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Preparation of Heterocycles via Visible-Light-Driven Aerobic Selenation of Olefins with Diselenides

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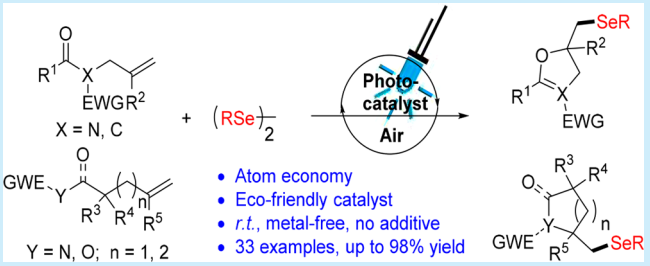
Supporting Information

ABSTRACT: The aerobic dehydrogenative cyclization of alkenes with easily accessible diselenides facilitated by visible light is reported. Notably, the features of this transition-metal-free protocol are pronounced efficiency and practicality, good functional group tolerance, atom economy, and high sustainability, since ambient air and visible light are adequate for the clean construction of five- and six membered heterocycles in yields of up to 98%.



Organoselenides, an important class of molecules with high pharmacological value, are widely found in a great number of biologically active compounds and natural products (Figure 1).[1] They also have numerous applications in organic synthesis.[2] In fact, the seleno group is a very useful and versatile functionality, because it can be easily removed either by oxidation or by reduction.[3] In recent decades, organo-selenium-mediated cyclization reactions used in either a hetero- or carbocyclic ring formation are well documented.[4] In particular, the addition of organoselenium cations to unsaturated compounds has been largely used as a crucial step in many important synthetic transformations.[5] The transformation is based on the mode of electrophilic cyclization to produce the corresponding five- or six-membered heterocycles such as oxazoline, isoxazoline, lactone, etc. Oxazolines are prevalent units found in a variety of naturally or biologically active compounds with several pharmocological properties (e.g., antiobiotic, antitumor, anti-inflammatory, and antifungal activity, Figure 1).[6] Furthermore, these structures play an important role in asymmetric synthesis, extensively serving as auxiliaries and ligands.[7] For these reasons, the development of practical and convenient methods for the construction of oxazolines is highly desirable. Although there are some approaches to the synthesis of seleno oxazolines based on a cyclization mode (Scheme 1), these procedures have certain disadvantages that include the need for heavy metals and/or heating conditions, the requirement of excess oxidants, and the generation of equivalents of toxic byproducts.[8]

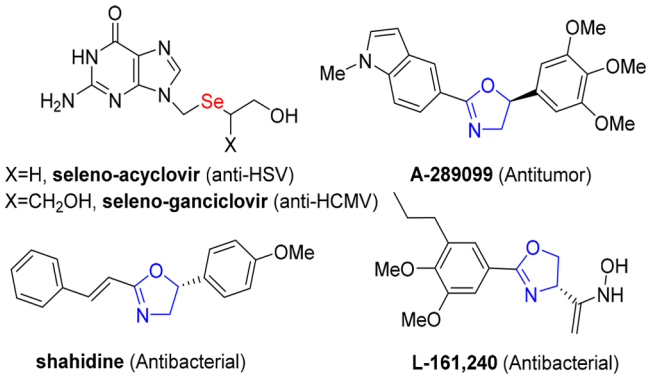
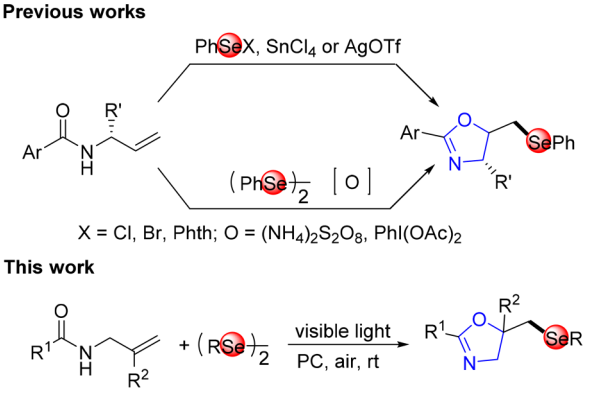


Figure 1. Examples of biologically active organoselenides and oxazolines.

