Advanced Synthesis & Catalysis

## Accepted Article

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**To be cited as:** *Adv. Synth. Catal.* 10.1002/adsc.202000858

**Link to VoR:** https://doi.org/10.1002/adsc.202000858

10.1002/adsc.202000858

FULL PAPER

DOI: 10.1002/adsc.202((will be filled in by the editorial staff))

# Visible-light Catalyzed [1+2+2] Cycloaddition Reactions Enabled by the Formation of Methylene Nitrones

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Received: ((will be filled in by the editorial staff))

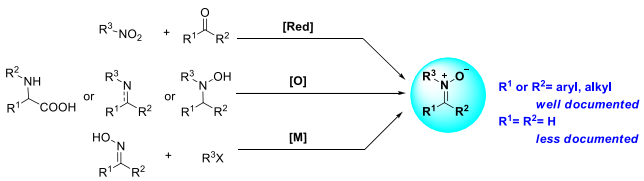
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

**Abstract:** Nitrones are key intermediates in organic synthesis. Herein, we report the first photo-redox synthesis of methylene nitrone intermediates from nitroarenes and arylamines. The highly reactive methylene nitrones are *in situ* trapped by alkenes to afford various isoxazolidines. This three-component reaction features the use of *N*,*N*-dimethylanilines or *N*-aryl glycines as C1 building blocks, which allow for the one-pot formal [1+2+2] cycloaddition from simple starting materials. A wide range of useful isoxazolidines can be obtained under mild conditions with moderate to good yields. Mechanistic investigations support the formation of methylene nitrone via selective N-$CH_3$ bond cleavage and methylene transfer.

**Keywords:** Methylene nitrone; C1 synthetic unit; [1+2+2] cycloaddition; Visible light; Redox

## Introduction

Nitrones are key intermediates in synthetic chemistry for the preparation of natural products and biologically active compounds (Scheme 1).[1] Nitrones, given their highly versatile reactivities, are extensively used in various fundamental synthetic transformations, such as nucleophilic additions, radical additions, 1,3-dipolar cycloadditions, [3+n] annulations, and C–H functionalization reactions, *etc.* In addition, nitrones have multiple applications in radical trapping, bioorthogonal labeling, and potential therapeutic agents. Thus, considerable effort has been devoted in developing methodologies for the efficient synthesis of nitrones.

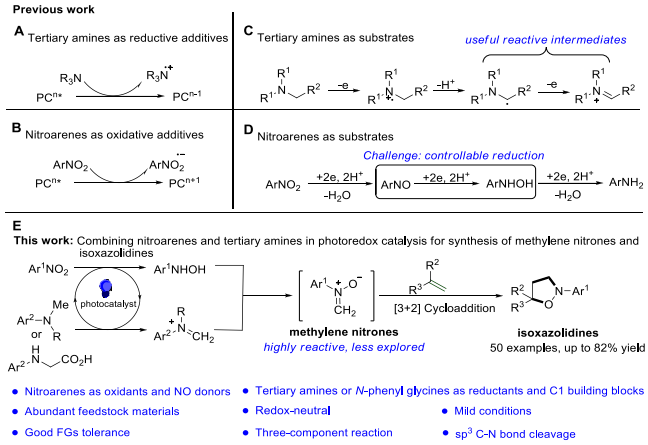



**Scheme 1.** Synthetic strategies of nitrones.

The classic approaches typically involve condensation reactions of carbonyl compounds with *N*-monosubstituted hydroxylamines. However, stoichiometric external reductants (Zn, $H_2$, $N_2H_4$•$H_2O$, *etc.*)[1a,2] and harsh conditions are generally required to prepare hydroxylamines from nitro precursors. Although the oxidation of amines, imines or hydroxylamines provides alternative approaches to accessing nitrones, the process largely suffers from the use of stoichiometric external oxidants (HgO, $MnO_2$, oxone, peroxides, *etc.*) and the limited compatibility of functional groups.[1a,3] The transition metal-catalyzed transformation of oximes by alkylation reactions is another efficient method for the synthesis of nitrones.[4] However, this strategy often requires the use of prefunctional substrates and a careful control of reaction conditions to avoid the mixing of products. From the viewpoint of sustainability, most of abovementioned processes create large amounts of environmentally toxic waste. Therefore, developing a catalytic method for nitrone synthesis under redox-neutral and environmentally benign conditions is highly desirable.[5] Besides, to the best of our knowledge, the synthesis and application of methylene nitrone ($R^1$= $R^2$= H, Scheme 1) remains largely underexplored, probably due to the high reactivity for isolation and the lack of suitable C1 building blocks.[6]

