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Divergent Synthesis of Aziridine and Imidazolidine Frameworks under Blue LED Irradiation

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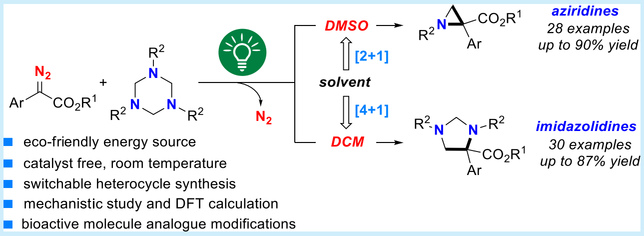
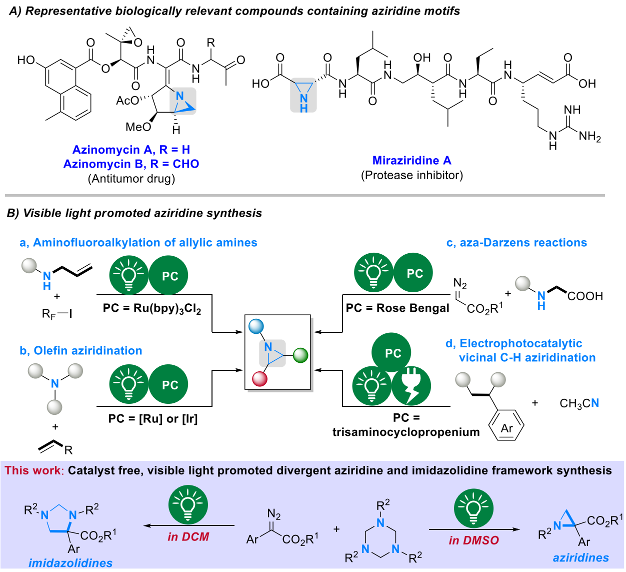
ABSTRACT: We develop a visible light-promoted divergent cycloaddition of α-diazo esters with hexahydro-1,3,5-triazines, leading to a series of aziridine and imidazolidine frameworks in average good yield, by simply changing the reaction media used. It is noteworthy that the reaction occurs under sole visible light irradiation without the need for exogenous photoredox catalysts. More significantly, a reasonable mechanism was proposed on the basis of the control experiments and density functional theory calculation results.



Aziridines are some of the smallest nitrogen-containing heterocycles that can be widely found in various natural isolates, pharmaceuticals, and biologically active molecules (Scheme 1A).[1] Moreover, aziridines are also known as highly versatile synthetic intermediates to undergo ring-opening functionalization due to their intrinsic ring strain.[2] Despite the fact that syntheses of aziridines have been extensively developed in the past several decades,[3] visible light-catalyzed synthesis of three-membered heterocyclic frameworks as a clean and sustainable route is rarely reported (Scheme 1B).[4] In early 2013, the group of Cho developed a visible light-promoted aminofluoroalkylation of allylic amines for the synthesis of CF_3-containing aziridines with $[Ru(bpy)_3]Cl_2$ as the photoredox catalyst.[5] Visible light-induced olefin aziridination[6] and aza-Darzens reaction[7] are alternative methods for the synthesis of these valuable building blocks. Recently, the Lambert group disclosed a vicinal C−H diamination reaction for the formation of aziridine derivatives through an electrophotocatalytic strategy.[8] Though elegant advances in light-induced synthesis of aziridines have been achieved, current methodologies still depend on metal-based or organic dye photoredox catalysts. On the contrary, the growing demand for sustainable chemistry makes development of versatile methods for the construction of both aziridines and other important heterocyclic systems from same easily accessed starting materials under benign conditions still urgent.

