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Synthesis of aziridines by visible-light induced decarboxylative cyclization of *N*-aryl glycines and diazo compounds

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A visible-light induced decarboxylative aza-Darzens reaction between *N*-aryl glycines and diazo compounds was developed, which affords various mono-substituted aziridines in good yields.

visible light, diazo compound, decarboxylation, aza-Darzens reaction

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Aziridines are versatile and powerful intermediates in organic synthesis, acting as precursors of many complex molecules due to the strain incorporated in their skeletons [1–5]. They are also key structural motifs which are widely found in natural products and biologically important molecules [6–9]. To date, a number of catalytic protocols have been developed for the synthesis of aziridines [10–16]. One of the oldest and most flexible methods is the Lewis or Bronsted acid-promoted aziridination of imines with diazo compounds [15,17–21]. These reactions proceed through the nucleophilic addition of diazo carbon to imines followed by *3-exo-tet* cyclization of the amide anions, which are often described as "aza-Darzens reactions".

Our group [22] have recently reported a visible-light induced oxidative coupling of tertiary amines and diazo compounds (Scheme 1). This process involves the nucleophilic addition of diazo compound to the *in situ* generated iminium ion [23–25], followed by the deprotonation of intermediate **A** to give β-amino-α-diazo compound. As a continuation of this work, we envisioned that the visible-light photoredox-mediated decarboxylation of *N*-aryl glycine would afford an α-amino alkyl radical [26,27], which could be further oxidized in the presence of oxygen to generate active imine [28]. The attack of imine by diazo compound would lead to intermediate **B**. In contrast to the intermediate **A**, intermediate **B** containing a negative amide anion might undergo a *3-exo-tet* cyclization instead of the deprotonation, which ultimately forms aziridine as the product. In this study, we endeavored to develop a decarboxylative aza-Darzens reaction between *N*-aryl glycines and diazo compounds for the synthesis of mono-substituted aziridines using visible-light photoredox catalysis [29–32].

Initially, when the mixture of *N*-phenyl glycine **1a**, ethyl diazoacetate **2a** and 1 mol% of Rose Bengal (RB) in MeCN was irradiated by a 5 W blue LED at room temperature for 6 h, we obtained the desired *N*-phenyl aziridine **3a** in 40% yield (Table 1, Entry 1). Several solvent such as 1,4-dioxane, DCE, MeOH, EtOH, and CF_3CH_2OH, were screened for this transformation, and MeOH was found to be the best one (Table 1, Entries 2–6). Further optimizations indicated eosin Y, eosin B, $Ru(bpy)_3Cl_2$ were also effective photo-

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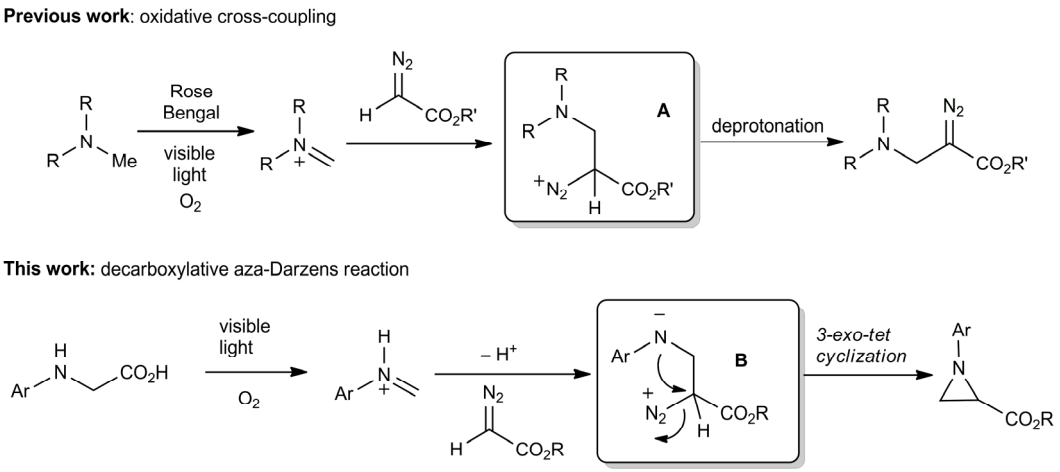
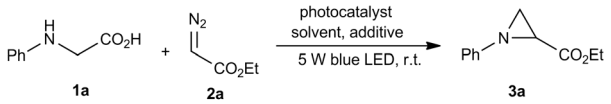


