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ORIGINAL PAPER

Mechanistic investigation of the base-promoted cycloselenoetherification of pent-4-en-1-ol

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Abstract The mechanism of phenylselenoetherification of pent-4-en-1-ol using some bases (pyridine, triethylamine, quinoline, 2,2′-bipyridine) as catalyst was examined through studies of kinetics of the cyclization, by UV-VIS spectrophotometry. It was demonstrated that the intramolecular cyclization is facilitated in the presence of bases caused by the hydrogen bond between base and alkenol's OH-group. The obtained values for rate constants have shown that the reaction with triethylamine is the fastest one. Quantum chemical calculations (MP2(fc)/6-311+G**// B3LYP/6-311+G**) show, that the transition state of the cyclisation is S_N2 like.

Keywords Alcohols · Cyclization · Kinetics

Introduction

Intramolecular cyclization of alkenols is one of the most important approaches for the stereoselective construction of oxygen heterocycles, which are present in the skeletons of several biologically active natural products and related compounds. Applications of selenium reagents in organic chemistry have developed over the past years, and comprehensive reviews on this area have appeared [1–11]. Tetrahydrofuran and tetrahydropyran derivatives can be prepared through cycloselenoetherification of alkenols under extremely mild experimental conditions [12–19]. This synthetic strategy has been used to prepare a large number of O-heterocycles, and most of these rings are incorporated into a great number of physiologically active natural products.

The reactions of phenylselenenyl halides and unsaturated alcohols are usually considered to be a two-step mechanism: electrophilic addition of the reagent to the double bond of the alkenols and nucleophilic attack of the hydroxylic oxygen results in the formation of a ring (Fig. 1).

However, such a mechanism is not unique. Indeed if the reaction of phenylselenenyl halides and alkenols is regarded as a nucleophilic displacement at bivalent selenium, several variations of this two-step mechanism can be envisioned: the first, analogous to the S_N1 mechanism at a saturated carbon atom, and second, analogous to S_N2 mechanism and finally an addition-elimination mechanism [20].

During recent years, there has been some investigation of the cyclization reactions of alkenols in the presence of some additives, which influences the increases of the yield of cyclic ether product [17, 21, 22]. The base mediated cyclizations have been much less studied, but in recent years some results has been achieved [15–19].

Consequently, in view of the above facts and as a part of ongoing investigation into catalyzed cycloselenoetherification reactions, our current interest is focused on the heterocyclizations using pent-4-en-1-ol as substrate, in which base plays an important role.

Recently, we presented an approach to cyclic ethers from pent-4-en-1-ol using PhSeX (X = Cl, Br) in the presence of pyridine [17, 18]. Procedure works smoothly resulting in

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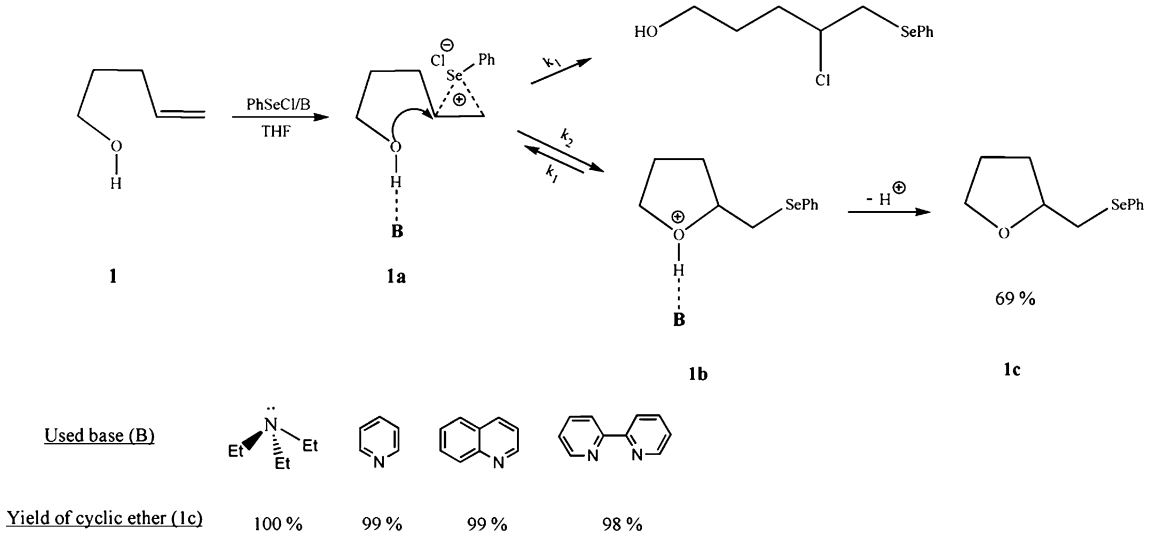

