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Oxidative Allylic Esterification of Alkenes by Cooperative Selenium-Catalysis Using Air as the Sole Oxidant

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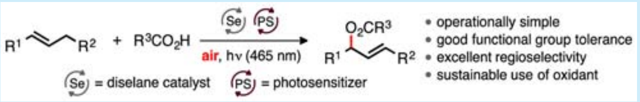
Ⓢ *Supporting Information*

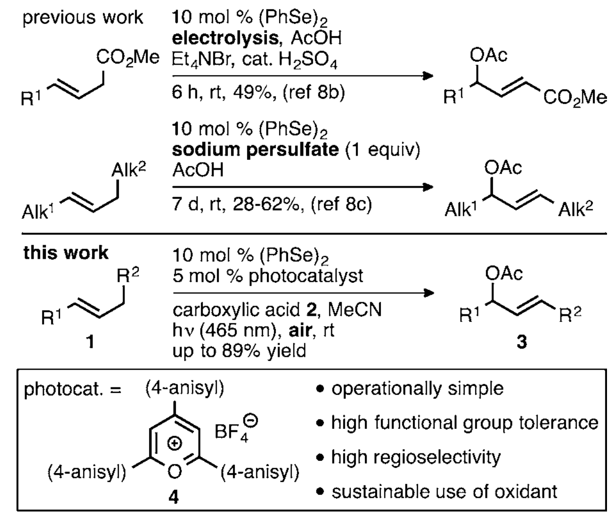
ABSTRACT: A new metal-free catalysis protocol for the oxidative coupling of nonactivated alkenes with simple carboxylic acids has been established. This method is predicated on the cooperative interaction of a diselane and a photoredox catalyst, which allows for the use of ambient air or pure O_2 as the terminal oxidant. Under the title conditions, a range of both functionalized and nonfunctionalized alkenes can be readily converted into the corresponding allylic ester products with good yields (up to 89%) and excellent regioselectivity as well as good functional group tolerance.



The oxidative derivatization of alkenes arguably constitutes one of the most paramount categories of organic transformations both in industrial and scientific contexts. Because of the economic and ecological profile of molecular oxygen, there has been a sustained and ever-increasing interest in the development of new reaction manifolds that capitalize on the use of O_2 as a terminal oxidant for the functionalization of alkenes.[1] Of particular interest in this context are reactions in which O_2 solely serves as an acceptor of electrons and protons from the substrate molecules but is otherwise not involved in the derivatization event, i.e., emulated or artificial oxidase reactions. While there has been notable progress in the development of transition-metal-catalyzed oxidase reactions,[1] there is still only a very limited number of reports documented in the literature that delineate analogous and equipotent metal-free catalysis concepts for the derivatization of simple alkenes.[2,3] As a matter of fact, selective O_2-reliant allylic oxidations that are exclusively driven by nonmetallic catalysts and in which the carbon−heteroatom bond formation occurs via carbophilic alkene activation[4] have remained elusive thus far.[2a,5]

In a series of independent investigations, both Pandey et al. and Ragains et al. showed that organoselanes and -diselanes can be readily oxidized under photochemical conditions using photosensitizers such as 1,4-dicyanonaphthalene (DCN) and $Ru(bpy)_3(PF_6)_2$, respectively.[6] Pandey et al. also showed that alkenes can be converted into β-selenenylated ethers and esters using stoichiometric quantities of $(PhSe)_2$ in the presence of DCN and O_2 under UV irradiation.[7] From these studies, we conjectured that photosensitizers with suitable redox potentials and photophysical properties in combination with organodiselanes might allow for the design of a cooperative catalysis manifold in which simple alkenes are directly converted into allylic oxidation products using O_2 or even air as the sole oxidant. A notable implication of such a catalytic regime is the fact that oxidants commonly employed in selenium catalysis (e.g., *N*-haloimides and -amides as well as hypervalent iodine reagents), which inevitably entail the production of significant amounts of waste, may be replaced by O_2 in certain cases. On the basis of this conceptual rationale, we reasoned that simple alkenes might be oxidatively coupled to carboxylic acids to give allylic esters[8] via light-dependent cooperative selenium catalysis (Scheme 1).

