Se…O interaction of the phenolic OH group results in an enhancement in the radical quenching antioxidant activity of the bis and tris-selenophenols. Consequently, the electron-donating group substituted bis-selenophenol shows comparable radical quenching activity with naturally occurring antioxidant vitamin E, while the tris selenol-bisphenol exhibit higher radical quenching activity than vitamin E. Also, the decomposing peroxide activity of tris selenol-bisphenol was found comparable with the ebselen molecule. The coordinating property of these pincer-types of bis-ortho-selenophenols for isolation of metal-chalcogen complexes will be presented in the future.

Experimental Section

General procedures

All reactions are carried out under an inert atmosphere. Anhydrous DMF was used with sealed septa, and 1,10 phenanthroline was used as received. Diphenyl diselenide, CuI, Mg turning, 2,6-dibromophenol, 4-amino-2,6-dibromophenol and 2,6-dibromo-4-methylphenol were obtained from commercially available source (Aldrich) and used as received. 4-Hydroxy-3,5-diiodobenzonitrile and 4-hydroxy-3,5-diiodobenzaldehyde were purchased from Alfa Aesar and used as received. TLC analysis of reaction mixtures was performed using silica gel coated aluminum plates. NMR spectra were recorded on a Bruker Bio Spin GmbH-400 MHz spectrometer operating at 400.13 (^{1}H), 100 (^{13}C), and 76.31 (^{77}Se) MHz. ^{1}H and ^{13}C chemical shifts were relative to the internal chloroform peak ($\delta =$ 7.24 ppm for ^{1}H and $\delta = 77.0$ ppm for ^{13}C NMR). The ^{77}Se NMR chemical shifts were relative to external diphenyl diselenide (Ph_2Se_2) in $CDCl_3$ ($\delta = 463.0$ ppm) relative to Me_2Se_2 ($\delta = 0$ ppm). High-resolution mass spectral (HRMS) analysis was performed for the ion of ^{80}Se on a quadrupole time of fight (Q-TOF) mass spectrometer equipped with both an ESI and APCI source. Silica gel (100–200 mesh size) was used for column chromatography.

2-(Phenylselanyl)phenol (**17**):[15] Copper iodide (86 mg, 0.45 mmol), 1,10-phenanthroline (81 mg, 0.45 mmol) and magnesium turning (144 mg, 6.0 mmol) were added into DMF (5 mL) in a single neck flask. Resulted brownish solution was stirred for 5 min and then 2-iodophenol (660 mg, 3.0 mmol), diphenyl diselenide (469 mg, 1.5 mmol), were added sequentially to same reaction flask. Brown coloured reaction mixture was refluxed at 110 °C using refluxing condenser under nitrogen atmosphere. Progress of reaction was monitored by TLC. Reaction mixture was refluxed for 6 h. After this, reaction mixture poured over 10% hydrochloric acid solution (40 mL) and stirred for 3 h. Extracted with ethyl acetate (15 mL × 3), concentrated over rotary evaporator, resulted brown solid which was purified by column chromatography using hexane/ ethyl acetate (8 : 2) over silica gel. Yield 0.67 g (90%), ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.67 (dd, $J = 8.0$, 1.2 Hz, 1H), 7.40 (td, $J = 8.0$,1.6 Hz, 1H), 7.30–7.20 (m, 5H), 7.12 (dd, $J = 8.0$,1.2 Hz, 1H), 6.94 (td, $J = 8.0$, 1.2 Hz, 1H), 6.47 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 138.0, 132.3, 130.8, 129.7, 129.5, 126.8, 121.4, 115.2, 114.8. ^{77}Se NMR (76 MHz, $CDCl_3$) δ 247. HRMS (*m/z*) calcd for $C_{12}H_{10}OSeNa$ $[M+Na]^+$ 272.9789, found 272.9839.

2-((2-Methoxyphenyl)selanyl)phenol (**18**):[15] Synthesis of **18** was carried out in a similar way as described for **17** from 2-((2-methoxyphenyl)selanyl)phenol. Yield 0.77 g (92%), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, $J = 4.0$ Hz, 1H), 7.40 (t, $J = 8.0$ Hz, 1H), 7.22 (t, $J = 8.0$ Hz, 1H), 7.10 (d, $J = 8.0$ Hz, 1H), 6.93 (d, $J = 8.0$ Hz, 1H), 6.87 (t, $J = 10.0$ Hz, 2H), 6.81 (t, $J = 10.0$ Hz, 1H), 6.63 (s, 1H), 3.96 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 156.7, 138.5, 132.3, 130.0, 128.1, 121.9, 121.3, 119.9, 115.1, 113.4, 110.5, 55.9. ^{77}Se NMR (76 MHz, $CDCl_3$) δ 198. HRMS (*m/z*) calcd for $C_{13}H_{13}O_2Se$ $[M+H]^+$ 281.0076, found 281.0106.

