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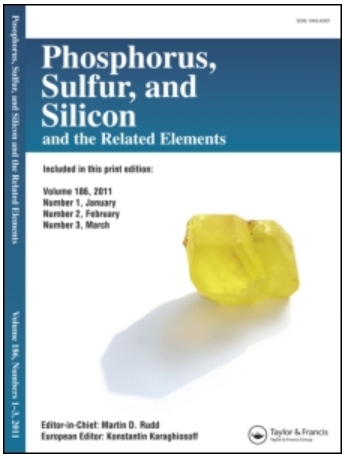

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Aspects of Intramolecularly Coordinated Organochalcogen Derivatives

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Aspects of Intramolecularly Coordinated Organochalcogen Derivatives

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Recent progress in the area of intramolecularly coordinated organochalcogens, in particular, organoselenium derivatives, is reviewed. Intramolecular coordination facilitates isolation of (a) stable organoselenenyl iodides, (b) chiral diselenides, (c) organotriselenides, d) cleavage of Te—C bond, e) metal-free synthesis of chalcogenaaza macrocycles, and f) isolation of cyclic selenenate esters. The synthesis of organoselenium compounds incorporating two ortho- coordinating groups is also discussed.

Keywords Ebselen; Glutathione peroxidase; Intramolecular Se···N coordination; Organoselenium; Seleninate ester

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INTRODUCTION

The chemistry of organoselenium derivatives, having intramolecular nonbonded E···D interactions **1** (where E is chalcogen and D is donor) has attracted current interest. Intramolecular coordination facilitates; (a) isolation of novel hypervalent, stable organoselenium compounds via intramolecular interaction of selenium with a nearby heteroatom (N, O, S etc.),[1] (b) chiral reagents for asymmetric synthesis,[2] (c) ligands for the isolation of monomeric MOCVD precursors,[3] (d) ligands for achiral and chiral catalysis,[4] and (e) glutathione peroxidase mimics.[5,6]

ACTIVATION OF Te–C BOND

Our group is having a long-standing interest in different aspects of the chemistry of organochalcogen compounds **2**–**9**[6–11] including, nonbonded chalcogen-heteroatom interactions (Figure 1). In continuation to this, we discuss here some recent results from our laboratory.

We are grateful to Department of Science and Technology, (DST) for financial support.
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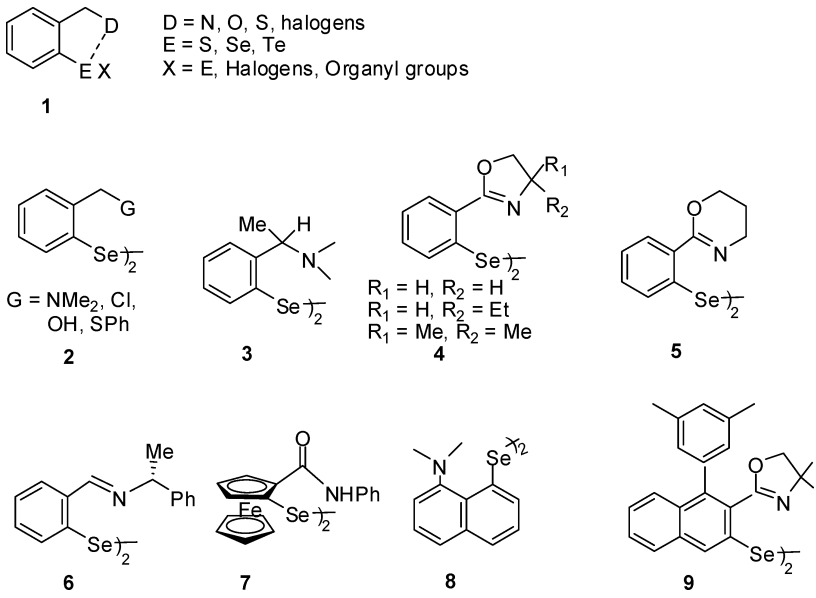