Scheme 1. Selenium-Catalyzed Oxidative Allylic Esterification Strategies



Traditional methods for the synthesis of this compound class usually rely on the use of preoxidized starting materials, such as allylic alcohols or halides, and often require harsh reaction conditions (e.g., strong Brønsted acids, high temperatures). The envisioned cooperative selenocatalytic approach, on the other hand, would provide a significantly streamlined and atom-economic[9] assembly of the allylic ester motif, since the adjustment of the desired oxidation state within the carbon framework and the C−O bond formation would take place in the

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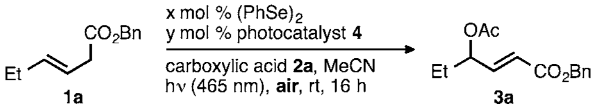
very same event using air as the sole oxidant. As a consequence of these considerations, we report herein the first allylic oxidation protocol for the conversion of nonpolarized alkenes into allylic esters via light-dependent cooperative selenium catalysis.

At the outset of our investigations, we identified 2,4,6-tris(4-methoxyphenyl)pyrylium tetrafluoroborate (**4**) as the photocatalyst of choice since the reduction potential of its excited state ($E_{1/2}^{red}$ [**4***/**10**] = +1.74 V vs SCE in MeCN)[10] was found to be sufficiently high to readily oxidize $(PhSe)_2$ ($E_{1/2}^{red}$ = +1.35 V vs SCE in MeCN)[11] but at the same time low enough to leave electron-neutral, nonconjugated alkenes intact ($E_{1/2}^{red} \geq +1.80$ V vs SCE in MeCN).[12,13] Thus, in initial experiments benzyl (*E*)-pent-3-enoate (**1a**) was reacted with acetic acid (**2a**) in various solvents (1:1; v/v) at room temperature under an atmosphere of air and irradiation at 465 nm using 10 mol % of $(PhSe)_2$ and 5 mol % of photocatalyst **4** (Table 1). We were pleased to find that the title procedure provided allylic ester **3a** in 27% when the reaction was conducted in toluene (entry 1). More polar solvents, such as THF (33%, entry 2) and DMF (29%, entry 3), resulted only in marginally improved yields. A significant increase in the yield was observed when dichloroethane and acetone were used as reaction media, which gave rise to target compound **3a** in 67% and 71% yields, respectively (entries 4 and 5). We believe that the difference in yield between toluene and THF on the one hand and dichloroethane and acetone on the other is most likely due to the insufficient solubility of photocatalyst **4** in the former solvents. The best result (83%, entry 6) was obtained in acetonitrile. Next, we varied the concentration of the carboxylic acid from 100 to 5 vol %.[13] These experiments revealed that 40 vol % of acetic acid gave the best yield (>95%, entry 7). Increasing the concentration of the alkene from 0.1 to 0.2 M (>95%, entry 8) had no negative impact on the yield.

Table 1. Optimization of Reaction Conditions[a]



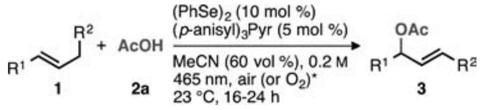
entry	*x* (mol %)/*y* (mol %)	solvent	concn **1**/**2** (M)	yield (%)
1	10/5	toluene	0.1/8.7	27
2	10/5	THF	0.1/8.7	33
3	10/5	DMF	0.1/8.7	29
4	10/5	DCE	0.1/8.7	67
5	10/5	acetone	0.1/8.7	71
6	10/5	MeCN	0.1/8.7	83
7	10/5	MeCN	0.1/7.0	>95
8	10/5	MeCN	0.2/7.0	>95
9	10/0	MeCN	0.1/7.0	0
10	0/5	MeCN	0.1/7.0	0
11[b]	10/5	MeCN	0.1/7.0	0
12[c]	10/5	MeCN	0.1/7.0	traces

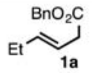
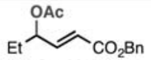
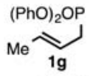
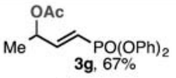
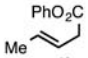
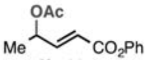
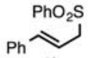
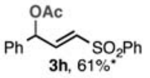
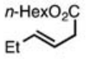
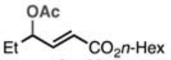
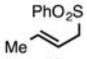
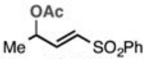
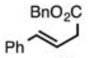
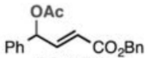
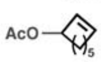
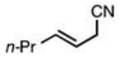
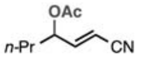
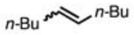
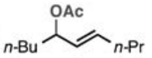
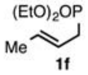
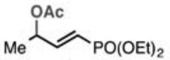
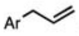
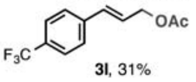
[a] Reactions were carried out on a 0.5 mmol scale in 5−2.5 mL of solvent for 16 h under an atmosphere of ambient air and with irradiation at 465 nm by an LED lamp. Yields were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [b] Reaction was performed in the dark. [c] Reaction was performed in the absence of air. DCE = 1,2-dichloroethane.

