Organoseleno-Catalyzed Synthesis of α,β -Unsaturated α' -Alkoxy Ketones from Allenes Enabled by $\text{Se}\cdots\text{O}$ Interactions

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Dedicated to Professor Benito Alcaide on the occasion of his 70th birthday

Supporting Information Placeholder

ABSTRACT: α,β -Unsaturated α' -alkoxy ketones have been prepared under mild conditions from allenes using water as the oxygen source and without the necessity of metals. The organocatalytic oxygenation-rearrangement sequence displays an exquisite chemo-, stereo-, and site-selectivity as well as good functional group compatibility. DFT calculations suggest that stabilizing noncovalent $\text{Se}\cdots\text{O}$ interactions may be responsible for the observed reactivity.

The α,β -unsaturated α' -alkoxy ketone moiety is a recurrent structural motif in natural products and bioactive molecules which has been also identified as a valuable platform for the preparation of more complex products.¹ Despite that the synthesis of the naked α -hydroxy ketone moiety can be smoothly accomplished from alkenes,² the preparation of the more functionalized α,β -unsaturated α' -alkoxy ketone scaffold is not an easy task.³ Consequently, the search for alternative protocols for this framework is highly desirable.

One subject in the continuously growing field of organocatalyzed reactions is the appearance of organoselenium catalysis

as a versatile synthetic tool.⁴ In particular, electrophilic transformations of isolated alkenes through selenium-based π -acid-type catalysis have been developed (Scheme 1a).⁵ Other π -systems have rarely been studied; only Zhao et al. have recently reported the organoseleno-catalyzed functionalization of alkynes (Scheme 1b) and the pyridination of 1,3-dienes (Scheme 1c).⁶ Although many efforts have been made in the preparation of selenoderivatives by the stoichiometric reaction of allenes with selenenylating reagents,⁷ the use of selenium catalysis in allene chemistry remains unexplored. We wish to report herein

the oxygenative rearrangement of the allene skeleton *via* organoselenium catalysis (Scheme 1d).

During our program focused on studying the reactivity of the allene moiety, an unanticipated observation captured our interest. The reaction of allenyl methyl ether **1a** with stoichiometric amounts of diphenyl diselenide in the presence of 1-fluoropyridinium triflate formed the unexpected α' -alkoxy enone **2a** as major product (25% yield) along with selenated adducts (Scheme 2a).⁷¹ Control experiments revealed that both the organoselenium compound and the oxidant were crucial for this transformation. Aimed at exploiting this accidental result in connection with a general synthetic protocol, we speculated that a selenium-catalyzed rearrangement-functionalization sequence of allenyl ethers could be established. For this proposal, we initially decided to reduce the stoichiometric quantity of (PhSe)₂ to catalytic amounts. Disappointingly, the use of 10 mol% (PhSe)₂ yielded α' -alkoxy enone **2a** in a diminished 12% yield. The major product (82% yield) of this reaction was enone **3a**, a Meyer–Schuster-type product lacking the methoxy moiety (Scheme 2b). We suspect that the catalytic version using 10 mol% is kinetically slow and higher catalyst loading is required. Noteworthy, when the reaction of allenyl methyl ether **1a** was catalyzed by 20 mol% (PhSe)₂, α,β -unsaturated α' -alkoxy ketone **2a** was obtained in a good 69% yield as single (*E*)-isomer (Scheme 2c). Similar figures, with just a slight improvement in yield, were obtained using 50 mol% of (PhSe)₂ (Scheme 2d). Consequently, we decided that 20 mol% of the organoselenium catalyst should be used as optimized amount for studying the scope of the organoseleno-catalyzed reaction of allenes. When the reaction of precursor **1a** was carried out replacing (PhSe)₂ by PhSeCl (20 mol%), a complicated mixture was obtained and product **2a** was obtained in a poor 14% yield.

Scheme 1. State-of-the-art and current work

Previous work

Current study (d)

Scheme 2. Impact of the diphenyl diselenide amount on the selenium-catalyzed rearrangement-functionalization sequence of allenyl methyl ether **1a**

