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1st World Sustainability Forum
1-30 November 2011

www. wsforum.org

Communication

Green Chemistry for Environmental Sustainability: An Example of "Bio-Logic" Approach

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Abstract: Hundreds of tonnes of hazardous waste are released to the air, water, and land by industry every hour of every day. The chemical industry is the biggest source of such waste and the number of agents considered toxic is continuously increasing due also to a series of more restrictive laws (REACH). The term Green Chemistry was coined in the 1990s, to bring focus to an increasing interest in developing more environmentally friendly chemical processes and products. In this term the Green Chemistry represents the most concrete answer of the scientific community to the pressing environmental needs and sustainability. There is a pool of clean technologies that are becoming widely studied or used between them catalysis is a well established one, well proven at the largest volume end of the chemicals industry. Green Chemistry begin by design and design derives from inspiration. Nature is the biggest chemical laboratory in the world and produces, every days tonnes of chemicals in absolutely eco-friendly and sustainable way. The secret of natural chemistry are the enzymes, "Why don't take inspiration from them to setup new green chemical processes?" An example of oxidative reactions inspired by the enzyme Gluathione Peroxidase will be discussed to highlight the reduction of produced waste, the reduction of energy requirement and the mild and eco-friendly conditions used.

Keywords: Green Chemistry, Waste Reduction, Sustainability.

1. Introduction

Hundreds of tonnes of hazardous waste are released to the air, water, and land by industry every hour of every day. The chemical industry is the biggest source of such waste and the number of agents considered toxic is continuously increasing due also to a series of more restrictive laws (REACH). Chemical manufacturing businesses produce waste such as processes residues spent catalysts or solvents effluent, treatment sledges and contaminated chemicals containers that can have an harmful impact on the environment.

For these reasons there is a growing interest in the new frontiers of the Green Chemistry and its application on the industrial productions of basic and fine chemicals as well as pharmaceuticals. With the term *Green Chemistry*, coined in 1990s, we define the inventions, design and applications of chemical products and processes to reduce or to eliminate the use and generation of hazardous substances, maximize the amount of raw material that ends up in the product, increase the energetic efficiency, minimize the waste production.
These general concepts constitute a new philosophy of making chemistry and produce chemicals and can be summarized in 12 rules :

1. It is better to prevent waste than to treat or clean waste after it is formed.
2. Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3. Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. Chemical products should be designed to preserve efficacy of function while reducing toxicity.
5. The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.
6. Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.
7. A raw material or feedstock should be renewable rather than depleting wherever technically and economically practicable.
8. Reduce derivatives - Unnecessary derivatization (blocking group, protection/ deprotection, temporary modification) should be avoided whenever possible.
9. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10. Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.
11. Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
12. Substances and the form of a substance used in a chemical process should be chosen to minimize potential for chemical accidents, including releases, explosions, and fires.

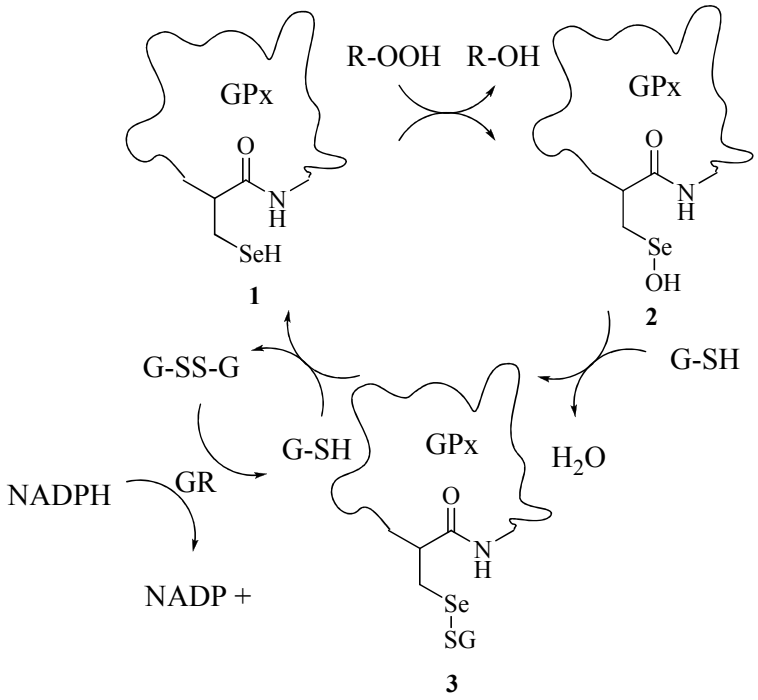
On the border between Science and Nature information can flow in both directions: from Science to Nature it helps to understand how living systems work and how we can interact with them modulating their activity; from Nature to Science it represents an inspiration source for design new materials and 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 applying the logic of the living systems is possible to setup new chemical reactions and 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 processes in "flow" in order to obtain a rapid and efficient scale-up for large scale productions.

