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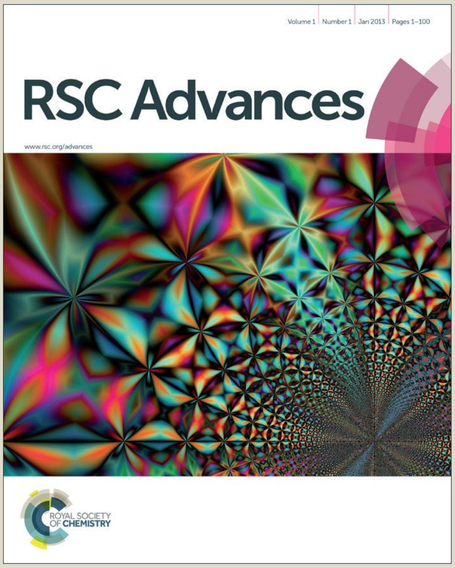

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Visible light-mediated decarboxylative amination of indoline-2-carboxylic acids catalyzed by Rose Bengal

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Abstract

A visible light-induced decarboxylative amination of indoline-2-carboxylic acids and azodicarboxylate esters has been developed, in which the oxidation of α-amino acids provides a versatile CO_2-extrusion platform to generate α-aminoalkyl radicals. Corresponding products were obtained with yields of up to 72% catalyzed by a metal-free photocatalyst under mild conditions.

Key words: photocatalysis; visible light; decarboxylative amination; indoline; Rose Bengal

Introduction

Visible light as renewable energy source has the advantages of being inexpensive, nonpolluting and abundant[1]. Photocatalysis driven by visible light under mild and green conditions has received widespread attention and has recently become an intriguing field of research in organic synthesis[2-4]. Different types of photocatalysis have been developed. For example, chiral organocatalysts (such as thioureas) have been used for enantioselective photoreaction in which substrate is combined to the chiral catalyst through hydrogen bonds providing a chiral environment[5-12]. Metal complexes have been reported as visible-light photocatalysts to perform a variety of photoredox reactions[13-15]. Many common visible light photocatalysts are polypyridyl complexes ruthenium and iridium, such as $Ru(bpy)_3^{2+}$ and

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$[Ir(ppy)_2(dtbbpy)]PF_6$[15]. However, the ruthenium and iridium salts have numerous disadvantages, including high cost, potential toxicity, and dwindling availability[16]. Contrastingly, organic dyes—such as eosin Y[16-18], Mes-AcrClO$_4$[19,20], fluorescein[21] and Rose Bengal[22-26]—are more environmentally friendly, inexpensive and more readily available[24-27] than their metallic counterparts. Recently, organic dyes have also been applied as effective visible light photoredox organocatalysts. Different types of mechanism for metal-free photoredox catalysis have been proposed, such as photoinduced electron or energy transfer process[28-35].

Over the past decade, decarboxylation reactions have widely received attention, largely due to the ability to change carboxylic acids—which are generally inexpensive and non-toxic—into more attractive reactants[36]. The following methods are often used to realize the CO_2-extrusion: transition metal catalyzed decarboxylation process[37,38] and radical-mediated processes, such as persulfate oxidation decarboxylation method under high temperature[39-41] and photoinduced single electron transformation[36,42-44]. Generally, radical decarboxylation of carboxylic acids has several advantages for synthetic organic chemistry: the elimination of CO_2 as the traceless byproduct does not influence the reaction system; furthermore, the resulting radical intermediates can be changed into more attractive, valuable chemical products with relative ease[45].

The indoline substructure is considered an advantageous backbone because it is found in many types of organisms, including pharmaceutical molecules[46,47], naturally occurring alkaloids, and many biologically active molecules[48,49]. Therefore, the synthesis of indoline derivatives has attracted much attention[50]. In 2012, the Nishibayashi group reported amination of protected indoline *via* α-aminoalkyl radicals by using an iridium complex photocatalyst under visible light[51]. Considering the importance of amination products of indoline, it is still desirable to develop more environmentally friendly methods for the synthesis of these compounds. Herein, we report the first metal-free decarboxylative amination reaction of *N*-protected indoline-2-carboxylic acids and azodicarboxylate esters catalyzed by an organic dye in the presence of visible light under mild conditions.

