

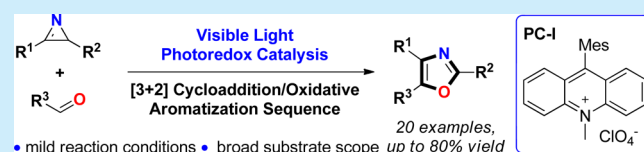
[3 + 2] Cycloaddition/Oxidative Aromatization Sequence via Photoredox Catalysis: One-Pot Synthesis of Oxazoles from 2*H*-Azirines and Aldehydes

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S Supporting Information

ABSTRACT: A novel [3 + 2] cycloaddition/oxidative aromatization sequence via visible light-induced photoredox catalysis is disclosed. It provides a general synthetic route to 2,4,5-trisubstituted oxazoles from easily accessible 2*H*-azirines and aldehydes under mild reaction conditions. The potential of this strategy was further demonstrated by the rapid synthesis of a cyclooxygenase-2 inhibitor as well as the success of employing electron-deficient alkenes and imines as the reaction partners.



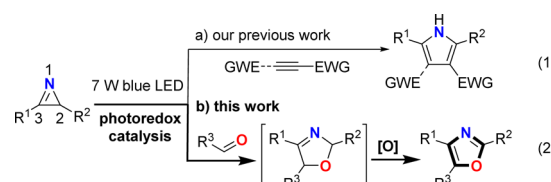
2*H*-Azirines, though a strained three-membered ring, are bench-stable and readily available reagents first reported by Neber and Burgard in 1932.¹ Due to their inherent reactivity, 2*H*-azirines have been extensively used as versatile precursors to prepare diverse *aza*-heterocycles through ring opening reactions.² Early reports indicated that cleavage of the C2–N bond can be achieved by treatment with heat³ or metal salts⁴ or through reaction with metal carbenes,⁵ delivering nitrene or 1,3-azadiene intermediates for a wide range of cycloaddition reactions. Alternatively, cleavage of the C2–C3 bond is also a viable path to form imino diradicals, nitrile ylides, or 2-azaallenyl radical cations under thermal conditions⁶ or irradiation with high-energy UV light.⁷ Usually, breaking the C2–C3 bond is more challenging than the C2–N bond because of its slightly higher bond energy than the latter.^{8,2c} Recently, our group realized this goal using visible light photocatalysis⁹ via a single-electron-transfer process.^{10,11} The key to success is the application of a commercially available organic dye photocatalyst.¹² In this work, we expand the success of this strategy to construct other useful *N*-heterocycles.

Oxazole derivatives are frequently found in natural products,¹³ pharmaceuticals,¹⁴ and as functional materials¹⁵ and usually display numerous significant bioactivities and unique properties. Encouraged by these findings, numerous strategies have been developed to forge this heterocyclic unit, mainly involving oxidation of oxazoline,¹⁶ metal/halogen-promoted intramolecular cyclization,¹⁷ or transition-metal-catalyzed bimolecular annulation.¹⁸ However, known approaches to accessing polysubstituted oxazoles often require poorly accessible starting materials and still face problems such as the need for high temperatures, tedious operations, and/or require transition metal catalysts.

Visible-light-induced photoredox catalysis has been identified as a green and sustainable synthetic method for the assembly of diverse heterocycles under mild reaction conditions.¹⁹ In this regard, we have investigated the photocatalyzed [3 + 2]

reaction via amine oxidation for the synthesis of pyrrolo[2,1-*a*]isoquinolines,^{20a} imidazoles,^{20b} and polysubstituted pyrroles¹⁰ (Scheme 1, eq 1). As a part of our continuing work,

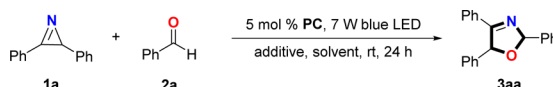
Scheme 1. Visible Light Photoredox-catalyzed Cycloaddition Reactions of 2*H*-Azirines



herein we disclosed the preparation of 2,4,5-trisubstituted oxazoles from 2*H*-azirines²¹ and commercially available aldehydes via a photoredox-catalyzed [3 + 2] cycloaddition/oxidative aromatization sequence (Scheme 1, eq 2).