Visible light photoredox catalysis has emerged as a powerful strategy in synthetic organic chemistry in the past decade because it allows for the design and development of new chemical transformations in an environmentally benign

manner.[7] A typical photocatalytic process is generally initiated by a single-electron transfer (SET) between an excited photocatalyst and an oxidative or reductive quencher to afford the corresponding redox-active species and an ion-radical species. In the previous work, low-cost ubiquitous tertiary amines and nitroarenes were employed as reductive additives and oxidative additives to quench the excited photocatalyst (Schemes 2**A** and 2**B**). In addition to acting as sacrificial additives, tertiary amines and nitroarenes were also used as substrates in photoredox catalysis (Schemes 2**C** and 2**D**). On one hand, tertiary amines were shown to undergo various visible-light promoted α-functionalization through the formation of reactive intermediates, including α-amino radicals and iminium ions (Scheme 2**C**).[7f,8] By harnessing the synthetic potential of α-amino radicals and iminium ions, various transformations, including nucleophilic addition, radical addition, and cross-coupling reactions, could be developed for the functionalization of amine substrates.[8a,9] New chemical transformations based on the C-N cleavage of iminium ions intermediates were seldom explored.[10] On the other hand, nitroarenes were mostly employed as oxidative additives rather than substrates in photocatalytic reactions.[11] Although the photocatalytic reduction of nitroarenes into the corresponding anilines have been realized, the controllable reduction towards nitrosoarenes or *N*-arylhydroxylamines and their subsequent transformations remain a challenge (Scheme 2**D**).[12]



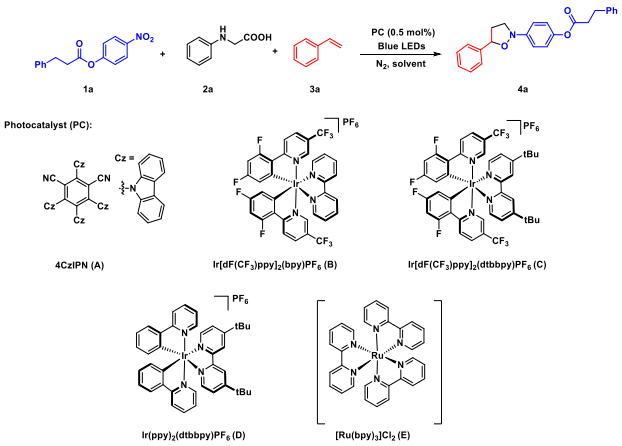

**Scheme 2.** Visible-light photoredox catalysis involving nitroarenes and tertiary amines.

On the basis of the redox properties of the tertiary amines and nitroarenes, we envisioned that nitrones could be accessed through the condensation of *in situ*-generated iminium ions and *N*-arylhydroxylamines from tertiary amines and nitroarenes under visible light photocatalysis, thus avoiding the need to use stoichiometric amounts of oxidants or reductants common in conventional approaches (Scheme 2**E**). Herein, we report the first redox-neutral visible-light photocatalytic reactions of nitroarenes and *N*,*N*-dimethylanilines (or *N*-aryl glycines) for the synthesis of highly reactive methylene nitrone intermediates, which are trapped by alkenes to afford a variety of useful isoxazolidines. This method entails several remarkable features, including abundant feedstock materials, a broad substrate scope, and mild conditions. To our knowledge, this process represents the first example of a highly efficient formal [1+2+2] three-component reaction for the rapid and convergent assembly of isoxazolidines, in which *N*,*N*-dimethylanilines or *N*-aryl glycines are used as C1 building blocks.

