Red-Light-Induced ^{n}Pr-DMQA^{+}-Catalyzed [3+2] Cycloaddition of Cyclopropylamines with Alkenes or Alkynes

Savannah M. Stull[a]
Liangyong Mei[b]
Thomas L. Gianetti*[a]

[a] Department of Chemistry and Biochemistry, University of Arizona, Tucson, AZ 85721.

[b] Department of Chemistry, Colgate University 13 Oak Dr, Hamilton, NY 13346.

tgianetti@arizona.edu

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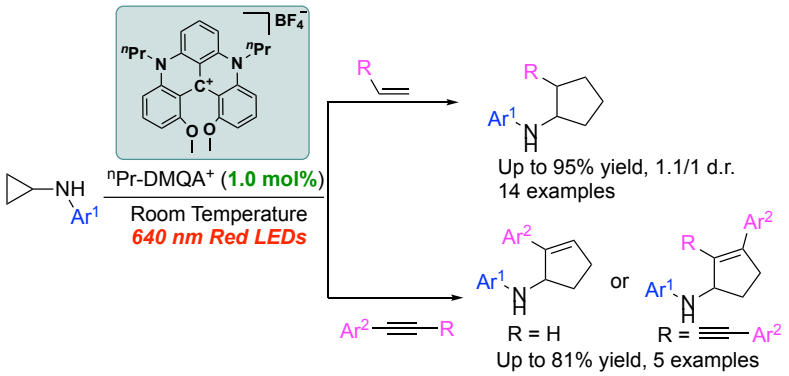

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Abstract A red-light-mediated [3+2] annulation of cyclopropylamines with akenes or alkynes in the presence of ^{n}Pr-DMQA^{+} has been reported. An array of cyclopentane or cyclopentene derivatives with diverse functional groups have been obtained in moderate to excellent yields under mild conditions.

Key words red light, photoredox catalysis, [3+2] cycloaddition, cyclopropylamine, ^{n}Pr-DMQA^{+}

Cyclopentyl functional group motifs are prevalent in a wide range of bioactive pharmaceuticals and natural products such as peramivir,[1] aristeromycin,[2] Prostaglandin $F_{2\alpha}$,[3] and Vibralactone[4] (Figure 1). As a consequence, various strategies to their synthesis have been developed.[5-9] Some of the representative examples are Pauson–Khand reaction,[5] Nazarov cyclization,[6] [3+2] cycloaddition,[7] ring-closing metathesis (RCM),[8] and intramolecular Henry reaction.[9] In particular, the visible-light-mediated [3+2] cycloaddition of cyclopropylamines caught our attention since it not only represents an atom-economical process, but also takes advantage of readily available and environmental-friendly visible light.[10] During the reaction, cyclopropylamine serves as a "three-carbon-atom" precursor by generating a crucial distonic radical cation intermediate through a radical mechanism.[10]