FIGURE 1

The key step in Fujiwara-Heck cross-coupling reaction between organic tellurides and alkenes was proposed to be the migration of an organic moiety from Te to Pd (transmetalation) in organic telluride-$PdCl_2$ complexes to afford the organopalladium species.[12] McWhinnie and co-workers have established the lability of organic groups from tellurium on reaction with metal compounds.[13] In this regard, the reactions of R_2Se (**10**) and R_2Te (**12**) (where R = 2-(4,4-dimethyl-2-oxazolinyl)phenyl)) with $HgCl_2$ and $Pd(COD)Cl_2$ were attempted (Scheme 1). The reaction of selenoether **10** with $HgCl_2$ afforded the expected complex $R_2Se.HgCl_2$ (**11**), which is stable in solution. In contrast, the analogous tellurium complex $R_2Te.HgCl_2$ undergoes slow dismutation in chlorinated solvents to give the fragments RTeCl (**13**) and RHgCl (**14**). Mechanistically, this cleavage can be explained through electrophilic substitution by mercury at the ipso carbon of one aromatic ring. It leads to the formation of the σ-intermediate, which results in polarization of the Te-C bond (Te^+-C^-). Rearomaticization in the presence of chloride ion generates **13** and **14** with completion of the aryl migration. The Te→N intramolecular nonbonding interactions may be the additional factor facilitating the polarization of the Te—C bond.[14] Similarly the reaction of tridentate tellurides **15** and **18** with $Pd(COD)Cl_2$ led to facile cleavage of the Te—C bond and isolation of the resulting organopalladium **17**,**20** and organotellurium products **16**,**19** respectively (Scheme 2).[15]

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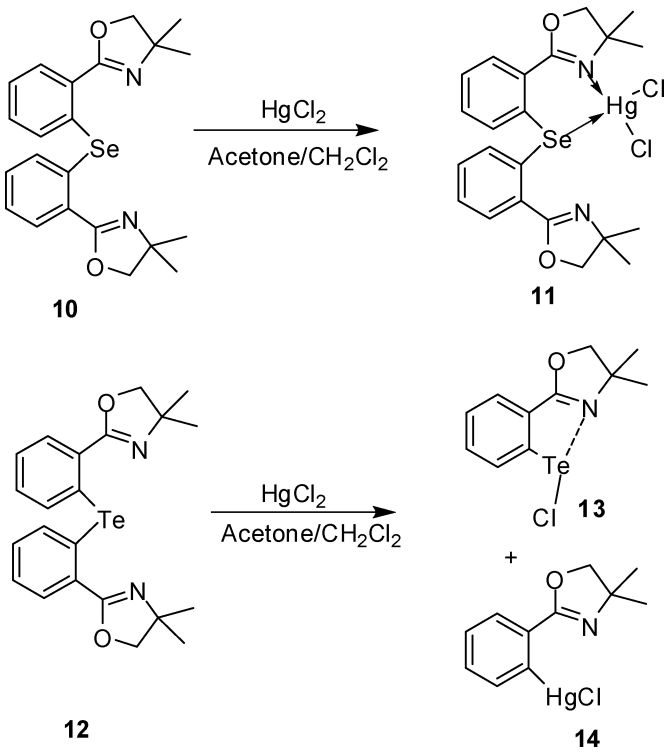

