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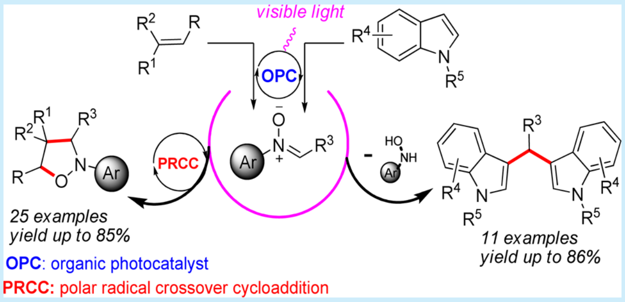
Visible-Light-Mediated Anti-Regioselective Nitrone 1,3-Dipolar Cycloaddition Reaction and Synthesis of Bisindolylmethanes

Lewei Zheng,[†] Fei Gao,[†] Chao Yang,*[,†] Guo-Lin Gao,[†] Yating Zhao,[†] Yuan Gao,[‡] and Wujiong Xia*[,†]

[†]State Key Lab of Urban Water Resource and Environment, Harbin Institute of Technology (Shenzhen), Shenzhen 518055, China
[‡]School of Chemistry and Chemical Engineering, Yantai University, #30 Qingquan Road, Laishan District, Yantai 264005, China

Supporting Information

ABSTRACT: The development of photoredox reactions of 1,3-dipolar cycloaddition of nitrones with alkenes is reported. It offers an efficient synthetic method to obtain isoxazolidine derivatives under mild conditions in synthetically useful yields. The nitrones are cyclized with oxidizable styrenes and aliphatic alkenes via a polar radical crossover cycloaddition reaction through photocatalytic reaction without additives. In addition, bis(indole)methanes can also be prepared through this method.

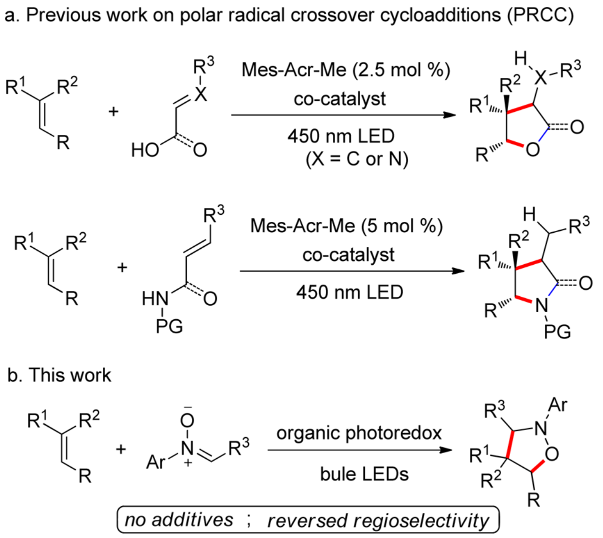


Functionalized heterocycles are highly prevalent and important structural motifs which can be found in many agrochemicals, pharmaceuticals, and materials.[1] In particular, the saturated heterocycles have already attracted great attention in the realm of drug discovery and organic synthesis.[2] An efficient and straightforward strategy for building blocks of diverse heterocycles and carbocyclic compounds is the cycloaddition reaction,[3] in which alkenes are used as one of most common and versatile feedstocks.[4]

Nowadays, the development of visible-light-mediated synthetic transformations has attracted more and more concern.[5] For example, Yoon and co-workers reported a new synthesis of cyclobutanes via intramolecular [2 + 2] enone cycloadditions upon irradiation with visible light.[6] Subsequently, they discovered a complementary method that could engage electron-rich alkenes in [2 + 2] cycloadditions through an oxidative quenching cycle.[7] Recently, a unique catalytic [3 + 2] cycloaddition reported by Nicewicz's group provided an access to the synthesis of tetrahydrofurans from alkenes and allylic alcohols via a polar radical crossover cycloaddition, which has also been utilized for synthesizing various heterocycles (PRCC, Scheme 1, a).[8]

With our continuous research interest in photochemical reactions, especially on the photochemical behavior of olefins,[9] we envisioned the radical cation intermediates that resulted from oxidative activation of olefins by photocatalyst might react with nitrone via 1,3-dipolar cycloaddition. Herein, we report a photocatalytic pathway to synthesize substituted isoxazolidine, in which the regioselectivity is contrary to that of the typical 1,3-dipolar cycloaddition reactions (Huisgen reaction) (Scheme 1, b).