Scheme 1. Biologically Relevant Compounds Containing Aziridine Motifs and Their Photopromoted Synthetic Methods



Since they were first discovered by Reinfield et al. at the beginning of the past century,[9] hexahydro-1,3,5-triazines have been recognized as efficient 1,*m*-dipoles in the synthesis of various important N-containing heterocycles through a cycloaddition process.[10] Among the reactions developed, α-diazo esters proved to be ideal cycloaddition partners with hexahydro-1,3,5-triazines in the presence of Lewis acids or transition metals.[11] Despite the fact that metal-catalyzed carbene-transfer reactions from α-diazo esters have been widely investigated for several decades,[12] visible light-promoted carbene generation/functionalization of α-diazo

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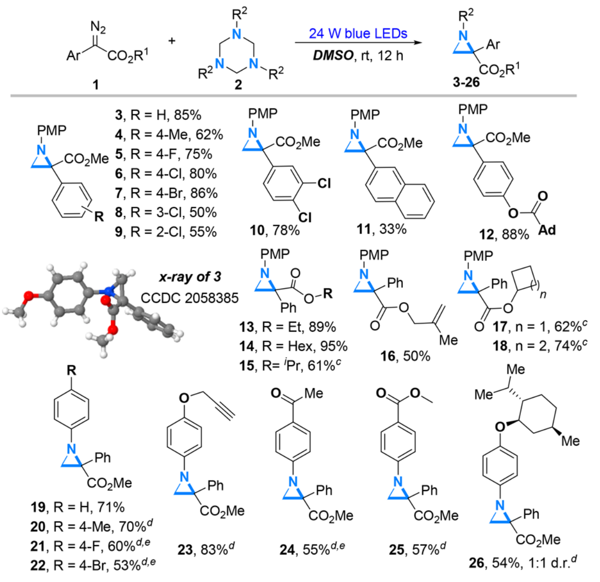
esters emerged in only 2018. Under blue LED irradiation, α-diazo esters can be activated by absorption of light in the visible region to form free singlet carbene species through nitrogen gas extrusion.[13] The groups of Davis, Zhou, Koenigs, Xiao, and many others have successfully applied this strategy to various chemical transformations, such as X−H insertion,[14] cyclopropanation and cyclopropenation,[15] Doyle−Kirmse reaction,[16] and other valuable reactions.[17] Compared with these well-developed processes, the applications of photo-generated carbene species using visible light from α-diazo esters toward the synthesis of important heterocyclic compounds are rarely reported.[18]

As part of our ongoing research interest in the development of heterocycle-oriented methodologies,[19] we herein report a solvent-controlled divergent cycloaddition of α-diazo esters with hexahydro-1,3,5-triazines promoted by visible light (Scheme 1c). It was found that aziridine derivatives were accessed in DMSO with good results. This method can also be applied to the facile synthesis of imidazolidine frameworks in DCM media. Appealing features of this protocol include (1) the use of visible light as a sole clean energy source, (2) the fact that exogenous photoredox catalysts are not required to run the process, and (3) the fact that both aziridines and imidazolidines can be easily accessed through simple alternation of the reaction solvents used.

We initially optimized the reaction conditions by reacting phenyldiazoacetate **1** and PMP-substituted hexahydro-1,3,5-triazine **2** in DMSO under blue LED irradiation. It was found that aziridine **3** could be obtained in 85% yield of the isolated product by using 3.0 equiv of **1** (compared with the *in situ*-formed formaldimine from **2**). Under the optimal reaction conditions (for details of the optimization, see the Supporting Information), the generality and the limitation of visible light-promoted formal [2+1] cycloaddition were then investigated (Scheme 2). First, a wide range of mono- or disubstituted α-diazo esters were examined. α-Diazo esters with different electron-donating substituents (methyl and acyloxyl) or electron-withdrawing groups (halogens, e.g., -F, -Cl, or -Br) transformed to the corresponding formal [2+1] cycloaddition products in good to high yields (Table 1 in the Supporting Information, **3**−**10** and **12**). The yields of heterocycles produced from *meta*- and *ortho*-substituted α-diazo esters were relatively lower than those derived from *para*-substituted α-diazo esters because of steric hindrance (**6** vs **8** and **9**). Note that aziridine product **11** bearing a naphthyl ring was also achieved, albeit with a low yield (33%). Next, the effect of the ester moiety of α-diazo esters was also investigated. We are grateful that different alkyl ester (**13**−**16**)- or cycloalkyl ester (**17** and **18**)-derived α-diazo esters showed good compatibility to produce the corresponding heterocyclic products in good yields. In addition, several hexahydro-1,3,5-triazines were applied as formaldimine precursors in this visible light-promoted formal [2+1] cycloaddition process. To our delight, when the aryl rings of hexahydro-1,3,5-triazines bearing different sensitive functional groups (e.g., halogens, alkyne, ketone, or ester) were used as surrogates of formaldimines, all reactions proceeded smoothly and furnished the expected aziridine products in good yields (**19**−**26**).