SCHEME 1

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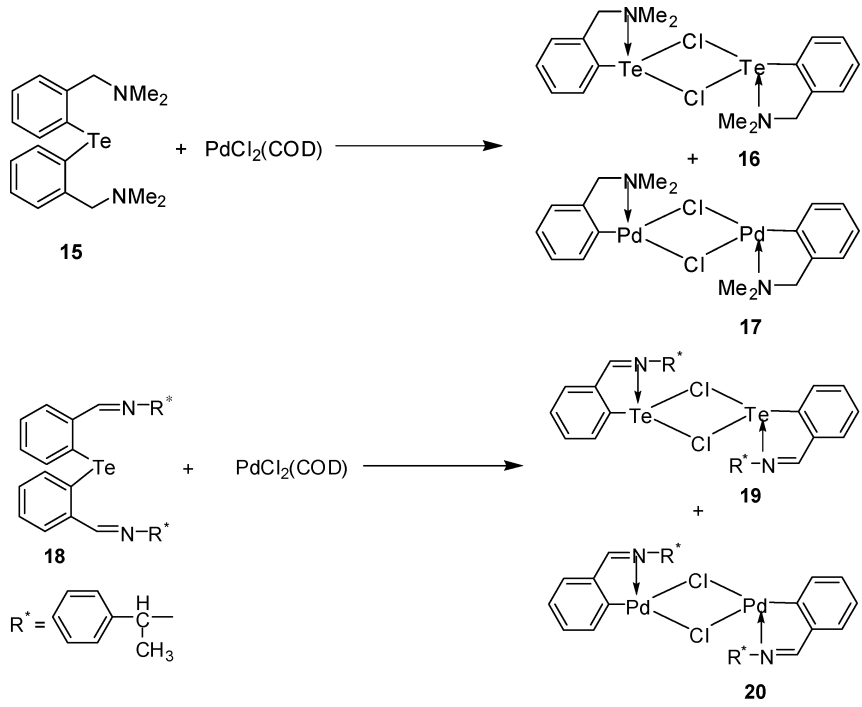
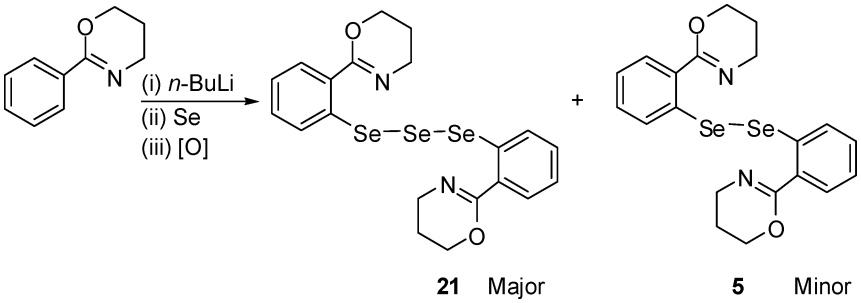
Isolation of Triselenide

The organoselenium compounds with coordinating nitrogen in close proximity of chalcogen in the form of oxazoline ring have been thoroughly studied by our group.[7] To study the chelate ring size effect, we have studied another substrate oxazine,[9] having coordinating nitrogen as a part of six membered heterocycle. The synthesis of diselenide **5** was attempted by the *ortho*-lithiation method. However, oxidative work-up of lithium arylselenolate afforded triselenide **21** as the major product (Scheme 3). Interestingly, in the previous reports, similar reactions using ligands, 2-phenyl-2-oxazoline, 4,4-dimethyl-2-phenyl-2-oxazoline, (*R*)-4-ethyl-4-hydro-2-phenyloxazoline, where nitrogen as a member of five-membered oxazoline ring, have afforded corresponding diselenides. Generally, bulky ligands such as dithiophenetriptycyl,[16] tris(trimethylsilyl)methyl[17] and 2,6-di[2,6-di(2,6-dimethylphenyl)tolyl]-4-tert-butylphenyl[18] have been used to isolate stable triselenides or tetraselenides. In this



SCHEME 2



SCHEME 3

case, triselenide **21** has been stabilized by intramolecular Se···N coordination.

Isolation of Mercury Tellurolate

To gain insight on the stability of organochalcogens having both intermolecular coordinating and sterically demanding groups,

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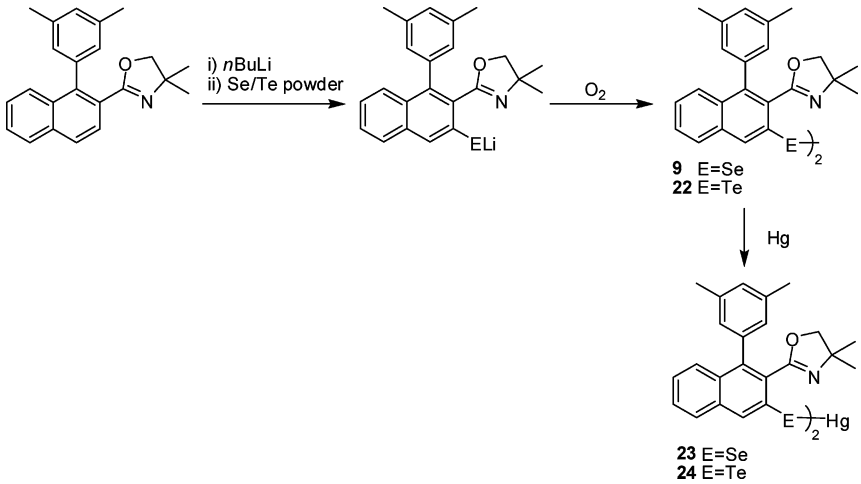