2,6-Bis(phenylselanyl)phenol (**19**): Copper iodide (57 mg, 0.3 mmol), 1,10-phenanthroline (54 mg, 0.3 mmol) and magnesium turning (72 mg, 3.0 mmol) were added into DMF (5 mL) in a single neck flask. Resulted brownish solution was stirred for 5 min and then 2,6-dibromophenol (250 mg, 1.0 mmol) and diphenyl diselenide (312 mg, 1.0 mmol) were added sequentially to same reaction flask. Brown coloured reaction mixture was heated under nitrogen atmosphere. Progress of reaction was monitored by TLC. Reaction mixture was stirred for 18 h. After this, reaction mixture poured over water (60 mL) and stirred for 3 h. Extracted with ethyl acetate (15 mL × 3), concentrated over rotary evaporator, resulted brown solid which was purified by column chromatography using hexane/ ethyl acetate (9.5 : 0.5) over silica gel. Yield 0.10 g (75%),^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 3H), 7.45-7.42 (m, 5H), 7.33-7.29 (m, 5H), 6.00 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 137.0, 132.4, 131.1, 129.6, 127.7, 122.9, 110.4. ^{77}Se NMR (76 MHz, $CDCl_3$) δ 426. HRMS (*m/z*) calcd for $C_{18}H_{15}OSe_2$ $[M+H]^+$ 428.9271, found 429.5766.

4-Methyl-2,6-bis(phenylselanyl)phenol (**20**): Synthesis of **20** was carried out in a similar way as described for **19** from 2,6-dibromo-4-methylphenol and diphenyl diselenide. Yield 0.33 g (81%), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.41 (m, 4H), 7.31-7.28 (m, 6H), 7.20(s, 1H), 6.71(s, 1H), 2.20(s,3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 136.3, 132.0, 131.5, 130.0, 129.5, 127.4, 116.1, 20.2. ^{77}Se NMR (76 MHz,

$CDCl_3$) δ 313. HRMS (*m/z*) calcd for $C_{19}H_{16}OSe_2Na$ $[M+Na]^+$ 442.9427, found 442.9409.

4-Amino-2,6-bis(phenylselanyl)phenol (**21**): Synthesis of **21** was carried out in a similar way as described for **19** from 4-amino-2,6-dibromophenol and diphenyl diselenide Yield 0.34 g (80%), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 8.0, 1.2 Hz, 4H), 7.43-7.35 (m, 8H), 7.28 (s, 1H), 5.32 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 156.7, 138.5, 132.3, 130.0, 128.1, 121.9, 121.3, 119.9, 115.1, 113.4, 110.5, 55.9. ^{77}Se NMR (76 MHz, $CDCl_3$) δ 262. HRMS (*m/z*) calcd for $C_{18}H_{14}NOSe_2$ $[M-H]^+$ 419.9404, found 419.9403.

2,6-Bis(hexylselanyl)phenol (**22**): Synthesis of **22** was carried out in a similar way as described for **19** from 2,5-dibromophenol and di-*n*-hexyl diselenide. Yield 30 mg (12%), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 2H), 7.19 (s, 1H), 5.80 (s, 1H), 2.78 (t, *J* = 8.0 Hz, 4H), 1.62-1.54 (m, 4H), 1.34-1.93 (m, 12H), 0.81 (t, *J* = 8.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 136.7 132.0, 110.0, 31.2, 30.0, 29.6, 29.3, 22.5, 14.0. ^{77}Se NMR (76 MHz, $CDCl_3$) δ 748.

3,5-Bis(^{n}hexylselanyl)-4-hydroxybenzaldehyde (**23**): Synthesis of **23** was carried out in a similar way as described for **19** from 3,5-dibromo4-hydroxybenzaldehyde and di-*n*-hexyl diselenide. Yield 0.12 g (32%), ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.89 (s, 2H), 7.55 (s, 1H), 2.86 (t, *J* = 8.0 Hz, 4H), 1.70–1.63 (m, 4H), 1.42–1.25 (m, 12H), 0.86(t, *J* = 6.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.8, 135.8, 31.2, 29.9, 29.4, 28.3, 22.5, 14.0. ^{77}Se NMR (76 MHz, $CDCl_3$) δ 196. HRMS (*m/z*) calcd for $C_{19}H_{12}O_2Se_2$ $[M-H]^+$ 449.0496, found 449.0514.