Scheme 1 Visible-light induced oxidative cross coupling and decarboxylative aza-Darzen reaction between amines and diazo compounds.

catalysts for the reaction, but they were not better than rose bengal (Table 1, Entries 7, 8 and 10). None of aziridine **3a** was detected when methylene blue was employed (Table 1, Entry 9). Although the Lewis acid has been reported to promote the aza-Darzens reaction between imines and diazo compounds, the addition of 0.2 equiv. of $Zn(OTf)_2$ has a negative effect on this photocatalytic reaction (Table 1, Entry 11). When the reaction was carried out in the open air condition, only 16% yield of **3a** was observed (Table 1, Entry 12). The diminished yield might be attributed to the low concentration of oxygen and the moisture in the air, which accelerate the decomposition of the active intermediate. The control experiments indicated the reaction could not proceed in the absence of either light or the photocatalyst (Table 1, Entries 13 and 14). A kinetic study demonstrated that the best reaction time is 6 h. The side products might be generated from the further oxidation of aziridine **3a** through iminium ions as reactive intermediates (for the details see the Supporting Information online) [33].

Table 1 Optimization of reaction conditions [a)]



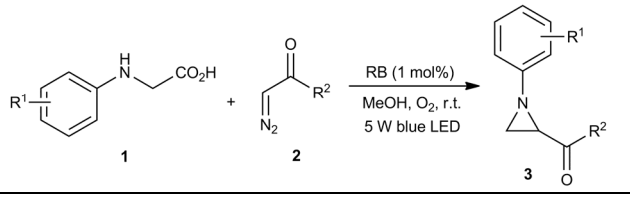
1a **2a** **3a**

Entry	Photocatalyst	Solvent	Yield (%) [b)]
1	rose bengal	MeCN	40
2	rose bengal	1,4-dioxane	15
3	rose bengal	DCE	<5
4	rose bengal	MeOH	79
5	rose bengal	EtOH	57
6	rose bengal	CF_3CH_2OH	33
7	eosin Y	MeOH	50
8	eosin B	MeOH	61
9	methylene blue	MeOH	0
10	$Ru(bpy)_3Cl_2$	MeOH	53
11 [c)]	rose bengal	MeOH	35
12 [d)]	rose bengal	MeOH	16
13 [e)]	rose bengal	MeOH	NT
14 [f)]	none	MeOH	NT

a) Reaction conditions: *N*-phenyl glycine **1a** (0.26 mmol), ethyl diazoacetate **2a** (0.2 mmol), photocatalyst (1 mol%), 5 W blue LED at r.t. under 1 atm of oxygen for 6 h; b) yields were determined by ^{1}H NMR spectroscopy using mesitylene as internal standard; c) 0.2 equiv. of $Zn(OTf)_2$ was added; d) in the open air; e) without light; f) in the absence of photocatalyst.

Having established the optimized reaction conditions, an investigation into the versatility and functional group tolerance of this reaction process was performed. First, the photocatalytic decarboxylative cyclization of various *N*-aryl glycines with ethyl diazoacetate was examined. As shown in Table 2, *para*-, *meta*-, and *ortho*-substituted *N*-phenyl glycines all worked well in the present system to afford the corresponding aziridines **3b–3d** in good to excellent yields (Table 2, Entries 2–4). Both electron-donating groups such as methoxy, and electron-withdrawing groups such as fluoro, chloro, and bromo could be well-tolerated (Table 2, Entries 5–8). Unfortunately, none of the desired product was detected when a strong electron-withdrawing NO_2 group was introduced to the *para*-position of *N*-aryl gylcine (Table 2, Entry 9). The reaction was found to be significantly affected by the *N*-protection groups, glycines protected by electron-withdrawing groups, such as Boc, Ts, and Ac, were not compatible for this transformation. Switching the ethyl group in diazoacetate to isopropyl, *n*-butyl or *tert*-butyl group led to desired aziridines **3j–3l** in slightly diminished yields (Table 2, Entries 10–12). We were pleased to find that diazoacetates with functional groups such as chloroethyl (**3m**), allyl (**3n**), cinnamyl (**3o**), and propargyl (**3p**) were also suitable substrates for the reaction (Table 2, Entries 13–16). Finally, diazo ketone was tested, and its cyclization with *N*-phenyl glycine gave the aziridine **3p** in the yield of 34% (Table 2, Entry 15). The low yield might be attributed to the weaker nucleophilicity of diazoketone.