Fig. 1 Mechanism of based mediated cycloselenoetherification of pent-4-en-1-ol

quantitative formation of the cyclic ether. Kinetic investigation of these reactions showed that all reactions follow the kinetics of the second order and pyridine presence increases values for rate constants [18]. We were interested in exploring how pent-4-en-1-ol behaves in the presence of other bases and have therefore undertaken a study of the reaction of these alkenol with PhSeCl in the presence of some other bases (triethylamine, quinoline, 2,2′-bipyridine) and its influence on the yield obtained, values of rate constants and mechanism of reaction.

Experimental section

To investigate the mechanism of the reaction between phenylselenenyl chloride PhSeCl and pent-4-en-1-ol in the presence and absence of some bases the kinetics were studied under the *pseudo*-first-order conditions at 15 °C in THF as a solvent. A conventional kinetic method for determination of the values of rate constants was used.

These reactions were studied spectrophotometrically using UV-VIS Perkin Elmer Lamda 35 spectrophotometer equipped with water thermostated cell. All reactions were followed at 15 °C. The temperatures of reaction mixtures were controlled throughout all kinetic experiments to ± 0.1 °C.

All solutions were prepared by measuring the calculated amounts of substances in THF. The reactions were initiated by mixing equal volumes of phenylselenenyl chloride and alcohol solutions in the quartz cuvette. During all experiments the concentration of phenylselenyl chloride was constant ($1 \cdot 10^{-4}$ M), while the concentration of alcohol was varied from $1 \cdot 10^{-3}$ M to $2.5 \cdot 10^{-3}$ M. For the experiments with the presence of bases, the concentration of bases was equimolar to phenylselenenyl chloride concentration.

Spectral changes, resulting from the mixing of phenylselenenyl chloride and alcohol solutions, were recorded over the wavelength range 220 - 600 nm to establish a suitable wavelength at which kinetic experiments could be performed. The *pseudo*-first-order rate constants, k_{obsd}, were determined according to the Eq. 1 by fitting all kinetic runs as a single exponential function.

$$A_t = A_0 + (A_0 - A_\infty)\exp(-k_{obsd}t) \quad (1)$$

The observed *pseudo*-first order rate constants, k_{obsd}, were calculated as the average value from two to five independent kinetic runs using computational program Microsoft Excel and Origin 6.1.

Results and discussion

The reaction between alcohol and phenylselenenyl chloride starts with electrophilic attack of phenylselenenyl group on the double bond of alkenol which results in formation of selenonium cation (Fig. 1, 1a). In the next phase of the reaction, nucleophile oxygen from hydroxyl group of alcohol attacks selenonium cation and formation of five-membered ring occurs. Finally, generation of cyclic phenylseleno ether (Fig. 1, 1c) ensues with elimination of proton from oxonium ion.

When reactions were performed in the presence of bases (triethylamine, pyridine, quinoline and 2,2-bipyridine) the yields of obtained cyclic ether increased to almost quantitative.

It appears that the presence of bases is beneficial to the cyclization process, whereas the bases could play

several roles: (i) its basic properties (ii) bases could enhance the nucleophilicity of the hydroxyl group of the alkenol and (iii) mediate the stabilization of oxonium ion intermediates by abstracting the hydrogen (1b, Fig. 1). With the goal to apply this reaction to retro-synthetic problems detailed knowledge of the mechanism is of fundamental importance, therefore we investigated the mechanistic details by kinetic measurements and quantum calculations.