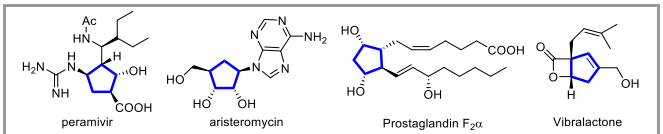
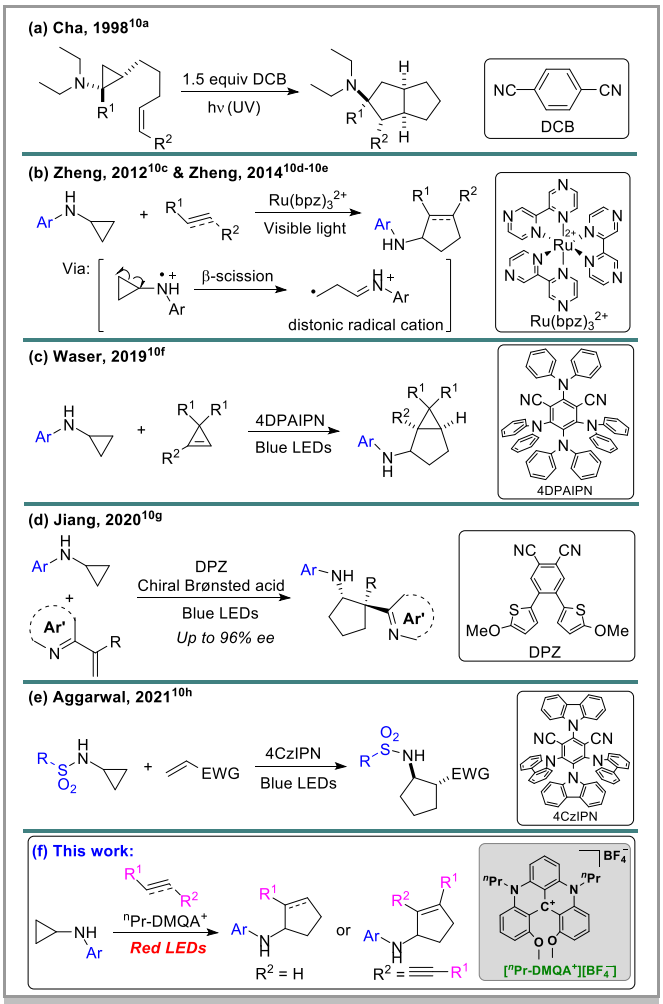


Figure 1 Selected examples of pharmaceuticals and natural products bearing a cyclopentane/cyclopentene core

Cha and coworkers pioneered this work by introducing a photo-mediated intramolecular [3 + 2] annulation of olefin-tethered cyclopropylamines,[10a] which built the foundation for any future developments (Scheme 1a). Nevertheless, the requirements of UV light and stoichiometric amounts of photosensitizer have rendered his protocol less than practical. However, over the past decade, the renaissance of modern visible-light-induced photoredox catalysis has brought new life to this reaction since its milder conditions can address the previously noted drawbacks.[11] As a result, the Zheng group showed several exquisite works on visible-light-mediated intermolecular [3+2] annulation of cyclopropylamines with olefins, alkynes, enynes, or diynes in the presence of $Ru(bpz)_3^{2+}$ (Scheme 1b).[10c-10e] Afterwards, Waser et al. presented the synthesis of bicyclo[3.1.0]hexanes through a 4DPAIPN-catalyzed [3 + 2] cycloaddition of cyclopropenes with aminocyclopropanes under blue light irradiation (Scheme 1c).[10f] Later, the Jiang group disclosed the asymmetric version of Zheng's original protocol by employing cooperative photoredox and chiral Brønsted acid catalysis in the presence of blue LEDs (Scheme 1d).[10g] Very recently, Aggarwal et al. introduced a diastereoselective blue-light-mediated 4CzIPN-catalyzed [3 + 2] cycloaddition of *N*-sulfonyl cyclopropylamines with electron-deficient olefins, which further expanded the substrate scope of this reaction (Scheme 1e).[10h] Despite the impressive progress to date, all the current protocols employ relatively high-energy blue or white light. In contrast, red light is featured with lower energy, higher penetration depth, less health risks, fewer side reactions, and more abundance from sunlight.[12] Therefore, developing a red-light-induced [3+2] cycloaddition of cyclopropylamine for the synthesis cyclopentane and cyclopentene derivatives is still highly desirable.

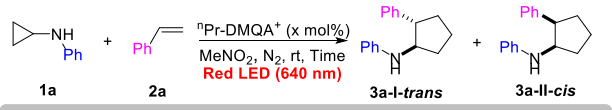
Recently, we demonstrated that the helicenium ion (*N*,*N*′-di-*n*-propyl-1,13-dimethoxyquinacridinium, ^{n}Pr-DMQA^{+}) is an efficient organic photocatalyst (PC) for red-light-mediated reactions.[13] This PC has successfully catalyzed a series of well-studied photo-catalyzed reactions, as well as a novel red-right-mediated cascade trifluoromethylation/dearomatization of