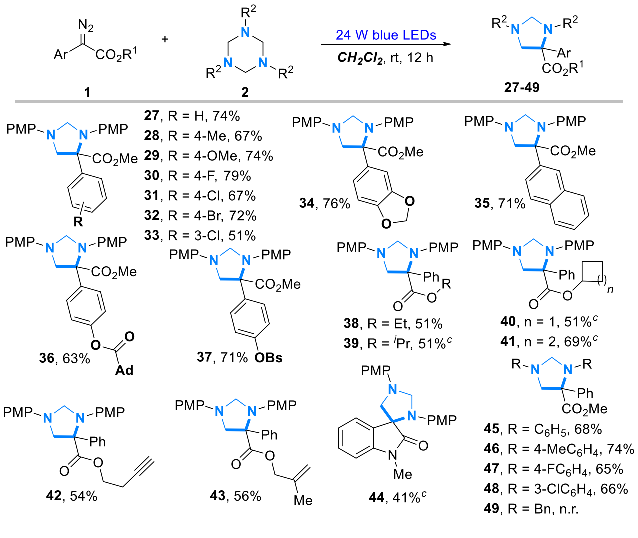
Scheme 2. Reaction Scope of Aziridines[a,b]



[a]Reaction performed with diazoalkane (0.45 mmol) and 1,3,5-triazine (0.05 mmol) in DMSO (2.0 mL) at rt under 24 W blue LED irradiation for 12 h. [b]Yield of the isolated product. [c]Diazoalkane (0.15 mmol) and 1,3,5-triazine (0.15 mmol). [d]Diazoalkane (0.15 mmol) and 1,3,5-triazine (0.05 mmol). [e]Twenty-four hours.

During the reaction optimization, we were pleased to find that the reaction media had a significant effect on product formation. When the solvent was changed from DMSO to DCM, a formal [4+1] cycloaddition adduct, imidazolidine **27**, was obtained in 74% yield of the isolated product after irradiation for 12 h (for details of the optimization, see the Supporting Information). As shown in Scheme 3, incorporation of both electron-rich and electron-deficient substituents on the phenyl ring of α-diazo esters generally afforded the corresponding imidazolidine in good yields (**28**−**37**). The relatively low yield of **33** might be due to the steric effect. More significantly, disubstituted α-diazo esters were also amenable substrates to afford product **34** in 76% yield. Apart from phenyl-derived α-diazo esters, methyl 2-diazo-2-(naphthalen-2-yl) acetate reacted well with PMP-protected hexahydro-1,3,5-triazine **2a** to give **35** in 71% yield. Importantly, the

Scheme 3. Reaction Scope of Imidazolidines[a]

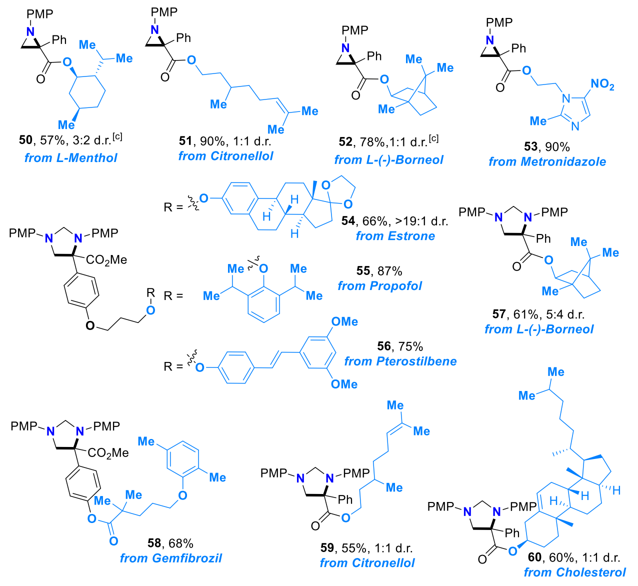


[a]Reaction performed with diazoalkane (0.2 mmol) and 1,3,5-triazine (0.1 mmol) in DCM (2.0 mL) at rt under 24 W blue LED irradiation.