For the kinetic part of the experiment conventional kinetics method on UV/VIS spectrophotometer was used [23]. All reactions were studied as reaction of pseudo-first order at 15 °C in THF as solvent. Reactions were investigated by following the dependence of the absorbance on reaction time at suitable wavelength. The observed rate constants as a function of total alcohol concentration can be described by the following equation:

$$k_{obsd} = k_1 + k_2[\text{alcohol}]. \quad (2)$$

In this equation, k_2 represents the second order rate constant for the forward reaction, which depends on alcohol concentration and k_1 shows the effects of parallel reaction on the substitution process. The rate constant k_1 is independent of the alcohol concentration. The values for the k_2 were calculated from the slopes of the plots k_{obsd} versus of the alcohol concentration while the values for k_1 were determined from the intercept of the observed lines (Fig. 2).

The experimental data are summarized in Fig. 2 and calculated values for rate constants are given in Table 1.

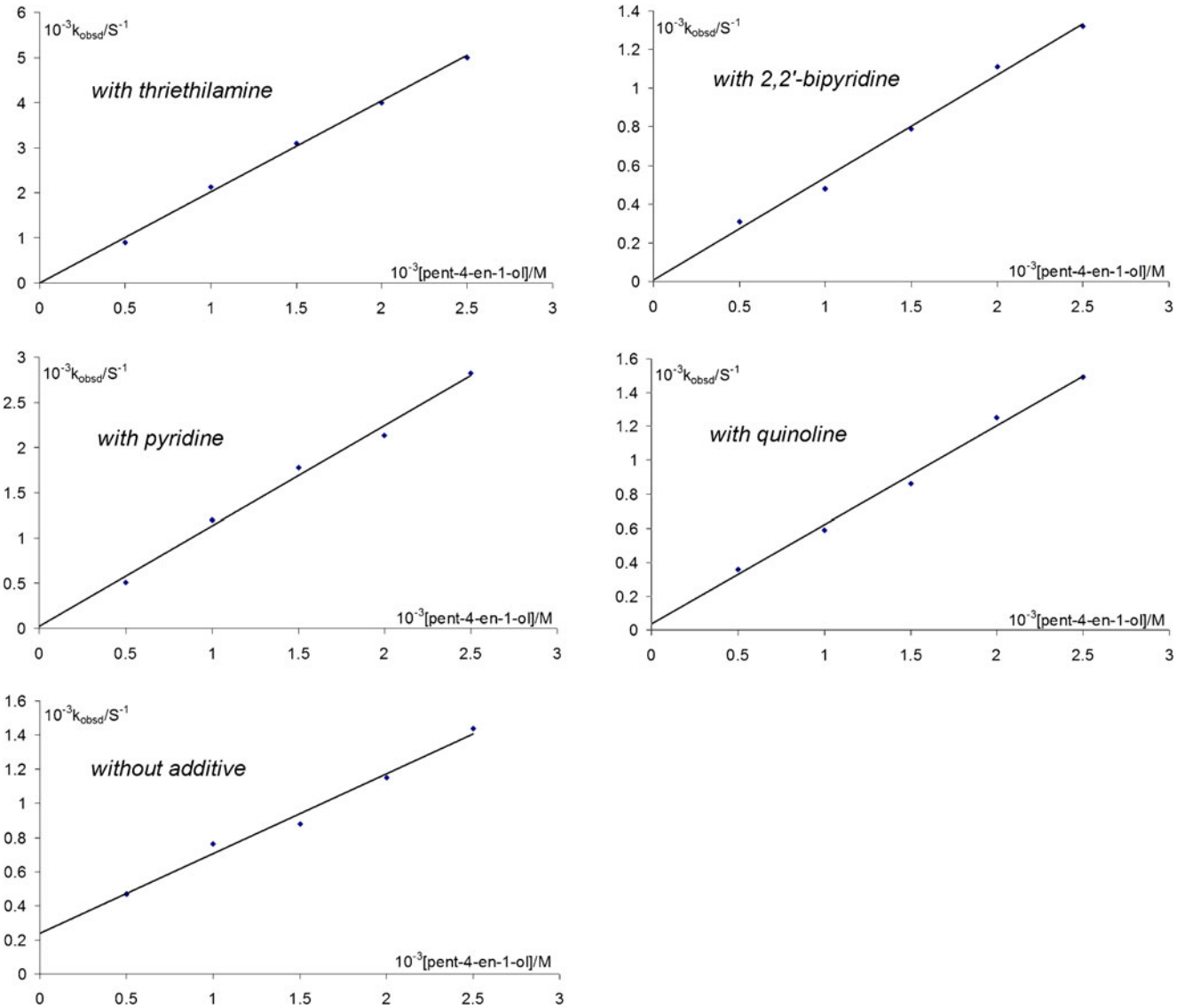

Fig. 2 *Pseudo*-first order rate constant, $k_{obsd.}$, as a function of concentration of alkenol for reaction between PhSeCl and pent-4-en-1-ol with and without base additive present (triethylamine, pyridine, 2,2′-bipyridine and quinoline) in THF as a solvent