Scheme 1. Seleno Cyclization of *N*-Alkenylamides



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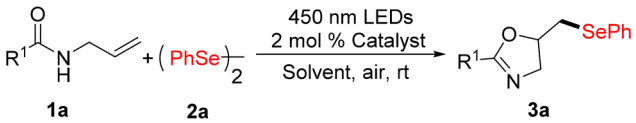
Undoubtedly, the employment of diselenides as the selenylating agent is preferred because diselenides are stable, easily accessible, and easy to handle during manipulations. In addition, in a series of independent investigations, both Pandey et al. and Breder et al. showed that diselenides can be readily oxidized to generate a $PhSe^+$ intermediate under photochemical conditions in the air.[9] Moreover, our group has reported visible-light-mediated aerobic selenation of (hetero)-arenes with diselenides through $PhSe^+$ electrophilic addition.[10] On the basis of our continuing interest in this field, we design the seleno functional cyclization of unsaturated compounds by photoredox catalysis using air as the sole oxidant. To the best of our knowledge, the use of visible-light catalysis to make seleno oxazolines through the reaction of olefinic amides with diselenides has not been reported to date. The method is considerably more advantageous in terms of green and sustainable chemistry than the available method because it (i) is simple to operate and cost-effective, (ii) uses O_2 as a terminal oxidant, and (iii) provides H_2O as the primary byproduct.

We commenced our study by using *N*-allyl-1-naphthamide (**1a**) and diphenyl diselenide (**2a**) as the model substrates for optimizing the reaction conditions, and the results are shown in Table 1. The selenative intramolecular cyclization of **1a** with

Table 1. Optimization of Reaction Conditions[a]



1a **2a** **3a**

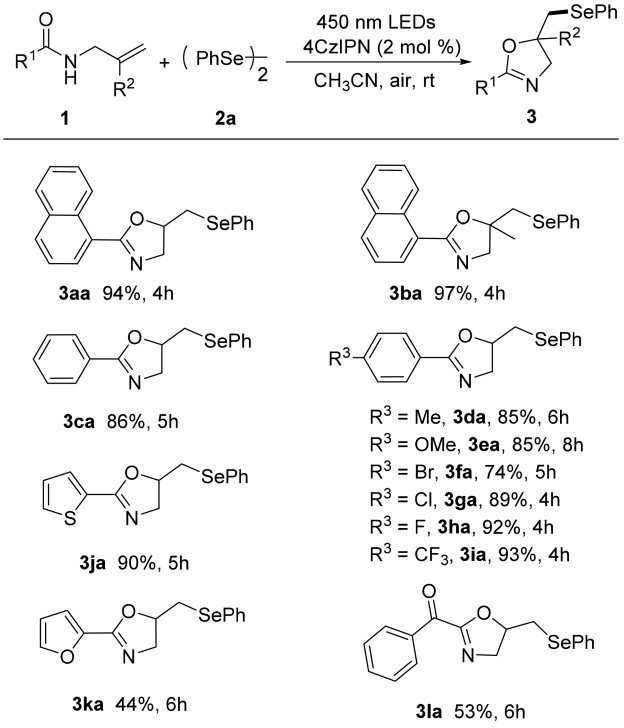
entry	catalyst	solvent	time (h)	yield[b] (%)
1	–	acetone	24	19
2	–	THF	24	22
3	–	DCE	24	50
4	–	CH_3CN	24	73
5	Riboflavin	CH_3CN	24	62
6	Eosin Y	CH_3CN	14	76
7	FIrPic	CH_3CN	10	81
8	Fluorescein	CH_3CN	11	85
9	Acr-Mes$^+$	CH_3CN	2	90
10	4-CzIPN	CH_3CN	4	94
11[c]	4-CzIPN	CH_3CN	24	0

[a]Reaction conditions: (R^1 = naphthalene-1-yl), **1a** (0.1 mmol), **2a** (0.06 mmol), catalyst (2 mol %), solvent (2 mL), in air at room temperature, irradiated by 3 W blue LEDs. The reaction was monitored by TLC. [b]Isolated yield. [c]Reaction was carried out in the dark.

