The 15th International Electronic Conference on Synthetic Organic Chemistry (ECSOC-15)

Bioinspired Use of Organoselenium Catalysts

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Abstract
Selenium-based reagents bear a high potential for the improvement of known reactions not only from an environmental and pharmaceutical point of view, but also as interesting reagents for the development of completely new synthetic transformations and as potential ligands in catalytic reactions. A variety of organoselenium compounds have been proved to be useful for organic synthesis over several decades. Organoselenium species can be introduced as either nucleophiles or electrophiles to other organic molecules, producing useful intermediates for organic synthesis. Optically active organoselenium derivatives and their application to highly selective asymmetric synthesis are also of current interest. Probably the most interesting aspect, which emerged in recent years, concerns the possibility of effecting some functional group conversions using catalytic amounts of the selenium reagent or using selenium containing compounds as chiral ligands in metal catalyzed reactions. The developments of all these catalytic processes represent the most important results which have been reported recently in this field and their conceptual and synthetic relevance considerably increases the use of some organoselenium derivatives as *Green Catalysts.* Considering that in Nature, the main biological function of selenium is associated with its incorporation in the form of selenocysteine (Sec) into certain proteins having redox motifs, different selenium containing compounds can be investigated as bio-inspired catalysts in the carbon-carbon multiple bond oxidation mediated by H_2O_2 in water. These catalysts resulted to be also interesting good GPx-mimics.

Keywords: Catalysis, Oxidation, Selenium, Biomimetic

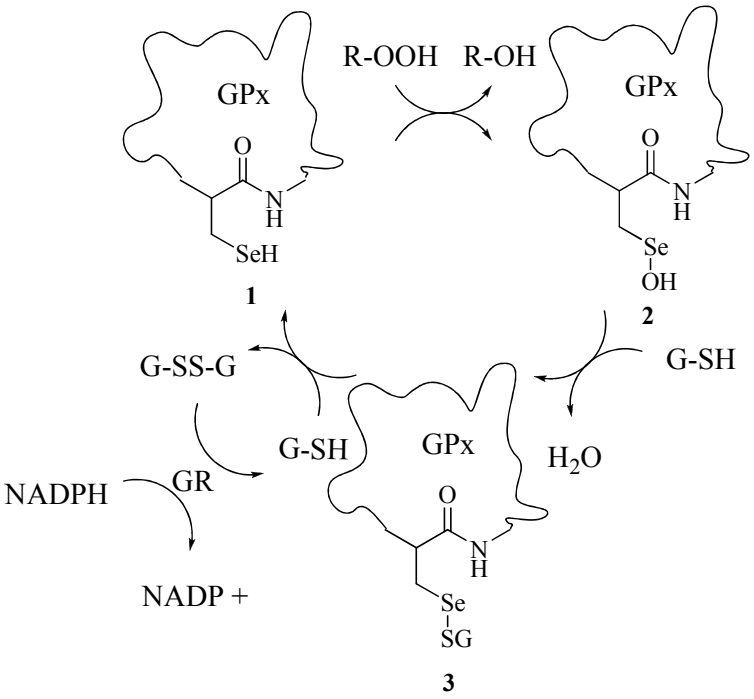
1. Introduction

On the border between Science and Nature information can flow in both directions: from Science to Nature it helps to understand how living systems work and how we can interact with them modulating their activity; from Nature to Science it represents an inspiration source for design new materials and processes that should be more efficient and environmentally benign. From a chemical point of view, Nature is the biggest laboratory in the world and produces tons of chemicals per day in a completely eco-friendly manner.