Our research group for several years has been involved in Selenium chemistry and recently we start to use organoselenium reagents as Green catalyst following a "Bio-Logic" approach.

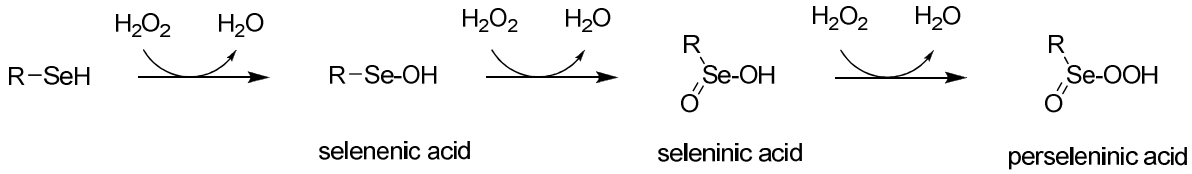
In Nature, the main function of selenium is associated with its incorporation in the form of selenocysteine into certain proteins having redox motifs: Glutathione Peroxidase (GPx), Iodothyronine Deiodinase (ID) and Thioredoxin Reductase (TrxR) are important members of this class and give direct evidence 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 the selenol, through the formation of the intermediate **3** subsequently reduced by a NADPH dependent reductase.[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.

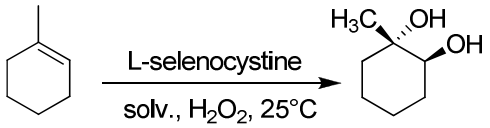


Scheme 2 Overoxidation of selenols

Epoxides are common intermediates for the stereoselective synthesis of 1,2-diols, important functional groups in natural products, such as carbohydrates and poliketides, as well as in many pharmaceuticals.[5] 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] or experimental conditions that cannot be generalized.[7]

2. Results and Discussion

In 2005 the Nobel laureate Noyori identified on the use of hydrogen peroxide for clean oxidations one of the three key developments in green chemistry, in particular the interest on hydrogen peroxide is based on its properties to react with organic compounds generating water as the only byproduct.[8] For these reasons recently we have studied general conditions for the dihydroxilation reactions, promoted by 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.[8]