After fixing a productive catalyst system, different tests were conducted to inspect the substrate scope of the above transformation. The generality of the reaction was first studied using differently-substituted allenyl methyl ethers **1**. The corresponding products **2a–m** were achieved in reasonable yields (40–76%) and good or great (*E*)-diastereoselectivity (Scheme 3). The reaction proved to be general because both, electron-donating (4-MeO and 4-Me) and electron-withdrawing groups (Cl and Br) were well accommodated. Interestingly, the bromine and chlorine moieties on the arene are compatible with enone formation conditions, which may offer further functionalization through selective cross-coupling protocols. Reactions of derivatives **1** bearing substituents on the phenyl nucleus at the *ortho*, *meta*, and *para* positions proceeded smoothly. Hetaryl moieties such as 2-thienyl were also well suited, albeit the *E/Z* ratio of **2l** (78:22) was lower compared to other examples. Next, substitution at the allene moiety was examined. Replacement of the methyl group by hydrogen also provided the desired α' -alkoxy enones **2h,i** in fair yields. To judge by the reactions of (1-methoxybuta-2,3-dien-2-yl)benzenes **1j,k**, the steric hindrance imparted by the phenyl group on the cumulene moiety did exert unquestionable influence on enone formation; the reaction of phenyl-allenes **1j,k** afforded adducts **2j,k** in a diminished yield (Scheme 3; **2b,d** vs **2j,k**). Noteworthy, the alkyne portion may also be tolerated and methyl ether **1m** provided α' -methoxy conjugated enynone **2m** with exquisite chemoselectivity (allene vs alkyne). Noteworthy, when allenyl methyl ether **1n** decorated with a methyl substituent at the terminal allene carbon was used as starting material, the reaction also worked well to provide the α' -methyl α' -methoxy *gem*-substituted enone **2n** (Scheme 3). However, when the protocol was applied to alkyl-substituted allenyl methyl ether **1o**, enone formation could not be achieved (Scheme 3). The (*E*)-stereochemistry of enones **2** was established by means of NOE experiments performed in compound **2c** (see Supporting Information).

Scheme 3. Controlled synthesis of α,β -unsaturated α' -alkoxy ketones **2a–n**

Scheme 4. Controlled synthesis of α,β -unsaturated α' -alkoxy ketones **2r–x**

Next, we sought to develop a more general protocol by replacing the methyl ether framework by different oxygenated functionalities. Initial efforts were a little bit frustrating because the reaction of allenol **1p** yielded enone **3b**, while allenyl acetate **1q** was unreactive.⁹ Fortunately, allenyl ethers **1r–x** bearing

an extra benzyl, allyl, propargyl and cumulenyl moieties provided the desired rearranged functionalized adducts **2r–x** in synthetically useful yields (Scheme 4). It should be noted that the mild reaction conditions allow for a complete chemoselectivity, with the unsaturated allyloxy, propargyloxy and allenyloxy components present in allene precursors **1** been transferred unaltered to the final rearranged products **2**. Simultaneously, functionalized α' -alkoxy enones (*E*)-**2r–x** were stereoselectively formed in a high *E/Z* ratio (up to 97:3) comparable to methyl ethers **2a–n**.

The accessible water of regular (HPLC grade) acetonitrile and THF was adequate for the reaction to progress profitably. In order to confirm the participation of adventitious water in the formation of polyfunctional adducts **2**, an ¹⁸O-labeling experiment was conducted (Scheme 5). Indeed, the use of H₂¹⁸O in the reaction of **1e** in anhydrous solvents resulted in the formation of ¹⁸O-labeled **2e**, as observed by high-resolution mass spectrometry (see Supporting Information). Besides, the possible participation of atmospheric oxygen in the formation of the carbonyl group can be ruled out in view of the observed drastic reduction of the yield of enone **2a** when conducting a control reaction in dehydrated solvents in the presence of an O₂ balloon (Scheme 5).

A possible pathway for the generation of functionalized enones **2** from allenes **1** through organoselenium catalysis is outlined in Scheme 6. First, and similar to the pathway proposed by Zhao and co-workers,^{6a} the selenium-based π -acid species PhSe(OTf) is originated from PhSeSePh by way of the oxidative reagent [pyF][OTf]. Subsequently, an alkenyl seleniranium **INT-1** may be formed through regioselective carbophilic interaction to the terminal allene double bond. The proposed formation of the cyclic selenium intermediate **INT-1** in a *syn* manner towards the OR¹ group is in agreement with recent reports on stabilizing noncovalent Se $\cdots$ O interactions.^{8,9} Then, controlled water attack to the three-membered heterocyclic species with concomitant release of ring strain and triflic acid liberation should afford enol **INT-2**, which is in equilibrium with its more stable keto-tautomer **INT-3**. The presence of free pyridine in the reaction medium should provoke the abstraction of the acidic hydrogen, that is associated with alcohol elimination and formation of selenoenone **INT-4**. Further [pyF][OTf]-mediated oxidation of the PhSe group in **INT-4** should give rise to selenonium species **INT-5**.¹⁰ α,β -Unsaturated α' -alkoxy ketones **2** would be finally formed by S_N2 displacement of the phenylselenonium moiety by the *in situ* generated alcohol, with concurrent loss of FH and regeneration of the selenium- π -acid catalyst.