Initially, we tested the formal [3 + 2] cycloaddition of 2*H*-azirine **1a** and benzaldehyde **2a** to obtain 2,5-dihydrooxazole **3aa** using 9-mesityl-10-methylacridinium perchlorate (PC-I) as the photocatalyst and 1,2-dichloroethane (DCE) as the solvent under the irradiation of a 7 W blue LED. Gratifyingly, the desired [3 + 2] reaction proceeded smoothly, giving 2,5-dihydrooxazole in 37% yield (Table 1, entry 1).²² By adding desiccant, the yield was improved (Table 1, entries 2–3), especially when 4 Å molecular sieves (MS) were used (Table 1, entry 2: 61% yield). Evaluation of the effect of solvent showed that halogenated solvent and acetonitrile were better than more polar solvents such as MeOH and DMF (Table 1, entries 2 and 4–7), with DCE still being the best solvent. Other reaction parameters such as concentration and substrate ratio were examined, although they did not lead to further improvement

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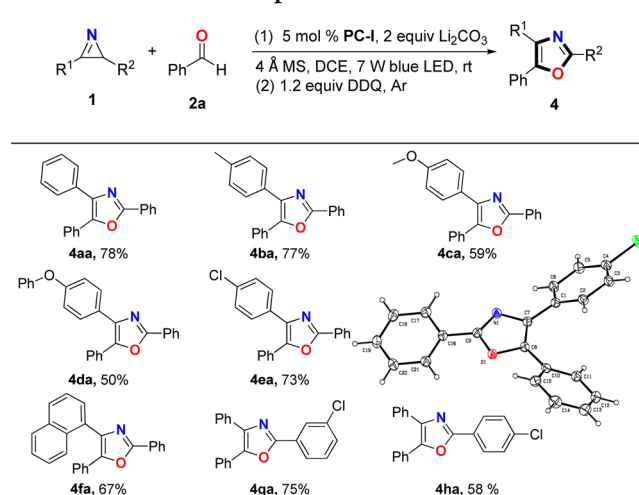
Table 1. Condition Optimization for 2,5-Dihydrooxazole^a


entry	PC	solvent	additive	yield ^b (%)
1	PC-I	DCE	—	37
2 ^c	PC-I	DCE	4 Å MS	61
3 ^c	PC-I	DCE	MgSO ₄	45
4 ^c	PC-I	DCM	4 Å MS	47
5 ^c	PC-I	MeCN	4 Å MS	45
6 ^c	PC-I	MeOH	4 Å MS	13
7 ^c	PC-I	DMF	4 Å MS	0
8 ^{c,d}	PC-I	DCE	4 Å MS/K ₂ CO ₃	70
9 ^{c,d}	PC-I	DCE	4 Å MS/Li ₂ CO ₃	77
10 ^{c,d}	PC-I	DCE	4 Å MS/Na ₂ CO ₃	69
11 ^{c,d}	PC-II	DCE	4 Å MS/Li ₂ CO ₃	0
12 ^{c,d}	PC-III	DCE	4 Å MS/Li ₂ CO ₃	22
13 ^{c,d,e}	PC-I	DCE	4 Å MS/Li ₂ CO ₃	0
14 ^{c,d}	—	DCE	4 Å MS/Li ₂ CO ₃	0

^aReaction conditions: **1a** (0.3 mmol), **2a** (1.5 mmol), photocatalyst (5 mol %), solvent (3 mL) at rt for 24 h under the irradiation of a 7 W blue LED. **PC-I**: 9-mesityl-10-methylacridinium perchlorate. **PC-II**: Ru(bpy)₃Cl₂·6H₂O. **PC-III**: Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆. ^bIsolated yield. ^c200 mg of desiccant was added. ^d2 equiv of base were added. ^eWithout visible light.

in efficiency.²³ Since aldehydes are prone to be oxidized to carboxylic acids, we postulated that a weak acidic environment was detrimental to this transformation.²⁴ Thus, a number of bases were introduced, and increased yields were indeed observed under these conditions (Table 1, entries 8–10). Among them, Li₂CO₃ greatly improved the reaction efficiency, delivering the cycloadduct in 77% yield (Table 1, entry 9). In addition, other transition metal photocatalysts, such as the ruthenium complex **PC-II** or iridium complex **PC-III**, were tested for the photocatalyzed cycloaddition reactions; however, very low yields resulted (Table 1, entries 11–12). Removing the light source or eliminating the photocatalyst from the optimal reaction conditions led to no product, indicating it is a photocatalytic process (Table 1, entries 13–14). To realize the one-pot synthesis of oxazole, an oxidizing agent, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), was added to the reaction system after total consumption of **1a**. After being stirred at room temperature for 14 h, to our delight, the desired oxazole **4aa** was isolated in 78% yield (Scheme 2, **4aa**). Other oxidants such as molecular oxygen and *N*-bromosuccinimide were tried as well, but no desired oxazole product was produced with these reagents.