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%

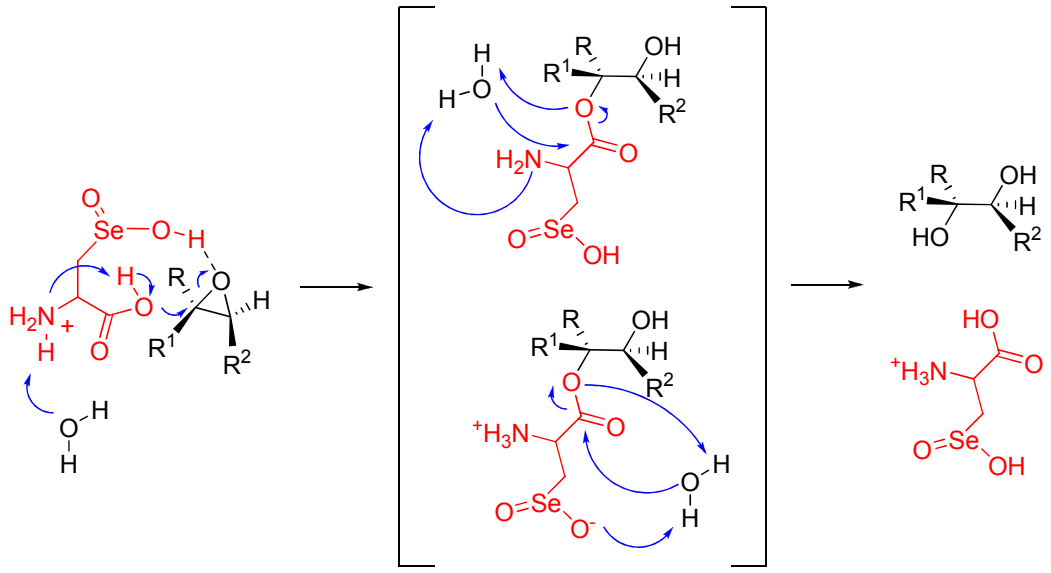
Table1 Preliminarily investigations

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 amino acid that constitutes the active site of the enzyme.

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.

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 resulting to be stereospecific with the exclusive formation of the *anti* isomer.

In our opinion the improvement of 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 3.

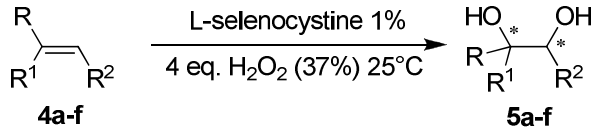


Scheme 3: Proposed mechanism for the ring opening reaction

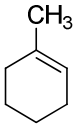
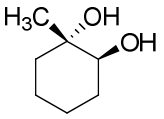
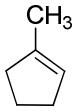
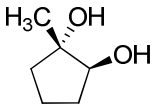
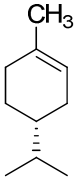
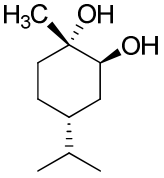
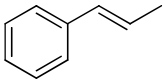
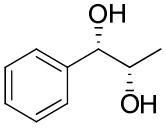
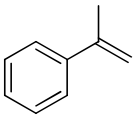
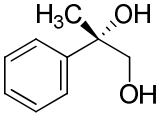
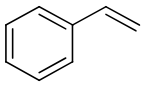
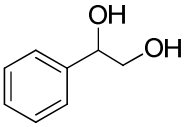
With the optimized conditions in hand we investigated the scope of the reaction starting from a series of substituted olefins.

The results are summarized in Table 2. In all the cases, with the only exception of □-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.[9]

Table 2 Dihydroxylation reaction, scope of the reaction

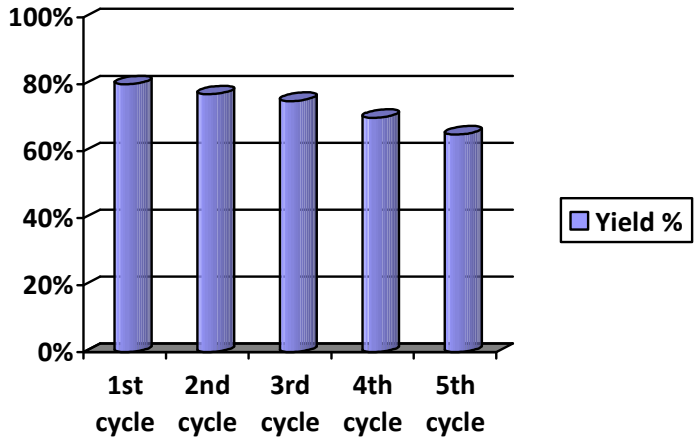


4a-f **5a-f**

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 4, for the first five cycles the yields resulted to be good, up to 60% and in addition without lost of enantioselectivity.



