Highlight on the reactivity of PhSeZnX

Bonifacio Monti,[a] Luca Sancineto,[a] Martina Palomba,[a] Luana Bagnoli,[a] Francesca Marini,[a] Eder Lenardao,[b] and Claudio Santi*[a]

[a] *Group of Catalysis and Organic Green Chemistry, Department of Pharmaceutical Sciences, University of Perugia, Via del Liceo 1, Perugia 06100, Italy – claudio.santi@unipg.it*

[b] *Laboratório de Síntese Orgânica Limpa (LASOL), Centro de Ciências Químicas, Farmacêuticas e de Alimentos (CCQFA), Universidade Federal de Pelotas (UFPel), P.O. Box 354, Pelotas 96010-900, Brazil*

Abstract: The first bench stable selenolates, PhSeZnHalides have been synthesized through a completely atom-economic oxidative insertion of the elemental zinc on the commercially available PhSeHalides. These reagents showed the characteristic nucleophilic reactivity which will be reviewed in this report. All of the reactions were strongly accelerated when effected in water suspension. Alkyl, aryl, vinyl and acyl substitutions, ring-opening reactions of epoxides and aziridines and Michael type addition will be described including the role of the zinc in the control of the chemoselectivity and stereoselectivity.

Keywords: Selenium, Zinc, Nucleophile

In 2008, the first bench-stable selenolates **1** were prepared by oxidative insertion of elemental zinc starting into the chalcogen-halogen bond of the commercially available PhSeX by refluxing the elemental zinc and the suitable selenenyl halide in THF (Figure 1). The procedure allowed the quantitative preparation of the reagent in a completely atom-economic fashion and therefore in perfect agreement with the green chemistry rules.[1]

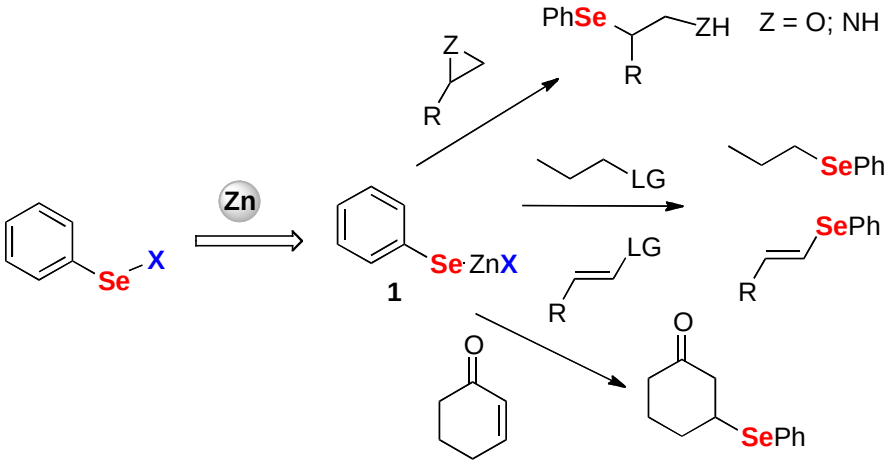
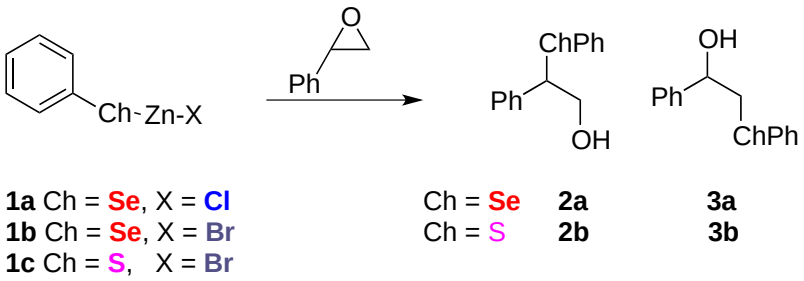


Figure 1. Synthesis and reactivity of PhSeZnX.