indole derivatives with Umemoto's reagent for the synthesis of CF_3-containing spirocyclic indolines.[13,14] In the reported works on visible-light-mediated [3+2] cycloaddition,[10c-10e] authors have shown that a key step is the oxidation of cyclopropylamine to the amine radical cation (ArRNH/ $ArRNH^{\bullet+}$ = ~ +1.0 V vs SCE[16]) through reductive quenching. With $E_{1/2}(C^{+*}/C^{\bullet})$ = +1.15 V and $E_{1/2}(C^{+}/C^{\bullet})$ = −0.78 V vs SCE[13] for ^{n}Pr-DMQA^{+}, we speculated that ^{n}Pr-DMQA^{+} will be competent to catalyze such transformation. Therefore, we herein present a ^{n}Pr-DMQA^{+}-catalyzed [3+2] annulation of cyclopropylamines with olefins or alkynes in the presence of red light, which provides a simple and more sustainable approach for the construction of functionalized cyclopentanes or cyclopentenes under mild conditions (Scheme 1f).



Scheme 1 (a-e) Previous Work on visible-light-mediated [3+2] cycloaddition of cyclopropylamines and (f) this work

For the initial examinations, we used *N*-cyclopropylaniline **1a** and styrene **2a** as the model substrates in the presence of ^{n}Pr-DMQA^{+} under red light irradiation to screen the optimal conditions and the results of these experiments are summarized in Table 1. The desired product *N*-(2-phenylcyclopentyl)aniline **3a** was obtained in 95% NMR yield, along with 1.1:1 d.r. (trans/cis) value, in nitromethane ($MeNO_2$) when the reaction was run with 3.0 mol% of ^{n}Pr-DMQA^{+} at r.t. for 18 h (Table 1, entry 1). By decreasing the catalyst loading we observed that 1.0 mol% of PC gave the best performance, furnishing **3a** in 95% NMR yield along with 1:1.1 d.r. value (entry 2 vs 3). The investigation of reaction time revealed that 6 h was sufficient to complete the reaction, giving rise to **3a** in 95% NMR yield along with 1:1.1 value in the presence of 1.0 mol% of ^{n}Pr-DMQA^{+} (entries 4-6). Thus, the use of $MeNO_2$ as the solvent, 1.0 mol % of ^{n}Pr-DMQA^{+} as the catalyst loading, and 6 h as the reaction time are the optimized reaction conditions (entry 5). Furthermore, in the absence of red light or ^{n}Pr-DMQA^{+}, no desired product **3a** was detected with mainly starting materials **1a** and **2a** recovered, which suggested the essential roles for both of red light and ^{n}Pr-DMQA^{+} (entries 7-8). Running the reaction under air lowered the reaction yield significantly, which is consistent with Zheng's work[10c] (entry 9).