Table 1 Rate constants for cycloselenoetherification of pent-4-en-1-ol with and without base additive present in THF at 288 K

T=288K	λ (nm)	k_2 ($M^{-1}s^{-1}$)	k_1 (s^{-1})
pent-4-en-1-ol	257	0.47±0.03	(2.4±0.5) × 10^{-4}
pent-4-en-1-ol and triethylamine	254	2.02±0.06	-
pent-4-en-1-ol and pyridine	258	1.11±0.06	-
pent-4-en-1-ol and quinoline	257	0.58±0.03	-
pent-4-en-1-ol and 2,2'- bipyridine	256	0.53±0.03	-

The catalytic role of bases has also been described by the second order rate constants, presented in Table 1. Data from Table 1 show that values for the k_1 constants are insignificant comparing with values for second order rate constants, k_2.

The reactions with bases are faster. The catalytic effect is slightly different depending on the type of bases that are used. Taking into account the results from Table 1, Et_3N increases the rate of reaction of pent-4-en-1-ol about four times. In the case of pyridine, the increase is about two times, while in the presence of Bipy and Qu the increase of the rate constants is smaller which can be explained by influence of steric hindrance on cyclization step.

From Fig. 3 some differences between the reactions with bases are remarkable. All lines in the reactions with bases start almost from the origin of the graph. This means that these reactions have no reverse or parallel runs, which is in agreement with the synthetically obtained yields (≈100%) for cyclization products in the reactions with bases as the catalyst (Fig. 1). In addition, it can be seen that there is excellent agreement between rate constants and basicity of used base-the fastest reaction is reaction with triethylamine, which is the strongest base.

Plot log k_2 vs. pKa of additive showed that bases used in these reactions increase the rate and yield with the same reaction mechanism (Fig. 4).

To get deeper insight into the reaction on a molecular level, we performed quantum chemical calculations for the pyridine facilitated and unfacilitated reaction between the reactants pent-4-en-1-ol and PhSeCl respectively their adduct.

All structures were fully optimized at B3LYP/6-311+G** [24–27] and characterized as minima or transition state structures by computation of vibrational frequencies (for minima, all frequencies are positive, NImag=0; for transition state structures, exactly one imaginary frequency is present, NImag=1). Being well aware of the limitations of DFT calculations, [28–32] we evaluated the energies by MP2(fc)/6-311+G** calculations (MP2(fc)/6-311+G**//B3LYP/6-311+G**+ZPE(B3LYP/6-311+G**)). When employing this approach, one has to keep in mind that activation barriers are generally somewhat different by MP2 compared to B3LYP [33] Gaussian 03 suites of programs were used throughout [34].

Independent, if pyridine is added or not, in the first step, the Ph-Se-fragment forms in a highly exothermic reaction with the alkenol's double bond a three-membered heterocyclic ring. This reaction can easily be understood and rationalized by Clark's σ-hole concept [35]. The σ-hole concept originally introduced with reference to halogen interactions, also known as halogen bonding, was subsequently extended to chalcogens, too [36–38]. If one half filled p orbital of an atom like selenium is involved in a covalent bond with an electronegative atom (here chlorine), electron deficiency in the outer, non-involved lobe of that orbital can be observed. This electron deficiency is associated with a positive electrostatic potential and concentrated approximately along the extension of the covalent bond. This positive potential will lead to an attractive interaction with the electron density of the C-C double bond and form a three-membered ring.