In this communication we report that using simple organic catalysts and the logic of the enzymatic systems is possible to setup new chemical reactions affording the synthesis of

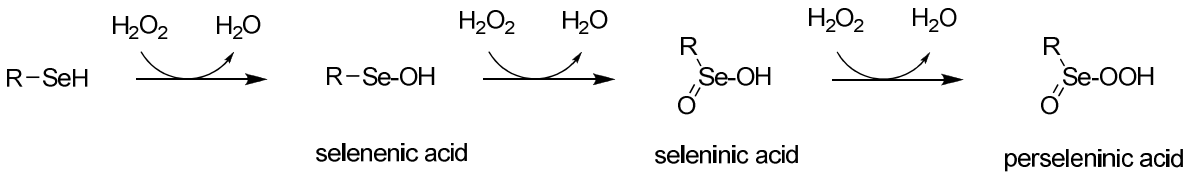
functionalized and useful chemicals in a greener way: non toxic reagents and solvents, efficient catalyst turnover, room pressure and temperature. At the same time it is possible to transfer this *know how* in the optimization of novel strategies to select new drugs candidates and to better understand the chemical mechanism of some biological reactions.

In Nature, the main function of selenium is associated with its incorporation in the form of selenocysteine into certain proteins having redox motifs: Glutathione Peroxidase (GPx), Iodothyronine Deiodinase (ID) and Thioredoxin Reductase (TrxR) are important members of this class and give direct evidence for the fact that selenium is an essential trace element.[1] Even if various oxidation states of selenium have been observed within proteins, at physiological pH the selenol moiety, that represents the catalytic site of the GPx, is fully dissociated conferring to the selenium atom a strong nucleophilicity towards the reaction with peroxides.[2] Selenolates are usually very unstable and reactive species but, in the enzyme, a –SeH group participates to the catalytic triad being stabilized by hydrogen bonds with a tryptophan and a glutamine residues. [2] It is known that in presence of oxidative stress the selenol **1** reduces the peroxides forming a selenenic acid **2** that rapidly reacts with the cofactor glutathione (GSH) regenerating, through the formation of the intermediate **3** subsequently reduced by NADPH dependent reductase, the selenol group closing the catalytic cycle. [3] (Scheme1)



Scheme 1 Catalytic reduction of peroxides mediated by GPx

It has been suggested that depleting the amount of cofactor GSH or in the presence of a large excess of oxidants, the selenenic acid produced in response to GPx oxidation may undergo further oxidation to seleninic acid and perseleninic acid. [4] (Scheme2) These latter are known to be effective oxidants and can be used to transform alkenes into epoxides through an oxygen transfer reaction.



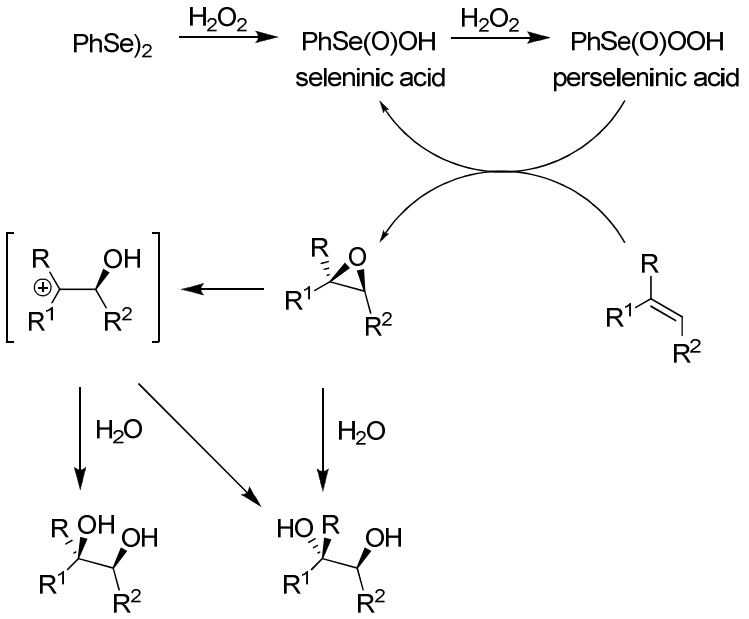
Scheme 2 Overoxidation of selenols

Epoxides are common intermediates for the stereoselective synthesis of 1,2-diols that are important functional groups in natural products, such as carbohydrates and poliketides, as well as in many pharmaceuticals. [5] In a different way vicinal diols can be prepared by direct dihydroxylation of double bonds and several oxidants have been used for this purpose even if most of the known methods present disadvantages related to the use of expensive and toxic transition metals. [6]