SCHEME 4

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2-[1-(3,5-dimethylphenyl)-2-naphthyl]-4,5-dihydro-4,4-dimethyl-1,3-oxazole was chosen as a precursor. The synthesis of corresponding diselenide **9** was accomplished by *ortho*-lithiation, selenium insertion into the C-Li bond, followed by oxidative work-up (Scheme 4).[8] The most interesting feature of the structure of diselenide **9** is the existence of both Se···N and Se···O interactions between selenium atoms and nitrogen/oxygen in the same molecule. Generally, for the structure of selenium compounds incorporating 2-phenyloxazoline, only Se···N interactions were observed. The unusual intramolecular Se···O interaction in the structure of diselenide **9** has been explained based on the different orientation of oxazoline ring due to steric crowding. One of the oxazoline rings is twisted in such a way that nitrogen of the ring pointed away and oxygen towards the selenium atom. The Se···N [2.976(8) Å] and Se···O [2.9815 Å] distances are comparable to the reported examples. In contrast, the ditelluride analogue showed only one type of (Te(1)···N(1), 2.718(3) Å) intramolecular interaction. The mercury selenolate **23** and tellurolate **24** complexes were prepared by oxidative addition of corresponding dichalcogenides with mercury metal in methanol.[19] These show high stability towards light, moisture, and air. Especially, no decomposition was observed for the mercury tellurolate **24**, when the solid was kept in contact with air or in solution. Thus, synthesis of a novel air stable and monomeric mercury tellurolate using a ligand having both sterically more demanding and intramolecular coordinating features has been achieved.

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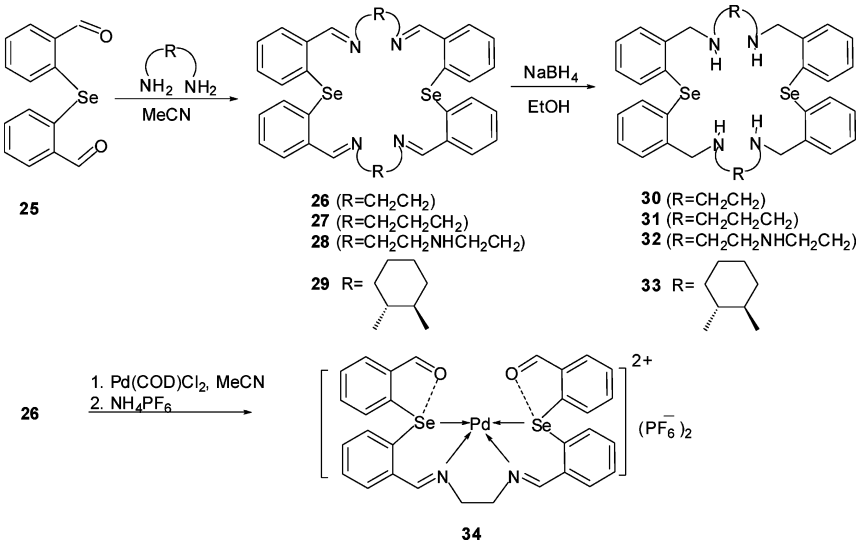
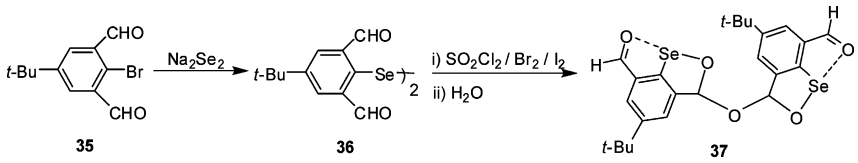
Template-Free Macrocycle Synthesis

