Photoactivated Formal [3 + 2] Cycloaddition of *N*-Aryl Cyclopropylamines

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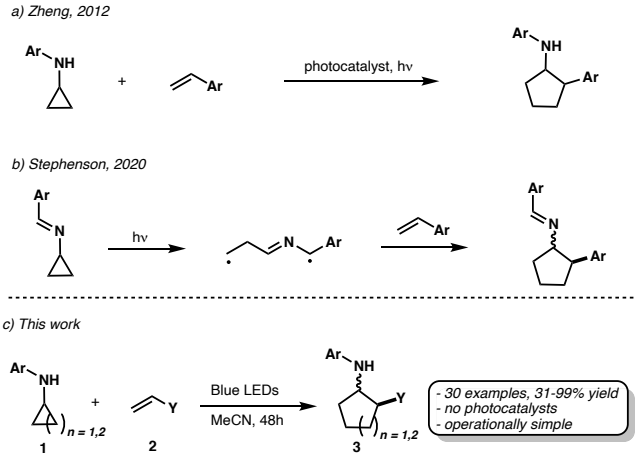
ABSTRACT: Organic transformations initiated by photochemical activation have been at the forefront of reaction discovery. We have seen the [2+2] photocycloaddition performed upon excitation of α,β-unsaturated carbonyl compounds, and more recently [3 + 2] cycloadditions of aryl cyclopropyl ketones have been reported. These methodologies required a photocatalyst and/or external activators, adding some limitations to the substrates used. Herein, we report a formal photochemical [3 + 2] cycloaddition using *N*-aryl cyclopropylamines and α,β-unsaturated carbonyl systems without the use of photocatalysts or additives. This simple method proceeding through a Single Electron Transfer (SET) offers a wide scope for the synthesis of *N*-arylaminocycloalkyl compounds in good to excellent yields.

Cyclopropanes have special and unique reactivity that can be attributed to the torsional and angular strain of the ring.[1] Recently, the use of transition metals to cleave cyclopropanes to form cyclopentane rings has been demonstrated.[2] The addition of an activating handle such as an attached nitrogen-based functional group, which allows the exploitation of C-C bond cleavage opening the formation of key intermediates.[3] From a radical formation perspective, cyclopropylamines can be employed in the formation of cyclopentanes through the formation of the nitrogen center radical initiating the β-scission of the three-membered ring.[4-6] However, most of these methods requires often the use of harsh conditions such as high energy light, or strong oxidants. Recently, modern visible-light photoredox catalysis has provided an attractive alternative method for the formation nitrogen and carbon centered radical.[7] In 2012, Zheng and coworkers reported a [3 + 2] photocatalytic cycloaddition of cyclopropyl anilines and styrenes for the synthesis of aminocyclopentanes (Scheme 1a).[8] Following these reports, other groups utilized organic dyes and Ir(III) based catalysts to perform diastereoselective and enantioselective [3 + 2] cycloadditions where the proceed through a stepwise process.[9] Recently, photoexcitation of cyclopropylimines to generate nitrogen-centered radicals has been shown to be an alternative strategy for the formation of amino-cyclopentanes (Scheme 1b).[10]

With this in mind, the process of photoinduced single electron transfers (SET) can be carried out using a diverse photoactivated molecules, leading to different free-radical reaction pathways and new methodologies in C-C bond formation. To broaden the scope of *N*-aryl cyclopropylamine **1** cycloaddition, we first examined the reaction with electron-poor olefins **2** and the use of other photoredox catalysts such as $Au_2dppm_2Cl_2$ (5 mol%). Initial results shown that the gold(I)-catalyzed photoredox cycloaddition of **1a** (Ar = Ph) and ethyl acrylate **2a** (Y = CO_2Et) using 365 nm LEDs gave **3aa** (Ar = Ph and Y = CO_2Et) in good yields as an inseparable mixture of diastereomers (dr = 3:2) (Scheme 1c). However, a control experiment revealed that irradiation (365 nm) of **1a** and **2a** in the absence of a photocatalyst gave the desired cycloadduct product **3aa** in 72% yield (dr = 3:2). This exciting result indicates that the initial SET could be triggered by photoexcitation of the cyclopropylaniline **1a**. This unexpected result prompted us to investigate the general applicability of this reaction. Herein, we report the synthesis of *N*-aryl aminocycloalkyl **3** harnessing a distinct activation mode.