By using diselenide/ammonium persulfate couple, we reported the first example of "one pot" dihydroxylation of olefins promoted by an electrophilic selenium species.[7] The diselenide, in the presence of an excess of ammonium persulfate, acts as a procatalyst on the generation of PhSe-sulfate that, at the end of the reaction, is regenerated by substitution. Despite of the interesting mechanism this method is limited in terms of general applicability, as only cyclic olefins could be dihydroxylated with high selectivity and good yields. In the field of the Green Chemistry there is a growing interest for reactions that use hydrogen peroxide as oxidant, which can reacts with organic compounds generating water as the only byproduct.[8] For these reasons and in order to find more general conditions for the dihydroxilation reactions, we investigated H_2O_2 as oxidant. Using as catalyst the commercial available diphenyl diselenide, the process affords 1,2-diols with high yields and a diastereoselectivity strongly dependent on the nature of the substrate.

The reaction carried out in a 3:1 mixture of H_2O/CH_3CN at room temperature requires 10% of catalyst in the presence of a large excess of peroxide (40 equivalents).[8]

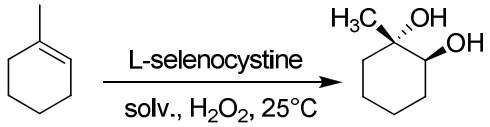
The proposed mechanism was essentially different from that reported for the ammonium persulfate: it consists in the oxidation of diphenyl diselenide to give benzeneseleninic acid, which can be overoxidized to the corresponding peracid. This latter is responsible for the olefin epoxidation but in water the epoxidic intermediate cannot be isolated and rapidly evolves to 1,2-diol according with a S_N2 ring opening mechanism or through the incipient formation of a carbocation, depending on the steric and electronic properties of the starting alkene. In the first case a stereospecific process produces the inversion of configuration of the carbon atom attacked by the water; in the second one the carbocation formation is responsible for the lost of selectivity.



Scheme 3 Olefin oxidation catalyzed by $(PhSe)_2$ in the presence of H_2O_2

The proposed mechanism involves an oxygen transfer reaction from the hydrogen peroxide to an organic substrate with the formation of a molecule of water, a process that results to be very similar to those catalyzed in Nature by the Glutathione Peroxidase (GPx). For these reasons we decided to investigate as pre-catalyst the L-Selenocysteine $(L\text{-}Sec)_2$, the commercially available dimer of the aminoacid that constitute the active site of the enzyme.
The second step of the reaction involves the ring opening of the epoxide. In Nature similar reactions are catalyzed by several epoxy-hydrolase. The proposed mechanism for this enzyme involves the acidic activation of the oxygen and the subsequent nucleophilic attack

of a carboxylic moiety leading to an intermediate that is subsequently hydrolyzed to the diols.[9] It should be envisioned that the carboxylic and the amino groups of the $(L\text{-}Sec)_2$ could participate in a similar mechanism increasing the catalytic efficiency in respect to diphenyl diselenide. In order to find the best reaction conditions, preliminary investigations were carried out starting from 1-methyl-1-cyclohexene **4a** using different reaction medium and different catalyst/oxidant ratios. The results are summarized in Table 1.