Finally, we also conducted a series of control experiments in which the reactions were performed in the absence of either of the catalysts, air, and light, respectively (entries 9−12). While no formation of allylic ester **3a** was recorded in the absence of any catalyst or light, only trace amounts of the product were detected when air was replaced by argon. These findings indicate that the title reaction is indeed proceeding via a cooperative mechanism.

With the optimized conditions in hand, investigations continued with the exploration of the scope and limitations of the title procedure. Initially, a series of different alkenes was reacted with acetic acid (**2a**) (Table 2). The use of *β*,*γ*-unsaturated esters **1a** and **1b**, which both contained aliphatic residues at the *γ*-position, resulted in very good isolated yields of 89 and 82%, respectively (entries 1 and 2). While *n*-hexyl ester **3c** was isolated in an acceptable yield of 69% (entry 3) the use of alkene **1d** furnished allylic ester **3d** only in trace amounts under the standard conditions. Changing from air to a neat O_2 atmosphere resulted in an improved reaction outcome with an isolated yield of 45% (entry 4). The exact reasons for the sluggish reactivity of styrene substrate **1d** under standard conditions remain unclear at the moment; however, we speculate that the increased steric demand of styrene derived alkenes may hamper the attack of the selenenium electrophile (cf. compound **5**, Scheme 1).

Table 2. Reaction Scope with Varying Alkenes[a]



entry	alkene	product	entry	alkene	product
1	 **1a**	 **3a**, 89%	7	 **1g**	 **3g**, 67%
2	 **1b**	 **3b**, 82%	8	 **1h**	 **3h**, 61%*
3	 **1c**	 **3c**, 69%	9	 **1i**	 **3i**, 65%*
4	 **1d**	 **3d**, 45%*	10	 **1j**	 **3j**, 89%
5	 **1e**	 **3e**, 83%	11	 $\mathbf{1k}_E$ $\mathbf{1k}_Z$	 **3k**, 81% (from $\mathbf{1k}_E$) 75% (from $\mathbf{1k}_Z$)
6	 **1f**	 **3f**, 68%	12	 **1l**	 **3l**, 31%

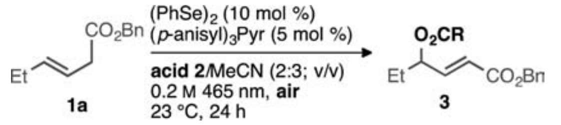
[a] Reactions were carried out on a 1 mmol scale (0.2 M) in acetonitrile for 16−24 h under an atmosphere of ambient air or O_2 (yields are marked with an asterisk) and with irradiation at 465 nm by an LED lamp. Yields refer to isolated compounds.

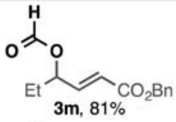
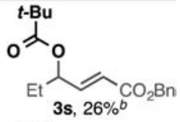
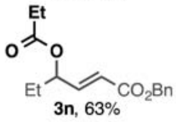
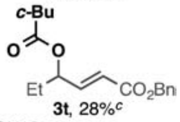
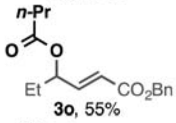
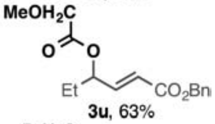
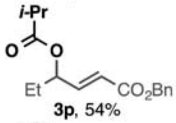
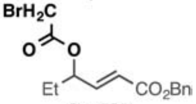
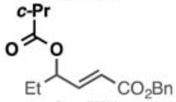
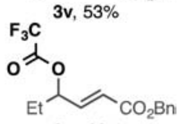
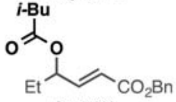
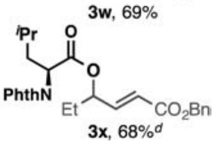
Next, we tested other functional groups, such as nitrile, phosphonate, and sulfone moieties. Conversion of nitrile **1e** under aerial conditions resulted in an isolated yield of 83% (entry 5). Application of phosphonates **1f** and **1g** provided access to the corresponding target allylic esters **3f** and **3g** in yields of 68 and 67%, respectively (entries 6 and 7). The oxidative allylic esterification of sulfones **1h** and **1i** proceeded best when neat O_2 was used as the oxidant, providing allylic esters **3h** and **3i** in 61 and 65% (entries 8 and 9). Next, we tested alkenes in which R^1 and R^2 equaled hydrocarbon residues (entries 10−12). Subjection of cyclooctene (**1j**) to the standard conditions under air furnished ester **3j** in 89% yield (entry 10). Both (*E*)-