Results and discussion

Initially, the model reaction of *N*-Boc-indoline-2-carboxylic acid (**1a**) with di-*tert*-butyl azodicarboxylate (**2a**) at room temperature in presence of a 32W household fluorescent light bulb

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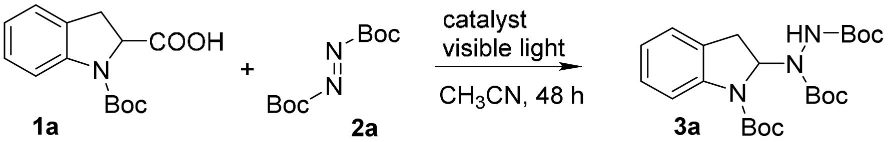
was employed to screen the reaction conditions.

At the beginning, a preliminary organic dye screening was performed to determine the most efficient photocatalyst for the model reaction (**Table 1**). The model reaction without catalyst only gave the product **3a** in a low yield of 20% under visible light (**Table 1**, entry 1). When eosin Y and fluorescein were introduced as photocatalysts, the product **3a** was obtained in yields of 34% and 35%, respectively (**Table 1,** entries 2 and 3). The best result of 46% yield was obtained by using Rose Bengal (**Table 1**, entry 4). The data indicated that the tested organic dyes indeed promoted the reaction. Therefore, Rose Bengal was chosen as the suitable photocatalyst for the reaction. To verify the effect of the visible light, the model reaction with Rose Bengal (2 mol%) was performed in dark, and as expected no reaction was observed (**Table 1**, entry 5). This control experiment revealed that visible light is essential for the catalytic operation of this new decarboxylative amination reaction. Next, the influence of molar ratio on the model reaction was investigated. When the molar ratio of 2:1 (**1a**:**2a**) was employed, the best yield of 52% was received (**Table 1**, entry 6). Thus, the molar ratio of 2:1 (**1a**:**2a**) was selected as the optimal condition (for details, please see the supporting information **Table S1**).

Table 1. Organic dye photocatalyst screening[a].



Entry	Catalyst	Yield (%)[b]
1	None	20
2	Eosin Y (5 mol%)	34
3	Fluorescein	35
4	Rose Bengal	46
5	Rose Bengal (in dark)	0
6	Rose Bengal[c]	52

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), CH_3CN (1.0 mL), and catalyst (2 mol%) under irradiation of 32 W fluorescent bulb at rt for 48 h.

[b] Isolated yield.

[c] **1a** (0.4 mmol).

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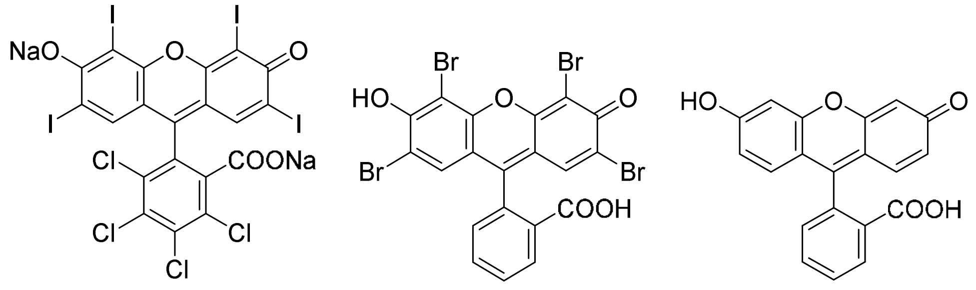
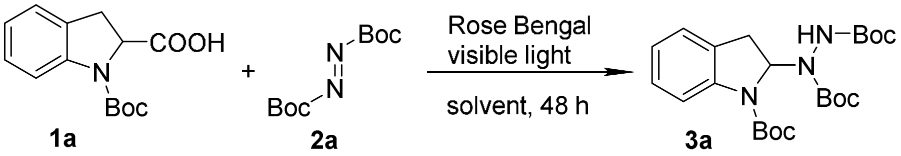


