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Visible-Light Photoredox Catalyzed Three-Component Cyclization of 2*H*-Azirines, Alkynyl Bromides, and Molecular Oxygen to Oxazole Skeleton

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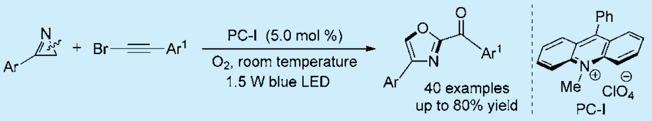
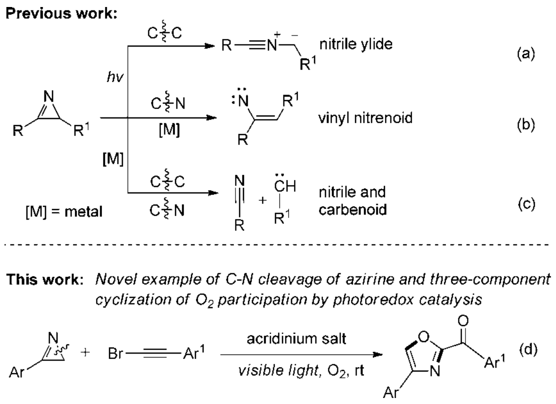
Supporting Information

ABSTRACT: A novel three-component cyclization of 2*H*-azirines, alkynyl bromides, and molecular oxygen under visible-light photoredox catalysis at room temperature has been developed, which provides a direct approach to a wide range of substituted oxazoles in moderate to good yields.



The unique 2*H*-azirines with highly strained three-membered *N*-heterocyclic motifs are known as reactive intermediates in organic synthesis.[1] Although 2*H*-azirines featured a C═N bond embedded in a highly strained three-membered cycle, they are stable enough to be isolated and stored for a long while. As a consequence, a variety of organic transformations concerning 2*H*-azirines have been reported.[2] Generally, the ring-opening of 2*H*-azirines underwent three possible bond cleavage models to release intermolecular strain. For instance, the direct C−C bond cleavage in 2*H*-azirines to generate nitrile ylides under light irradiation (Scheme 1a);[3] the C−N bond cleavage in 2*H*-azirines by transition-metal catalysis to form vinyl nitrenoid intermediates (Scheme 1b);[4−6] and the simultaneous cleavage of both C−C and C−N bonds generates carbenoid species and nitriles (Scheme 1c).[7] Recently, 2*H*-azirines have been used for the synthesis of *N*-containing compounds.[8] In particular, 2*H*-azirines bearing an aryl group at the C-3 position are attractive because of their unique activity. Although many advances have been made on azirine chemistry in the last decades, development of mild and green chemical transformations of azirines is highly desirable.

Scheme 1. Representative Bond Cleavage of 2*H*-Azirines



Most recently, visible-light-induced photoredox catalysis has offered a valuable strategy for organic transformations,[9,10] and a number of elegant works have been reported by MacMillan,[9a,b] Yoon,[9c] Sanford,[9d] Glorious,[9e] Stephenson,[9f] Nicewicz,[10a−e] Xiao,[10f,g] and others.[10h−l] This rapidly expanding field has enabled the invention of a series of bond formations, which are impossible to be constructed previously via the classic methods.

It is well-known that molecular oxygen is always considered an atom-economical, environmentally benign, and abundant source.[11] In general, oxygen acts as a sink for electrons coming from catalysts, and which also can be incorporated into the products. More often, exploring the novel synthesis of oxygen-containing compounds via molecular oxygen incorporation is much more practical and valuable. To our knowledge, few reports exist referring to aerobic chemical process in the presence of photoredox catalyst,[10k,l] but less on molecular oxygen incorporation. Based on these understandings and our recent works on photochemistry,[12] we herein first report an O_2-participated three-component cyclization of 3-aryl-2*H*-azirines with 1-aryl-2-bromoacetylenes in the presence of acridinium salt as a photoredox catalyst under visible light irradiation at room temperature (Scheme 1d). The photoredox-catalyzed C−N bond cleavage of azirines and incorporation of oxygen atom into oxazoles from O_2 proceed smoothly under mild and energy-efficient conditions.