Such three-membered ring systems are not uncommon in organoselenium chemistry. In the case of the $Ph\text{-}Se^+$ attack

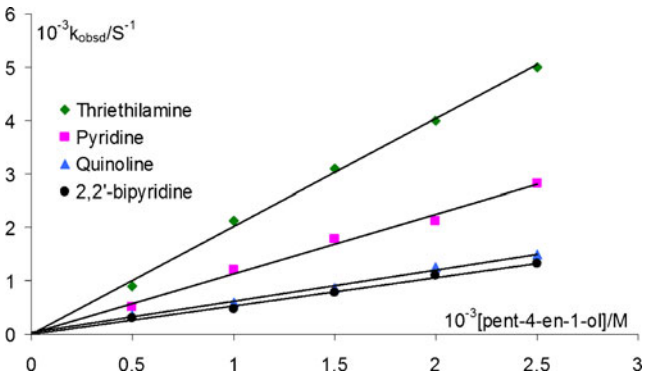

Fig. 3 Comparison of triethylamine, pyridine, quinoline and 2,2′-bipyridine catalytic influence on the rate of direct reaction

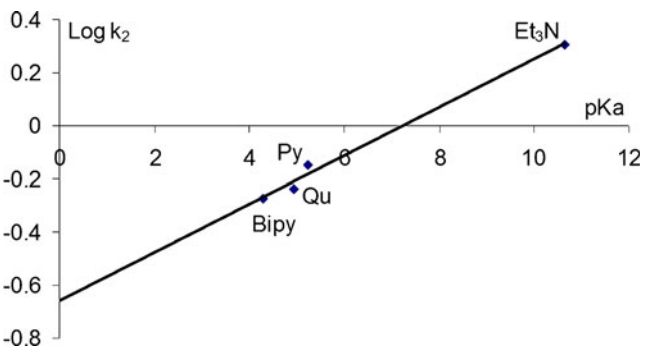

Fig. 4 Plot of log k_2 vs. pKa of additives for the cycloselenoetherification of pent-4-en-1-ol with base present

onto a triple bond Poleschner and Seppelt were even able to get x-ray structures of such ring systems [39]. The liberated energies are with more than 50 kcalmol^{-1} surely exaggerated due to the large electrostatic contribution. Additionally the positive charge of the Ph-Se^{+} fragment will be stabilized by the newly formed three-membered ring. (Unsupported: MP2 (fc)/6-311+G**// B3LYP/6-311+G**: 65.9 kcalmol^{-1}, B3LYP/6-311+G**: 52.4 kcalmol^{-1}; Pyridine supported: MP2(fc)/6-311+G**//B3LYP/6-311+G**: 73.2 kcalmol^{-1}, B3LYP/6-311+G**: 59.3 kcalmol^{-1}) (see Figs. 5 and 6). In both cases, the bonds of the formed triangal are very similar. While the Se-C_{CH2}-bond is identical with 2.04 Å the C-C bond in the unsupported case is 1.45 Å insignificantly 0.01 Å longer. The biggest difference one can see is in the inner Se-C_{CH}-bond, which is in the unsupported system 2.13 Å and in the pyridine facilitated one 2.17 Å. In both molecules the shortest and therefore strongest Se-bond is that one forming in the product CH_2-Se-Ph moiety. A comparison of the distances between the HO-group and the carbon atoms of the former double bond already shows which carbon atom will react with the oxygen atom. The HC-O-distance is in the pyridine-mediated molecule 2.68 Å, while the unmediated structure has 2.79 Å distance. The H_2C-O distance is in both cases clearly longer than 3 Å. The first significant differences between base mediated, here pyridine, and unmediated reaction is the S_N2 like ring closing transition state. While in the pure reaction a barrier of 12 kcalmol^{-1} (MP2(fc)/6-311+G**// B3LYP/6-311+G**) appears, in the pyridine supported case the barrier lowered to 3 kcalmol^{-1}. Based on DFT values the energy barrier reduces by around 8 kcalmol^{-1}, too, but vanishes nearly in the case of the pyridine supported reaction. Within the framework of early and late transition states, the assisted transition appears earlier than the unassisted. In the aided one is the Se-CH-bond only elongated by 0.2 Å to 2.38 Å, while the pure is already elongated to 2.87 Å. The C-C bond and the Se-CH_2-bond in the selenocycle show no real relevant change. In contrast to the oxygen-carbon distances, responsible for the ring formation, which shorten, as expected. In the pyridine case it is diminished by 0.3 Å to 2.33 Å and in the base free by more than 0.4 Å to 2.32 Å. Additionally the H_2C-O-distances get shorter in both pathways by around 0.4 Å. The hydrogen bond between OH-group and pyridine does not change, as expected.