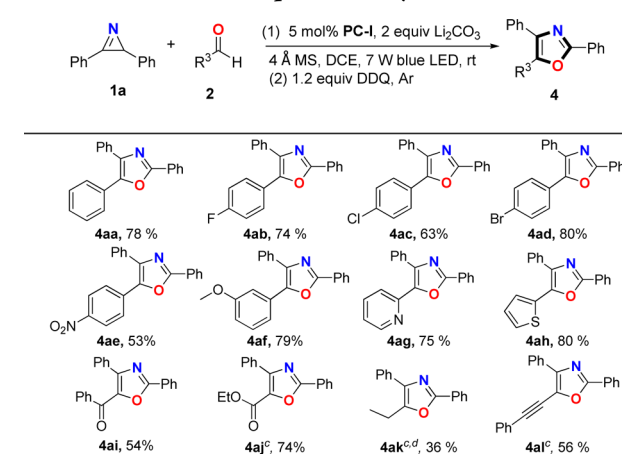
Having established the optimal conditions, we started to probe the scope of 2,3-disubstituted 2*H*-azirines that participated in this cycloaddition (Scheme 2). When electron-donating (Me, OMe, OPh) and electron-withdrawing (Cl) groups were introduced to the C3-phenyl ring adjacent to the C=N bond, the reaction worked well, generating the corresponding oxazoles in moderate to good yields (**4ba**–**4ea**, 50%–77%). Moreover, the structure of **4ea** was unambiguously determined by X-ray diffraction analysis.²⁵ Sterically hindered substrates can also be tolerated by this transformation. For example, when naphthyl-substituted 2*H*-azirine **1f** was applied, the desired oxazole **4fa** was afforded in 67% yield. Modification of the substitution of the C2-phenyl ring also proved to be viable. 2*H*-Azirines with R² possessing Cl at the *meta*- or *para*-positions of

Scheme 2. Substrate Scope of 2*H*-Azirines^{a,b}

^aReaction conditions: **1** (0.3 mmol), **2a** (1.5 mmol), **PC-I** (5 mol %), DCE (3 mL) at rt under the irradiation of a 7 W blue LED for 24–61 h. DDQ was added after the complete consumption of substrate **1** and stirred at rt for 14–34 h. ^bIsolated yield.

the benzene ring underwent this reaction with good efficiency (**4ga**: 75% yield; **4ha**: 58% yield). 2*H*-Azirines with alkyl or heteroaromatic substituents were also examined; however, only a trace amount of products were observed.

Next, the scope of aldehyde components was examined in this [3 + 2] cycloaddition/oxidative aromatization sequence. As highlighted in Scheme 3, benzaldehydes bearing *para*-F/Cl/Br/

Scheme 3. Substrate Scope of Aldehydes^{a,b}

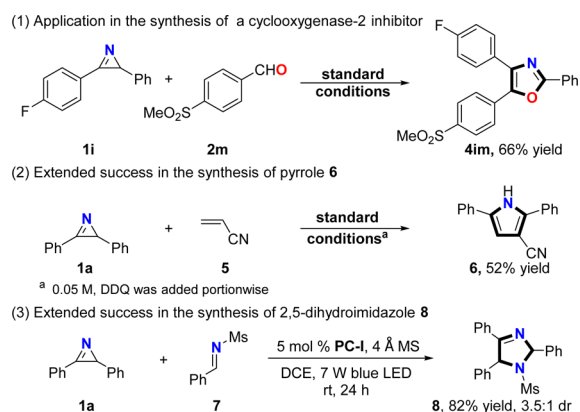
^aReaction conditions: **1a** (0.3 mmol), **2** (1.5 mmol), **PC-I** (5 mol %), DCE (3 mL) at rt under the irradiation of a 7 W blue LED for 24–97 h. DDQ was added after complete consumption of substrate **1a** and stirred at rt 14–25 h. ^bIsolated yield. ^cThe second step was run at 50 °C. ^d10 equiv of aldehyde and 0.6 equiv of DDQ were used.

NO₂ substituents proved to be compatible with this reaction system, giving the desired oxazoles in moderate to good yields (**4ab**–**4ae**, 53%–80% yield). When *meta*-anisaldehyde was applied to the reaction conditions, the corresponding product **4af** was delivered in 79% yield, albeit after an extended reaction time. To our delight, heteroaryl aldehydes reacted well with 2*H*-azirine **1a**. For instance, when pyridyl and thienyl aldehydes were used, the corresponding heterocycle-substituted oxazoles were afforded in 75% (**4ag**) and 80% yields (**4ah**), respectively.