## Results and Discussion

Initially, we started our investigation by identifying reaction conditions suitable for performing the three-

**Table 1.** Optimization of the reaction conditions.[a]



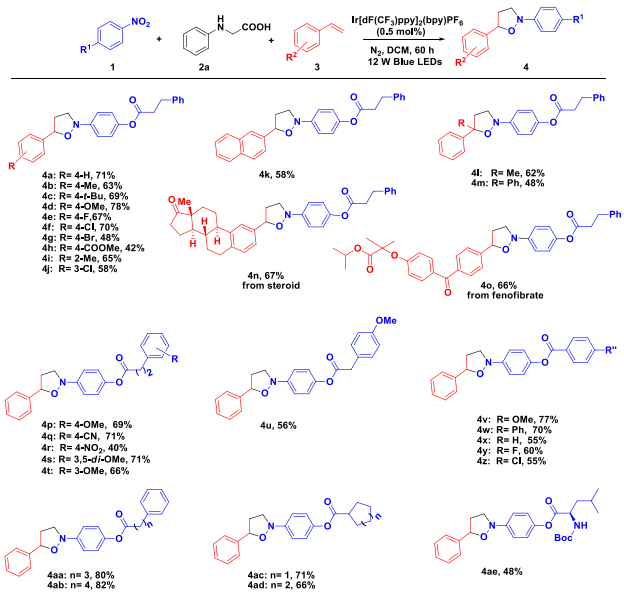

| Entry | Photocatalyst | Additive[b] | Solvent | Yield [%][c] |
|---|---|---|---|---|
| 1 | **A** | - | DCM | 38 |
| 2 | **B** | - | DCM | 60 |
| 3 | **C** | - | DCM | 52 |
| 4 | **D** | - | DCM | 58 |
| 5 | **E** | - | DCM | 34 |
| 6 | **B** | - | THF | 36 |
| 7 | **B** | - | toluene | 55 |
| 8 | **B** | - | $CHCl_3$ | 45 |
| 9 | **B** | - | DCE | 34 |
| 10 | **B** | - | PhCl | 26 |
| 11 | **B** | - | xylene | 37 |
| 12 | **B** | 3Å MS | DCM | 40 |
| 13 | **B** | 4Å MS | DCM | 38 |
| 14 | **B** | $Na_2SO_4$ | DCM | 41 |
| 15 | **B** | $MgSO_4$ | DCM | 54 |
| 16[d] | **B** | - | DCM | 65 |
| 17[e] | **B** | - | DCM | 70(71[h]) |
| 18[f] | **B** | - | DCM | 68 |
| 19 | - | - | DCM | 0 |
| 20[g] | **B** | - | DCM | 0 |

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.3 mmol), **3a** (0.3 mmol), photocatalyst (0.0005 mmol), solvent (2 mL) under 12 W blue LEDs for 24 h at 25 °C.
[b] 20 mg additive.

[c] NMR yield using $CH_2Br_2$ as internal standard.
[d] 48 h.
[e] 60 h.
[f] 72 h.
[g] No light.
[h] Isolated yields.

component cycloaddition of 4-nitrophenyl 3-phenylpropanoate (**1a**) and styrene (**3a**) with *N*-phenyl glycine (**2a**) as C1 unit. As expected, the reaction did proceed and the desired isoxazolidine **4a** could be obtained in 38% yield (Table 1, entry 1) when using 0.5 mol% of 4CzIPN ($E_{1/2}^{red}$ = +1.35 V *vs.* SCE in MeCN)[13] as the photocatalyst and irradiating with two 12 W blue LEDs for 24 h in DCM. Given the successful implementation of Ir(III) and Ru(II) photocatalysts in previous photoredox reaction,[7a,7g,13c,14] a range of Ir(III) and Ru(II) photocatalysts were evaluated (entries 2-5). To our delight, the reaction was significantly improved when $Ir[dF(CF_3)ppy]_2(bpy)PF_6$ ($E_{1/2}(*Ir^{III}/Ir^{II})$= +1.32 V *vs.* SCE in MeCN)[14c,15] was used as the photocatalyst (entry 2). Subsequently, we conducted further investigations on the effect of reaction media, including THF, toluene, $CHCl_3$, DCE, PhCl and xylene. The reaction proceeded poorly in other solvents and DCM remained to be the optimal choice (entries 2, 6-11). In addition, several additives were screened and failed to improve the yield (entries 12-15). The yield of **4a** could be readily improved to 70% by increasing the reaction time to 60 h (entries 16-18). The control experiments indicated that photocatalyst and light irradiation are essential for the success of this transformation (entries 19-20).