On the basis of recognizing photoredox catalysis, we set out to test the model reaction of 3-phenyl-2*H*-azirine (**1a**) with 1-phenyl-2-bromoacetylene (**2a**) using organic dye as photoredox catalyst under visible light irradiation in air at room temperature, as shown in Table 1. Initially, we found that green LED was capable of enabling the cycloaddition of **1a** with **2a** in CH_3CN under 9-phenyl-10-methylacridinium perchlorate catalysis (PC-

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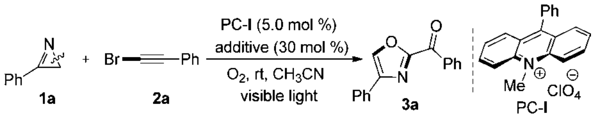
Table 1. Optimization of the Reaction Conditions[a]



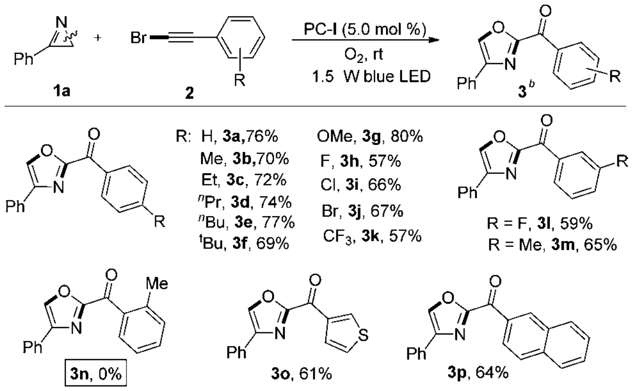
entry	light source	additive	yield (%)[b]
1	green LED		7
2	white LED		n.r.
3	blue LED (1.5 W)		62
4	blue LED (3 W)		64
5	blue LED (6 W)		25
6	blue LED (1.5 W)	PhSSPh	46
7	blue LED (1.5 W)	TBHP	24
8	blue LED (1.5 W)	Et_3N	n.r.
9	blue LED (1.5 W)	PivOH	43
10	blue LED (1.5 W)		77[c], 76[c,d]
11	blue LED (1.5 W)		n.r.[e]
12			n.r.

[a] Reaction conditions: **1a** (0.40 mmol), **2a** (0.20 mmol), PC-**I** (5.0 mol %), CH_3CN (1.0 mL) under air atmosphere with light irradiation for 24 h. [b] Isolated yield. [c] CH_3CN/DCE (V/V = 1:1, 1.0 mL), [d] O_2 atmosphere (balloon). [e] In absence of PC-I. n.r. = no reaction.

I), albeit with the formation of product **3a** in 7% yield (entry 1). Single crystal X-ray diffraction further confirmed the structure of oxazole backbone (Supporting Information for detail). Subsequently, screening of light source indicated that white LED did not promote the model reaction (entry 2). To our delight, employing blue LED (1.5 W) irradiation for 24 h on the reaction generated **3a** in 62% yield (entry 3). The power of blue LED was examined, and 3 and 6 W blue LED provided the desired product **3a** in 64 and 25% yields, respectively (entries 4 and 5). Addition of additives, such as PhSSPh, *tert*-butyl hydroperoxide (TBHP), NEt_3, and PivOH, resulted in lower yields of **3a** (entries 6–9). Furthermore, improved yield of **3a** was achieved by using mixed solvent of CH_3CN/DCE in equal volume (entry 10), and comparable result was obtained when carried out in O_2 (entry 10). As expected, no reaction occurred in the absence of PC-**I** or light irradiation (entries 11 and 12). Inferior results were obtained when the other solvents, such as DCE, DMF, MeOH, and THF, were investigated under the similar conditions (SI, Table S1, entries 1–4). Further, the screening of some organic dyes as photocatalysts demonstrated that PC-**I** was an optimal photocatalyst among the examined acridinium salts, and the results are also summarized in Table S1 (entries 5–11).

Based on the optimal reaction conditions, we turned our attention to investigate the scope of the substrates. First, the scope of alkynyl bromides in the reaction was examined, as described in Scheme 2. The visible-light-induced cyclization of 3-phenyl-2*H*-azirine (**1a**) with an array of 1-aryl-2-bromoacetylenes smoothly underwent optimal conditions to generate the corresponding substituted oxazoles as desired products. Obviously, the aryl substituents of **2** bearing both electron-withdrawing and electron-donating groups on the *para*-position of the benzene rings exhibited good tolerance. For example, *para*-methyl, *para*-ethyl, *para*-(*iso*)propyl, *para*-butyl, *para*-(*tert*)butyl, and *para*-methoxyl substituted phenyl-2-bromoacetylenes reacted with **1a** to afford the corresponding products (**3b–g**) in 69–80% yields. The reactions also proceeded well when the reactions of **1a** with 1-aryl-2-bromoacetylenes with F, Cl, Br, and CF_3 at *para*- or *meta*-position of the phenyl rings were performed under the standard reaction conditions, providing the desired products (**3h–m**) in 57–67% yields. An obvious steric effect was observed when 1-(*ortho*-methyl-substituted phenyl)-2-bromoacetylene reacted with **1a**. No products including desired **3n** were obtained, and the starting materials were recovered and unchanged. It should be noted that 3-(bromoethynyl)thiophene and 2-(bromoethynyl)naphthalene as substrates reacted with **1a** to give **3o** and **3p** in 61 and 64% yields, respectively.