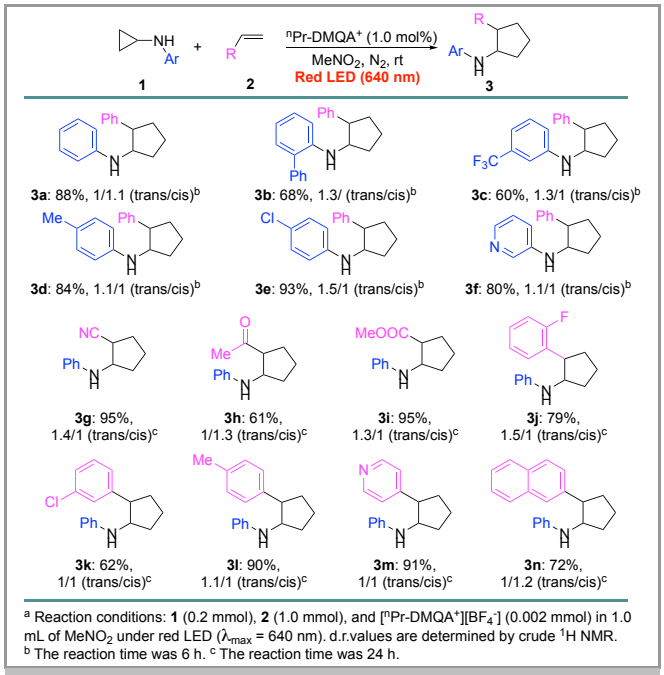


Entry[a]	Catalyst Loading (x mol %)	Time [h]	Yield [%][b]	d.r.[c]
1	3.0	18	95	1:1.1
2	1.0	18	95	1:1.1
3	0.5	18	71	1:1.1
4	1.0	8	95	1:1.1
5	***1.0***	***6***	***95***	***1:1.1***
6	1.0	4	73	1:1.1
7[d]	1.0	20	n. d.[e]	-
8	-	20	n. d.[e]	-
9[f]	1.0	20	65	1:1.1

[a] The reaction was conducted with **1a** (0.2 mmol), **2a** (1.0 mmol) and PC (x mol%) in $MeNO_2$ (1.0 mL). [b] NMR yield by using 1,3,5-trimethoxybenzene as internal standard. [c] Determined by crude ^{1}H NMR. [d] In dark. [e] Not detected. [f] In the presence of air.

Table 1 Optimization of red-light-mediated ^{n}Pr-DMQA^{+}-catalyzed [3+2] cycloaddition

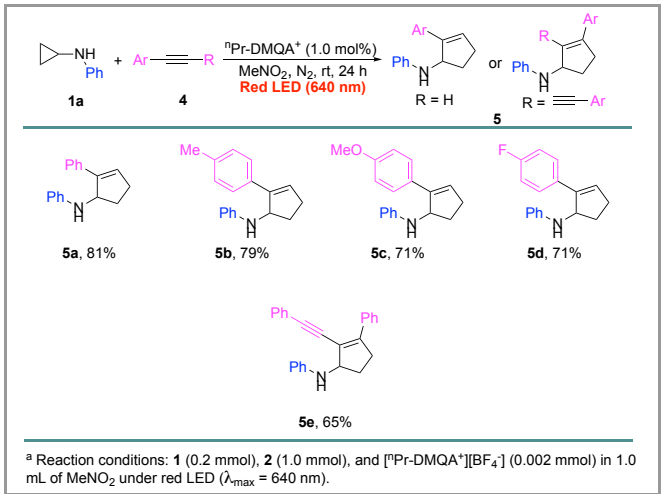
With the optimal conditions in hand, we next sought to explore the substrate scope of this red-light-induced [3+2] cycloaddition (Table 2). Using styrene **2a** as a model substrate, cyclopropylamines with different aromatic groups **1a**–**1f** were tested. The electronic properties, or substitution patterns on the phenyl ring of **1,** did not have much impact the reaction outcome, delivering the corresponding cyclopentane derivatives **3a**-**3f** in 60-93% yield. For example, substrate **1b** with phenyl group at the *ortho* position yielded the desired product **3b** smoothly in 68% yield. **3c** was also isolated in 60% yield when **1c** with trifluoromethyl group at the *meta* position reacted with **2a**. In addition, **1d**-**1e** with methyl or chloro groups at the *para* position provided the 5-membered carbocycles **3d**-**3e** in moderate yields. **1f** with 3-pyridyl group was also suitable for this [3+2] annulation, furnishing **3f** in 80% yield. Then, a wide range of alkenes **2b**-**2i** with diverse useful functional groups such as cyano (**2b**), ketone (**2c**), ester (**2d**), and halide (**2e**-**2f**) were examined, and the reactions proceeded smoothly when reacting with *N*-cyclopropylaniline **1a**. In details, olefins **2b**-**2d** with strong electron-withdrawing groups afforded **3g**-**3i** in 61-95% yield. **3j**-**3n** were also obtained in 62-91% yields when styrene derivatives **2e**-**2i** reacted with **1a**. Though the reaction had relatively poor diastereoselectivities, most of the two *trans* and *cis* diastereomers were fully isolated via flash column chromatography, except for **3b**, **3c**, **3j**, and **3m**.



