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Visible-Light Photocatalytic Decarboxylative Alkyl Radical Addition Cascade for Synthesis of Benzazepine Derivatives

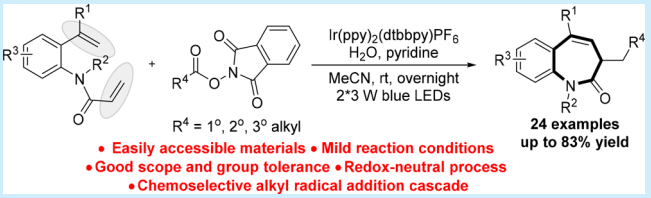
Yu Zhao,[†] Jia-Rong Chen,[†] and Wen-Jing Xiao*[,†,‡]

[†]Hubei International Scientific and Technological Cooperation Base of Pesticide and Green Synthesis, Key Laboratory of Pesticides and Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, 152 Luoyu Road, Wuhan 430079, China

[‡]State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China

Supporting Information

ABSTRACT: A visible-light photocatalytic decarboxylative alkyl radical addition cascade reaction of acrylamide-tethered styrenes for the synthesis of benzazepine derivatives is described. This protocol features broad substrate scope, excellent functional group tolerance, and mild reaction conditions, affording the seven-membered rings in good yields. This method was also applied for efficient grafting of the benzazepine scaffold into the pharmaceutically active ursolic acid scaffold.



Radical cascade reactions serve as an excellent way to construct various structually diverse and complex carbocycles and heterocycles, which exist in many pharmaceuticals, bioactive molecules, and natural products.[1] This strategy can usually meet a criteria of ideal synthesis,[2] enabling the design of an atom-, step-, and redox-economic process. In order to develop more environmentally friendly alternatives, we need to avoid the use of harsh reaction conditions and stoichiomeric radical initiators that are typically involved in the traditional methods for radical generation. Toward this target, visible-light photoredox catalysis provides an attractive tool to produce various reactive radicals for initiating radical reactions and assembly of diverse carbocyclic and heterocyclic skeletons.[3] In this context, we also have a longstanding interest in visible light photocatalytic heterocycle synthesis.

Benzazepine derivatives are a significant family of seven-membered heterocycles that exhibit unique bioactive and pharmaceutical properties (Figure 1).[4] The development of novel and efficient methods for their synthesis has attracted considerable attention from the synthetic community. Typically, the benzazepine skeletons could be assembled by transition-metal-catalyzed coupling,[5] Beckmann rearrangement,[4a] radical reactions,[6] and others.[7] For instance, the Shi group reported an elegant Fe- or Cu salt-catalyzed CF_3 radical addition cascade for the synthesis of CF_3-containing polycyclic benzazepine derivatives in a highly chemoselective fashion (Scheme 1a).[6c] Recently, the Li group has also developed a Ag-mediated decarboxylative radical addition/annulation cascade for construction of 2*H*-benzo[*b*]azepin-2-ones using stoichiomeric $K_2S_2O_8$ as oxidant (Scheme 1b).[6d] Inspired by these impressive advances, we envisaged that visible light induced redox-neutral radical addition cascade would provide a facile route to benzazepine skeletons.

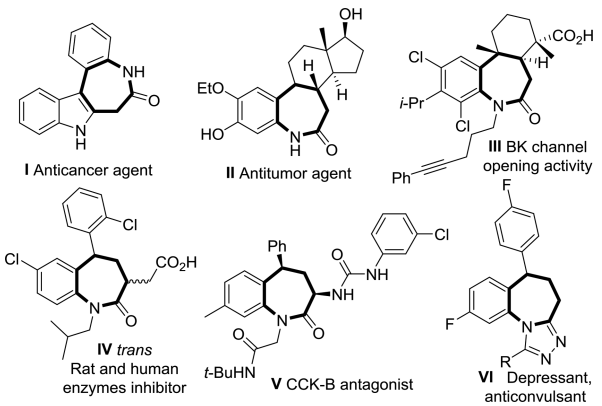


Figure 1. Examples of biologically active compounds containing benzazepine scaffold.