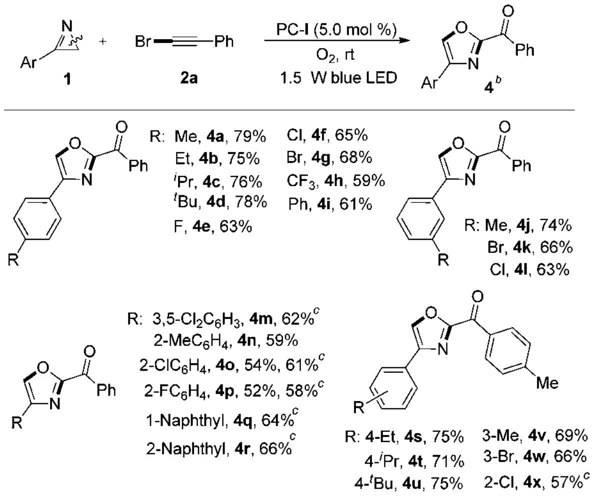
Scheme 2. Scope of Alkynyl Bromides[a]



[a] Reaction conditions: **1a** (0.40 mmol), **2** (0.20 mmol), PC-**I** (5.0 mol %), CH_3CN/DCE (V/V = 1:1, 1.0 mL), room temperature, air, 1.5 W blue LED for 24 h. [b] Isolated yield.

Subsequently, the generality of 2*H*-azirine was also investigated and is summarized in Scheme 3. It is noteworthy that excellent group tolerance was observed when a number of substituted 2*H*-azirines were examined in the cycloaddition reactions. 3-Aryl-2*H*-azirines attached electron-donating groups (Me, Et, *i*-Pr and *t*-Bu) at *para*-position of the phenyl rings reacted with **2a** to provide the corresponding products (**4a–d**) in good yields. Meanwhile, the reactions of 2*H*-azirines with a (*para*-fluoro)phenyl, (*para*-chloro)phenyl, and (*para*-bromo)-phenyl at 3-position with **2a** afforded the desired products (**4e–g**) in 63–68% yields. Moreover, 3-aryl-2*H*-azirines bearing a CF_3 or C_6H_5 group on the *para*-position of benzene ring gave the anticipated products **4h** and **4i** in 59 and 61% yields, respectively.

Scheme 3. Scope of 2*H*-Azirines[a]

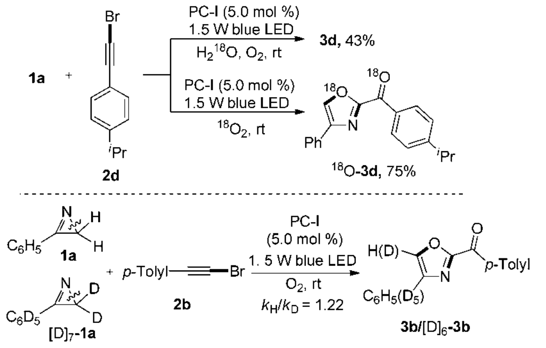


[a] Reaction conditions: **1** (0.40 mmol), **2a** (0.20 mmol), PC-**I** (5.0 mol %), CH_3CN/DCE (V/V = 1:1, 1.0 mL), room temperature, air, 1.5 W blue LED for 24 h. [b] Isolated yield. [c] 36 h

The cycloaddition of **2a** with 3-(*meta*-substituted phenyl)-2*H*-azirines proceeded smoothly under optimal conditions to give products (**4j**–**l**) in accepted yields. However, an obvious steric effect was observed for the formation of **4m**–**p** by using 3-(*ortho*-substituted phenyl)-2*H*-azirines as one of the substrates. The reactions of 3-(3,5-Cl_2-phenyl)-2*H*-azirine, 3-(naphthalen-1-yl)-2*H*-azirine, and 3-(naphthalen-2-yl)-2*H*-azirine, as well as 3-(2-Cl-phenyl)-2*H*-azirine and 3-(2-F-phenyl)-2*H*-azirine with **2a** generated the target products (**4m**, and **4o**–**r**) in satisfactory yields after 36 h. In addition, the cycloaddition of several aryl-substituted 2*H*-azirines with 1-(4-methylphenyl)-2-bromoacetylene under the optimized reaction conditions were examined, and the according products (**4s**–**x**) were obtained in 57–75% yields.