[a] Reaction conditions: **1** (0.2 mmol), **2** (1.0 mmol), and [^{n}Pr-DMQA^{+}][BF_4^-] (0.002 mmol) in 1.0 mL of $MeNO_2$ under red LED (λ_{max} = 640 nm). d.r.values are determined by crude ^{1}H NMR. [b] The reaction time was 6 h. [c] The reaction time was 24 h.

Table 2 Substrate scope of red-light-mediated ^{n}Pr-DMQA^{+}-catalyzed [3+2] cycloaddition of cyclopropylamine with alkenes

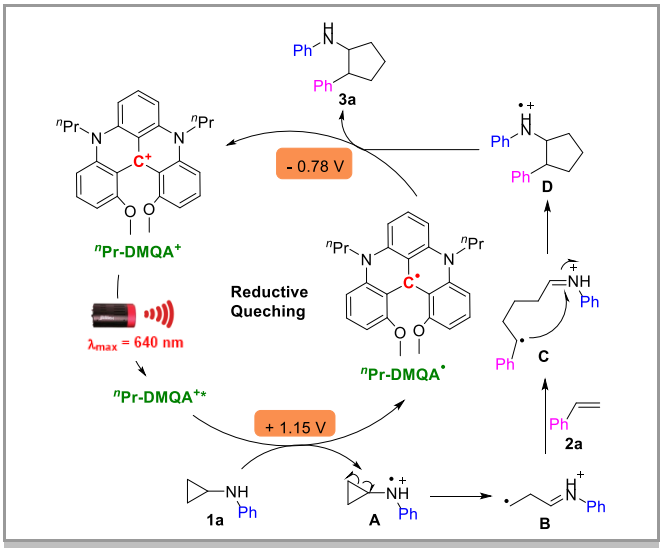
Notably, under optimal reaction conditions, the [3 + 2] addition of cyclopropylamine with alkynes could also be achieved with a broad substrate scope (Table 3). The corresponding cyclopentene products **5a**-**5d** were obtained in 71-81% yields when electron-neutral, electron-deficient, or electron-rich terminal alkynes **4a**-**4d** reacted with **1a.** Moreover, a dialkyne substrate was also compatible under standard reaction conditions, affording the desired product **5e** in 65% yield. It is noteworthy that **5e** was obtained in a much higher yield compared to the yield in the literature,[10d] presumably due to the relatively milder condition with red light in this protocol.



[a] Reaction conditions: **1** (0.2 mmol), **2** (1.0 mmol), and [^{n}Pr-DMQA^{+}][BF_4^-] (0.002 mmol) in 1.0 mL of $MeNO_2$ under red LED (λ_{max} = 640 nm).

Table 3 Substrate scope of red-light-mediated ^{n}Pr-DMQA^{+}-catalyzed [3+2] cycloaddition of cyclopropylamine with alkynes

Based on previous work,[10,13,14] we propose the reaction mechanism for these transformations as shown in Scheme 2. Firstly, the ^{n}Pr-DMQA^{+}* is formed under irradiation of red light, which undergoes a single electron transfer process with cyclopropylamine **1a** to generate the nitrogen radical cation intermediate **A.** Due to the inherent torsional and angular strain of cyclopropane ring, **A** undergoes β-scission of the strained cyclopropane ring to form a β-carbon radical iminium ion **B**, followed by attacking the styrene **2a** to produce another stabilized distonic radical cation species **C**. Intramolecular addition of the *in situ*-formed radical to the iminium ion within intermediate **C** furnishes another nitrogen radical cation species **D**. Lastly, **D** is reduced by the ^{n}Pr-DMQA$^{\bullet}$ to form the final product **3a** as well as and ground state of ^{n}Pr-DMQA^{+} to complete the catalytic cycle.



Scheme 2 Plausible Reaction Mechanism

In conclusion, we have disclosed a ^{n}Pr-DMQA^{+}-catalyzed [3+2] cycloaddition of cyclopropylamines with alkenes or alkynes in the presence of red light, which provides a facile and efficient route for the construction of functionalized 5-membered carbocycles. A mechanism involving reductive quenching of a critical distonic radical cation species is proposed. The employment of low energy red light enables this approach to serve as a complementary option for the current white- or blue-light-mediated protocols in the literature. Further investigation of this red-light-mediated [3+2] annulation of cyclopropylamines with other interesting substrates are underway in our laboratory.