2a was studied in the absence of a photocatalyst under blue LEDs irradiation using air as the oxidant to form oxazoline **3a** (entries 1–4). After investigating the effect of the solvent on this cyclization, CH_3CN was found to be the best solvent (entry 4); poor yields (19–50%) of **3a** were obtained when acetone, THF, and DCE were used as the solvent (entries 1–3). For further optimization, various photoredox catalysts were examined (entries 5–10). We were delighted to obtain the desired product **3a** in 90% yield of isolated product, when using 2 mol % of 9-mesityl-10-methylacridinium perchlorate (Mes-Acr$^+$) as the photocatalyst (entry 9), presumably owing to the high oxidative power of Mes-Acr$^+$ (E*red = 2.06 V vs SCE) compared to that of other catalysts.[11] Notably, the organo photocatalyst 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN) was found to provide the best result, offering selenation product **3a** in 94% yield (entry 10). Moreover, the absence of light irradiation completely quenched the reaction, proving that a light mediated reaction was involved (entry 11).

With the optimized cyclization reaction conditions in hand, we examined the scope by first varying the allylic amides (Scheme 2). Various unsaturated amides were competent

Scheme 2. Scope of Cyclization of *N*-Alkenylamides[a,b]



[a]Reaction conditions: **1** (0.1 mmol), **2a** (0.06 mmol), and 4CzIPN (2 mol %) in CH_3CN (2.0 mL) were irradiated with 3 W blue LEDs in air at rt. The reaction was monitored by TLC. [b]Isolated yield.

electrophilic addition partners: *N*-allylamides **1** with electron-donating substituents, such as 1-naphthyl, phenyl, 4-methyl and 4-methoxy groups, performed well with diphenyl diselenide (**2a**), affording the desired seleno oxazoline products **3aa**, **3ca**–**3ea** with 85–94% yields. 1,1-Disubstituted alkene **1b** was subjected to the reaction conditions and gave methyl derivative **3ba** in 97% yield. Synthetically attractive groups (F, Cl, Br, CF_3) in substrates **1** were also tolerated in this reaction providing the products **3fa**–**3ia** in high to excellent yields. The reaction of heteroaryl substituted amides proceeded smoothly to afford the corresponding products **3ja** and **3ka** in 90% and 44% yields, respectively. Surprisingly, benzyl substituted amides **1l** furnished oxo-oxazoline **3la** with a 53% yield.

Next, a diverse array of substituted diselenides were employed as substrates to explore the scope of this reaction (Scheme 3). Different electron-donating groups (Me, OMe) or 1-naphthyl (**2b**, **2c**, **2g**, **2h**) were tolerated with very limited influence on the yields (71%–80% yields), whereas 1,2-bis(3,4,5-trimethoxyphenyl) diselane gave the product (**3ae**) in moderate yield. Furthermore, steric effects did not significantly affect the reaction, and on using ortho-substituted diselenides the corresponding products (**3ad**, **3af**) were obtained in 75%

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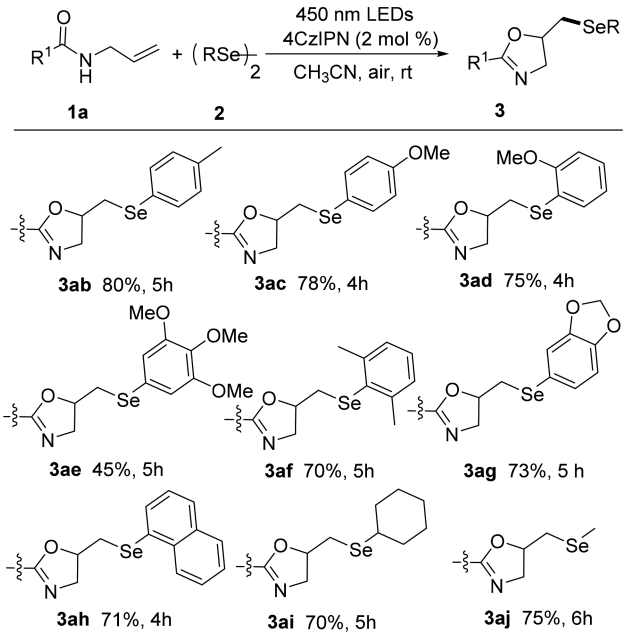
Scheme 3. Scope of the Reaction of Diselenides[a,b]