reaction was tolerated well with many sensitive functional groups, such as esters (**36** and **37**), a carbon−carbon double bond (**42**), and a triple bond (**43**). It was noteworthy that carbene cyclopropanation or cyclopropenation products were not observed in the cases of substrates containing unsaturated double or triple bonds. Then, substituent modification of the ester group in diazoalkane components was investigated. It was found that replacement of the methyl group in **1** with other primary alkyl groups (**38**), a secondary alkyl group (**39**), and cyclic alkyl groups (**40** and **41**) all proved to be successful, providing the corresponding imidazolidine heterocycles in moderate to good yields (51−69%). To our delight, spiro-imidazolidine **44** could be successfully obtained in moderate yield through the reaction of cyclic diazo compounds with 1,3,5-triazine **2a** under our optimal reaction conditions. Moreover, different aryl-substituted hexahydro-1,3,5-triazines were also examined, thus giving the corresponding imidazolidines in good yields (**45**−**48**). Note that alkyl-substituted hexahydro-1,3,5-triazine was not suitable in the current reaction system (**49**).

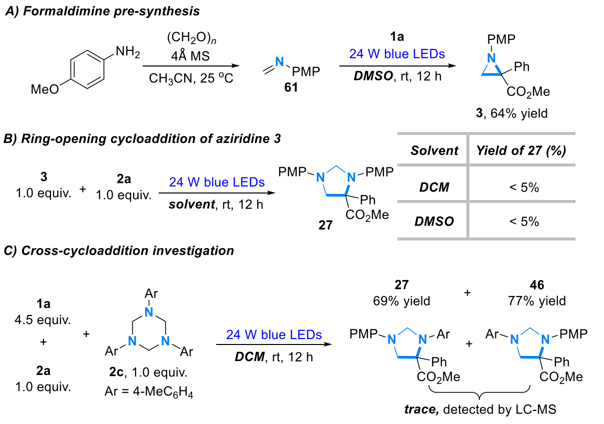
To further explore the potential application of this method in the pharmaceutical industry, we tested visible light-promoted selective cycloaddition chemistry on late-stage modifications of several biologically active molecules. As shown in Scheme 4, the [2+1] cycloaddition process could be further applied to the synthesis of aziridines containing biologically important complex molecules by using L-menthol, citronellol, L-(−)-borneol, and metronidazole as examples (**50**−**53**, respectively). We also introduced some natural products or drug-derived complex molecules, such as estrone, propofol, pterostilbene, gemfibrozil, L-(−)-borneol, citronellol, and cholesterol, into diazoalkane starting materials. To our satisfaction, all o fthese α-diazo esters reacted well in DCM under only blue LED irradiation, affording the corresponding imidazolidine-modified complex structures in good yields (**54**−**60**, 55−87% yields).

Scheme 4. Bioactive Molecule Analogue Modifications



Some control experiments were conducted as shown in Scheme 5 to better understand the reaction mechanism. Initially, formaldimine **61** was presynthesized and applied to react with α-diazo esters **1a** in DMSO under standard reaction conditions (Scheme 5A). After irradiation for 12 h, the desired aziridine **3** could be obtained in 64% yield, indicating the formaldimine was formed during the formation of aziridine. In addition, performing the reaction of aziridine **3** with **2a** under blue LED irradiation in DCM or DMSO resulted in the formation of only imidazolidine **27** in very low yield [<5% (Scheme 5B)]. These results indicated that the formation of imidazolidine **27** through the ring-opening cycloaddition of aziridine **3** with *in situ*-generated formaldimine from 1,3,5-triazine **2a** might not be the predominate way. The reactions of various aryl-substituted 1,3,5-triazines with methyl 2-diazo-2-phenylacetate **1a** under standard reaction conditions were also examined (Scheme 5C). After irradiation for 12 h, imidazolidines **27** and **46** were isolated in 69% and 77% yields, respectively. In contrast, only a trace amount of the cross-cycloaddition product was detected by LC-MS analysis, which further excluded the formation of formaldimine from hexahydro-1,3,5-triazines in the case of the imidazolidine formation process.