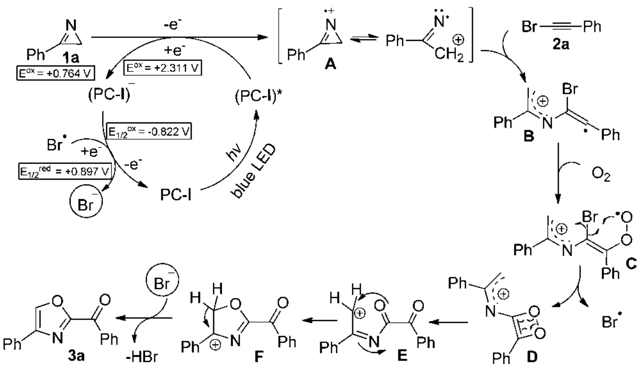
To gain insight into the reaction mechanism of oxygen participated cycloaddition, several control experiments were conducted. First, addition of TEMPO (1.0 equiv) into the reaction of **1a** with **2a** suppressed the cycloaddition completely (Scheme S2, SI), indicating that a radical process may be involved in the reaction. Subsequently, when **1a** reacted with (iodoethynyl)benzene, (phenylethynyl)copper, and ethynylbenzene under standard reaction conditions, no product **3a** was obtained, demonstrating that only C–Br bond can be effectively cleaved under blue LED irradiation (Scheme S2). Moreover, addition of ^{18}O-labeled water into the model reaction did not give ^{18}O-**3d** (Scheme 4). However, when the reaction was performed in $^{18}O_2$ atmosphere for 24 h, ^{18}O-**3d** was isolated in 75% yield, which was further confirmed by HRMS (Figure S1, SI). These results clearly illustrated that oxygen atom in oxazole **3d** comes from O_2 in air, not from H_2O (Scheme 4). In addition, deuterium-labeling study using $[D]_7$-**1a** unambiguously showed that the cleavage of C–H bond in the reaction is not a rate-determining step (Scheme 4). It is important to note that EPR spectra did not provide any information for the formation of superoxide radical anion ($O_2^{-\bullet}$) or singlet $^1O_2$ during the reaction. Inversely, a vinyl peroxyl radical **C** (Scheme 5) is considered as the key intermediate in the aerobic transformation (Figure S4, SI).

Scheme 4. Selected Control Experiments



On the basis of the above control experiments and mechanistic studies, a possible pathway for this cyclization is outlined in Scheme 5. Initially, a single-electron oxidation of 2*H*-azirine **1a** (E^{ox} = +0.764 V) by the excited state of organic catalyst (PC-**I**)* (E^{ox} = +2.311 V) generated a radical cation **A**[13] and (PC-**I**)$^-$.[10f] Then an addition of **A** to alkynyl bromide **2a** provided intermediate **B**. The formed **B** reacted with O_2 to afford peroxyl radical **C**, followed by a 4-endo alkene cyclization at very fast rate[14] to generate intermediate **D** along with the formation of Br radical. Next, the obtained Br radical as an oxidant gained one electron from formed (PC-**I**)$^-$ to reset catalyst PC-**I**, which proves feasible on the basis of half-peak redox potential of $Br^\bullet$/Br^- ($E_{1/2}{}^{red}$ = +0.897 V)[15] and (PC-**I**)$^-$/PC-**I** ($E_{1/2}{}^{ox}$ = −0.822 V). The fragmentation of **D** afforded **E**, followed by intermolecular cyclization to generate **F**. Finally, the obtained **F** underwent *β*-H elimination assisted by Br^- to form desired **3a** and HBr.

Scheme 5. Proposed Reaction Mechanism



In conclusion, we have developed a novel methodology to build oxazole skeleton using acridinium salt (PC-**I**, 5.0 mol %) as an organic photocatalyst at room temperature under visible light irradiation. The radical cycloaddition proceeded smoothly to generate oxazoles in moderate to good yields under mild reaction conditions, and which provides an alternative approach to functionalized oxazoles. The initial experiments have been carried out to gain insight into the possible reaction pathway, and additional efforts to gain a better understanding of this transformation are currently underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01696.

Full experimental details and characterization data for all products (PDF)

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Notes

The authors declare no competing financial interest.

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