**Table 2.** Substrate scope when using *N*-aryl glycines as C1 synthetic unit.[a,b]

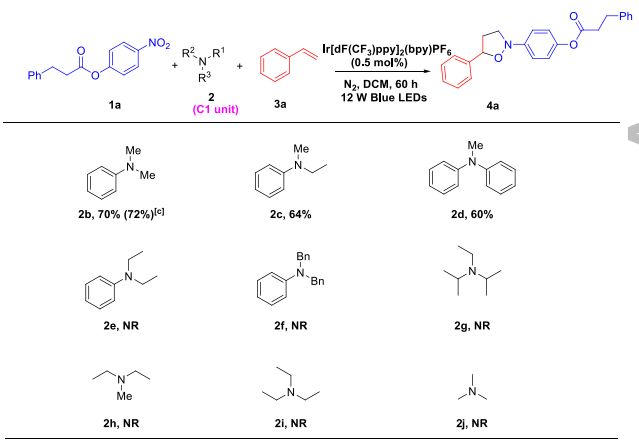



[a] Reaction conditions: **1** (0.1 mmol), **2a** (0.3 mmol), **3** (0.3 mmol), $Ir[dF(CF_3)ppy]_2(bpy)PF_6$ (0.0005 mmol), DCM (2 mL) under 12 W blue LEDs for 60 h at 25 °C.
[b] Isolated yields.

With the optimized conditions in hand (Table 1, entry 17), next we investigated the substrate scope of this [1+2+2] cycloaddition reaction and the results were shown in Table 2. Firstly, this reaction generally exhibited a broad substrate scope with respect to styrenes. Various styrene derivatives bearing electron-neutral or electron-donating groups proceeded smoothly to give the desired isoxazolidines **4a**−**4d** in good yields (63%−78%). The electron-deficient styrenes bearing substituents such as halides and ester groups were also tolerated in the reaction with moderate to good efficiencies (**4e**−**4h**, 42%−70% yields). Styrene derivatives with substituents at the *ortho*- and *meta*-positions also worked well, providing **4i**−**4j** in 58%−65% yields. 2-Vinyl naphthalene afforded the product **4k** in 58% yield. In addition, the isoxazolidines **4l**−**4m** bearing a quaternary carbon center could also be constructed from the corresponding 1,1-disubstitued alkenes under the standard reaction conditions. The structure of **4m** was unambiguously determined by X-ray single-crystal analysis.[16] Notably, to illustrate the utility of this method in synthesis, the alkenes derived from bioactive estrone and fenofibrate were smoothly converted into the corresponding isoxazolidines **4n**−**4o** in 67% and 66% yields, respectively.

Subsequently, the scope of nitroarene substrates was explored with reacting with *N*-phenyl glycine **2a** and styrene **3a**. A range of structurally diverse 4-nitrophenol esters, which served as the NO donors, were examined in this [1+2+2] cycloaddition reaction and afforded the products in moderate to excellent yields (**4p**−**4ae**, 40%−82%). Various functional groups on the phenyl ring, such as –OMe, –CN, $–NO_2$, –Ph, –F, and –Cl, were well compatible in the current transformation (**4p**−**4ab**), whereas $–NO_2$ substituent made the transformation a little sluggish, providing lower yield (**4r**, 40%). In addition, 4-nitrophenol esters derived from cyclic carboxylic acids and α- amino acid were also tolerated, providing the corresponding isoxazolidines **4ac**−**4ae** in 48%–71% yields.