Scheme 1. Previous Work and Our Protocol



Initially, the reaction was carried out by addition of nitrone **1a** to the solution of β-methylstyrene **2a** in dichloromethane using pyrylium salt **3a** as the photoredox catalyst under irradiation with blue LEDs. We were pleased to find that the desired cycloaddition product **4a** was produced in 85% yield after 12 h (Table 1, entry 1). The increase of catalytic loading of photocatalyst had no effect on the reaction result (Table 1, entry 2). However, decreasing the load of **2a** resulted in diminished yield (Table 1, entry 3). Replacing CH$_2$Cl$_2$ with other solvents, including MeCN, THF, and 1,2-DCE, provided a lower yield (Table 1, entries 4−6). Further investigation showed that the product still could be furnished with a yield of 59% under air atmosphere (Table 1, entry 7). Control

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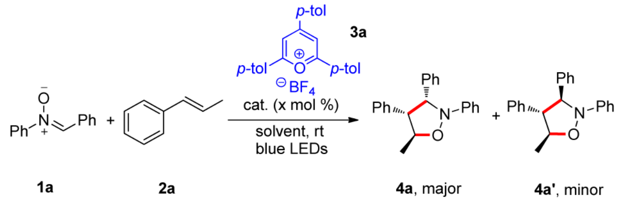
Table 1. Optimization of Nitrone Cycloaddition[a,b]



entry	cat. (mol %)	solvent	yield[b] (%)
1	**2.5**	**CH_2Cl_2**	**85**
2	5	CH_2Cl_2	84
3[c]	2.5	CH_2Cl_2	76
4	2.5	MeCN	78
5	2.5	THF	53
6	2.5	1,2-DCE	80
7[d]	2.5	CH_2Cl_2	59
8	0	CH_2Cl_2	trace
9[e]	2.5	CH_2Cl_2	trace

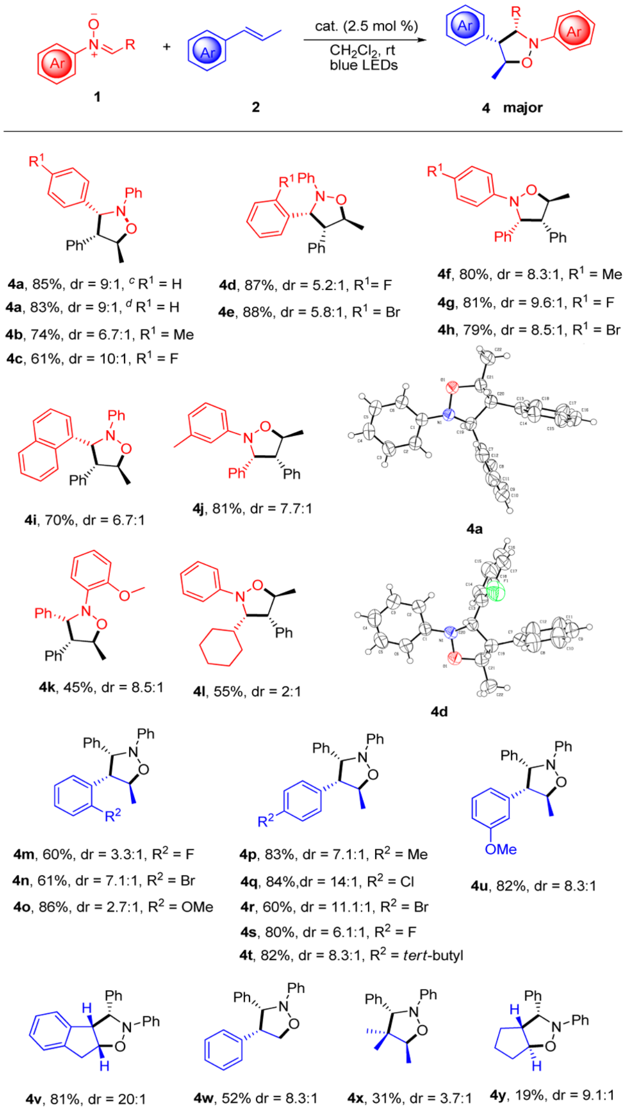
[a] Reaction conditions: nitrone **1a** (0.3 mmol), **2a** (0.45 mmol), and catalyst **3a** were dissolved in the dry solvent (4 mL) under N_2 atmosphere, and stirred under blue LEDs. [b] Isolated yield. [c] **2a** (0.36 mmol). [d] Under air. [e] In the dark.