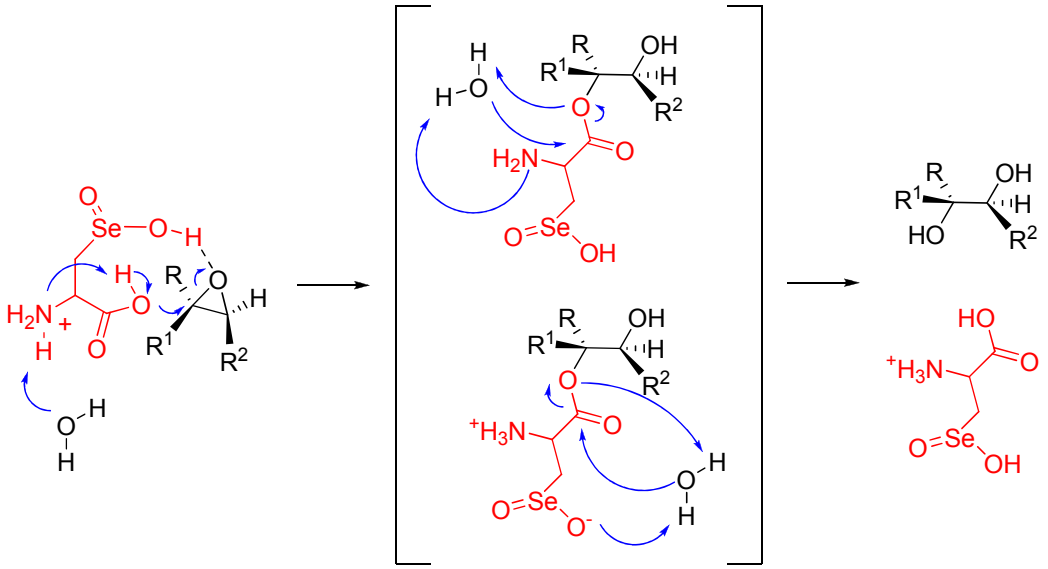
4a **5a**

	Cat.(%)	Solvent	H_2O_2(eq)	t(h)	Yield
a	1%	CH_2Cl_2	2	24	30%
b	1%	H_2O/CH_3CN 3:1	2	24	30%
c	1%	H_2O	2	24	30%
d	1%	H_2O	2	48	38%
e	2%	H_2O	2	48	15%
f	1%	H_2O	4	48	70%
g	1%	H_2O	4	96	75%

Table1 Preliminarily investigations

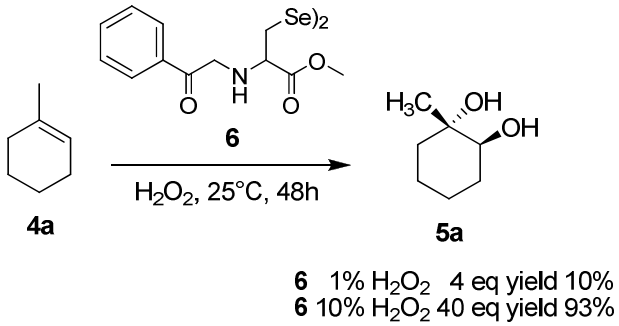
From these results it is evident that $(L\text{-}Sec)_2$ showed a better turnover in respect to diphenyl diselenide affording appreciable yields using a reduced amount of catalyst (1% vs 10%) and oxidant (4 equivalents vs 40 equivalents). It is also interesting to underline that the reaction has been efficiently effected in water at room temperature and resulted to be stereospeficic with the exclusive formation of the *anti* isomer.

In our opinion the improvement on catalytic efficiency observed for $(L\text{-}Sec)_2$ as well as the higher stereoselectivity should be explained suggesting an "epoxyhydrolase-like" mechanism with the involvement of the carboxylic and the amino moieties as shown on the Scheme 4.



Scheme 4: Proposed mechanism for the ring opening reaction

In order to support the proposed mechanism we repeated the reaction using the catalyst **6** (provided by Prof. Micho Iwaoka) in which the carboxylic acid is protected as methoxy ester and cannot participate to the ring opening reaction. In this case after 48 hours 1,2-diol **5a** has been obtained in 93% of yield using 10% of diselenide **6** and only 19% using 1% of catalyst. (Scheme 5) These results suggest that there are two simultaneous mechanism for the ring opening reaction and that the free carboxylic moiety is necessary to accelerate the process probably following an epoxyhydrolase-like mechanism.



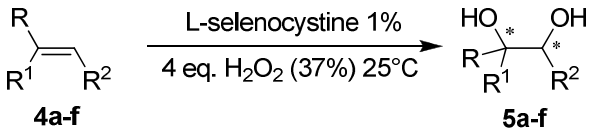
Scheme 5: Dihydroxylation reaction catalyzed by **6**

With the optimized conditions in hand we investigated the scope of the reaction starting from a series of substituted olefins.