**Table 3.** Investigation when using tertiary amines as the C1 synthetic unit.[a,b]



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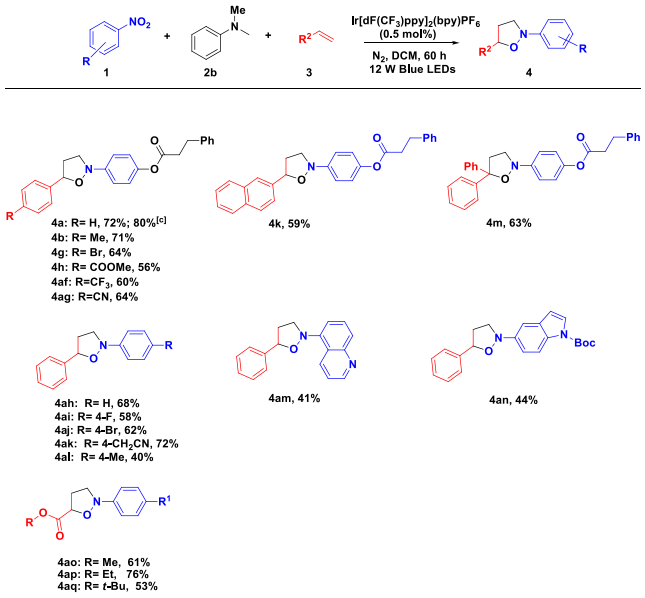
[a] Reaction conditions: **1a** (0.1 mmol), **2** (0.3 mmol), **3a** (0.3 mmol), Ir[dF($CF_3$)ppy]$_2$(bpy)$PF_6$ (0.0005 mmol), DCM (2 mL) under 12 W blue LEDs for 60 h at 25 °C.
[b] NMR yield using $CH_2Br_2$ as internal standard.
[c] Isolated yield.

Given the success of the cycloaddition with *N*-phenyl glycine as the C1 units, next we turned our attention to investigate the use of more challenging tertiary amines (Table 3). It was found that *N*-methylanilines **2b**−**2d** could also play as the methylene sources of final isoxazolidine products. Among them, *N*,*N*-dimethylaniline **2b** was the best choice and delivered the product in 70% yield, whereas other anilines proceeded with lower efficiency. In contrast, no reaction occurred when *N*,*N*-diethylaniline **2e** or *N*,*N*-dibenzylaniline **2f** was subjected to the reaction conditions. Moreover, nonaromatic tertiary amines **2g**−**2j** were demonstrated to be invalid in the current transformation, which suggested that aromatic amine moiety is essential for the selective N-$CH_3$ bond cleavage.

**Table 4.** Substrate scope when using *N*,*N*-dimethylaniline as the C1 synthetic unit.[a,b]




[a] Reaction conditions: **1** (0.1 mmol), **2b** (0.3 mmol), **3** (0.3 mmol), Ir[dF($CF_3$)ppy]$_2$(bpy)$PF_6$ (0.0005 mmol), DCM (2 mL) under 12 W blue LEDs for 60 h at 25 °C.
[b] Isolated yields.
[c] 1 mmol scale for 120 h.

Subsequently, we further demonstrated the generality of this protocol with *N*,*N*-dimethylaniline as the C1 building block and the results were summarized in Table 4. Cycloaddition of electron-neutral groups (4-H, 4-Me) and electron-withdrawing groups (4-Br, 4-COOMe, 4-$CF_3$ and 4-CN) substituted styrenes gave the products in 56−72% yields. To explore the practicality of this method, a 1 mmol scale experiment was performed with 4-nitrophenyl 3-phenylpropanoate (**1a**) and styrene (**3a**) with *N*,*N*-dimethylaniline (**2b**) as C1 unit. The addition product **4a** could be obtained in 80% yield with 0.5 mol% photocatalyst albeit longer reaction time was required to ensure complete conversion. Donating groups such as –$CH_3$, –$CH_2CN$ at the *para*-position of the aromatic ring, all underwent the desired radical cycloaddition reaction smoothly to afford the corresponding isoxazolidines **4ah**–**4al** in moderate to good yields (40%–72%). The nitro-heteroaromatic compounds, such as 5-nitroquinoline and 5-nitroindole, also proved to be suitable substrates for this reaction, providing the target products **4am** and **4an** in 41% and 44% yields, respectively. Moreover, various acrylates were also capable acceptors in the reaction to give the corresponding products **4ao**–**4aq** in 53%–76% yields.