We expect that this transformation will be very useful in constructing such oxazoles in a regioselective manner.²⁶ In addition to the aforementioned aldehydes, the reaction went smoothly with phenylglyoxal hydrate (**4ai**: 54% yield) and ethyl glyoxylate (**4aj**: 74% yield) as substrates. Notably, the ester group can be removed to obtain a 2,4-disubstituted oxazole or further transformed to the oxazole analogue of urocanic acid, which shows immunosuppressive activity.^{26,27} In addition, after increasing the amount of aldehyde, propanal can also undergo this transformation, affording the desired product **4ak** in an acceptable yield (36%). Lastly, 5-alkynyl substituted oxazole **4al** can be readily prepared in moderate yield (56%) by using alkynyl aldehyde **2l**. Compared with existing methods that use transition-metal-catalyzed cross-coupling reactions or multistep synthesis from arylacrylic acids,²⁸ this strategy features a simple procedure and mild conditions.

To further explore the potential of this method, the cyclooxygenase-2 inhibitor²⁹ **4im** was synthesized in a good yield (Scheme 4, eq 1: 66% yield) in a single pot. Apart from

Scheme 4. Synthetic Potentials of this Protocol

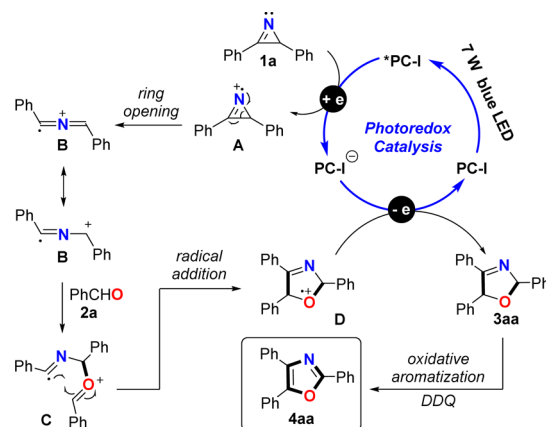


aldehydes, the electron-deficient alkene acrylonitrile **5** can be utilized in this reaction, affording pyrrole **6** in moderate yield (Scheme 4, eq 2: 52% yield). It is worthy to note that imine **7** can also participate in the visible-light-photocatalyzed [3 + 2] cycloaddition reaction, affording the 2,5-dihydroimidazole product **8** in a good yield and moderate diastereoselectivity (Scheme 4, eq 3: 82% yield, 3.5:1 dr),³⁰ although it did not undergo the oxidative aromatization step under standard conditions.

On the basis of our previous work¹⁰ and literature reports,⁷ a plausible mechanism for this transformation was proposed as shown in Scheme 5. 2H-Azirine **1a** can be converted to 2-azaallenyl radical cation **B** after single-electron oxidation by the excited photocatalyst and homolytic cleavage of the C–C bond. Then, nucleophilic attack of benzaldehyde **2a** on **B** would result in the formation of cation radical **C**, which could undergo subsequent intramolecular radical addition to afford the new cation radical **D**. After that, this transient species would be readily reduced by a low-valent photocatalyst, delivering the cycloadduct **3aa** and regenerating the photocatalyst PC-I. Finally, the oxidative aromatization of 2,5-dihydrooxazole **3aa** furnished the desired oxazole product **4aa**.

In summary, we have developed a [3 + 2] cycloaddition/oxidative aromatization sequence through visible-light-induced photoredox catalysis. This process provides a new approach for the one-pot synthesis of multisubstituted oxazoles from readily

Scheme 5. Plausible Reaction Mechanism



available 2H-azirines and aldehydes. It features a broad substrate scope and mild reaction conditions (i.e., 7 W LED irradiation and organic dye catalyst). Significantly, this strategy enabled the synthesis of a cyclooxygenase-2 inhibitor in one simple operation and can be further applied to the synthesis of biologically important pyrroles and 2,5-dihydroimidazoles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01994.

Experimental procedures, characterization data, and NMR spectra (PDF)

Crystallographic data for *cis*-**8** (CIF)

Crystallographic data for **4ea** (CIF)

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Notes

The authors declare no competing financial interest.

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- (23) Please see the [Supporting Information](#) for details.
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