Stereoselectivity in phenylselenoetherification of (*Z*)- and (*E*)-hex-4-en-1-ols facilitated by pyridine and some Lewis acids

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Abstract: *Studies on the stereoselective phenylselenoetherification of (Z)- and (E)-hex-4-en-1-ols is described. (Z)-Alkenol is envisage to facilitate the 5-exo favored cyclization, while (E)-isomer facilitate the 6-endo favored cyclization. Diastereomeric ratio of the cyclic products depends on counterion and reaction temperature. We found that external additives, such as pyridine and some Lewis acids coordinating to the electrophilic species are used to control the course of cyclizations with high degrees of efficiency and improve the level of stereoinduction. The course of cyclization can be directed as desired by the choice of the electrophile and the additives used in the reaction.*

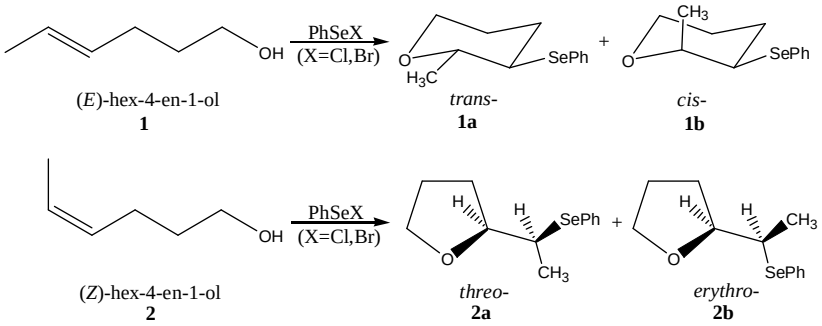
Cyclization of unsaturated alcohols leading to cyclic ethers is well documented in a literature as convenient pathways in the synthesis of natural products and related compounds[1]. Different electrophilic selenium reagents and a variety of reaction conditions have been employed and recent reviews are highlighting the broad scope of this general process[2].

Substituted tetrahydrofuran and tetrahydropyran rings are common in many natural products and play important role as building blocks for the synthesis of various biologically active organic target molecules[3]. Stereoselective synthesis[4] of substituted cyclic ethers is important and received considerable attention[5] since cyclic ether units are frequently found in polyether antibiotics[6], C-glycosides[7] and polyene mycotoxins[8].

In recent years, we have studied intramolecular cyclization of some Δ^4- and Δ^5-alkenols by means of phenylselenyl halides[9]. Outcome of this reaction is influenced by the nature of selenium reagent used, and the reactivity of the selenium electrophile also depends of the nature of counterion. Although standard conditions can be used for these cyclizations, the interactions between the selenium electrophile, counterion, the solvent and the substrate are not fully understood, and we describe herein our recent investigations towards selective cyclizations.

In this context we initiated our study of phenylselenoetherification of (*Z*)- and (*E*)-hex-4-en-1-ols. The reason that selecting the reaction and the substrates are as follows: 1) *cis*-homoallylic alcohol is envisage to facilitate the *5-exo* favored cyclization, while *trans*-isomer facilitate the *6-endo* favored cyclization; 2) although phenylselenoetherification is generally known to give low stereoselectivity[10], it is advantageous in generating two endocyclic prochiral centers. We herein describe successful results of our investigation for the development of disubstituted cyclic ethers by high level of stereoinduction.

Cyclization reaction of (*E*)- (**1**) and (*Z*)-hex-4-en-1-ols (**2**) were carried out with two electrophilic selenium reagents, PhSeCl and PhSeBr, in dichloromethane as a solvent, at different reaction temperature yielding regioselectively tetrahydropyrans (*trans*- (**1a**) and *cis*- (**1b**)) and tetrahydrofurans (*threo*- (**2a**) and *erythro*- (**2b**)) respectively (Scheme 1). We have also done the same reactions under kinetic conditions, in the presence of base – pyridine.



Scheme 1. Phenylselenoetherification of (*E*)- and (*Z*)-hex-4-en-1-ols

The experimental results, summarized in Table 1, show that more electrophilic PhSeCl was used to drive reaction more completely and maintain better stereoselectivity, but the poorer electrophile, PhSeBr, gave reversal stereoselectivity. The results reveal the effect of reaction temperature which drove the reaction further towards completion and better stereoselectivity. Superior results are obtained with pyridine. Conversion to cyclic ethers was quantitative with increased and reversal stereoselectivity regardless to reagent used. (*E*)-Hex-4-en-1-ol affords six-membered *cis*-isomer predominantly, while (*Z*)-hex-4-en-1-ol affords five-membered *erythro*-isomer as unique product.

Table 1. Phenylselenoetherification of (*E*)- and (*Z*)-hex-4-en-1-ols at different temperature and in the presence of pyridine

Reagent	**Yields and ratio (a:b) of cyclic products/%**		
	(*E*)-hex-4-en-1-ol (1)		
	-78 °C	**0 °C**	**r.t.**
PhSeCl	85 (87:13)	83 (75:25)	81 (69:31)
PhSeCl/Py	100 (95:5)	100 (74:26)	100 (24:76)
PhSeBr	77 (80:20)	-	65 (65:35)
PhSeBr/Py	100 (92:8)	100 (86:14)	100 (20:80)
	(*Z*)-hex-4-en-1-ol (2)		
PhSeCl	78 (98:2)	75 (85:15)	72 (70:30)
PhSeCl/Py	100 (23:77)	100 (5:95)	100 (0:100)
PhSeBr	83 (33:67)	-	75 (30:70)
PhSeBr/Py	100 (14:86)	100 (8:92)	100 (0:100)

We also studied the reactivity and stereoselectivity of these reactions in the presence of equimolar ammount of some Lewis acids which were considered as the perspective candidates. $ZnCl_2$, $FeCl_3$ and $AlCl_3$ were tested at room temperature. As it can be seen from the results obtained Lewis acids promoted cyclization process (Table 2). In all cases reactions were high yielded. Diastereomeric ratio was improved and reversal stereoselectivity in the reactions with PhSeBr was not noticed. (*Z*)-Hex-4-en-1-ol affords five-membered *threo*-isomer, while (*E*)-hex-4-en-1-ol affords six-membered *trans*-isomer predominantly. In the presence of Lewis acids reactivity of selenium electrophile is independent of nature of counterion.

All used additives can bound counter ion from reagent, increase electrophilicity of PhSe group, and eliminate X^- as a concurrent of hydroxyl group in cyclization step. They could also enhance the

nucleophilicity of hydroxyl group of the alkenol and also mediate the stabilization of the oxonium ion intermediates.

Table 2. Phenylselenoetherification of (*E*)- and (*Z*)-hex-4-en-1-ols in the presence of Lewis acids

Substrate	Yields and ratio (a:b) of cyclic products/%			
	PhSeCl			
	No additives	$ZnCl_2$	$FeCl_3$	$AlCl_3$
1	81 (69:31)	92 (98:2)	89 (76:24)	91 (72:18)
2	72 (70:30)	96 (97:3)	98 (86:14)	89 (93:7)
	PhSeBr			
1	65 (65:35)	95 (95:5)	96 (82:18)	99 (97:3)
2	75 (30:70)	98 (96:4)	99 (95:5)	95 (92:8)

In summary, we found that external additives, such as pyridine and Lewis acids coordinating to the electrophilic species are used to control the course of cyclizations with high degrees of efficiency and improve the level of stereoinduction. The course of cyclization can be directed as desired by the choice of the electrophile and the additives used in the reaction.

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