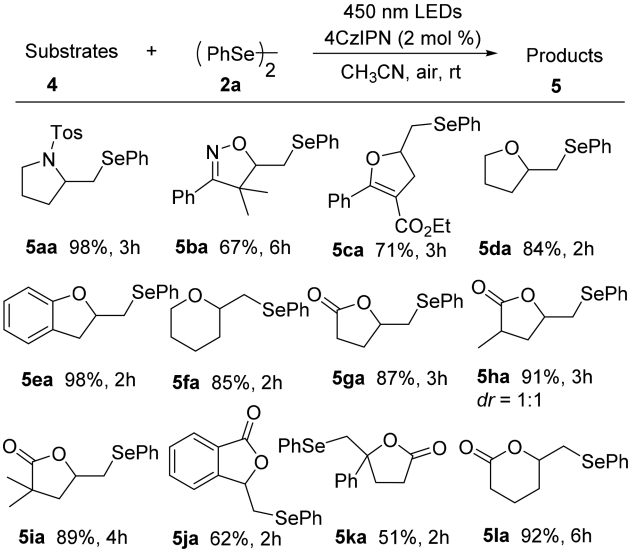


[a]Reaction conditions: (R^1 = naphthalene-1-yl) **1a** (0.1 mmol), **2** (0.06 mmol), and 4CzIPN (2 mol %) in CH_3CN (2.0 mL) were irradiated with 3 W blue LEDs in air at rt. The reaction was monitored by TLC. [b]Isolated yield.

and 70% yields, respectively. Importantly, the dialkyl diselenides were good reaction partners and provided oxazoline (**3ai**, **3aj**) in good yields.

Encouraged by our results with allylic amides, we shifted our focus to investigate the scope of the nucleopilic reagent (Scheme 4). As we expected, formation of *Ts*-protected pyrrolidine **5aa** proceeded in 98% yield while isoxazoline **5ba** was formed in a moderate 67% yield. Ethyl 2-benzoylpent-4-enoate and 2-allylphenol were efficient substrates and afforded products (**5ca**, **5ea**) in 71% and 98% yields. The selenocyclization of enol resulted in 84% and 85% yields of seleno tetrahydrofuran (**5da**) and a tetrahydro-2*H*-pyran derivative (**5fa**). Using the alkenoic acids as substrates, we observed the construction of five- and six-membered lactone rings (**5ga**–**5la**) in moderate to excellent yields. Notably, **5ha** was isolated as an ∼1:1 mixture of diastereomers in 91% combined yield. The similar diselenide-mediated aerobic intramolecular cyclizations of alkenoic acids and alcohols have been disclosed by Breder and co-workers.[12] In all these cases, however, seleno-free heterocycles were produced instead of seleno-containing structures.

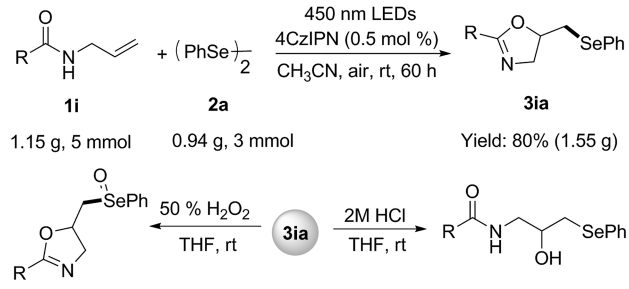
Scheme 4. Scope of Cyclization of Unsaturated Compounds[a,b]



[a]Reaction conditions: **4** (0.1 mmol), **2a** (0.06 mmol), and 4CzIPN (2 mol %) in CH_3CN (2.0 mL) were irradiated with 3 W blue LEDs in air at rt. The reaction was monitored by TLC. [b]Isolated yield.