Mixed selenium and nitrogen donor macrocycles are attractive synthetic targets for several reasons. These ligands contain *hard* and *soft* binding sites in close proximity within the same macrocyclic cavity, and, therefore, can coordinate both *hard* and *soft* guest ions, or molecules. Selenium in a macrocycle is useful for structural investigation using ^{77}Se NMR spectroscopy. In addition, selenium has a greater σ-donating ability than N, O, and S, which may influence complexation properties. Finally, incorporation of selenium, which is a larger atom, into macrocyclic ligands should change the size of the cage cavity thus leading to interesting coordination behavior. The macrocyclic ligands were prepared from the precursor bis(*o*−formylphenyl) selenide, **25**, which itself was synthesized from *o*−bromotoluene.[20] Several 22-, 24-, and 28-membered macrocyclic Schiff base type ligands **26–33** were isolated in high yield (Scheme 5).[21,22] The intramolecular nonbonded interaction plays an important role in the template-free syntheses of Schiff base selenaaza macrocycles. Macrocycle **26** showed two Se···N nonbonded interactions with the distances of 2.723 Å and 2.729 Å which are slightly shorter than that observed in **30** (2.773 Å) where only one interaction is present. These interactions lead to the interesting reactivity of the macrocycles toward complexation with different metal ions. Reaction of **26** with $Pd(COD)Cl_2$, unexpectedly, resulted into complex



SCHEME 5



35 36 37

SCHEME 6

34 where one arm of the macrocycle hydrolyzed into two formyl groups. Crystal structure of complex **34** showed weak nonbonded Se···O interactions (2.855 Å). Extending the series, we have reported new selenaaza **29** macrocycle and its reduced form **33** by replacing ethylenediamine by cyclohexylenediamine.[23] The resulting macrocycle has shown nonbonded interaction comparable to that observed for **26**. The macrocycle has shown usual reactivity toward the metal ion Ni(II) and Co(II).

Isolation of Stable Selenenate Ester

Selenenic acid is a highly reactive species formed during the catalytic cycle of glutathione peroxidase (GP_x).[5] Selenenate esters can be considered as a protected form of the selenenic acid. We have synthesized and structurally characterized cyclic selenenate ester **37** stabilized by Se···O interaction. The reaction of diselenide **36** with halogenating regent ($SO_2Cl_2/Br_2/I_2$) followed by quenching with water has unexpectedly afforded the novel selenenate ester **37** (Scheme 6).[24] Diselenide **36** was synthesized by the treatment of the precursor bromo compound **35** with disodium diselenide. The Se···O distances (2.604 Å and 2.465 Å) are considerably shorter than sum of their van der Waals radii.

This is a nice example of the application of nonbonded interactions to isolate the rather unstable organoselenium compounds. It is interesting to note that there is no intramolecular interaction between any of the oxygen atoms and the selenium atoms in **36**. The structure shows that all four oxygen atoms of the formyl groups point away from the selenium centers.[24] The novel cyclic selenenate ester **37** and its precursor diselenide **36** exhibit almost 7- and 6-fold enhancement in the GP_x like antioxidant activity as compared to Wilson's catalyst [bis2-(*N*, *N*-dimethylbenzylamine) diselenide],[25] respectively.

The mechanistic pathway has been discussed for the catalytic cycle of selenenate ester based on ^{77}Se NMR studies and the previous report by Back et al.[26] Four closely related ^{77}Se NMR signals were obtained when two equivalents of H_2O_2 were added to a solution of selenenate ester **37**. These signals can be assigned to the cyclic seleninate **38**. Addition of two equivalents of PhSH resulted in one additional signal corresponding to selenenate **37**. The addition of two more equivalents of