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Supporting Information

General information, substrate synthesis and characterization, mechanistic investigation, experimental procedures, as well as NMR spectroscopy data can be found in the supporting information.

Conflict of Interest

The authors declare no competing financial interest. The authors declare no competing financial interest.

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(17) General procedure for the red-light-induced ^{n}Pr-DMQA^{+}-catalyzed [3+2] cycloaddition of 1 with alkenes 2

In a N_2 glove box, the substrate **1** (0.2 mmol, 1.0 eq.) and alkene **2** (1.0 mmol, 1.2 eq.) were added to an oven-dried (overnight) Schlenk tube containing a stirring bar, followed by adding 1.0 mg of [^{n}Pr-DMQA^{+}][BF_4^{-}] (0.002 mmol, 1.0 mol%) in 1 mL of degassed $MeNO_2$ (transferred from a 10 mL stock solution of [^{n}Pr-DMQA^{+}][BF_4^{-}] (10.0 mg) in degassed $MeNO_2$). The Schlenk tube was then sealed, removed from the glove box, and the solution was stirred at room temperature under red LED (λ_{max} = 640 nm) irradiation. After completion of the reaction, the mixture was concentrated under reduced pressure on a RotaVap. The crude product was purified by flash chromatography (FC) on silica gel (eluent: Hexanes/Et_2O = 25/1 ~ 6/1) to yield the desired product **3**.

Trans-N-(2-phenylcyclopentyl)aniline (**3a-I**):[10c] Yield (20 mg, 42% yield). A colorless oil. R_f = 0.3 (Hexanes/EtOAc = 20/1). FC (Hexanes/Et_2O = 99/1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 8.0, 8.0 Hz, 2H, ArH), 7.25 – 7.21 (m, 3H, ArH), 7.12 (dd, *J* = 8.0, 8.0 Hz, 2H, ArH), 6.65 (dd, *J* = 8.0, 8.0 Hz, 1H, ArH), 6.48 (d, *J* = 8.0 Hz, 2H, ArH), 4.01 (dd, *J* = 12.0, 6.0 Hz, 1H, CH), 3.46 (dd, *J* = 15.0, 7.5 Hz, 1H, CH), 3.37 (bs, 1H, NH), 2.22 – 2.07 (m, 3H, CH_2), 2.02 – 1.94 (m, 1H, CH_2), 1.89 – 1.76 (m, 2H, CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.91, 140.84, 129.18, 128.77, 128.43, 126.59, 117.01, 113.32, 57.57, 48.15, 32.01, 28.94, 22.19.

Cis-N-(2-phenylcyclopentyl)aniline (**3a-II**):[10c] Yield (22 mg, 46% yield). A colorless oil. R_f = 0.2 (Hexanes/EtOAc = 20/1). FC (Hexanes/Et_2O = 99/1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 4H, ArH), 7.22 (dd, *J* = 7.5, 7.5 Hz, 1H, ArH), 7.13 (dd, *J* = 7.5, 7.5 Hz, 2H, ArH), 6.67 (dd, *J* = 7.5, 7.5 Hz, 1H, ArH), 6.55 (d, *J* = 7.5 Hz, 2H, ArH), 3.80 (bs, 1H, NH), 3.80 (dd, *J* = 13.0, 7.0 Hz, 1H, CH), 2.93 (dd, *J* = 17.0, 8.0 Hz, 1H, CH), 2.38 (ddd, *J* = 21.0, 14.5, 7.5 Hz, 1H, CH_2), 2.26 – 2.19 (m, 1H, CH_2), 1.94 – 1.82 (m, 2H, CH_2), 1.81 – 1.75 (m, 1H, CH_2), 1.66 – 1.58 (m, 1H, CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.16, 143.83, 129.25, 128.69, 127.48, 126.54, 117.19, 113.47, 61.58, 53.27, 33.59, 33.55, 23.46.