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Oxidative selenofunctionalization of allenes: convenient access to 2-(phenylselanyl)-but-2-enals and 4-oxo-3-(phenylselanyl)pent-2-enoates†‡

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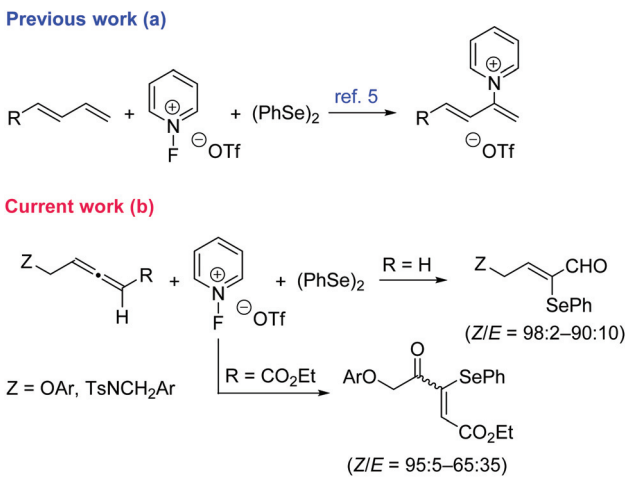
The controlled preparation of two types of α-seleno-α,β-unsaturated carbonyls, namely, α-selenoenals and α-selenoenones, has been accomplished directly from allenes through metal-free oxidative selenofunctionalization reactions. The decisive role of organoselenium and 1-fluoropyridinium reagents has been disclosed. The divergent reactivity due to the presence or absence of an ethoxycarbonyl moiety at the allene end has also been studied. A tentative pathway implying selective electrophilic addition of the selenium reagent to the allene moiety followed by adventitious water attack and concomitant oxidation has been proposed.

Introduction

Allenes (1,2-dienes) have attracted considerable interest in chemistry research due to their availability and unique reactivity, which allows for the selective synthesis of different functionalized organic molecules.[1] On the other hand, the organoselenium motif is the central structural element of a variety of biologically active molecules.[2] Besides, selenium-containing organic compounds are attractive to medicinal chemists because organic molecules bearing selenated moieties can enhance their pharmacological properties.[3] As a result, several synthesis protocols toward organoselenium derivatives have been described starting from allenes.[4] Inspired by the recently described organoselenium-mediated C–H pyridination of 1,3-dienes using 1-fluoropyridinium reagents (Scheme 1a),[5] we decided to test the related C–H functionalization of 1,2-dienes. However, we did observe the selective formation of α-selenoenals and α-selenoenones (Scheme 1b),[6] probably *via* the controlled electrophilic addition of the selenium reagent to the allene moiety followed by adventitious water attack and concomitant oxidation. 1-Fluoropyridinium compounds[7] as oxidative functionalization reagents have several advantages over classical oxidants based on heavy metals, such as low toxicity and high functional group tolerance. Herein we report this appealing reactivity which allows one to obtain two different types of α-seleno-α,β-unsaturated carbonyls from allenes.

Results and discussion

Starting materials, allenes **1a–h** unsubstituted at the proximal C=C double bond and allenoates **2a–f**, were prepared from



Scheme 1 Previous report and the current study of the reactivity of dienes with the 1-fluoropyridinium/1,2-diphenyldiselane system.

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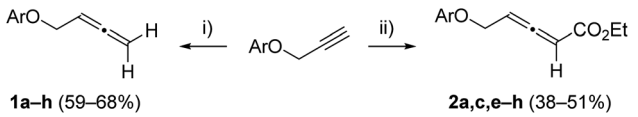
†In memory of Prof. Ángel Vidal.

‡Electronic supplementary information (ESI) available: Experimental procedures, compound characterization data, and copies of NMR spectra for all new compounds. See DOI: 10.1039/c9qo00561g

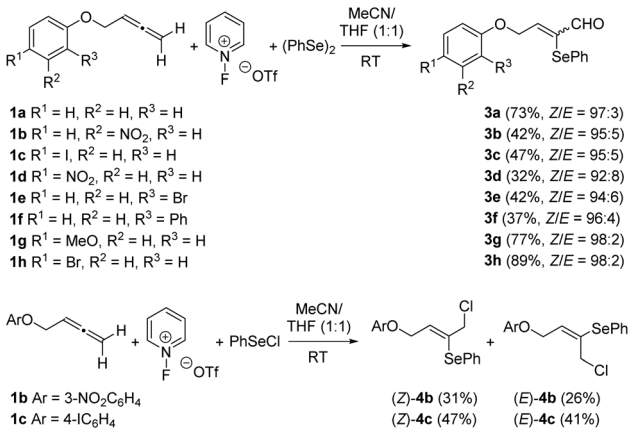


Scheme 2 Synthesis of allene precursors. (i) $(CH_2O)_n$, iPr_2NH, CuBr, dioxane, reflux, 2 h. (ii) $N_2{=}CHCO_2Et$, Et_3N, CuI, CH_3CN, rt.

common terminal alkyne precursors using the Crabbé reaction[8] or treatment with ethyl diazoacetate,[9] respectively (Scheme 2 and see the ESI for details‡).