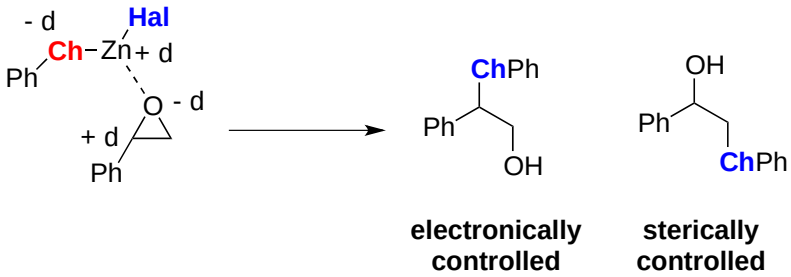
Successively, using a similar procedure the corresponding zinc thiolate **1c** was prepared starting from the PhSBr easily available by bromination of the corresponding diphenyldisulfide.[2]

Zinc chalcogenolates **1** were used for the synthesis of β-hydroxychalcogenides **2** via ring opening reaction of styrene oxide, as shown in Scheme 1.[1,2] The reaction with organochalcogenolates **1a** and **1b** proceeded trough the formation of the electronically controlled isomers **2a** or **2b**, respectively.



Scheme 1. Zinc chalcogenolates in ring opening of epoxides.

This highlighted that such reagents combine the properties of a strong chalchogen-centered nucleophile with those of a Lewis acid (Scheme 2).

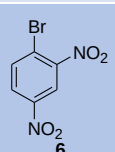
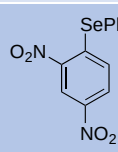
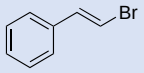
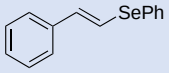
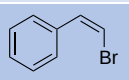
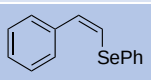
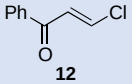
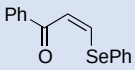
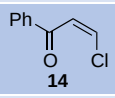
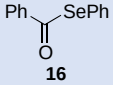
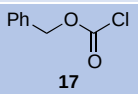
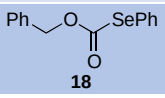


Scheme 2. Zinc controlled ring opening mechanism.

The most interesting aspect of these reactions is correlated to the rate acceleration observed in water under heterogeneous conditions in which compounds **2a** and **3a** were obtained in almost quantitative yields in 2h instead of the 24h required in THF (see Table 1).[1]

Table 1. Reaction conditions in ring opening of epoxides.					
Reagent	**Medium**	**Time (h)**	**Yield %**	**Product ratio**	**Ref**
1a	THF	24	100	88 : 12	1
1a	H_2O	2	100	80 : 20	1
1b	THF	24	20	56 : 44	1
1b	H_2O	2	--	--	1
1c	THF	0.25	99	89 : 11	2
1c	H_2O	6	40	89 : 11	2
All of the reactions have been performed using styrene oxide as substrate.					

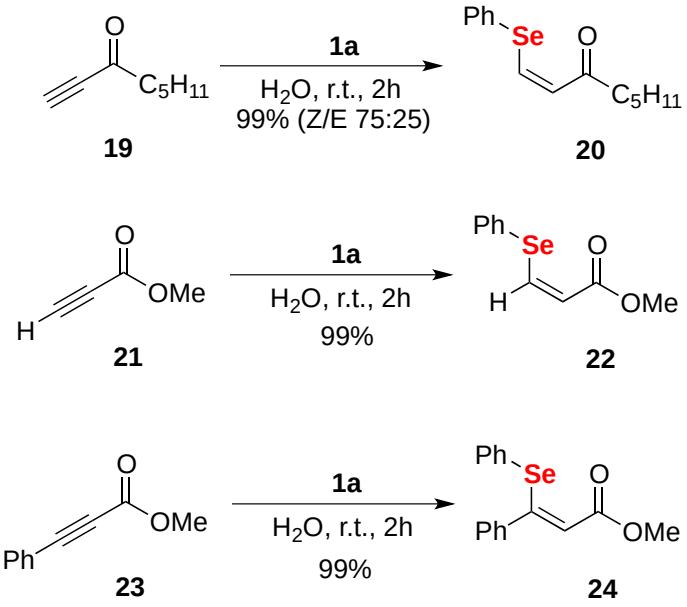
A number of nucleophilic substitutions were reported using as nucleophile PhSeZnCl (**1a**), representative examples are illustrated in Table 2.[1-4] In all the cases the *on water* conditions showed a rate acceleration when compared with the same reaction effected in THF.