Rose Bengal **Eosin Y** **Fluorescein**

Figure 1. Structures of the tested organic dyes

The choice of solvent is an important factor to promote this process. Various solvents were tested with 2 mol % of Rose Bengal as a photocatalyst under visible light (**Table 2**). Among the tested solvents, the best yield of 52% was obtained in CH_3CN (**Table 2**, entry 1). The reactions in CH_2Cl_2 and $ClCH_2CH_2Cl$ both resulted in a moderate yield of 50% (**Table 2**, entries 2 and 3). The reactions in the other tested solvents did not give better results (**Table 2**, entries 4-12). A trace amount of product **3a** was observed in cyclohexane (**Table 2**, entry 13). Based on the results, CH_3CN was selected as the most suitable solvent for the reaction.

Table 2. Solvent screening[a].



Entry	Solvent	Yield (%)[b]
1	CH_3CN	52
2	CH_2Cl_2	50
3	$ClCH_2CH_2Cl$	50
4	$CHCl_3$	38
5	EtOAc	44
6	*n*-BuOAc	40
7	EtOH	38
8	CH_3OH	33
9	Toluene	22
10	DMF	16
11	DMSO	9
12	1,4-Dioxane	8
13	Cyclohexane	trace

[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), solvent (1 mL), and Rose Bengal (2 mol%) under irradiation

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of 32 W fluorescent bulb at rt for 48 h.

[b] Isolated yield.

Next, the influence of solvent volume, catalyst dosage, and wattage of lamp were all investigated. The optimized reaction conditions were found to consist of the following: a volume of 0.5 mL (CH_3CN), a Rose Bengal dosage of 1 mol%, and a fluorescent lamp wattage of 23 W (for details, please see the supporting information **Tables S2- S4**).

With the optimal conditions in hand, we investigated the substrate scope of the visible light-mediated Rose Bengal catalyzed decarboxylative amination reaction. In general, various azodicarboxylate esters readily participated in this reaction to generate amination products of indoline in moderate to good yields. Unfortunately, the 2,2-azobisisobutyric acid dimethyl ester (**2n**) failed to give the desired product **3n** and the starting material **2n** was intact (**Table 3**, entry 13), probably due to the electronic effect (N connects to alkyl instead of ester carbonyl group like the others). *N*-Boc, Cbz protected indoline carboxylic acids could be successfully applied and provided the desired products in moderate to good yields (**Table 3**, entries 1-8). When indoline carboxylate acid with strong electron withdrawing protecting group *–sulfone* was used, a low yield of 21% was observed (**Table 3**, entries 9 and 10). A low yield of 36% was obtained when *N*-benzoyl protected indoline carboxylate acid was employed as a substrate, likely due to its poor solubility in CH_3CN (**Table 3**, entry 11). However, the presence of the free NH group of indoline carboxylic acid resulted in the formation of indole **4** and di-*tert*-butyl hydrazine-1,2-dicarboxylate **5** instead of amination product **3n** (**Scheme 1**). The data indicated that the protecting group on nitrogen atom of indoline carboxylate acid has great influence on the decarboxylative amination reaction. This reaction can be expanded to other cyclic system that incorporates α-oxy group (2,3-dihydrobenzofuran-2-carboxylic acid) providing the corresponding amination adduct **3l** in a low yield of 21% (**Table 3**, entry 12). In addition, *N*-Boc-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (**1m)** can also participate in the reaction giving the corresponding product **3m** with a yield of 19% (**Scheme 2**). For all the reactions, 2 equiv of indoline carboxylate acids (**1**) was used to react with azodicarboxylate esters (**2**). In the most cases, nearly all azodicarboxylate esters (**2**) were consumed, with indoline carboxylate acids (**1**) left and unknown by-products were observed. For the model reaction, a conversion rate of 99%