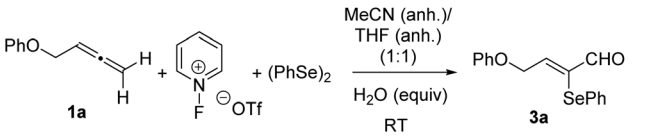
To screen the reactivity of the allene moiety towards C–H pyridination, terminal allene **1a** was selected as the model substrate. In the event, the incorporation of the pyridine nucleus did not occur and α-phenylseleno-α,β-unsaturated aldehyde **3a** was formed instead regio- and stereoselectively in 73% yield (Scheme 3). Next, we examined the reaction scope by varying the substitution of the arene moiety. Several substituents of different electronic demands were well tolerated. All the reactions progressed satisfactorily to provide the required α-selenoenals **3b–h** as almost single (*Z*)-isomers in fair yields (Scheme 3).[10] However, electron-withdrawing substituents at the arene moiety were counterproductive for the process, as 3- and 4-nitrobenzene provided the required products **3b** and **3d** in diminished yields. The presence of bulky substituents at the *ortho*-position such as in **3e** and **3f** was also unfavourable for the reaction yields. Taking into account the presence of both a PhSe group and a carbaldehyde functionality in adducts **3**,[11] we decided to modify the reaction conditions. The replacement of $(PhSe)_2$ with PhSeCl yielded a chromatographically separable 1 : 1 mixture of (*Z*)- and (*E*)-(1-chloro-4-aryloxybut-2-en-2-yl)(phenyl)selanes **4** (Scheme 3). The use of alternative oxidants such as Oxone or Selectfluor resulted in complicated reaction mixtures, thus highlighting the important role of the 1-fluoropyridinium reagent.

Owing to the structure of adducts **3**, we suspect the involvement of adventitious water. Aiming to evaluate the effect of water on this transformation, strictly dehydrated acetonitrile



Scheme 3 Synthesis of α-phenylseleno-α,β-unsaturated aldehydes **3** through the oxidative selenofunctionalization of allenes **1**.

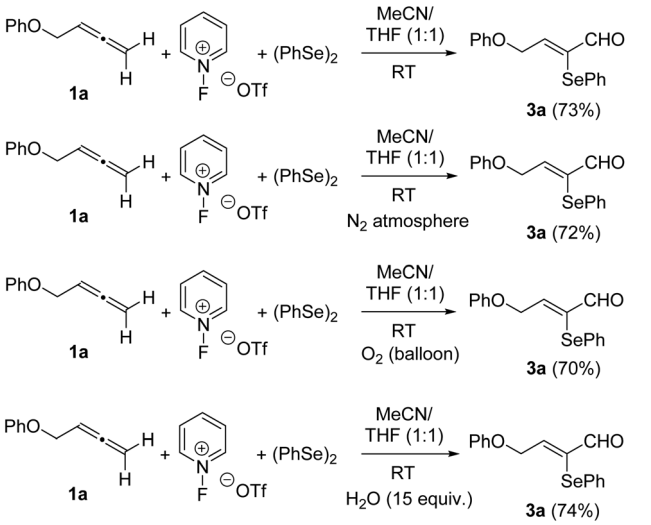
Table 1 Effect of water addition on the selenofunctionalization reaction of allene **1a** [a]



Entry	H_2O (equiv.)	Yield **3a** [b] (%)
1	0	8
2	1	26
3	2	51
4	5	70
5	10	73

[a] Unless otherwise noted, all reactions were carried out using 0.3 mmol of allene **1a**, 0.3 mmol of $(PhSe)_2$, and 0.36 mmol of $[PyF]^+[OTf]^-$. [b] Yield of the pure, isolated product.

and tetrahydrofuran were used as solvents followed by the controlled addition of water (Table 1). The use of rigorously anhydrous solvents resulted in almost the absence of reaction (entry 1, Table 1), while the addition of 1 equiv. of water produced a diminished yield (26%) of **3a** (entry 2, Table 1). The addition of the high amounts of water was beneficial and gave rise to product **3a** in reasonable yields (entries 3–5, Table 1). However, the alternative participation of oxygen from the air could not be discarded. To gain some insights into the reaction mechanism, control experiments were carried out. When the reaction of allene **1a** was conducted under a N_2 atmosphere under otherwise identical conditions, the yield remained almost unchanged (Scheme 4). Similar yields were obtained with the inclusion of an O_2 balloon. The addition of 15 equivalents of water to the standard reaction resulted in almost no variation in the isolated yield of **3a** (Scheme 4), which unquestionably proved that the amount of water available in regular solvents[12] was enough for the reaction to



Scheme 4 Control experiments for the formation of α-selenoenal **3a**.