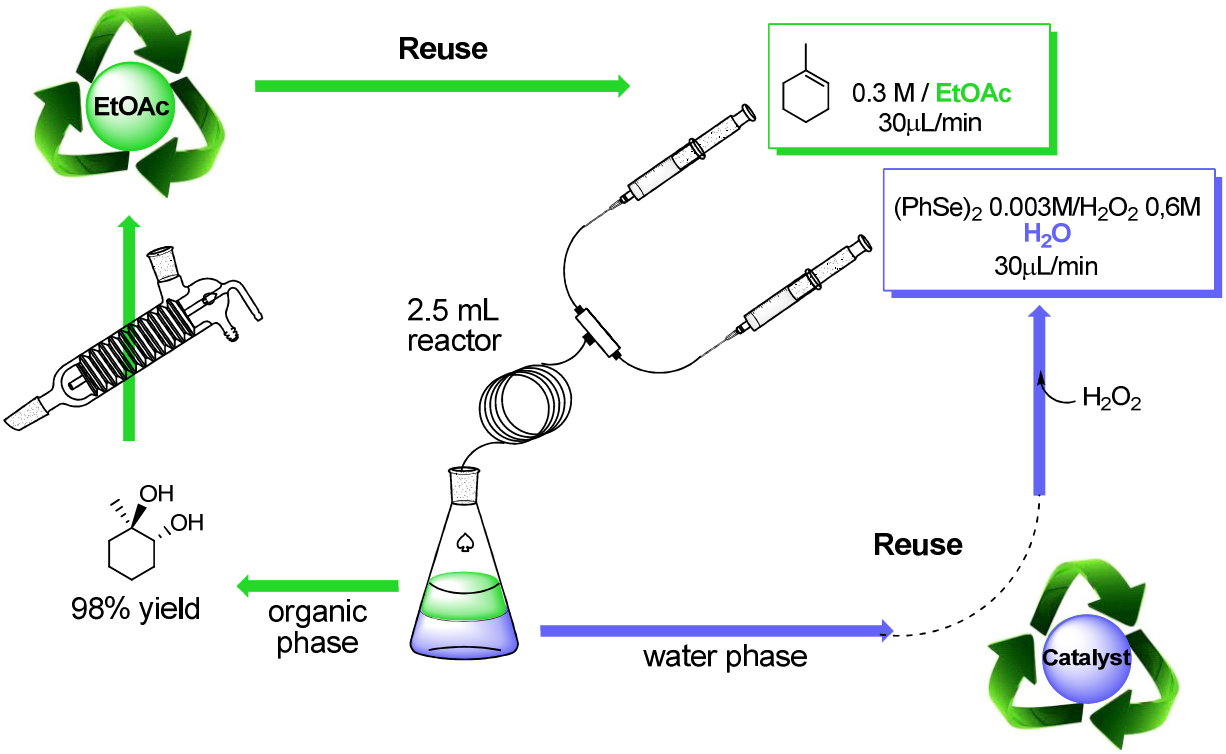
Scheme 4: turnover of the catalyst

Considering the high recyclability of the catalyst, we setup the first example of "continuous" grams-scale synthesis of diols toward an hydrogen peroxide oxidation of olefins catalyzed by diphenyl diselenide. As shown on the Scheme 5, a solution of cyclohexene (0,3M in EtOAc) and a solution of $(PhSe)_2$ (0,03M), dissolved in water by treatment with H_2O_2 (0,6M), were fluxed (3mL/min) through a T-junction in a 2,5ml reactor.

The two phases collected at the end of the reactor were separated. The aqueous layer, containing the catalyst, can be reused for a next cycle while the diols can be obtained from the organic phase by solvent distillation in 98% of yields. (Scheme 5)

This example, that take inspiration from the natural role of Selenium in GPx enzyme, presents a series of notable improvements in term of greenest of the process that can be summarized on the following points:

- use of simple and fully recyclable catalysts
- non hazardous and reusable solvents can be chosen
- the reaction is effected with non toxic and easily available oxidant
- the reaction proceeds with excellent atom economy without waste production
- the reaction proceeds with high energetic efficiency: room temperature and atmospheric pressure.