Scheme 5. Mechanistic Studies



Solvent	Yield of 27 (%)
DCM	< 5%
DMSO	< 5%

On the basis of the experimental results presented above and previous reports, a plausible reaction mechanism is proposed in Figure S1.[11,13] Under visible light irradiation, photolysis of aryl diazoacetate gives a carbene species (**Int-A**) with the release of nitrogen gas. It is well-known that heteroatom nucleophiles can react with carbene species to generate ylide intermediates.[13] To understand the pathways of this divergent heterocycle formation process, free energy surfaces are calculated by gradient-corrected density functional theory with dispersion corrections (M06-2X/cc-pVTZ) in Gaussian 09 (version E.01).[20] As the reaction was performed in DCM, direct reaction of 1,3,5-triazine with **Int-A** provides **Int-B** by ylide formation with a reaction free energy of −16.81 kcal/mol. Ring opening of **Int-B** gives zwitterionic intermediate **C** via the cleavage of the C−N bond with a free energy barrier of 7.33 kcal/mol, which subsequently transfers to **C′** through neighboring σ-C−N bond rotation with a very low energy of isomerization of 0.1 kcal/mol. In chairlike **Int-C**, the chair distortion of the triazine ring corresponds to a very low frequency mode (41 cm^{-1}), suggesting that the innate flexibility of the ring is an important factor in the deformation to facilitate the final cyclization. Finally, an intramolecular substitution of **C′** provides imidazolidine **45**, together with the release of formaldimine. The rate-determining step occurs with connection of the C−C bond (TS2) in forming product **45**.

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The free energy of 9.61 kcal/mol for this step (at 298 K) is consistent with the experimental temperature.

To experimentally explain the formation of aziridine, a formal [2+1] cycloaddition is first proposed in Figure S1b (path A) with the solvent effect of DMSO. The reaction is triggered by mixing **Int-A** and formaldimine (**Int-D**), where **Int-D** is generated by dissolution of 1,3,5-triazine. Then, the reaction of the nitrogen atom of formaldimine with carbene species **A** gives ylide **Int-E**. The combination of two reactants with very high reactivity decreases the free energy of −38.54 kcal/mol for the system. The Mulliken charge distribution of **Int-E** reveals a substantial polarization of the $C^1{=}N{-}C^2$ bonds [$q(C^1) = -0.28$, and $q(C^2) = 0.30$], indicating the possibility of the connection of two polarized C atoms. Therefore, **Int-E** subsequently undergoes intramolecular cyclization via **TS3** to provide aziridine **19** with a barrier of only 8.19 kcal/mol. In addition to this [2+1] cycloaddition mechanism, we also tried to consider an alternative pathway shown in Figure S1b (path B). With the solvent effect of DMSO, chairlike **Int-C** is generated by the ring opening of **Int-B** via **TS1** (in DMSO) with a barrier of 6.93 kcal/mol, which might also lead to the formation of aziridines. However, DFT calculation reveals that the energy barrier reaches 41.9 kcal/mol upon cyclization to form aziridines **19** with the departure of two groups of formaldimine. On the basis of natural population analysis of **Int-C** (in DMSO), we hypothesize the electrostatic attraction between the polarized $C^3{=}N{-}C^4$ [$q(C^3) = -0.08$, and $q(C^4) = -0.36$] has difficulty in triggering the dissociation of the ring. Therefore, the favored pathway in the formation of aziridine **19** is the [2+1] cycloaddition shown in path A with a rate-determining free energy barrier of 8.19 kcal/mol.

In summary, we developed a visible light-promoted divergent cycloaddition of α-diazo esters with hexahydro-1,3,5-triazines. Under environmentally benign blue LED irradiation, series of aziridine and imidazolidine frameworks could be obtained in good to excellent yields by simply changing the reaction solvent. In addition, the synthetic value of this benign protocol was further demonstrated by successful construction of aziridines and imidazolidines containing important natural isolates and drug-based complex molecules. Mechanistic studies based on control experiment results and DFT calculations revealed that both 1,3,5-triazines and the *in situ* formation of formaldimines could serve as carbene trapping reagents to form key nitrogen ylide intermediates.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00979.

Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 2058385 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 Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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