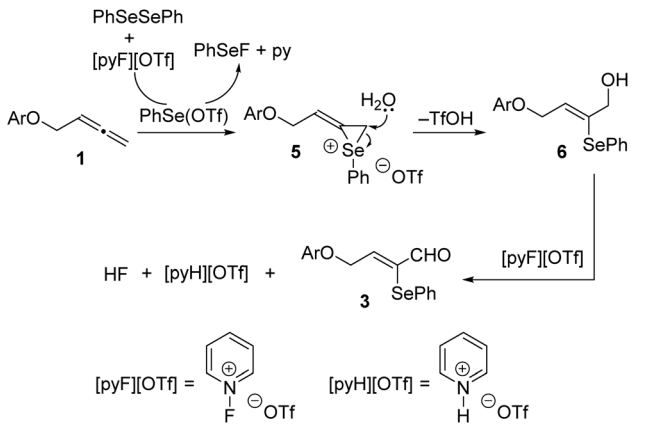
proceed efficiently. From the above results, it is apparent that the carbaldehyde oxygen of **3a** came from water.

A possible mechanistic pathway for the formation of α-selenoenals **3** from allenes **1** is depicted in Scheme 5. Initially, the generation of the electrophilic species PhSe(OTf) takes place through the oxidation of $(PhSe)_2$ promoted by 1-fluoropyridinium triflate. Next, the discriminating reaction with the terminal double bond of the allene moiety of allenes **1** provides intermediate 1-phenylseleniran-1-iums **5**, which after regioselective nucleophilic water attack are converted into 2-(phenylselanyl)but-2-en-1-ols **6**. Although merely speculative at this time, the origin of the detected stereoselectivity may be due to the favourable *syn* arrangement of the PhSe and CH_2OAr moieties with the latter acting as a directing group. The final oxidation of the hydroxyl functionality assisted by the 1-fluoropyridinium reagent provides α-phenylseleno-α,β-unsaturated aldehydes **3**.

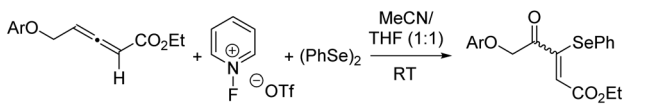
The oxidative selenofunctionalization of ethoxycarbonyl-allenes **2** was then surveyed under the optimized reaction conditions for the formation of α-selenoenals **3**. In the event, the regioselectivity was totally reverted. The reactions proceeded to form the corresponding 4-oxo-3-(phenylselanyl)pent-2-enoates **7** in fair yields and good to moderate stereoselectivities (Scheme 6). In every single case, a ketone group was formed and placed at the former carbon(sp^2) of the distal allene C=C double bond.[13] Contrary to α-selenoenals **3**, products **7** were not formed as almost single (*Z*)-geometrical isomers.[10] We suspected that the presence of the ethoxycarbonyl moiety brings about a different stereoelectronic environment which makes the selenofunctionalization and further water attack difficult, resulting in a lower stereoselectivity.

Based on the mechanistic proposal of Scheme 5, a plausible pathway for the formation of adducts **7** is depicted in Scheme 7. Initially, the electrophilic attack of the benzeneselenyl species to the more electron-rich allene C=C double bond takes place regioselectively to generate phenylseleniran-1-iums **8**. A subsequent nucleophilic water attack can be produced at either carbon of the cations **8**, but the site-selectivity is total and seleno-functionalized allylic alcohols **9** are exclusively formed. Probably, the formation of intermediates **9** is also the (*Z*)/(*E*)-stereodetermining step. Oxidation of the hydroxyl group at intermediates **9** provides final products **7** and releases pyridin-1-ium triflate and hydrogen fluoride. Alternatively, the hydroxy group of intermediates **9** may arise not from external water, but from the ester group of starting allenes **2** based on the proposal by Fu and Ma.[4f] To clarify the effective engagement of external water in the selenofunctionalization of ethoxycarbonyl-allenes, an ^{18}O-labeling experiment was performed (Scheme 8). Hence, the reaction of allene **2g** was carried out under otherwise optimal conditions, but in the presence of one equivalent of $H_2{}^{18}O$ with an isotope abundance of 97%. In the event, the resulting 4-oxo-3-(phenylselanyl)pent-2-enoate **7g** was ^{18}O-labeled (*ca.* 50%) as detected by mass spectrometry (see the ESI‡), suggesting the involvement of adventitious water in this transformation.