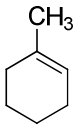
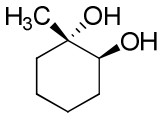
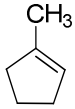
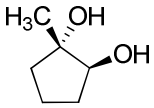
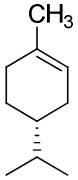
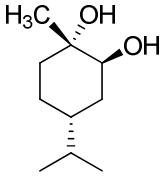
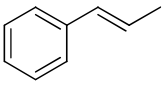
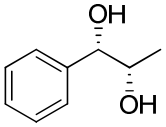
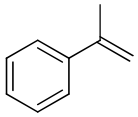
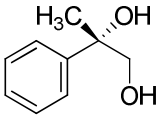
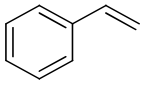
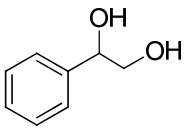
The results are summarized in table 2. In all the cases, with the only exception of β-methylstyrene the reactions were stereospecific affording the formation of the *anti* isomer.

The stereochemistry and the absolute configuration have been attributed by comparison of the physical data with those reported in literature. [10]

Table 2 Dihydroxylation reaction, scope of the reaction

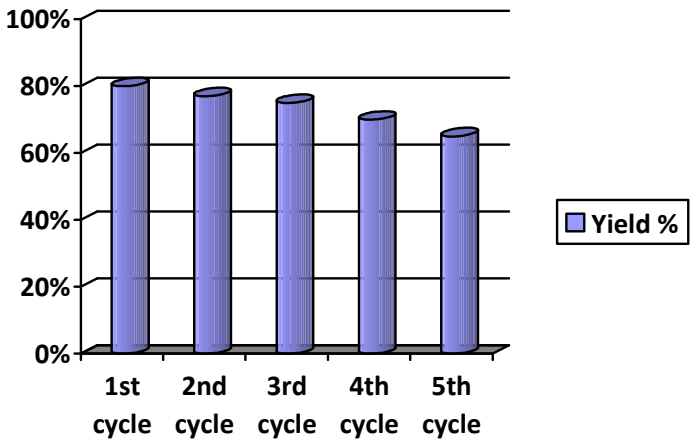


4a-f **5a-f**

Substrate	Product	t(days)	Yield	*e.e.*
 **4a**	 **5a**	2	80%	99%
 **4b**	 **5b**	2	70%	62%
 **4c**	 **5c**	7	65%	100 %
 **4d**	 **5d**	7	45% *syn/anti* 66/34	-
 **4e**	 **5e**	10	68%	20%
 **4f**	 **5f**	10	80%	0

Starting from 1-methyl-1-cyclohexene **4a** the synthesis of 1,2-*trans*-diol **5a** proceeds with a very high facial selectivity (*e.e.* 99%). The enantiomeric excesses have been calculated by NMR analysis using, as chiral shift reagent the europium tris[3-(trifluoromethyl-hydroxymethylene)-(+)-camphorate]. For some substrates, in order to increase the yields longer reaction time was needed and we observed that the good stereo and enantioselectivity, obtained in the case of cyclic alkenes, are quite completely lost when the double bond is substituted with an aromatic ring.

In order to better evaluate the turnover and the recyclability of $(L\text{-}Sec)_2$ at the end of the reaction, the organics were extracted with Et_2OAc and the water phase, containing the catalyst, reused for further dihydroxilations adding 1 equivalent of oxidant and 1 equivalent of substrate. As reported on Scheme 6 for the first five cycles the yields resulted to be good, up to 60% without lost of enantioselectivity .



Scheme 6: turnover of the catalyst

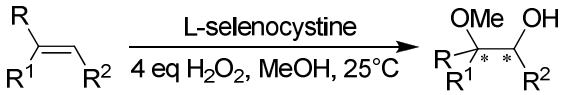
Using as solvent methanol instead of water the regiospecific formation of the corresponding methoxy alcohols can be obtained (Scheme 7).