experiments revealed that either light or photocatalyst was necessary for the reaction (Table 1, entries 8 and 9). Furthermore, other photoredox catalysts, e.g., $Ru(bpy)_3Cl_2$ and $Ir(ppy)_2(bpy)PF_4$, failed to yield the desired product.

With the identified suitable reaction conditions in hand, we turned our attention to the selection of substituted nitrones which were tolerated with the reaction conditions to afford the corresponding products in high yields with good diastereoselectivity regardless of the substitution pattern (Scheme 2, **4a–h**, **4j**, **4k**). When the *cis-β*-methylstyrene **2a** was used instead of the *trans-β*-methylstyrene **2a**, identical mixtures of diastereomers were obtained, which demonstrated the loss of the geometry of **2a** during the reaction. It should be pointed out that the nitrone with a naphthalene was also suitable for the reaction to afford the desired product in good yield (**4i**). In addition, a moderate yield was obtained when the substituent of nitrone **1** was an alkyl group (**4l**). However, *N*-alkyl nitrones, like *N*-benzylideneethanamine oxide, failed to obtain the product. The structures of these products were identified by 1D, 2D NMR spectral analysis, and as bonus, the structures of **4a** and **4d** were further confirmed by X-ray crystallographic analysis (Supporting Information (SI)).[10]

We then assessed the scope of the alkenes using the nitrone **1a** as the representative substrate under optimal reaction conditions. All *β*-methylstyrene derivatives could be employed to provide the desired products in good yields regardless of the substitution pattern (**4m–u**), in which the electron-rich *β*-methylstyrenes were more efficient than the electron-poor ones, except for ethene-1,1,2-triyltribenzene owing to the steric effect. When the styrene was subjected to the reaction conditions, the corresponding product was obtained in moderate yield (**4w**). However, when the aromatic group was substituted with an electron-withdrawing group, such as 1-nitro-2-vinylbenzene, no desired product was obtained. Moreover, the reaction of 2-methyl-2-butene with nitrone **1a** also furnished the cycloadduct in 31% yield (**4x**), while the cyclopentene proved to be less efficient, affording the product **4y** in 19% yield. Finally, indene was also tolerated with the optimal reaction conditions to form the product **4v** in good yield. Finally, isoxazolidine **4e** was selected for further transformation (see the SI for details).

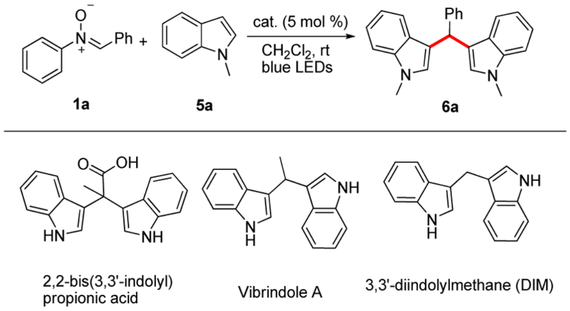
Scheme 2. Screening of Alkene with Various Nitrones[a,b]