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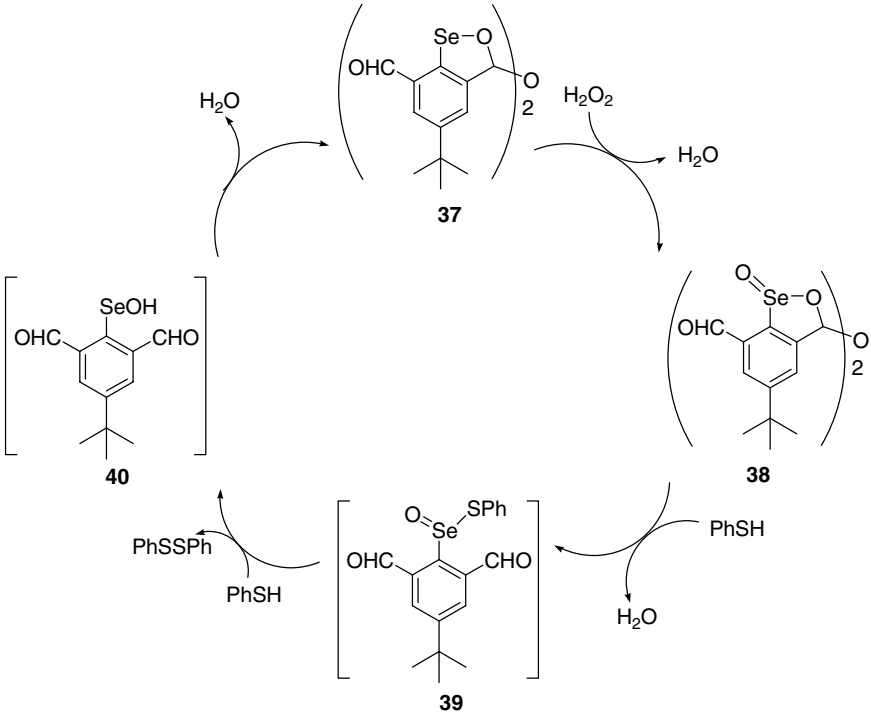
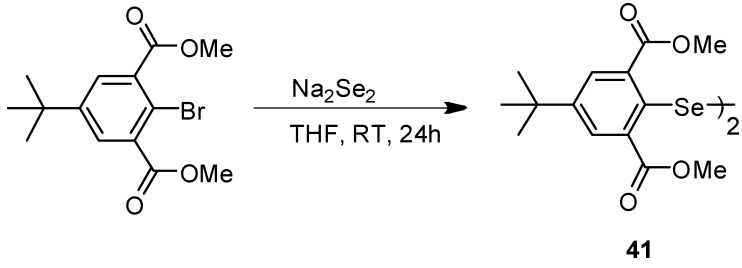
PhSH resulted in only the signal corresponding to selenenate **37** being observed (Scheme 7).



SCHEME 7

The formation of selenenate ester **37** can be explained by ring opening by the thiol, followed by breakdown of the hemiacetal to form thioseleninate **39**. These results corroborated the observations made by Back et al. that compounds containing Se···O bonds can be equally effective catalysts as the commonly studied Se···N derivatives.