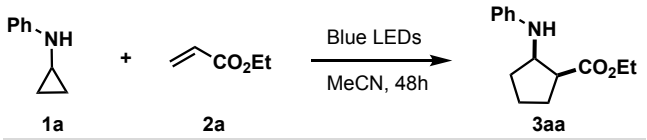
Scheme 1. Previous and present work in the formal [3 + 2] cycloadditions of aryl cyclopropylamines.



Initial optimization revealed that cycloaddition proceeded as well as with UVA and blue LEDs (365 and 465 nm, respectively). Although complete conversion was achieved in a shorter time with 365 nm (24h) irradiation compared to 465 nm (48 h), better yields were obtained using visible light thus avoiding product degradation. The equivalent number of **2a** was found to be an important factor in the yield of the reaction (entries 1-4). The desired aminocyclopentane **3aa** was obtained in 95% yield using 10 equivalents of ethyl acrylate. (Entry 4). Next, a screening of solvents was examined (Entries 4-8). Reactions performed in acetonitrile provided the best yield (Entry 4) while a lower yield was observed in a protic solvent such as ethanol (Entry 5). Interestingly, a reversal of the diastereoselectivity of the reaction was observed when the reaction was performed in non-protic and less polar solvents (Entries 6-8). By optimizing the reaction conditions, we found that the reaction in 0.2M afforded **3aa** in 98% yield (88% isolated) (Entry 10). Increasing the concentration above 0.2M proved to be disadvantageous for the yield as the reaction mixture became too viscous (Entry 11). Lower yields were observed when the photochemical cycloaddition was performed in an open flask (Entry 12). Finally, control experiments showed that no trace of the desired product was observed when the solution was heated to

80°C in the absence of light, only the starting product **1a** was recovered (Entry 13).

Table 1. Optimization of Reaction Conditions



1a 2a 3aa

entry	**2a** (equiv)	solvent	[M]	**3aa** (%)[a]	dr[b]
1	1	MeCN	0.1	72	3:2
2	2	MeCN	0.1	56	3:2
3	5	MeCN	0.1	45	3:2
4	10	MeCN	0.1	95	3:2
5	10	EtOH	0.1	78	3:2
6	10	CyH	0.1	75	1:2
7	10	DCE	0.1	73	2:3
8	10	PhH	0.1	88	2:3
9	10	MeCN	0.05	79	3:2
10	10	MeCN	0.2	98 (88)	3:2
11	10	MeCN	0.5	85	3:2
12[c]	10	MeCN	0.2	70	1:1
13[d]	10	MeCN	0.2	0 (71)	-

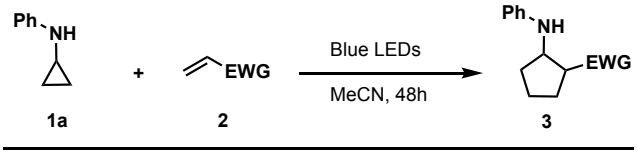
[a]NMR yield. [b]Determined by crude ^{1}H NMR analysis. [c]Reaction run without degassing and in normal atmosphere. [d]Heating at 80°C in the absence of light.

Having identified the optimal reaction conditions, we explored the reaction scope by examining different olefin substituents. Irradiation of **1a** in the presence of monosubstituted acrylates gave the desired compounds in good yields (Scheme 2, **3aa**-**3ac**). Cycloaddition with methyl methacrylate **2d** led to the formation of **3ad** in quantitative yield, albeit with modest diastereoselectivity, whereas a higher diastereoselectivity was achieved with the use of a trisubstituted olefin such as **2e**, giving the cycloaddition product **3ae** in 57% yield (dr = 9:1). Methyl vinyl ketone **2f** led to the formation of **3af** in 57% yield along with a side product **3ae'** (16%) resulting of a Michael addition. To our delight, the reaction scope was expended to styrene (**2g**), vinyl phenyl sulfone (**2h**), and acrylonitrile (**2i**), also provided moderate to excellent yields of the desired products (**3ag**, 84%, dr = 3:2; **3ah**, 65%, dr = 6:1; **3ai**, 99%, dr = 2:1).