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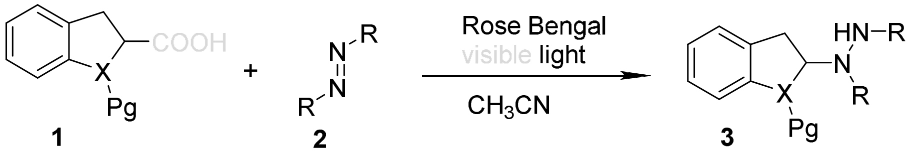
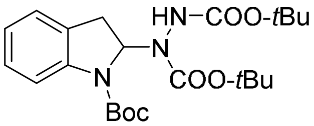
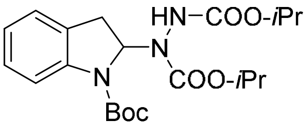
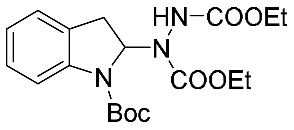
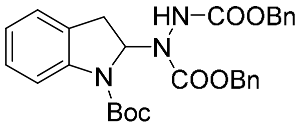
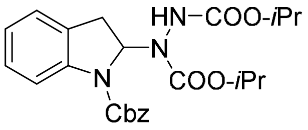
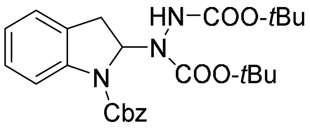
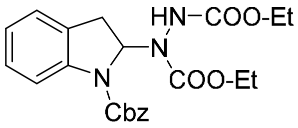
was determined after 48 h (**5** generated from reduction of **2a** was investigated as one of the by-prodcts) (**Table 3**, entry 1). This method represents a general procedure for the amination of indolines at the C-2 position. All the products obtained (**3a-3m**) are new compounds, and their structures have been determined by ^{1}H NMR, ^{13}C NMR and HRMS (for details, please see the Supporting information).

Table 3. Substrate scope[a].



Entry	Product No.	Product	Time (h)	Yield (%)[b]
1	**3a**		48	66 (99[c])
2	**3b**		48	72
3	**3c**		48	51
4	**3d**		48	42
5	**3e**		48	66
6	**3f**		48	63
7	**3g**		48	54

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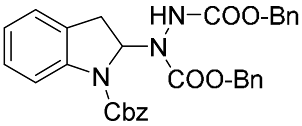
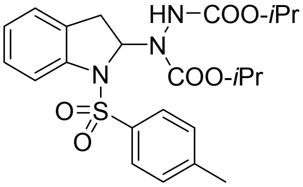
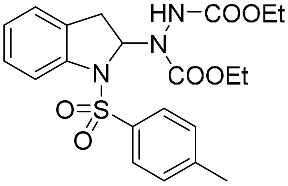
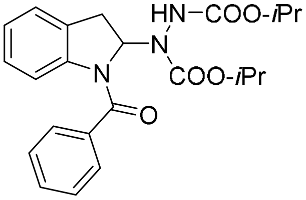
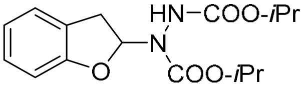
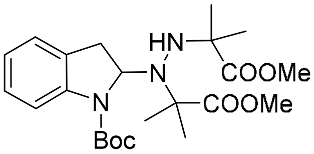
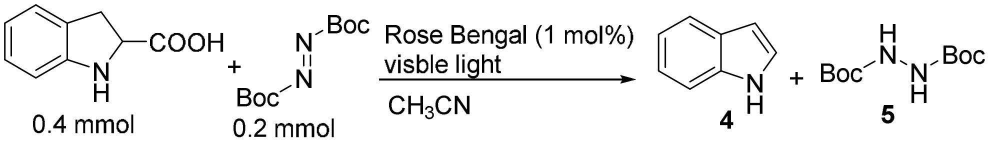
8	**3h**		48	42
9	**3i**		48	21
10	**3j**		48	22
11	**3k**		48	38
12	**3l**		58	22
13	**3n**		48	--

[a] Reaction conditions: **1** (0.4 mmol), **2** (0.2 mmol), CH$_3$CN (0.5 mL), and Rose Bengal (1 mol%) under irradiation of 23 W fluorescent bulb at rt.