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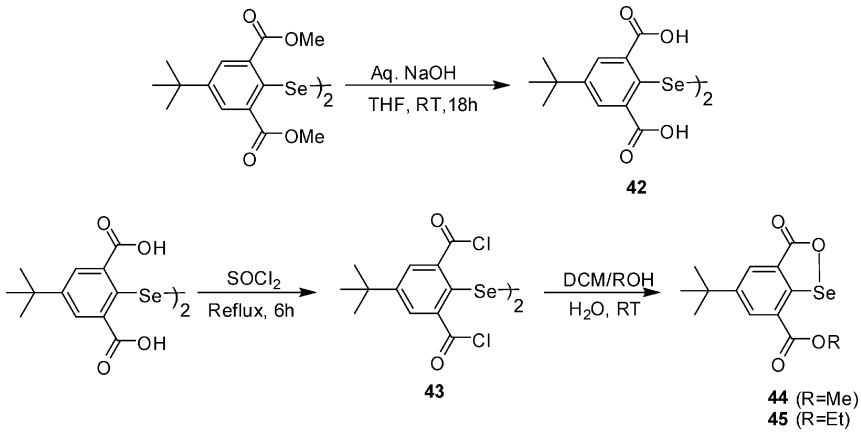
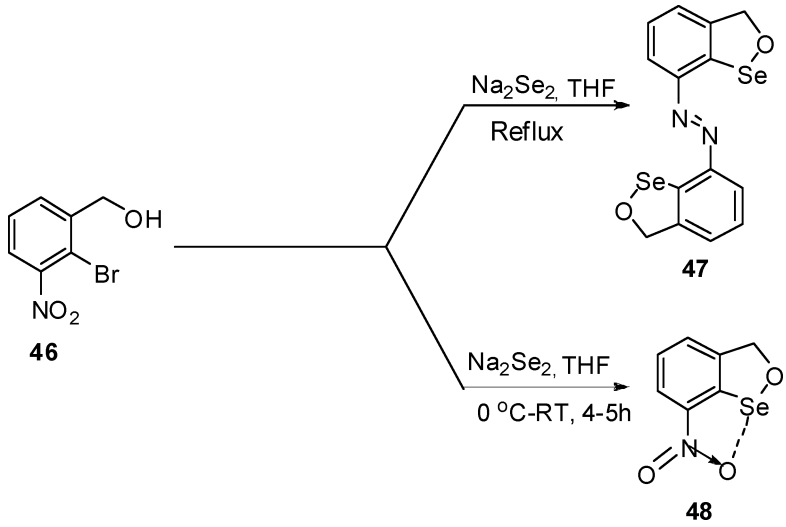


SCHEME 9

We have recently extended the study of GP_x-like activity to diselenides with two *ortho* esters group atoms. Diselenide **41** was synthesized by using Na_2Se_2 as the selenenating agent (Scheme 8).[27]

The diselenide upon hydrolysis with NaOH in H_2O/THF medium gave the hydrolyzed diselenide **42**, which was used to prepare new cyclic selenenate esters **44**, **45** (Scheme 9).[27]



SCHEME 10

Novel selenenate ester **48**, which is stabilized by a *ortho*-coordinating nitro group could be synthesized by treating

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3-nitro-2-bromobenzylalcohol[28] **46** with Na_2Se_2 at room temperature. Interestingly, the treatment of 3-nitro-2-bromobenzylalcohol with Na_2Se_2 at reflux temperature gives an azoselenenate ester **47** instead of nitroselenenate ester **48** (Scheme 10).[29]

Se···OH Interaction

Although Se···O interactions are weaker than the corresponding Se···N interactions, the compounds containing Se···O interactions do play a significant role in imparting enhanced GPx-like antioxidant properties. Tomoda and co-workers synthesized a series of organoselenium compounds **49** (Figure 2) having intramolecular Se···O interaction and studied the strength of this interaction by NMR and full NBO analysis.[30] Wirth reported diselenides **50** containing an oxygen atom in close proximity to the selenium atoms and found significant GP_x-like catalytic activity.[31] Back et al. and Singh and co-workers have also reported high to moderate catalytic activity for five membered seleninate ester **51**, spirodioxaselenanonane **52** and the corresponding benzo analogues **53**, **54**.[32,6]

The remarkable activity of the five membered esters and their benzo analogues **51-54** in coupled reductase GPx assay**,** prompted us to synthesize the first seven membered cyclic seleninate ester. The cyclic seven membered seleninate ester **57** was synthesized from the diselenide of 2-phenoxyethanol (Scheme 11). The synthesis of bis(2-phenoxyethanol) diselenide **55** was carried out by *ortho*-lithiation route, followed by the insertion of selenium and oxidation.[33]