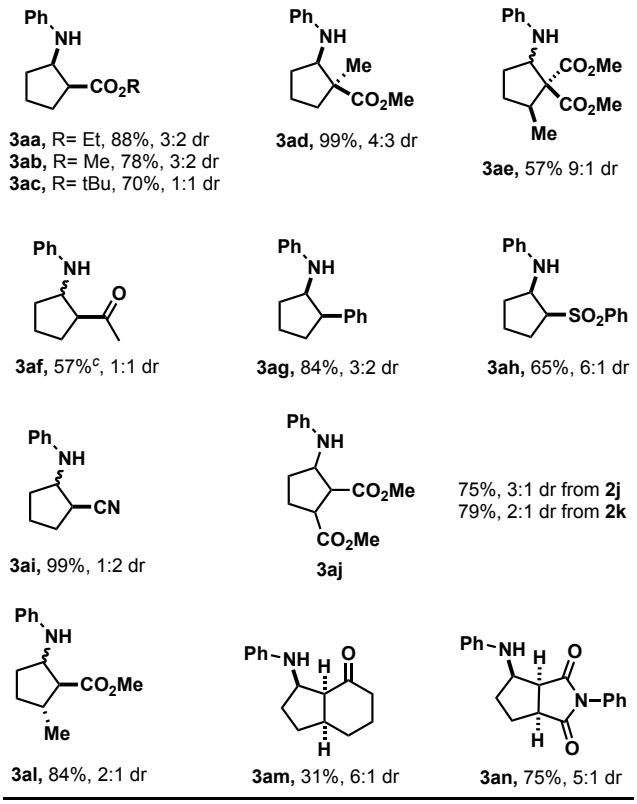
To gain more mechanistic insight, we then performed the reaction with dimethyl maleate (**2j**) and dimethyl fumarate (**2k**). The corresponding aminocyclopentanes **3aj** were isolated in 79% and 75% yields, respectively. Based on ^{1}H and ^{13}C NMR analyses, both reactions converged to the same mixture of diastereomers. These results demonstrate that the olefin geometry was not preserved in the final product supporting the premise that the reaction proceeds through a SET pathway. In addition, no conversion of methyl maleate **2j** to fumarate **2k** under these conditions was observed. Interestingly, reaction with cyclohexenone (**2m**) and N-phenylmaleimide (**2n**) proceeded smoothly with **1a** to give the *endo* products **3am** and **3an** as the major diastereomer in 31% and 75% yields respectively.

As shown in Scheme 3, we examined the scope of the reaction with different *N*-arylaminocyclopropanes **1**. Initially, the electronic properties of the aryl unit appear to have little impact on the desired reactivity. Reactions with *para* substituted electron-rich aryl units such as methoxy (**1b**) and methyl (**1c**) or bearing an electron-withdrawing group such as Cl (**1d**) and ester (**1e-f**) allowed the formation of the desired products (**3ba-fa**) in good yields. However, we observed a significant decrease in yield using the *p*-trifluoromethyl substituent (**3ga**, R= CF_3, 29%, dr = 1:1). This indicates that the electron density of the aryl amine can influence the SET process. High yields were obtained with *o*- and *m*-methoxy substituted cyclopropylamines **1h** and **1i** as well as with **1j**. The steric hindrance of the cyclopropylamine substituent has no influence on the reaction outcome, as shown by the reaction of *o*-phenyl and 2-naphthalenes **1k** and **1l**. Both provided the desired aminocyclopentanes (**3ka** and **3la**) in 84% and 99% yields, respectively. It is worth mentioning that the pyridine group is well tolerated under the reaction conditions, which is in contrast to the Rh(II)-catalyzed version.[2] The compound **3ma** was isolated in 95% yield.

Scheme 2. Substrate Scope of the Olefins[a]