A similar reaction has been reported by Sonoda and Chang, who separately have stated that a solution of SeO_2 in MeOH is able to generate firstly the epoxide by the formation of the peroxyselenious acid (Scheme 7) and then the metoxy-alchol of norbornene and 4-aryl-1,2,3,6-tetrhydropyridine, respectively. [11]

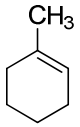
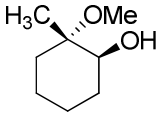
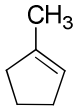
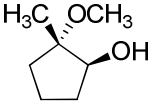
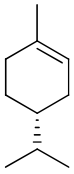
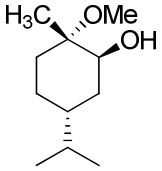
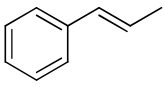
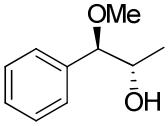
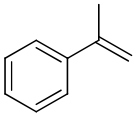
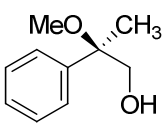
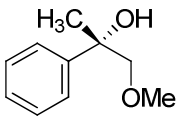
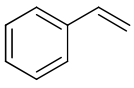
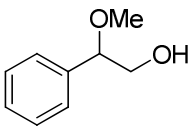
The authors described this reaction using an excess of catalyst. Now we report that it should be realized using a catalytic amount L-Sec (1%) 2 equivalent of H_2O_2 at room temperature.

The results summarized on Table 3 evidence that the yields are higher than those observed for the dihydroxylation even if the stereoselectivity is considerably reduced.

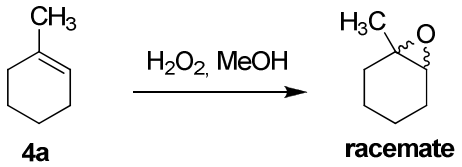
Table 3 Methoxyhydroxylation: scope of the reaction



4a-f **7a-f**

Substrates	Products	t(d)	Yield	*e.e.*
 **4a**	 **7a**	2	93%	30%
 **4b**	 **7b**	2	80%	38%
 **4c**	 **7c**	7	70% *syn/anti* 44/56	-
 **4d**	 **7d**	7	57% *syn/anti* 10/90	-
 **4e**	 **7e**  **8**	7	50% 1:1	10% (**7e**) 10% (**8**)
 **4f**	 **7f**	7	80%	0

Surprisingly the enantiomeric excess of 1-methyl-1-methoxy-cyclohexan-2-ol is considerably lower than that obtained for the corresponding 1,2-diol indicating that probably in MeOH a side *non-catalyzed* epoxidation occurs arising the racemic product. In this regard we carried out a reaction in absence of catalyst, obtaining the formation of the racemic epoxide. (Scheme 8) We also observed that in the above mentioned conditions the catalyst was recovered in the form of the methyl esther derivative, according to the mechanism reported on Scheme 4.



Scheme 7 Not-catalyzed methoxyhydroxylation reaction

The ability of organoselenium compounds to reduce hydrogen peroxide can be evaluated by NMR using as probe reaction the oxidation of a thiol into the corresponding disulfide. This is the same reaction catalyzed in Nature by glutathione peroxidase and can be used to evaluate and compare the GPx-like activity for different organoselenium compounds.

In a typical procedure the oxidation of dithiotreitol (DTT) was performed in D_2O and followed by ^{1}H-NMR spectroscopy modifying the procedure reported by Iwaoka *et al.* [12] Resonances at δ = 2.58 e 3.64 ppm relative to (DTT_{red}) decreased respect to the increasing intensity of the signals centered at δ = 2.85, 3.04 e 3.55 ppm relative to (DTT_{ox}).

In figure 1 we report the comparison between the results obtained using as catalyst L-selenocystine, PhSeZnCl, and diphenyl diselenide, respectively. The time required to convert DTT_{red} to DTTox by 50% (T50) can be conveniently used as parameter to compare the GPx-like activity of different compounds.

It is interesting to observe that T50 for PhSeZnCl (128 sec) is higher than T50 measured for the dimer of the natural amino acid L-Sec_2 (64 sec) but shorter respect that measured for $(PhSe)_2$ (192 sec).