and (*Z*)-dec-5-ene ($\mathbf{1k}_E/\mathbf{1k}_Z$) were converted to product **3k** in 81 and 75% yield, respectively, thus indicating that the double bond geometry does not play a significant role in these reactions (entry 11). Eventually, we exposed monosubstituted alkene **1l** to the catalysis protocol, yielding corresponding cinnamyl acetate **3l** in 31% together with 9% of 2-acetoxy-5-(trifluoromethyl)indane (entry 12).

Having demonstrated the feasibility, selectivity, and functional group tolerance of the oxidative allylic esterification of acetic acid with various alkene substrates, we then turned our attention to the generalization of this new selenium catalysis protocol toward other carboxylic acids. Consequently, a representative series of different carboxylic acids with varying pK_a values and steric demands was tested next (Table 3). For this part of our investigation, benzyl hex-3-enoate (**1a**) was chosen as the model substrate. The conversion of **1a** with formic acid under an atmosphere of air led to allylic ester **3m** in an isolated yield of 81% (entry 1). In order to determine whether there is any correlation between the yield of the ester products and the steric demand of the acid, we tested propionic acid as well as several isomeric forms of butanoic and pentanoic acid. Starting with propionic acid, the corresponding allylic ester derivative **3n** was obtained in 63% yield (entry 2). Within the series of butanoic acids, all isomeric forms, i.e., butyric acid (55%, entry 3), isobutyric acid (54%, entry 4), as well as cyclopropanecarboxylic acid (57%, entry 5), led to similar yields. In contrast to the homogeneous reaction outcomes observed within the butanoic acid series, the set of homologous pentanoic acids displayed a marked structural correlation between sterics and yield. While use of isovaleric acid (entry 6) furnished ester **3r** in a yield of 53%, its sterically more congested analogs pivalic and cyclobutanecarboxylic acid (entries 7 and 8) resulted in merely 26 and 28% isolated yield, respectively. It is noteworthy that the conversion of the latter acid was significantly slower (96 h) than any other acid tested.

Table 3. Reaction Scope with Varying Carboxylic Acids[a]



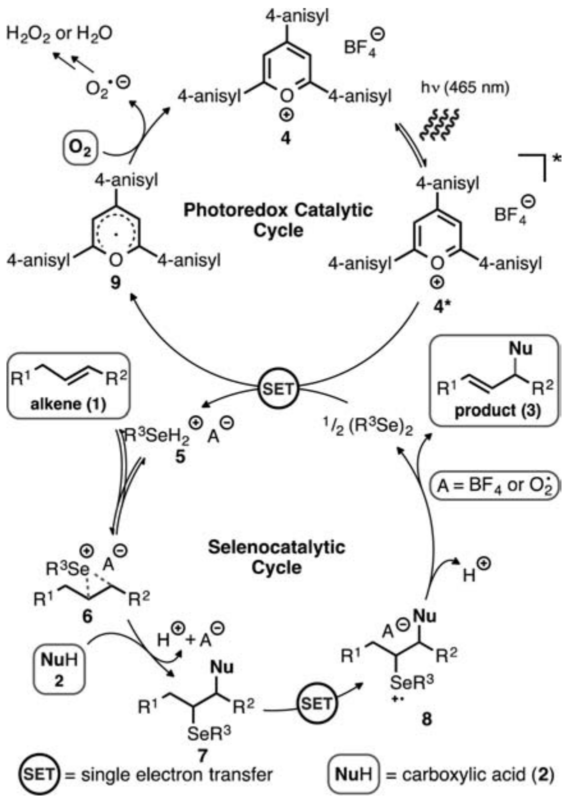
entry	product	entry	product
1	 **3m**, 81%	7	 **3s**, 26%[b]
2	 **3n**, 63%	8	 **3t**, 28%[c]
3	 **3o**, 55%	9	 **3u**, 63%
4	 **3p**, 54%	10	 **3v**, 53%
5	 **3q**, 57%	11	 **3w**, 69%
6	 **3r**, 53%	12	 **3x**, 68%[d]