Table 2 Visible-light induced decarboxylative cyclization of *N*-aryl glycines **1** and diazo compounds **2** [a]

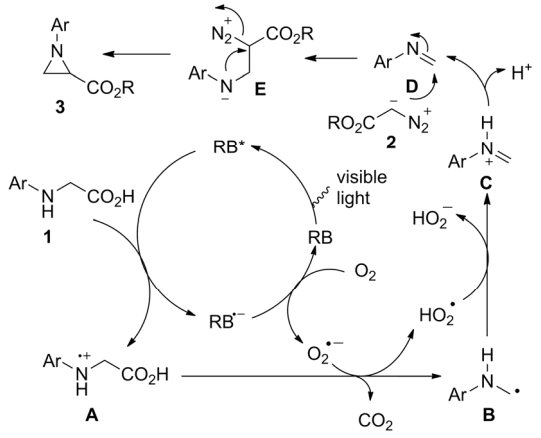


Entry	R^1	R^2	Product	Yield (%) [b]
1	H	OEt	**3a**	75
2	*p*-Me	OEt	**3b**	70
3	*m*-Me	OEt	**3c**	62
4	*o*-Me	OEt	**3d**	92
5	*p*-OMe	OEt	**3e**	60
6	*p*-F	OEt	**3f**	52
7	*p*-Cl	OEt	**3g**	71
8	*p*-Br	OEt	**3h**	70
9	*p*-NO_2	OEt	**3i**	0
10	H	O^{i}Pr	**3j**	49
11	H	O^{n}Bu	**3k**	67
12	H	O^{t}Bu	**3l**	51
13	H	OCH_2CH_2Cl	**3m**	52
14	H	$OCH_2CH{=}CH_2$	**3n**	48
15	H	$OCH_2CH{=}CHPh$	**3o**	54
16	H	$OCH_2C{\equiv}CH$	**3p**	55
17	H	*p*-ClC_6H_4	**3q**	34

a) Reaction conditions: *N*-aryl glycine **1** (0.26 mmol), diazo compound **2** (0.2 mmol), rose bengal (RB, 1 mol%), MeOH (0.8 mL), O_2 balloon, 5 W blue LED at room temperature for 6 h; b) isolated yields.

The nucleophilicity of ethyl diazoacetate is 4.91, while the *N* parameter of diazoketone is around 3.96 [34].

A plausible mechanism for the present visible-light induced decarboxylative cyclization of *N*-aryl glycines and diazo compounds was proposed in Scheme 2. Initially, photoexcitation of RB by visible light generates excited RB*, which is readily quenched by *N*-aryl glycine to give the cation radical **A**. Decarboxylation of **A** leads to α-amino alkyl radical **B**. Further oxidation of **B** by superoxide radical gives iminium ion **C**, which then deprotonates to generate active imine **D**. Finally, aziridines **3** were formed by the nucleophilic addition of diazo compounds on the C=N bond, followed by an intramolecular nucleophilic attack of the nitrogen atom on another carbon atom with N_2 as the leaving group.



Scheme 2 Plausible mechanism.

In conclusion, we have developed a metal-free, visible-light induced decarboxylative cyclization of *N*-aryl glycines and diazo compounds. The reaction provides a useful alternative route to mono-substituted aziridines by using easily available amino acid derivatives as the starting materials. Further investigation on the scope as well as the synthetic applications is ongoing in our group.

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Conflict of interest The authors declare that they have no conflict of interest.

Supporting information The supporting information is available online at http://chem.scichina.com and http://link.springer.com/journal/11426. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

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