Table 2. Nucleophilic substitution using 1a and 1c.				
Entry	**Substrate**	**Product**	**Yield %**	**Ref**
1	Et-I **3**	Et-Se-Ph **4**	100	1
2	Et-OTs **5**	Et-Se-Ph **4**	90	1
3	 **6**	 **7**	50	1
4	 **8**	 **9**	94	3
5	 **10**	 **11**	83	3
6	 **12**	 **13**	99	3
7	 **14**		85	3
8	 **15**	 **16**	60	4
9	 **17**	 **18**	60	3

Primary halides (**3**) and tosylates (**5**) demonstrated to be excellent leaving groups in substitution processes promoted by the zinc selenolate (entries 1 and 2) and the negative influence of the

sterical hindrance on the reaction rate indicates that a S_N2 mechanism is involved. Similarly, activated bromoaryl derivatives such as compound **6** underwent nucleophilic aromatic substitution, affording the corresponding diarylselenide **7** (Entry 3). An interesting stereo-controlled mechanism has been described in the case of vinylic nucleophilic substitution. The reaction proceeded with retention of the stereochemistry in the case of non functionalized vinyl halides (entries 4 and 5) whereas, when an acyl substituent is present on the carbon-carbon double bond, the process is stereo-convergent affording the *Z*-vinyl selenide **13** starting from both *Z*- and *E*-chloro vinyl derivatives **12** and **14** (entries 6,7). Based on DFT calculations it has been suggested that the stereo-convergence is due to the interaction of the zinc atom that can be coordinated by the carbonyl group driving the nucleophilic attack to the formation of the *Z*-isomer. Recently, PhSeZnCl (**1a**) and PhSeZnBr (**1b**) were successfully used in on water condition for the synthesis of selenoesters starting from the acid chlorides [4](Table 2 entry 8) as well as from chloroformyl derivatives [4](Table 2 entry 9).

In the case of Michael addition to aldehydes, ketones and esters the reactivity of **1a** appeared to be dependent on the nature of the substrate.[3] When the unsaturation is a double bond, the best results were obtained in THF whereas, moving to the electron-deficient alkynes, the *on-water* rate acceleration was demonstrated, indicating that the solvent probably acts in the activation of the substrate rather than the zinc selenolate complex. As reported in Scheme 3, the reactions were characterized by very high yields (ranging from 85% to 100%) associated to a high stereoselectivity in favor of the *Z* isomer.[5]



Scheme 3. Reactions with alkynes.

When the electron withdrawing group (EWG) is an ester (see as examples **21** and **23**) the reaction is stereospecific (only the *Z* isomers **22** and **24** are formed) but the stereoselectivity decreases as increases the reactivity toward the 1,4 addition; aldehydes showed indeed a 80/20 *Z/E* ratio while ketones produced a *Z*/*E* ratio of 75/25.

In conclusion, this highlight focus the attention on a new class of nucleophilic selenium reagents that can be easily prepared and stored as stable solids over non-inert conditions. These reagents allow avoiding the use of conventional organic solvents introducing the possibility to apply unconventional green procedures and reusable medium such as water. In this latter case the strong rate acceleration represents an interesting characteristic of these reagents affording time and energy saving protocols to effect a number of conversions.

Acknowledgments

Financial support from the Dipartimento di Scienze Farmaceutiche, Università degli Studi di Perugia "Fondo per il sostegno della Ricerca di Base 2015" and Fondazione Cassa di Risparmio di Perugia (2014.01000.021) are gratefully acknowledged. The authors also thank Regione Umbria: project "POR Umbria 2007–2013" for the fellowship to Luca Sancineto. Eder J. Lenardão is Bolsista CAPES—Processo No. BEX 6391/14-1. This article is part of the divulgative activity of the international multidisciplinary "SeS Redox and Catalysis" network.

References

(1) Santi, C.; Santoro, S.; Battistelli, B.; Testaferri, L.; Tiecco, M. *Eur J Org Chem* **2008**, *2008*, 5387.
(2) Propersi, S.; Tidei, C.; Bagnoli, L.; Marini, F.; Testaferri, L.; Santi, C. *J Sulfur Chem* **2013**, *34*, 671.
(3) Santoro, S.; Battistelli, B.; Testaferri, L.; Tiecco, M.; Santi, C. *Eur J Org Chem* **2009**, *2009*, 4921.
(4) Santi, C.; Battistelli, B.; Testaferri, L.; Tiecco, M. *Green Chem* **2012**, *14*, 1277.
(5) Battistelli, B.; Lorenzo, T.; Tiecco, M.; Santi, C. *Eur J Org Chem* **2011**, *2011*, 1848.