In order to gain insights into the reaction mechanism, a series of mechanistic studies were performed. Firstly, the desired product was inhibited in the presence of radical scavengers TEMPO or $O_2$, which indicated that a radical pathway might be involved in the reaction (Scheme 3a). Next, when the deuterated *N*,*N*-dimethylaniline **2b'** was subjected to the standard reaction with **1a** and **3a**, the $CD_2$-labelling product **4a'** was obtained with 62% yield

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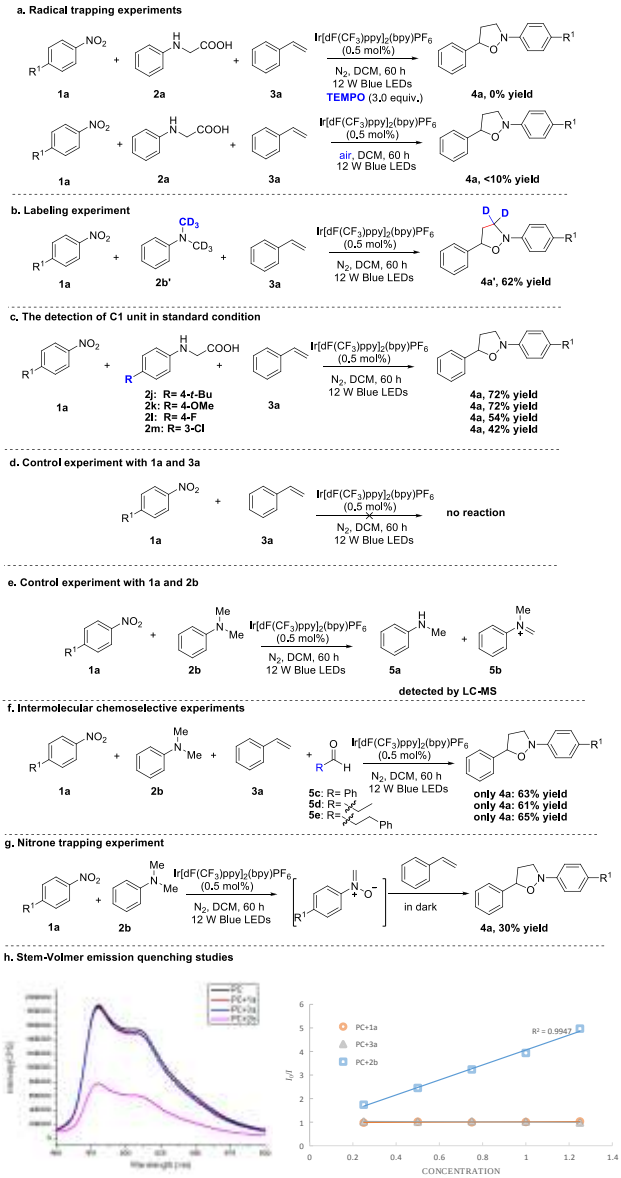
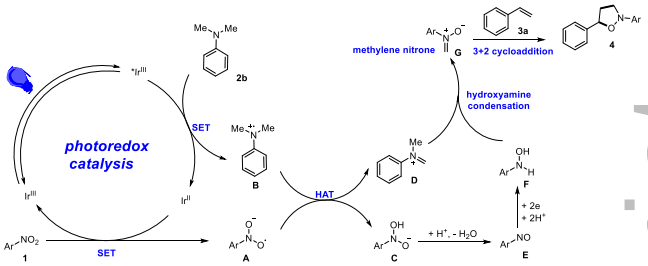



**Scheme 3.** Mechanistic studies.

(Scheme 3b), which unambiguously demonstrated that *N*,*N*-dimethylaniline was the C1 building blocks for the isoxazolidine products. Similarly, when *N*-phenyl glycines **2j**–**2m** with different substituted groups were employed in this reaction (Scheme 3c), the same product **4a** was delivered, which indicating that the methylene in the product is generated from the *N*-phenyl glycines. In contrast, when **1a** and **3a** were subjected to the standard reaction conditions without *N*-phenyl glycines or tertiary amines, neither intermediate nor isoxazolidine products were detected (Scheme 3d). These findings were different from previous reports,[6,9d] hinting the possibility of a novel mechanism. To verify the active intermediates, the photoredox reaction of nitroarene **1a** and *N*,*N*-dimethylaniline **2b** in the absence of olefins was conducted under irradiation. The intermediates **5a** and **5b** were detected by ESI-MS techniques (Scheme 3e), suggesting that selective *N*-methyl C-N bond cleavage might occur *via* photoredox single-electron transfer and hydrogen atom transfer process. Besides, only single product **4a** was afforded when the model reaction proceeded in the presence of a range of aromatic and alkyl aldehydes (**5c**–**5e**). These results indicated that the C1 synthon might be the *N*-methylene iminium rather than formaldehyde (Scheme 3f).[5a] In addition, the stepwise synthesis was carried out and styrene could trap the preformed intermediate in dark conditions (Scheme 3g). Finally, the Stern-Volmer studies of photocatalyst demonstrated that the excited photocatalyst Ir* was quenched by the amine **2b** (Scheme 3h).