Scheme 5: turnover of the catalyst

Further experiments were ongoing in order to setup the same reaction using chiral as well as supported catalysts and in order to setup a complete automatic flow system.

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.

References and Notes

[1] Shchendrina, V. A.; Novoseleov, S. V.; Malinouski, M. Y.; Gladyshev, V. N. Identification and characterization of a selenoprotein family containing a diselenide bond in a redox motif. *Proc. Natl. Acad. Sci.* **2007**, *104*, 13919- 13924.

[2] Roy, G.; Sarma, B.K.; Phadnis, P. P.; Mugesh, G. *J. Chem. Sci.* **2005**, *117*, 287-303.

[3] Epp, O.; Ladenstein, R.; Wendel, A. The Refined Structure of the Selenoenzyme Glutathione Peroxidase at 0.2-nm Resolution. *Eur. J. Biochem.* **1983**, *133*, 51-69.

[4] Bhabak, K. P.; Mugesh, G. *Chem.. Eur. J.* **2008**, *14*, 8640-8651.

[5] Nicolaou, K. C.; Snyder, S. A.; Classics in Total Synthesis II, Wiley-VCH, Weinheim, **2003** and references cited therein.

[6] a) Hudlicky, M. Oxidations in Organic Chemistry, ACS Monograph Series 186, American Chemical Society, Washington, DC, **1990**, p 174; b) Haines, A. H. in: Comprehensive Organic Synthesis, 1st edn., (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, Vol. 7, p 437; c)

Johnson, R. A.; Sharpless, K. B. in: Catalytic Asymmetric Synthesis, 2nd edn., (Ed.: I. Ojima), Wiley- VCH, New York, Weinheim, **2000**, p 357; d) Criegee, R. *Justus Liebigs Ann. Chem*. **1936**, *522*, 75–97; e) Criegee, R.; Marchand, B.; Wannowius, H. *Justus Liebigs Ann. Chem*. **1942**, *550*, 99–133; c) Schroder, M. Chem. Rev. **1980**, *80*, 187–213; f) Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263–4265; g) Nomura, K.; Okazaki, K.; Hori, K.; Yoshii, E. *J. Am. Chem. Soc*. **1987**, *109*, 3402–3408; h) Coleman, J. E.; Ricciuti, C.; Swern, D. *J. Am. Chem. Soc*. **1956**, *78*, 5342 – 5345; i) Ogino, T. *Tetrahedron Lett*. **1980**, *21*, 177–180; j) Weber, W. P.; Shepherd, J. P. *Tetrahedron Lett*. **1972**, *13,* 4907–4908; k) Ogino, T.; Mochizuk,i K. *Chem. Lett*. **1979**, *8,* 443–446; l) Plietker, B.; Niggemann, M. *J. Org. Chem*. **2005**, *70*, 2402 – 2405; m) Ho, C. M.; Yu, W.-Y.; Che, C.-M. *Angew. Chem*. **2004**, *116*, 3365–3369; n) Ho, C.-M.; Yu, W.-Y.; C.-M., Che *Angew. Chem. Int. Ed.* **2004**, *43*, 3303–3307.

[7] Santi, C.; Tiecco, M.; Testaferri, L.; Tomassini, C.; Santoro, S.; Bizzoca, G. Diastereo and Enantioselective Synthesis of 1,2-Diols Promoted by Electrophilic Selenium Reagents. *Phosphorus Sulfur* **2008**, *183*, 956-960.

[8] Santoro, S.; Santi, C.; Sabatini, M.; Testaferri, L.; Tiecco, M. Eco-Friendly Olefin Dihydroxylation Catalyzed by Diphenyl Diselenide. *Adv. Synth. Catal.* **2008**, *350*, 2881-2884.

[9] a) Kita, Y.; Yoshida, Y.; Mihara, S.; Furukawa, A.; Higuchi, K.; Fang, D.-F.; Fujioka, H. *Tetrahedron* **1998**, *54*, 14689-14704; b) Archer, I. V. J.; Leak, D. J.; Widdwson, D. A. *Tetrahedron Lett.* **1996**, *37*, 8819-8822.