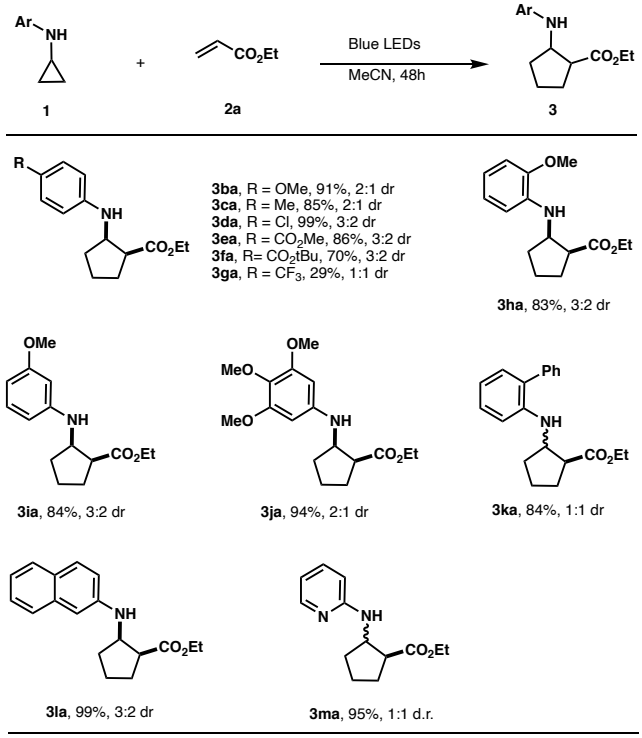
1a 2 3



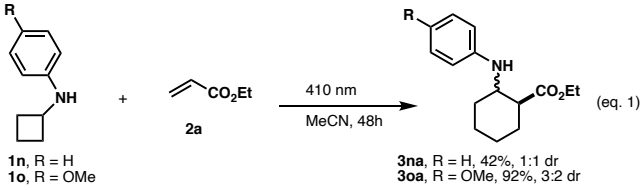
[a]Isolated yield. [b]Diastereomeric ratio determined by ^{1}H NMR analysis. [c]16% of 1,4-addition product (**3ai'**).

We were wondering if a similar photochemical process could be realized with *N*-arylcyclobutylamine leading to a formal [4+2]-cycloaddition (eq. 1). Irradiation of *N*-phenyl cyclobutylamine **1n** and methyl acrylate **2a** with blue LEDs did not lead to the complete conversion of the starting product, the desired product was obtained in low yield (<10%). However, performing the same reaction under 410 nm LEDs led to the formation of cyclohexylamine **3na** in 42% yield (dr = 1:1). We observed an increase in yield with the *p*-methoxy aryl substituent, the formal [4+2] cycloaddition product **3oa** was isolated in 92% yield (dr = 3:2) (eq. 1).

Scheme 3. Aryl Cyclopropylamine Scope

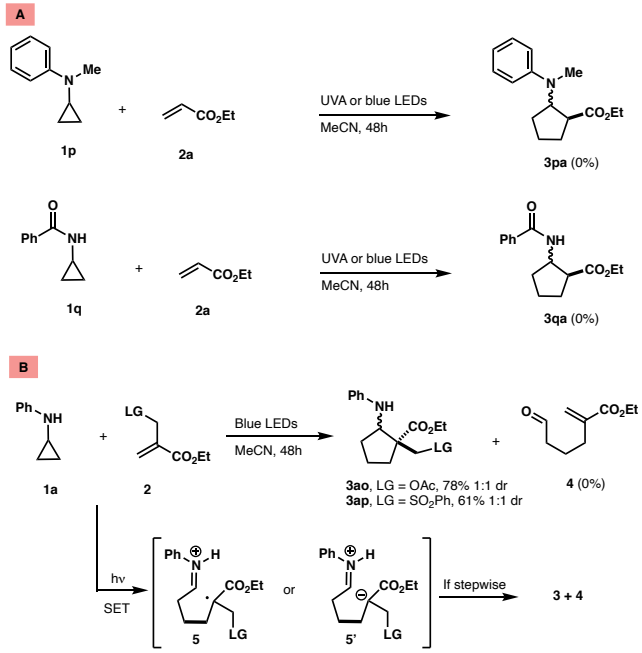


To gain further mechanistic insight, we performed a series of experiments. We first examined the effect the amine substitution, *N*-methyl-*N*-arylcyclopropylamine **1p** and carbamate **1q** were irradiated in the presence of ethyl acrylate **2a** under standard conditions (Scheme 4A). After 48h of irradiation using either UVA or blue LEDs, only starting material was recovered in both cases. These results indicates that the *N*-aryl and NH groups are essential for the SET to occur. Based on the results of the cyclization of methyl maleate and fumarate (Scheme 2), it can be assumed that the reaction proceeds via a SET process involving the simultaneous formation of cationic and anionic radical intermediates.