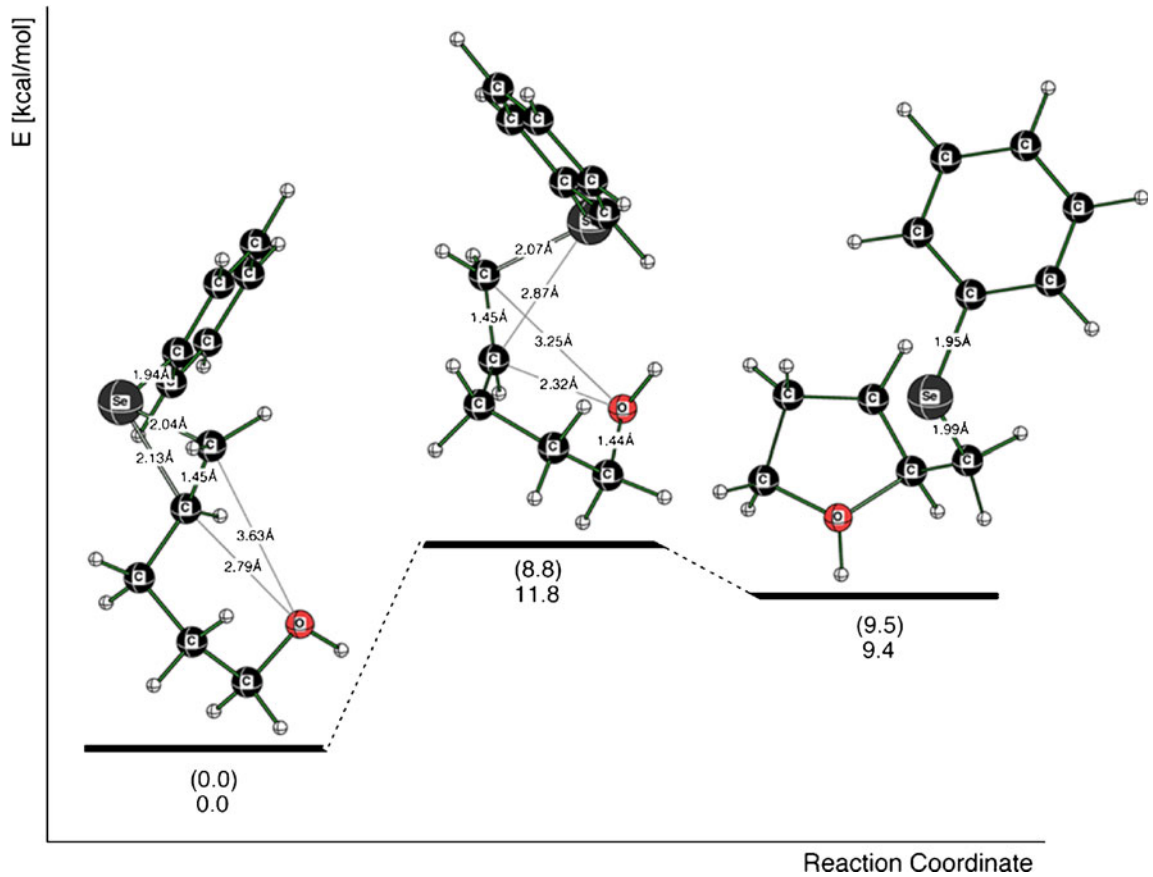

Fig. 5 Calculated reaction pathway for the cycloselenoetherification mediated by Ph-Se^{+} without hydrogen bond bound pyridine