4-Hydroxy-3,5-bis(phenylselanyl)benzaldehyde (**24**): Synthesis of **24** was carried out in a similar way as described for **19** from 4-hydroxy-3,5-diiodobenzaldehyde and diphenyl diselenide. Column chromatography of the reaction mixture by hexane/ ethyl acetate (8:2) on silica gel provided two fractions: first fraction is bis-selenide **24**. Yield 0.19 g (75%), ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 7.82 (s, 2H), 7.50-7.46 (m, 4H), 7.44 (s, 1H), 7.38–7.30 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.5, 158.6, 136.3, 133.1, 131.1, 129.8, 128.3, 128.2, 118.7. ^{77}Se NMR (76 MHz, $CDCl_3$) δ 320. HRMS (*m/z*) calcd for $C_{19}H_{14}O_2Se_2Na[M+Na]^+$ 456.9220, found 456.9201.

4-Hydroxy-3,5-bis(phenylselanyl)benzonitrile (**25**): Synthesis of **25** was carried out in a similar way as described for **19** from 4-hydroxy-3,5-diiodobenzonitrile and diphenyl diselenide. Column chromatography of the reaction mixture by hexane/ ethyl acetate (8:2) on silica gel provided two fractions: first fraction is bis-selenide **25**. Yield 0.19 g (45%), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.46 (m, 6H), 7.40–7.35 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 137.1, 133.6, 130.1, 128.8, 127.5, 119.3, 117.9, 105.9. ^{77}Se NMR (76 MHz, $CDCl_3$) δ 327. HRMS (*m/z*) calcd for $C_{19}H_{13}NOSe_2Na$ $[M+Na]^+$ 453.9223, found 453.9218.

5,5′-Selenobis(4-hydroxy-3-(phenylselanyl) benzaldehyde) (**26**): Second fraction from the reaction mixture of **24** provided triseleno-bisphenol **26**. Yield 94 mg (30%), ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (s, 2H), 7.95(d, *J* = 2.0 *Hz*, 2H), 7.88 (t, *J* = 4.0 Hz, 2H) 7.58 (s, 1H), 7.45–7.41 (m, 4H), 7.35–7.29 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.2, 159.5, 138.0, 137.2,132.4, 131.3, 129.9,128.4, 128.3 118.6, 116.1. ^{77}Se NMR (76 MHz, $CDCl_3$) δ 308, 258. HRMS (*m/z*) calcd for $C_{26}H_{18}O_4Se_3Na$ $[M+Na]^+$ 656.8594, found 656.8597.

5,5′-Selenobis(4-hydroxy-3-(phenylselanyl)benzonitrile) (**27**): Second fraction from the reaction mixture of **25** provided triseleno-bisphenol **27**. Yield 0.23 g (38%), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 4.0 Hz, 2H), 7.55 (d, *J* = 2.0 Hz, 2H), 7.48–7.46 (m, 5H), 7.42–7.36 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 139.0, 138.4, 132.1, 130.2, 128.9, 127.5, 119.8, 117.4, 115.7, 106.4. ^{77}Se NMR (76 MHz, $CDCl_3$) δ 320, 265. HRMS (*m/z*) calcd for $C_{26}H_{17}N_2O_2Se_3$ $[M+H]^+$ 628.8782, found 628.8789.

3-(*n*-Hexylselanyl)-4-hydroxy-5-iodobenzaldehyde (**28**): Synthesis of **28** was carried out in a similar way as described for **26** from 4-hydroxy-3,5-diiodobenzaldehyde and di-*n*-hexyldiselenide. Synthesis of **28** was carried out in a similar way as described for **17** from di ^{n}hexyl diselenide and 4-hydroxy-2,5-diiodobenzaldehyde. Yield 0.22 g (68%), ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 8.20 (s, *J* = *2.0* Hz, 1H), 8.03 (t, *J* = *2.0* Hz, 1H), 7.49 (s, 1H), 7.24 (s, 1H), 2.79 (t, *J* = *8.0* Hz, 2H), 1.68–1.60 (m, 2H), 1.39–1.24 (m, 6H), 0.85 (t, *J* = *8.0* Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7, 160.6, 142.400, 138.5, 131.6, 116.4, 81.6, 31.1, 30.3, 30.1, 29.2, 22.4, 14.0. ^{77}Se NMR (76 MHz, $CDCl_3$) δ 175. HRMS (m/z) calcd for $C_{13}H_{16}INO_2Se$ $[M-H]^+$ 410.9355,found 410.9367.