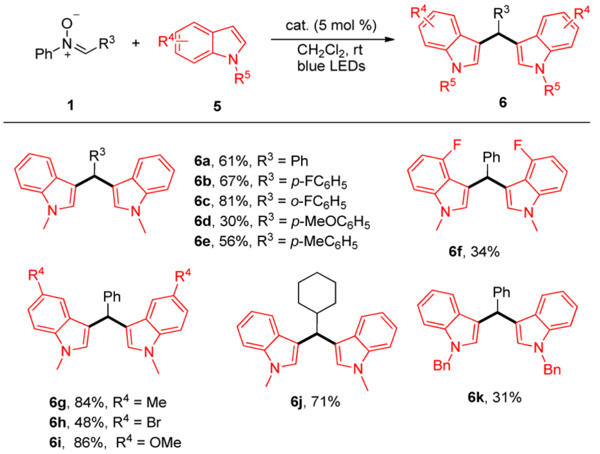
[a] Reaction conditions: nitrone **1a** (0.3 mmol), **2** (0.45 mmol), and catalyst **3a** (2.5 mol %) were dissolved in the dry CH_2Cl_2 (4 mL) under N_2 atmosphere, stirred under blue LEDs. [b] Isolated yield. [c] The *trans-β*-methylstyrene **2a** was used. [d] The *cis-β*-methylstyrene **2a** was used.

To extend the scope of the reaction, 1-methylindole **5a** was subjected to the reaction conditions. Interestingly, bisindolylmethane **6a** was obtained in 61% yield instead of the 1,3-dipolar cycloaddition product (Scheme 3). The bisindolylmethanes are important structural motifs of natural products and pharmaceuticals,[11] e.g., 3,3′-diindolylmethane (DIM), 2,2-bis(3,3′-indolyl)propionic acid, and vibrindole A, which exhibit a number of biological properties such as antibacterial, anti-inflammatory, antifungal, and antimicrobial activity.[12] Therefore, it encourages us to explore such an interesting reaction in detail. As shown in Scheme 4, electron-withdrawing and electron-donating groups on either nitrone or methylindole were both tolerated to furnish the corresponding products in moderate to good yields (**6a–i**). When the R^3 of **1** was replaced by an alkyl group, the reaction proceeded smoothly to form the

Scheme 3. Synthesis of Bisindolylmethane



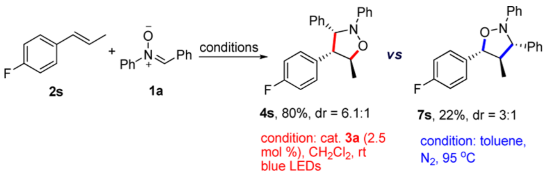
Scheme 4. Screening of Indole with Various Nitrones[a,b]



[a] Reaction conditions: nitrone **1** (0.3 mmol), **5** (0.9 mmol), and catalyst **3a** (5 mol %) were dissolved in the dry CH$_2$Cl$_2$ (4 mL) under N$_2$ atmosphere, and stirred under blue LEDs. [b] Isolated yield.

product in good yield (**6j**). Furthermore, a substrate bearing a benzyl group at the *N* atom of indole was also suitable for the reaction, giving the desired product in 31% yield (**6k**).

To differentiate our protocol with the typical thermo 1,3-diploar cycloaddition reaction, 1-fluoro-4-(prop-1-enyl)benzene **2s** and nitrone **1a** were selected as the representative substrates to react under different conditions. As shown in eq 1, the cycloaddition product **7s** was obtained in 22% yield under thermal conditions, while the product **4s** was obtained in a yield up to 80% under photocatalytic conditions. More importantly, the regioselectivity of **4s** was contrary to the product **7s**, which suggested that our methdology could be structurally complementary to the typical 1,3-diploar cycloaddition reaction (Huisgen reaction).