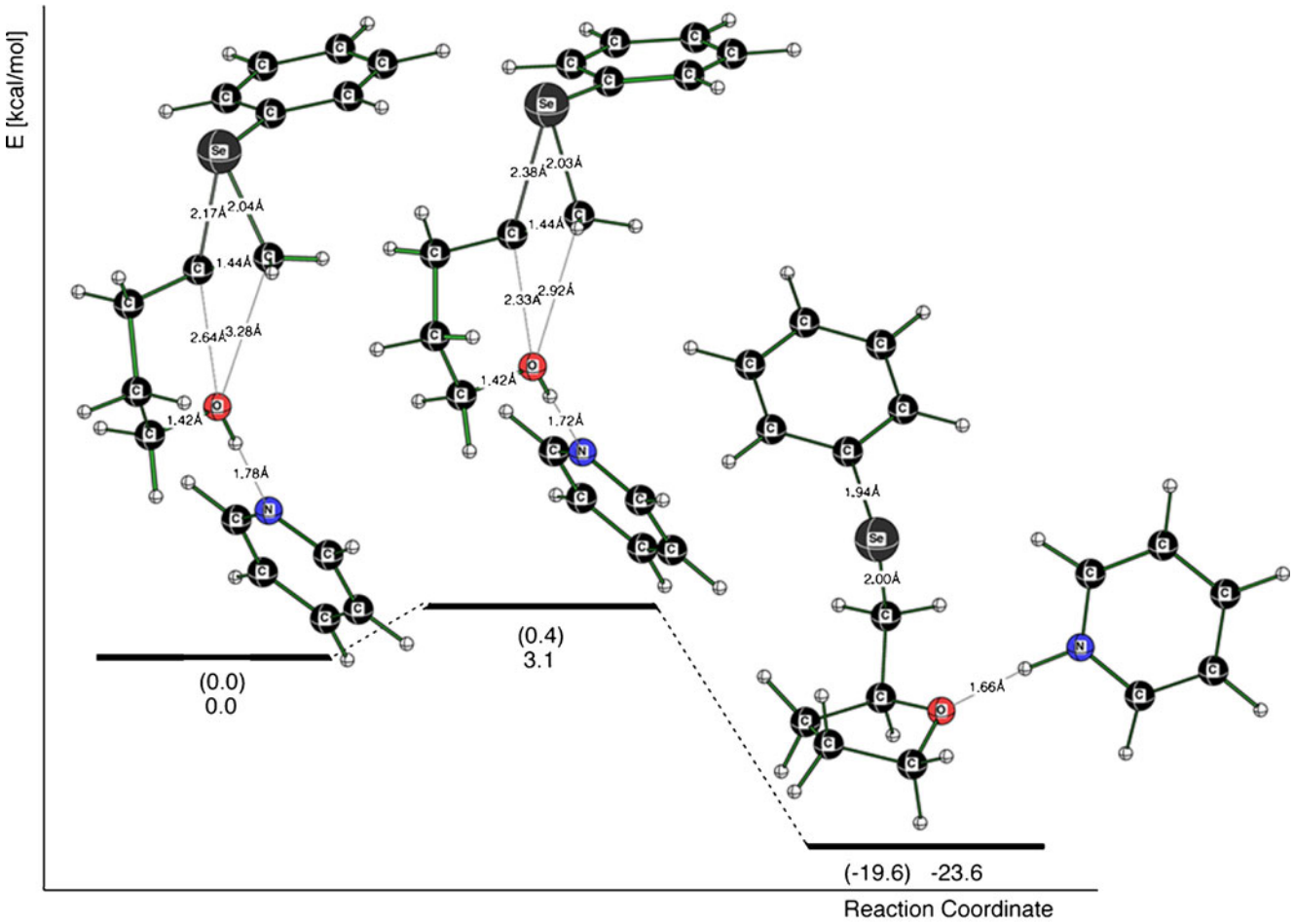

Fig. 6 Calculated reaction pathway for the cycloselenoetherification mediated by Ph-Se^{+} with hydrogen bond bound pyridine

In the product this hydrogen bond changes completely, as the proton now breaks the bond to the ether oxygen and binds to the pyridine ring, keeping a strong hydrogen bond to the oxygen atom of 1.66 Å. We attribute to this proton migration the drastic relative stability difference in both investigated reaction pathways. While the pyridine accepts the former hydroxyl proton and a neutral five membered heterocycle 20 kcal mol^{-1} more stable than the educts is formed, it is in the base free pathway the hydrogen atom still at the heterocycle's oxygen atom leading to products more than 9 kcal mol^{-1} higher in energy than the educts. In the case of DFT calculations this value is even higher at the transition state. This protonated ether oxygen is not only energetically very unfavorable; it is the first step to the back reaction, the ether cleavage. Both clear reasons for the lower amount of product observed in the experiment without base.

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