[a] Reactions were carried out on a 1 mmol scale (0.2 M) in acetonitrile for 16−24 h under an atmosphere of ambient air and with irradiation at 465 nm by an LED lamp. Yields refer to isolated compounds. [b] The reaction time was 72 h. [c] The reaction time was 96 h. [d] 5 equiv of *N*-phthaloylleucine were reacted with **1c** under an O_2 atmosphere.

Furthermore, we examined functionalized derivatives of acetic acid in order to elucidate any potential correlation between their acidity and the yield. Therefore, we independently reacted substrate **1a** with *α*-methoxy (entry 9; pK_a = 3.53),[14] *α*-bromo (entry 10; pK_a = 2.86),[14] and trifluoroacetic acid (entry 11; pK_a = 0.23)[14] under the standard conditions. The respective allylic esters **3u−w** were isolated in yields ranging between 53 and 69%. These findings clearly showcase that the title procedure remains effective within at least 4 orders of magnitude of pK_a values, thus underscoring the overall utility of the cooperative selenium catalysis concept. Another noteworthy feature of this method is the fact that even amino acids can be used as reactants. Conversion of phthaloyl-protected leucine with alkene **1c** under an O_2 atmosphere resulted in an isolated yield of 68% as a 1:1 mixture of diastereomers (entry 12).

From a series of control experiments (see the Supporting Information), we learned that the reaction proceeds through acyloxy selenation intermediate **7** (Nu = acyloxy, Scheme 2). Furthermore, we found that selenide **7** can be readily converted into ester **3** in the presence of photocatalyst **4** but without

Scheme 2. Mechanistic Hypothesis for the Cooperative Selenium-Catalyzed Oxidative Esterification of Alkenes



additional (PhSe)$_2$. As a matter of fact, under these conditions (PhSe)$_2$ is regenerated from compound 7. From these preliminary results, we formulate the mechanistic hypothesis depicted in Scheme 2. In this scenario, excited photocatalyst **4*** may initially activate (PhSe)$_2$ via single-electron transfer (SET) followed by fragmentation of the resulting radical cation to give ArSe$^+$ species **5**.[7,15] The reduced sensitizer **9**, in turn, may undergo oxidation by molecular oxygen. Subsequent excitation of photocatalyst **4** would eventually complete the photoredox catalytic cycle. The transiently generated selenenium cation **5** presumably reacts with the olefin moiety to give seleniranium intermediate **6**,[16] which on its part is directly attacked by a nucleophile, leading to 1,2-selenofunctionalized species **7**. Intermediate **7** is most likely also oxidized by excited photocatalyst **4***,[17] which subsequently leads to the elimination of the PhSe group and restoration of the carbon−carbon double bond.

In summary, we have disclosed an unprecedented and very efficient selenium-catalyzed oxidase protocol exemplified in the oxidative allylic esterification of carboxylic acids with nonactivated alkenes. The title method is characterized by a good functional group tolerance and allows for the use of a wide range of different carboxylic acids including amino acids. The suitability of amino acid derivatives in this protocol is noteworthy as this feature may allow for the design of a novel oxidative ligation strategy in the context of depsipeptide syntheses. Consequently, this procedure opens a new avenue toward the economic and sustainable incorporation of oxygen functionalities into unsaturated hydrocarbon architectures. We believe that this cooperative selenocatalytic concept of artificial, light-dependent oxidase reactivity will expediently complement current methodology in the realm of oxidation chemistry. Efforts toward the development of an asymmetric variant of the title protocol as well as its elaboration into other oxidative bond-forming processes are currently ongoing in our laboratories.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01130.

Experimental procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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(17) In this context, we speculate that the conversion of intermediate **7** into radical cation **8** may be inhibited by (PhSe)$_2$ at sufficiently high concentrations of the latter in comparison to the concentration of intermediate **7**. This assumption is supported by the observation that compound **7a** (Nu = AcO, R^1 = Et, R^2 = CO$_2$Bn) furnishes product **3a** only in low quantities when additional (PhSe)$_2$ is present. We also hypothesize that intermediate **7** represents the resting state of the catalytic cycle.