3-(*n*-Hexylselanyl)-4-hydroxy-5-iodobenzonitrile (**29**): Synthesis of **29** was carried out in a similar way as described for **26** from 4-hydroxy-3,5-diiodobenzenitrile and di-*n*-hexyl diselenide. Yield 0.25 g (80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = *2.0* Hz, 1H), 7.79 (d, *J* = *2.0* Hz, 1H), 7.24 (s, 1H), 2.78 (t, *J* = 8.0 Hz, 2H), 1.65–1.58 (m, 2H), 1.39–1.24 (m, 6H), 0.86 (t, *J* = *8.0* Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 143.7, 140.4, 116.8, 116.4, 106.3, 81.2, 31.1, 30.5, 30.1, 29.2, 22.5, 14.0. ^{77}Se NMR (76 MHz, $CDCl_3$) δ 183. HRMS (m/z) calcd for $C_{13}H_{15}INOSe$ $[M-H]^+$ 407.9358, found 407.9372.

2,6-Dibromo-4-(hexylselanyl)phenol (**30**): Synthesis of **30** was carried out in a similar way as described for **26** from 4-hydroxy-3,5-dibromobenzenitrile and di-*n*-hexyl diselenide. Yield 0.28 g (38%)^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 2H), 5.81 (s, 1H), 2.79 (t, *J* = 6.0 Hz, 2H), 1.63–1.55 (m, 2H), 1.35–1.27 (m, 2H), 1.22-1.18 (m, 4H), 0.81 (t, *J* = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 136.7, 122.5, 110.0, 31.2, 30.0, 29.6, 29.3, 22.5, 14.01. ^{77}Se NMR (76 MHz, $CDCl_3$) δ 309.5.

4-((Phenylselanyl)methyl)phenol (**31**): Synthesis of **31** was carried out in a similar way as described for **19** from diphenyl diselenide and 2,6-dibromo-4-methylphenol. Yield: 0.17 g (22%), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.54 (m, 4H), 7.33–7.29 (m, 5H), 5.75 (s, 1H), 4.26 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.0, 131.9, 131.3, 131.8, 129.7, 128.0, 126.5, 108.3, 19.9. ^{77}Se NMR(76 MHz, $CDCl_3$) δ 344.

4-(hydroxymethyl)-2,6-bis(phenylselanyl)phenol (**32**): Formation of **32** was achieved by using the mild reducing agent $NaBH_4$ in the ethanolic solution of **24** followed by the workup with $NaHCO_3$, ethyl acetate and water. The organic layer than filtered through sodium sulfate and dried over rotatory evaporator. Yield 87%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 6.5, 3.0 Hz, 1H), 7.37 (s, 1H), 7.30 (dd, *J* = 7.2, 3.5 Hz, 2H), 6.89 (s, 1H), 4.51 (s, 1H). ^{13}C NMR (126 MHz, CDCl3) δ 153.8, 134.6, 134.3, 132.4, 129.5, 129.4, 127.7, 116.9, 64.3.^{77}Se NMR (76 MHz, $CDCl_3$) δ 318. HRMS (m/z) calcd for $C_{19}H_{16}O_2Se_2Na$ $[M+Na]^+$ 458.9376, found 458.9395.

6,6′-selenobis(4-(hydroxymethyl)-2-(phenylselanyl)phenol) (**33**): Synthesis of **33** was carried out in a similar way as described for **26**. Yield 80%. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.03 (s, 1H), 7.29 (d, *J* = 3.2 Hz, 3H), 7.36 (d, *J* = 2.0 Hz, 1H), 7.40 (dd, *J* = 6.4, 3.1 Hz, 2H), 7.42 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.2, 135.1, 134.8, 134.6, 131.9, 129.6, 129.5, 127.6, 116.6, 115.5, 64.1. ^{77}Se NMR (76 MHz, $CDCl_3$) δ 308, 249. HRMS (m/z) calcd for $C_{26}H_{22}O_4Se_2Na$ $[M+Na]^+$ 660.9080, found 660.8939

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Organoselenium · Antioxidants · Phenols · Chalcogen · Radicals · Copper Catalysis

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