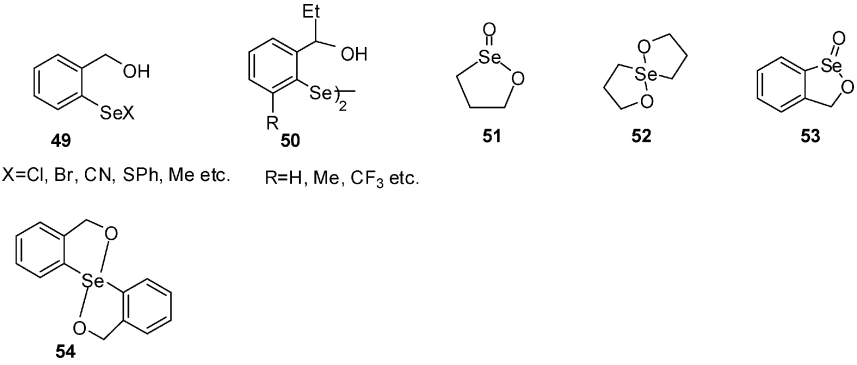

FIGURE 2 Please provide caption for Figure 2>

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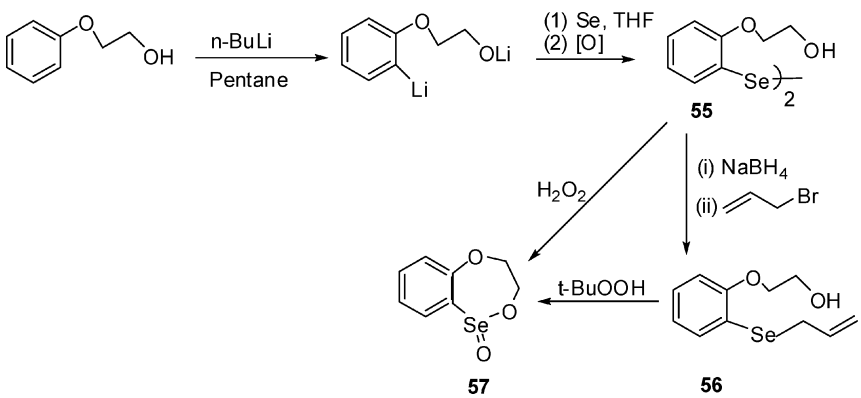

SCHEME 11

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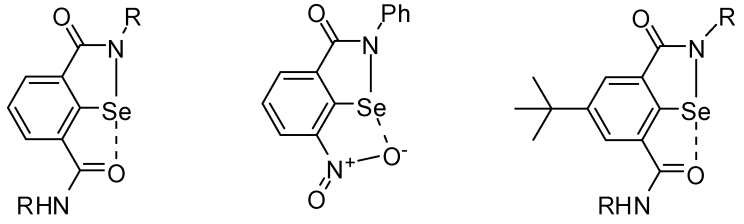
Ebselen Analogues as GPx Mimics

Synthesis of ebselen and its anologues has attracted considerable interest due to their promising GP_x-like activities and their therapeutic values.[34] Kersting and DeLion[35] isolated intramolecularly coordinated ebselen **58** (Figure 3).

Compounds **59**, **60** showed much better GPx activity than ebselen.[36] The significant enhancement in the initial reduction rate for *t*-BuOOH was essentially due to the Se···O intramolecular interaction. An attempted synthesis of intramolecularly coordinated organodiselenides by the reaction of N,*N*-dialkyl/diphenyl-2-bromo-5-*tert*-butylisophthalamide with Li_2E_2 (E = S, Se, Te), interestingly, afforded ebselen derivatives.

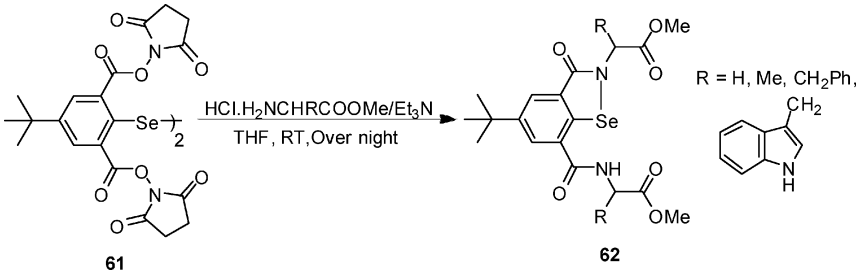
This prompted us to explore the synthesis and GP_x activity of intramolecularly stabilized ebselen analogues with amino acids and peptide chains. We have recently synthesized and characterized a few



58 **59** **60**

FIGURE 3

ebselen analogues **62** which have intramolecularly coordinating amino acids by active ester method (Scheme 12).[27]



SCHEME 12

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