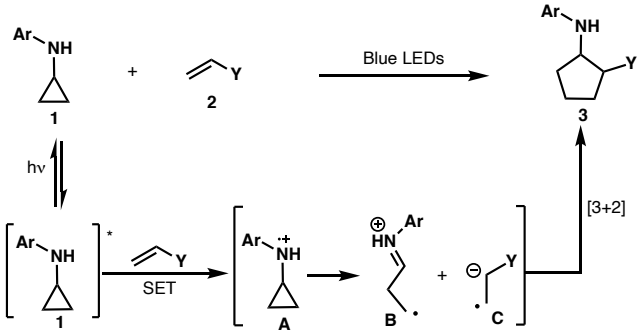
To examine if the photochemical cycloaddition proceeds through a stepwise or concerted process, cyclopropyl amine **2a** was irradiated in the presence of allylic acetate **2p** and allylic sulfone **2o** (Scheme 4B). One could reason that if this reaction involves radical or anionic intermediates such **5** or **5'**, a mixture of compounds **3** and **4** would be observed due to the elimination of the leaving group. In both cases, only the cycloadducts **3ap** and **3ao** were isolated in 78% and 61% yields as a mixture of diastereomers. Elimination product such as **4** or its derivatives were not observed in the crude reaction mixture or nor isolated. Finally, resubmission of *trans*-**3aa** and *cis*-**3aa** separately to the reaction conditions in the presence of methyl acrylate **2b** did not lead to the formation of diastereomers, only starting material was recovered. At the outset, these results suggest that the reaction could proceed by a concerted mechanism. However, a stepwise process in which the addition onto the iminium would be faster than the elimination should not be ignored. This is different from previous photoredox-catalyzed [3+2] cycloadditions that propose a stepwise radical or anionic cycloaddition.[8-10]

Scheme 4. Mechanistic studies



With these results in hand, we propose the following mechanism (Scheme 5). After the photoexcitation of **1**, one can envisage a SET between **1** and **2** promoting the formation of a nitrogen centered radical cation **A** which undergoes a rapid strain-induced β-scission ring opening and the radical anion **C**. The newly formed radical alkyl iminium **B** would recombine with **C** resulting in the formation of **3**. The need for secondary aryl cyclopropylamines also supports the formation of a complex bound by hydrogen-bonding, as tertiary amines were not compatible with the methodology. The charge transfer could be facilitated by the H-bonding between **1** and **2** by stabilizing the complex and increasing the electrostatic attraction. On the other hand, given the electron rich nature of the *N*-aryl cyclopropylamine **1** in the presence of electron accepting compounds such as **2**, the formation an electron donor-electron (EDA) complex could be at play.[11]

Scheme 5. Proposed Mechanism



In summary, we have developed an operationally simple light-mediated formal [3 + 2] cycloaddition of *N*-aryl cyclopropyl amines and electron deficient alkenes to afford aminocyclopentanes in good to excellent yields. The reaction scope is broad including various alkenes and cyclopropylamines providing key evidences that the reaction mechanism involves a photoinduced SET process. New forays into the use of diverse *N*-aryl cyclobutylamine derivatives including mechanistic investigations are underway and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
General experimental procedures, detailed synthetic procedures, and analytical data for all compounds mentioned (PDF)

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The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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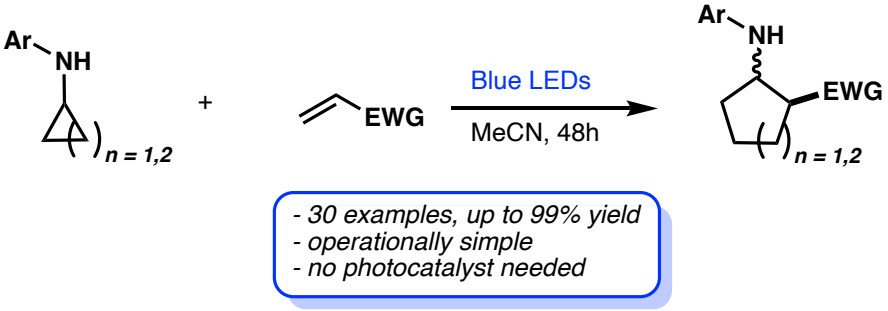

- *30 examples, up to 99% yield*
- *operationally simple*
- *no photocatalyst needed*