**Scheme 4.** Proposed mechanism for visible-light catalyzed [1+2+2] cycloaddition reactions

Based on the above experiments, a possible mechanistic pathway for this reaction was proposed as depicted in Scheme 4. Upon visible-light irradiation, the iridium(III) photocatalyst would produce the long-lived and highly oxidizing excited state *Ir(III) species ($^*Ir[dF(CF_3)ppy]_2(bpy)^+$ ($E_{1/2}(^*Ir^{III}/Ir^{II})$= +1.32 V *vs.* SCE in MeCN). Reductive quenching of the excited $^*Ir^{III}$ photocatalyst by *N*,*N*-dimethylaniline **2b** whose oxidation potentials fall in the 0.7 V *vs.* SCE[9c,17] would generate the nitrogen radical cation **B** and the reduced $Ir^{II}$ photocatalyst. Subsequent single electron oxidation of the $Ir^{II}$ photocatalyst with nitrobenzene **1** regenerates the $Ir^{III}$ photocatalyst and yields the nitrobenzene radical anion **A**,[7b,18] which then undergoes hydrogen atom transfer process with **B** to afford *N*,*N*-dihydroxyamine anion **C** and the imine cation **D**.[11a,19] **C** is transformed into nitrosobenzene **E** and subsequent *N*-phenylhydroxylamine **F** *via* a series of reduction and protonation processes. Subsequently, condensation of hydroxylamine **F** with the imine cation **D** leads to the methylene nitrone **G**. Finally, trapping of the highly reactive methylene nitrone **G** with styrene **3a** results in the formal [1+2+2] cycloaddition product **4**.

## Conclusion

In summary, we have developed the first visible-light-catalyzed [1+2+2] cycloaddition reaction. This formal [1+2+2] cycloaddition reaction involves the *in situ* formation of highly reactive methylene nitrone intermediates from nitroarenes and arylamines by visible-light photoredox catalysis, in which the methyl or methylene moiety of arylamines (either *N*,*N*-

dimethylanilines or *N*-aryl glycines) was employed as the C1 building blocks and nitrobenzenes acts as NO donors. A variety of useful isoxazolidines were accessed smoothly with moderate to good yields (50 examples, up to 82% yield). The method features redox-neutrality, simple starting materials, mild reaction conditions, broad substrate scope and good functional group tolerance. Preliminary mechanistic studies support the formation of methylene nitrone *via* selective N-$CH_3$ bond cleavage and methylene transfer.

## Experimental Section

**General Procedure for the Synthesis of Products**

To a solution of **1a** (0.1 mmol) and **2a** (0.3 mmol) in DCM (2 mL) was added **3a** (0.3 mmol) and $Ir[dF(CF_3)ppy]_2(bpy)PF_6$ (0.0005 mmol). The reaction mixture was degassed by bubbling a stream of nitrogen for 5 min at 0 °C, then stirred at 25 °C and irradiated with two 12 W blue LEDs with a fan placed nearby for cooling. After 60 h, the mixture was concentrated under reduced pressure and crude product was purified by flash column chromatography on silica gel to afford the title compound.

## Acknowledgements

*This work was financially supported by the National Natural Science Foundation of China (No. 81972824), Guangdong Provincial Key Laboratory of Chiral Molecule and Drug Discovery (No. 2019B030301005), Guangdong Basic and Applied Basic Research Foundation (No. 2020A1515011513) and National Engineering and Technology Research Center for New drug Druggability Evaluation (Seed Program of Guangdong Province, No. 2017B090903004).*

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10.1002/adsc.202000858

FULL PAPER

# Visible-light Catalyzed [1+2+2] Cycloaddition Reactions Enabled by the Formation of Methylene Nitrones

*Adv. Synth. Catal.* **2020**, *Volume*, Page – Page

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