Carboxylic acids are abundant and inexpensive chemical feedstocks. With the development of visible-light photoredox catalysis, carboxylic acids and their derivatives can undergo single-electron transfer to form the alkyl radicals by decarboxylation. As such, synthetically useful transformations can take place,[3h,8] such as atom abstraction, radical−radical cross coupling, radical addition, and radical transmetalation.[9] In terms of the radical addition reactions, we found that the alkyl radicals could directly add to activated or unactivated alkenes.[10] Inspired by these contributions, we anticipated that the visible light induced decarboxylative alkyl radical chemoselective addition casacde to acrylamide-tethered styrene would lead to

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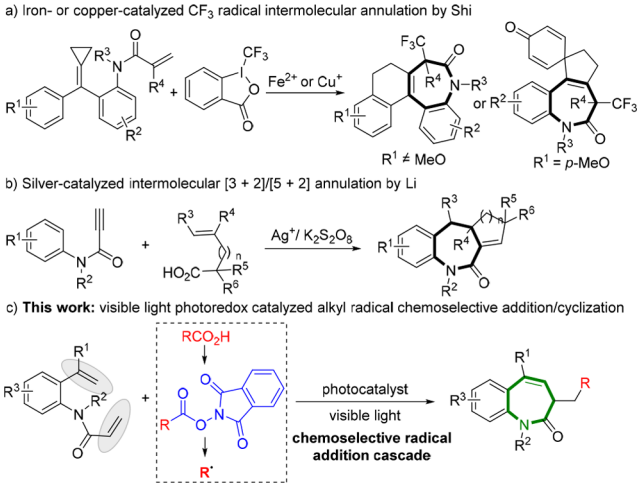
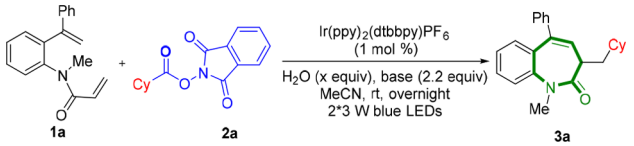
Scheme 1. Intermolecular Radical Addition Cascade for the Construction of the Benzazepine Scaffolds



benzazepine derivatives. Herein, we describe our preliminary results.

The investigation of the alkyl radical addition cascade began with acrylamide-tethered styrene and cyclohexyl *N*-(acyloxy)-phthalimide (NHP ester) as model substrates, 1 mol % of $Ir(ppy)_2(dtbbpy)PF_6$ as photocatalyst, and CH_3CN as the solvent under irradiation of 2*3 W blue LEDs (Table 1).[11]

Table 1. Reaction Optimization[a]



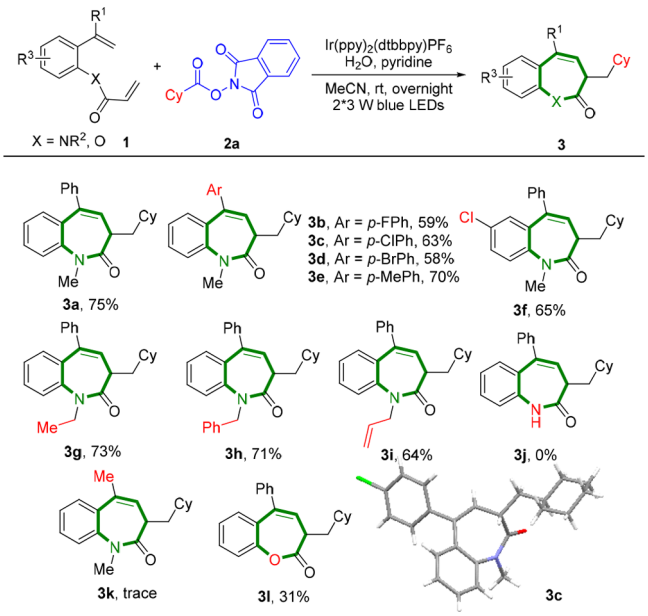
entry	H_2O (x equiv)	base	yield[b] (%)
1	5	no	69
2	10	no	71
3	50	no	62
4	10	pyridine	74
5	10	$NaHCO_3$	69
6	10	K_2CO_3	43
7[c]	10	pyridine	75
8[d]	10	pyridine	no
9[e]	10	pyridine	no
10[f]		pyridine	19

[a]**1a** (0.20 mmol), **2a** (0.22 mmol), photocatalyst (1 mol %), 2.2 equiv of base, 2.0 mL of MeCN, overnight, 2*3 W blue LEDs, rt. [b]Isolated yield. [c]1.2 equiv of pyridine was added. [d]Without photocatalyst. [e]Without visible light irradiation. [f]Without H_2O.

When 10 equiv of H_2O were added to this system, the desired product **3a** was obtained in 71% yield. Addition of less or more distilled water led to a slight decrease to 69% and 62% yields, respectively (entries 1−3). Subsequently, the addition of extra bases to this system, including organic and inorganic bases, led to a significant change in the reaction efficiency (entries 4−6). When pyridine was used as the base, the yield of the desired product **3a** rose to 74%. By decreasing the loading of pyridine to 1.2 equiv, the desired product **3a** was obtained in 75% yield (entry 7). Control experiments of this radical addition cascade were performed, either without the photocatalyst, in the absence of visible light irradiation, or without extra H_2O, and none or very low yield of **3a** was observed, confirming that this radical cascade reaction was a photocatalytic process (entries 8−10).