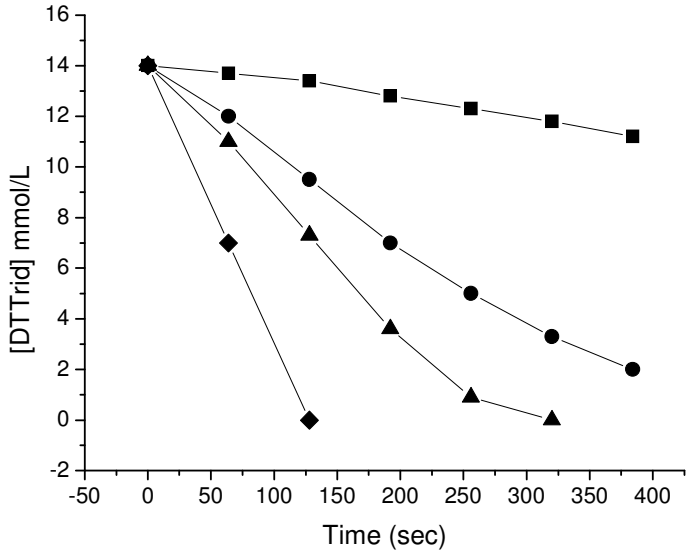
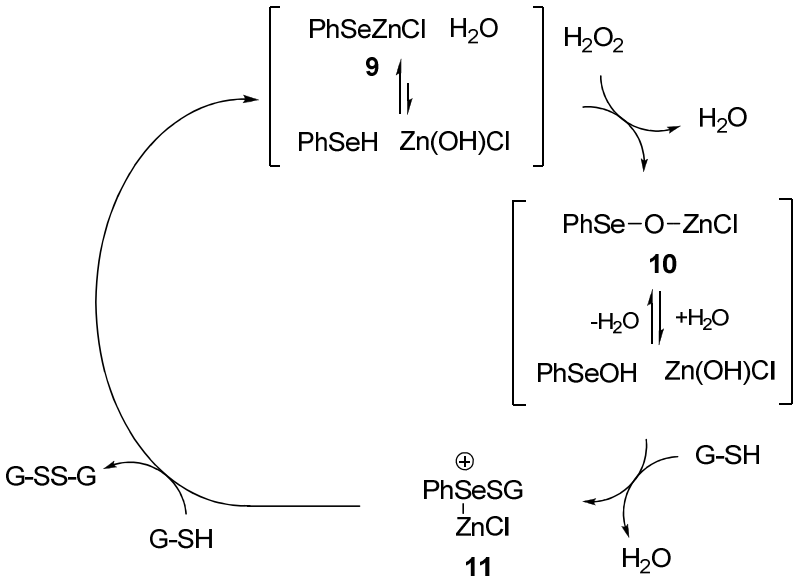


Figure 1. Comparison of the catalytic activity for the oxidation of DTT: without catalysts (■), $(PhSe)_2$ [1,4*10^{-3}N] (●), PhSeZnCl [1,4*10^{-3}N] (▲), L-Sec_2 [1,4*10^{-3}N] (♦).

These experimental evidences suggest that PhSeZnCl acts not simply as precursor of the selenenic acid intermediate, as reported for diphenyl diselenide, but reasonably a zinc containing Lewis acid plays an active role in the catalytic cycle as proposed on Scheme 2.



Scheme 8. Proposed mechanism for GPx-like activity of **9**

The mechanism proposed in Scheme 8 was also supported by the evidence that the presence of a stoichiometric amount of zinc chloride produces an increased catalytic activity of diphenyl diselenide in the oxidation of GSH with hydrogen peroxide.

Further investigations based on biological assay will be done to demonstrate the effective correlation between the proposed catalytic mechanism and an actual GPx-like activity in the cells. The bio-logic approach described in the present communication will be applied to effect other oxidative convertions.

Acknowledgments

Financial support from M.I.U.R. (Ministero Italiano Università e Ricerca), National Projects PRIN2007 (Progetto di Ricerca d'Interesse Nazionale), Consorzio CINMPIS, Bari (Consorzio Interuniversitario Nazionale di Metodologie e Processi Innovativi di Sintesi), Regione Umbria: "Fondo Sociale Europeo", are gratefully acknowledged.

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