To further expand the study of the 1,2-diene skeleton under these metal-free oxidative selenofunctionalization conditions, differently functionalized allenes **10–13** were surveyed



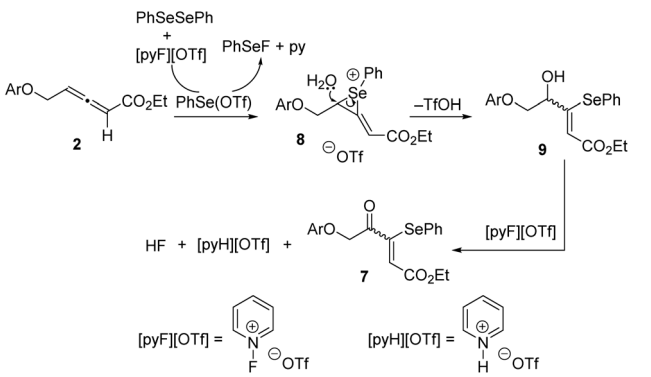
Scheme 5 Proposed reaction pathway for the 1-fluoropyridinium triflate-assisted formation of α-selenoenals **3**.



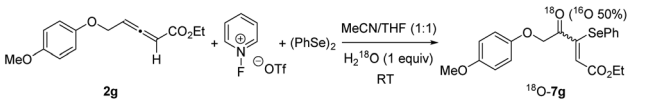
2a Ar = Ph
2c Ar = 4-IC_6H_4
2e Ar = 2-BrC_6H_4
2f Ar = 2-PhC_6H_4
2g Ar = 4-$MeOC_6H_4$
2h Ar = 4-BrC_6H_4

7a (63%, *Z*/*E* = 90:10)
7c (33%, *Z*/*E* = 75:25)
7e (47%, *Z*/*E* = 80:20)
7f (38%, *Z*/*E* = 65:35)
7g (53%, *Z*/*E* = 80:20)
7h (43%, *Z*/*E* = 95:5)

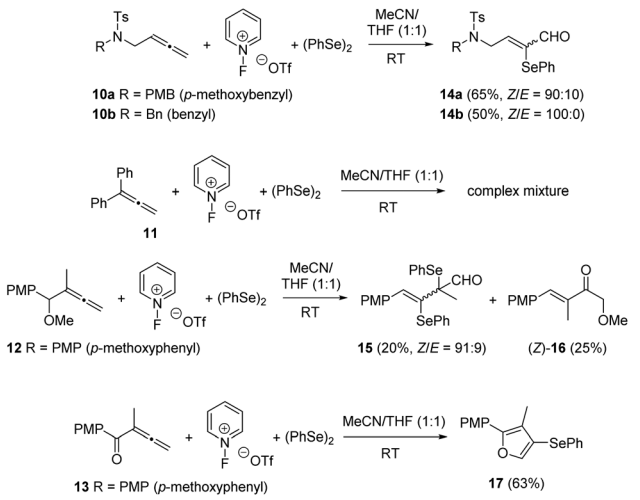
Scheme 6 Synthesis of α-selenoenones **7** through the oxidative selenofunctionalization of allenes **2**.



Scheme 7 Proposed reaction pathway for the 1-fluoropyridinium triflate-assisted formation of α-selenoenones **7**.



Scheme 8 ^{18}O-Labeling experiment.



Scheme 9 Reactivity of functionalized allenes **10–13** under oxidative selenofunctionalization conditions.

(Scheme 9). Interestingly, allenamides **10a** and **10b** reacted smoothly to furnish the appropriate α-selenoenals **14a** and **14b** in reasonable yields with good *Z*-stereoselectivity. The behaviour of *gem*-disubstituted allenes **11** and **12** was less rewarding. The added steric bulk resulted in a complex reaction mixture for diphenyl allene **11**, while allene **12** was suitable for this transformation. Surprisingly, the reaction of 1-methoxy-4-(1-methoxy-2-methylbuta-2,3-dien-1-yl)benzene **12** resulted in a separable mixture of selenoenal **15** and non-selenated enone **16**. By contrast, allenone **13** failed to provide the corresponding α-selenoenone, giving instead selenated furan **17**.

Conclusions

In conclusion, we present the controlled preparation of two types of α-seleno-α,β-unsaturated carbonyls, namely, α-selenoenals and α-selenoenones, directly from allenes through metal-free oxidative selenofunctionalization reactions by a subtle variation of the substituents at the allene end. Consequently, the effect of the presence of an ethoxycarbonyl moiety at the allene end on the outcome of the process has been established. The decisive role of the organoselenium and 1-fluoropyridinium reagents has also been disclosed.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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