With the optimized reaction established, we examined the substrate scope for the reaction of acrylamide-tethered styrenes **1** with **2a** (Scheme 2). It was found that this reaction can

Scheme 2. Scope of Acrylamide-Tethered Styrenes 2a[a,b]



[a]**1** (0.20 mmol), **2a** (0.22 mmol) and $Ir(ppy)_2(dtbbpy)PF_6$ (1 mol %), 10 equiv of water, 1.2 equiv of pyridine, in MeCN (2.0 mL) at rt under irradiation by 2*3 W blue LEDs overnight. [b]Isolated yield.

tolerate a variety of substituents on the benzene ring tethered alkene. Reactions of **1b−e** containing an electron-donating (e.g., methyl) or electron-withdrawing (e.g., fluoro, chloro, bromo) functional groups worked well to deliver the corresponding products **3b−e** in 58−70% yields. When R^3 is a chloro group, product **3f** can be isolated in 65% yield. Subsequently, we investigated the influence of the *N*-protected groups. It was found that with those groups, such as ethyl, benzyl and allyl, the reaction could give the desired products **3g−i** in 64−73% yields. In contrast, the reaction of *N*-free acrylamide-tethered styrene did not work under the standard conditions. Surprisingly, when we utilized the 1,1-phenylmethyl alkene tethered acrylamide as a radical acceptor, no desired product **3k** was observed, probably because the benzyl radical intermediate was not sufficiently stable. Note that the acrylate-tethered styrene **1l** could also react with **2a** to give the product **3l** in 31% yield. Importantly, the X-ray crystal structure analysis of product **3c** was determined, thus demonstrating the feasibility of this strategy for the construction of benzazepines.

For the next stage of this investigation, a set of radical sources was assessed by examining the generality of the alkyl radical addition cascade (Scheme 3). We were pleased to observe that this reaction exhibited broad substrate scope, and the aliphatic primary, secondary, and tertiary carboxylic acids reacted smoothly with **1a**. For example, the reaction with the primary carbon-centered radical derived from phenylpropionic acid gave rise to desired product **4a** in 40% yield. Moreover, the acyclic and cyclic secondary carbon-centered radicals worked well to afford the products **4b−i** in 49−73% yields. Functional

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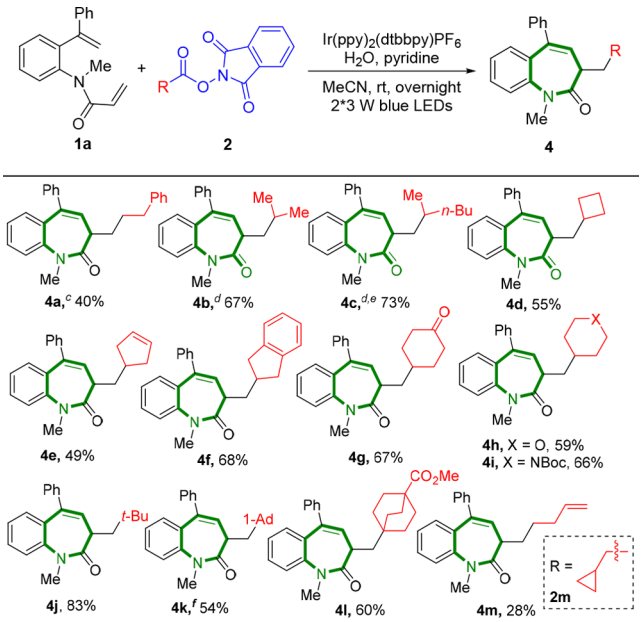
Scheme 3. Scope of the Alkyl Radical Precursors 2[a,b]