Scheme 5. Labeling and control studies

Scheme 6. Rationalization for the formation of α,β -unsaturated α' -alkoxy ketones **2 by organoselenium catalysis**

Density Functional Theory (DFT) calculations at the dispersion-corrected PCM(MeCN)-B3LYP-D3/def2-TZVPP//PCM(MeCN)-B3LYP-D3/def2-SVP level¹¹ were carried out to gain more insight into the suggested occurrence of a $\text{Se}\cdots\text{O}$ noncovalent interaction in the initial stages of the transformation. To this end, we computed the reaction involving allene **1b** and PhSeOTf which leads to the corresponding seleniranium **INT-1b** (see Figure 1). Our calculations indicate that the formation of **INT-1b** occurs concertedly via **TS**, a saddle point associated with the simultaneous (yet asynchronous) formation of the new C–Se bonds and the rupture of the $\text{Se}\cdots\text{OTf}$ bond. The low barrier ($\Delta G^\ddagger = 4.6$ kcal/mol) and the high exergonicity ($\Delta G_R = -15.6$ kcal/mol) computed for this reaction is fully compatible with a process occurring at room temperature. Interestingly, the $\text{Se}\cdots\text{O}$ distance in either **TS** or intermediate **INT-1b** (3.199 and 3.029 Å, respectively) are shorter than the sum of their respective van der Waals radii (3.42 Å), therefore suggesting a significant noncovalent interaction involving these atoms. The occurrence of this stabilizing intramolecular interaction can be computationally visualized and confirmed by means of the NCIPLOT method.¹² As clearly shown in the inset of Figure 1, there exists a significant noncovalent attractive interaction (green surface) between the oxygen and selenium atoms in **INT-1b**.¹³

Moreover, the crucial role of this $\text{LP}(\text{O})\cdots\text{Se}$ noncovalent interaction in the process is supported by comparing the reaction profile involving the OAc counterpart of **1b** (see Figure S1 in the Supporting Information). For this system, the $\text{Se}\cdots\text{O}$ distance of the corresponding transition state is much longer (3.333 Å) therefore indicating a weaker $\text{Se}\cdots\text{O}$ interaction as a consequence of the reduced donor ability of the oxygen atom. As a result, the computed barrier for this transformation is significantly higher ($\Delta G^\ddagger = 7.4$ kcal/mol) and the process becomes

much less exergonic ($\Delta G_R = -8.5$ kcal/mol) than the reaction involving its OMe counterpart **1b**.

Figure 1. Computed reaction profile for the formation of intermediate **INT-1b** from **1b** and PhSeOTf . Relative free energies and bond lengths are given in kcal/mol and angstroms, respectively. All data have been computed at the PCM(MeCN)-B3LYP-D3/def2-TZVPP//PCM(MeCN)-B3LYP-D3/def2-SVP level. Inset: Contour plots of the reduced density gradient isosurfaces (density cutoff of 0.03 a.u.) for compound **INT-1b**. The green surfaces indicate attractive non-covalent interactions.

To sum up, an organocatalyzed direct synthesis of α' -alkoxy enones from allenyl ethers under mild conditions with adventitious water as the oxygen source and without the involvement of metals has been satisfactorily accomplished. This chemo-, stereo-, and site-selective oxygenative rearrangement process involves an organoselenium-based π -acid-type catalysis. DFT calculations provide further support to the occurrence of a stabilizing $\text{LP}(\text{O})\cdots\text{Se}$ noncovalent interaction which significantly facilitates the transformation.¹⁴

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.

Experimental procedures, characterization data of new compounds, copies of NMR spectra, computational details, and alternative reaction pathway (PDF).

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Notes

The authors declare no competing financial interest.

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(9) The failure of allene **1q**, bearing an AcO group instead of an alkoxy moiety, may be tentatively explained through a weaker Se···O interaction, which should not impart stabilization enough to the putative phenylseleniranium intermediate **INT-1q**.

(10) The application of selenonium cations as Lewis acids in organocatalytic reactions has been recently documented: He, X.; Wang, X.; Tse, Y.-L.; Ke, Z.; Yeung, Y.-Y. Applications of Selenonium Cations as Lewis Acids in Organocatalytic Reactions. *Angew. Chem. Int. Ed.* **2018**, *57*, 12869–12873.

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(13) A similar interaction is found by the NCIPLOT method for the saddle point **TS**.

(14) Taking into account both that electrophiles are usually added to the internal double bond of the allene moiety¹⁵ as well as the possibility of isomerization of 2,3-allenols to 2-oxy-1,3-diene under certain conditions,¹⁶ another possible mechanism (see Scheme S1 in the Supporting Information) may be contemplated: Precursors **1** should be converted under acidic conditions to allene-type allyl cations **I** through OP release. Next, π bond migration followed by water attack should form 2-oxy-1,3-dienes **II**, which can isomerize to enones **3**. Next, PhSe^+ can react with intermediates **II** to form α -PhSe-ketones **INT-4**, which followed by oxidation and displacement should generate α,β -unsaturated α' -alkoxy ketones **2**. The formation of compounds **3a,b** might go through the picture depicted in Scheme S1. However, we think that this alternative path is not operative for the formation of compounds **2a–n** and **2r–x**, because it may not account for the different reactivity observed for AcO-allene **1q** and alkoxy-allenes **1a–n** and **1r–x**.

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