To demonstrate the utility of this visible-light-mediated protocol, we conducted the reaction between **1i** (5 mmol, 1.15 g) and **2a** (3 mmol, 0.94 g) in the presence of 4CzIPN (0.5 mol %) on a gram scale (Scheme 5). To our delight, the corresponding product **3ia** was obtained in 80% isolated yield with a prolonged time. Furthermore, functional group transformations of **3ia** were also pursued. Treatment of selenide **3ia** with H_2O_2 lead to the formation of selenoxides **6a** in 89% yield. Besides, the oxazoline moiety of **3ia** could also be easily hydrolyzed at room temperature, delivering vicinal amino alcohol **6b** in high yield.

Scheme 5. Gram-Scale Seleno Cyclization of 1i and Derivatization of Oxazoline 3ia



The photoluminescence of 4CzIPN was quenched by diphenyl diselenide (**2a**) with a rate constant of 6.03×10^2 $L{\cdot}mol^{-1}$. In contrast, the quenching rate constant of 4CzIPN with *N*-allyl-1-naphthamide (**1a**) was much smaller (1.16×10^2 $L{\cdot}mol^{-1}$) (see SI, Figure S3). This result indicated that the photoreaction may be mainly initiated by the interaction between the excited 4CzIPN and diselenide. The oxidation potential of diphenyl diselenide **2a** is 1.35 V (vs SCE),[13] and the reduction potential of the excited 4CzIPN is 1.35 V (vs SCE).[14] Thus, the electron transfer from **2a** to the excited 4CzIPN is thermodynamically feasible for seleno intramolecular cyclization.

On the basis of our observations and literature reports,[12a,15] a plausible mechanism is proposed in Scheme 6. Under visible-light irradiation, 4CzIPN is converted to the excited 4CzIPN*. A single electron transfer between diphenyl diselenide **2a** and 4CzIPN* affords the $\mathbf{2a}^{\bullet+}$ radical cation and generates the $4CzIPN^{\bullet-}$ radical anion. The photoredox cycle is completed by the molecular oxygen oxidation of $4CzIPN^{\bullet-}$ to the ground state. Subsequent reaction of diselane radical cation $\mathbf{2a}^{\bullet+}$ with *N*-alkenylamide **1c** produces seleniranium cation **A** and 0.5 equiv of diphenyl diselenide **2a**.[16] Finally, the desired product **3c** is generated via intramolecular nucleophilic cyclization of intermidate **A**.

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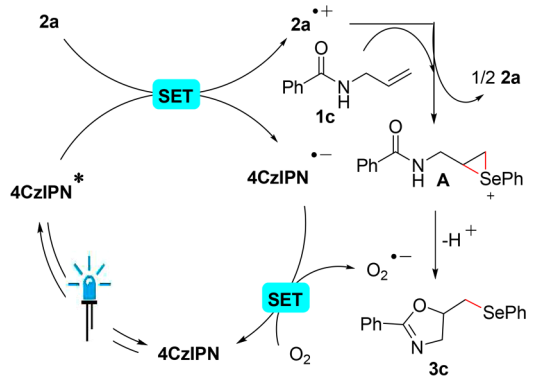
Scheme 6. Postulated Cyclization Reaction Mechanism



In conclusion, we have developed an economical and highly efficient methodology for the synthesis of heterocycles through selenation of alkenes with diselenides using molecular oxygen as a terminal oxidant under visible-light irradiation. Various aryl/alkyl diselenides and alkenes were suitable for this transformation and afforded heterocycles (such as oxazoline, isoxazoline, pyrrolidine, lactone, etc.) in excellent yields. Notably, the products can be used as direct precursors to construct an array of important molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03738.

Detailed experimental procedures, mechanism studies, and full spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(16) The detailed procedure for the reaction of diselane radical cation **2a**$^{\bullet+}$ with *N*-alkenylamides **1c** is still unclear at this point. Diselane radical cation **2a**$^{\bullet+}$ may undergo heterolytic cleavage of the Se−Se bond to generate the cation $[PhSe]^+$ and the radical [PhSe·] or dimerize to a tetrameric dication $[(PhSe)_4]^{2+}$. Both $[PhSe]^+$ and $[(PhSe)_4]^{2+}$ are efficient selenium-π-acid intermediates, which could be trapped by *N*-alkenylamide **1c**. For a detailed kinetic and thermodynamic analysis of the diselenide mediated anodic cyclizaion, please see ref 15a.

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