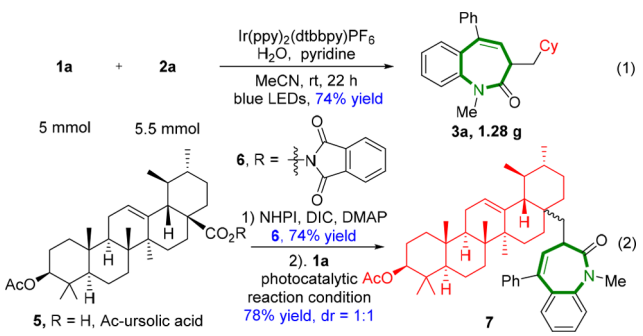


[a]**1a** (0.20 mmol), **2** (0.22 mmol) and $Ir(ppy)_2(dtbbpy)PF_6$ (1 mol %), 10 equiv of water, 1.2 equiv of pyridine, in MeCN (2.0 mL) at rt under irradiation by 2*3 W blue LEDs overnight. [b]Isolated yield. [c]The ratio of **1a** to **2** is 1.5:1. [d]5 mol % of $Ir(ppy)_2(dtbbpy)PF_6$ was used. [e]Diastereomeric ratio was 1:1, which was determined by ^1H NMR analysis. [f]37 h.

groups, such as vinyl, ether, Boc-protected amine, and carbonyl, can be toleranted in this reaction. Tertiary radical sources, including the sterically hindrance radical containing the 1-adamantyl group, could be employed for this reaction to generate the corresponding products **4i–k** in 54–83% yields. In addition, when we utilized NHP ester **2m** of cyclopropyl acetic acid as a radical precursor, a 28% yield of ring-opened product **4m** was obtained, confirming the involvement of radical intermediate in the process.

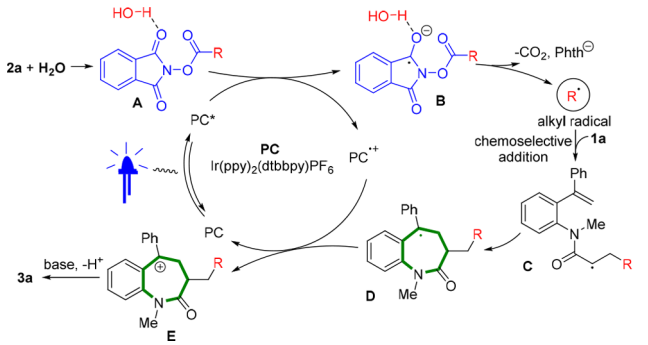
To showcase the scalability of this photocatalytic radical addition cascade, a gram-scale reaction was performed using the model substrates **1a** and **2a**, giving the product **3a** in 74% yield (Scheme 4, eq 1). Furthermore, it is well-known that ursolic acid has excellent pharmaceutical activity.[12] Using this radical addition cascade, we were able to assemble the "two privileged scaffolds" between ursolic group and benzazepine, providing **7** in 58% isolated yield by using the Ac-protected ursolic acid as starting material (Scheme 4, eq 2).

Scheme 4. Synthetic Application



To gain further insight into the mechanism, we have performed some control experiments, including addition of TEMPO as radical-trapping agent, with D_2O and without extra H_2O.[11] The experimental results suggested the involvement of radical intermediates and activation of the alkyl *N*-(acyloxy)-phthalimide by its hydrogen-bonding interaction with water.[10d] Accordingly, we proposed a plausible mechanism forthe photocatalytic chemoselective alkyl radical addition cascade (Scheme 5). First, this photocatalyst (PC) is photoexcited to its

Scheme 5. Proposed Mechanism



excited state (PC*) and oxidized by a complex of **2a** binded by hydrogen bonding. This reducing complex **B** undergoes decarbonation, to afford the alkyl radical intermediate. Subsequently, this alkyl radical reacts with **1a**, followed by the chemoselective radical addition cascade process, to form the benzyl radical intermediate **D**. Finally, this key intermediate **D** further undergoes oxidation and dehydrogen, completing the photocatalytic cycle by affording the final product **3a**. As demonstrated in Scheme 2, the reaction of substrates with electron-rich aryl groups (e.g., **3a** and **3e**) gave better yields than those with electron-deficient groups (e.g., **3b–d,f**), indicating that the stability of **D** is essential and the formation of **D** should be the rate-determining step.

In conclusion, we have successfully developed a novel and efficient method for the facile synthesis of benzazepine derivatives. The key to success is the photocatalytic decarboxylative alkyl radical generation and its chemoselective addition cascade to the alkene. This protocol features broad substrate scope and excellent functional group tolerance under very mild reaction conditions. Furthermore, application of this method enables access to the efficient installation of the pharmaceutically active ursolic group onto the benzazepine scaffold.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03588.

Experimental procedures and full spectroscopic data for all new compounds (PDF)

Accession Codes

CCDC 1582448 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge

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Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

*E-mail: wxiao@mail.ccnu.edu.cn.

ORCID

Jia-Rong Chen: 0000-0001-6054-2547

Wen-Jing Xiao: 0000-0002-9318-6021

Notes

The authors declare no competing financial interest.

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