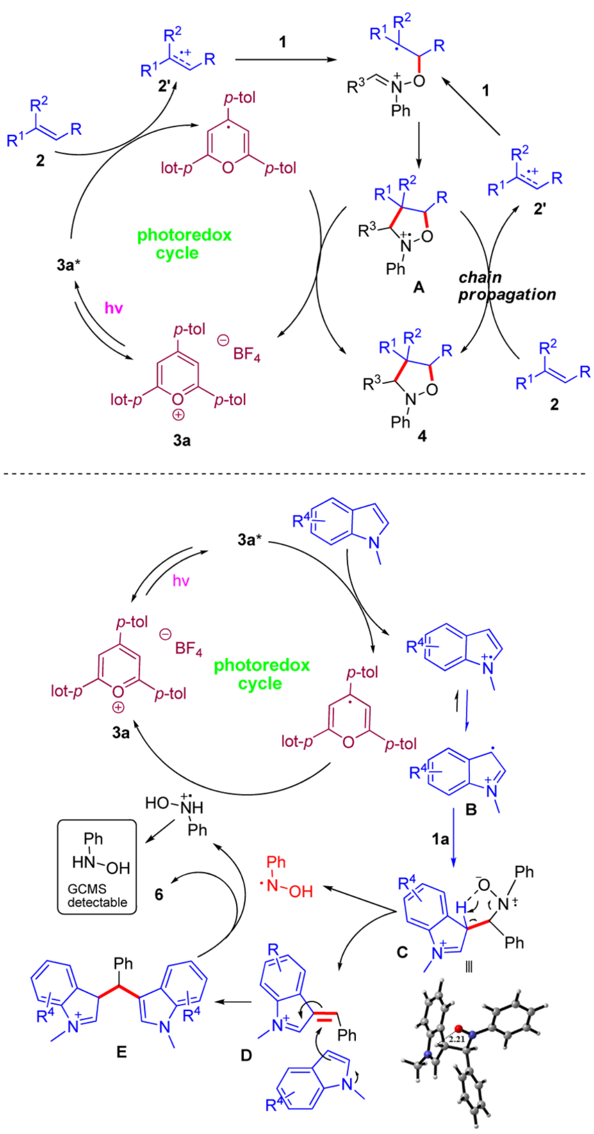
(eq 1)

Before the mechanism was proposed, the quantum yield of the reaction was measured with **1a** and **2a**. Compounds **1a** (0.3 mmol) and **2a** (0.45 mmol) were irradiated at 420 nm light under standard conditions. According to the prior procedure,[13] a photon flux of 7.34×10^{-10} was calculated by ferrioxalate actinometry. Thus, the quantum yield was defined as $\Phi = 9$, which demonstrated the chain process of the reaction strongly.

In addition, the Stern−Volmer quenching experiments were also carried out, which showed that **2a** and **5a** were more efficiently than **1a** to quench the excited state of **3a** (SI).

On the basis of the above results, a plausible mechanism was proposed as shown in Scheme 5. Upon irradiation, photocatalyst **3a** was excited to its excited state **3a***, which then oxidized alkene **2** to form the radical cation intermediate **2′** via the reductive quenching process. The electrophilic addition of **2′** with nitrone **1** followed by a radical addition led to the intermediate **A**, which then acted as an oxidant to regenerate the photocatalyst **3a**, affording the final product **4**. On the other side, according to the quantum yield measurements, a radical chain propagation step was probably involved between intermediate **2′** and alkene **2** during the transformation.

Scheme 5. Proposed Mechanism



On other hand, when the alkene is replaced by an indole, excited state **3a*** accepted one electron from indole, generating the radical cation intermediate **B**, which could react with nitrone **1a** via radical addition process to form the intermediate **C**. DFT calculations showed that the configuration of intermediate **C** at the lowest energy indicated the distance is 2.21 Å between the hydrogen atom of C3 of indole and the oxygen atom, which is ideal for hydrogen abstraction. Therefore, cationic intermediate **D** was formed from **C** after elimination of phenylhydroxylamine radical and could react with another equivalent of indole to form intermediate **E**. Deprotonation of **E** led to the final product **6**, along with the detectable phenylhydroxylamine by GC−MS analysis.

In summary, we have discovered an efficient and mild method to access isoxazolidine via visible-light-mediated cycloaddition which is antiregioselective to the typical 1,3-dipolar nitrone cycloaddition reactions. The reaction is highlighted by its synthetically useful yields and low catalyst loading without other additives. Meanwhile the bis(indole)-methanes can also be obtained in this protocol by simply changing to indole substrates, which demonstrate the potential application of this method in organic synthesis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02251.

Experimental procedures and spectral data for all compounds (PDF)
X-ray data for compound **4a** (CIF)
X-ray data for compound **4d** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: xyyang@hit.edu.cn. Fax: (+86)-451-86403760.
*E-mail: xiawj@hit.edu.cn. Fax: (+86)-451-86403760.

ORCID

Wujiong Xia: 0000-0001-9396-9520

Notes

The authors declare no competing financial interest.

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(10) CCDC 1491708 (**4a**) and 1491709 (**4d**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif (see the Supporting Information for X-ray data for 4a and 4d).

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