[b] Isolated yield (average of two trials, error: ±4%).

[c] Conversion rate.



Scheme 1. The reaction of unprotected indoline carboxylate acid.

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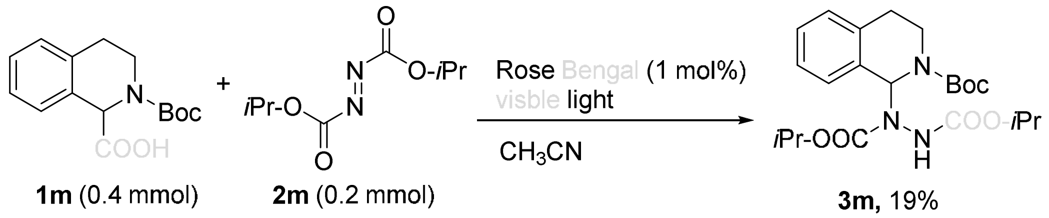
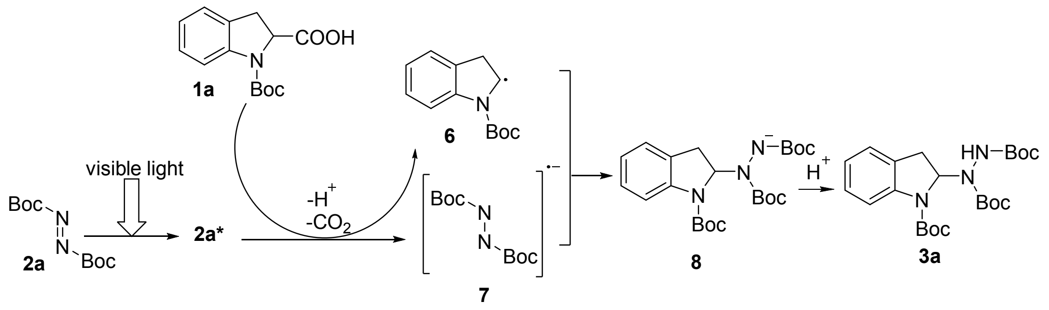


Scheme 2. The reaction of **1m** and **2m**.



Scheme 3. Possible pathway without catalyst

In order to gain more insight into the mechanism of the visible light-mediated Rose Bengal catalyzed decarboxylative amination reaction, fluorescence experiments with di-*tert*-butyl azodicarboxylate **(2a)** were performed. The absorption maximum of **2a** is centered at λ_{max} = 205 nm with a significant absorption in the UV region. However, **2a** exhibits a weak absorption in the visible light region at λ = 402 nm (ξ = 36 $L \cdot mol^{-1} \cdot cm^{-1}$) (the spectrum shown in the Supporting information). Considering the product yield was 20% without the presence of a catalyst (**Table 1**, entry 1), we speculated that **2a** could be the light absorber. In the absence of Rose Bengal, product is probably formed *via* the process shown in **Scheme 3**. Upon light absorption, **2a** accepts a photon from the visible light to generate excited state **2a***. Reductive quenching of **2a*** by *N*-Boc-indoline-2-carboxylic acid (**1a**) through single-electron transfer gives the corresponding radical anion (**7**). At the same time, α-aminoalkyl radical **6** is formed and CO_2 is extruded. The radical-radical coupling of **6** and **7** gives intermediate **8**. The protonation of **8** provids the product (**3a**). Because **2a** has a weak absorption in the visible light region, the reaction without catalyst only gave a low yield.

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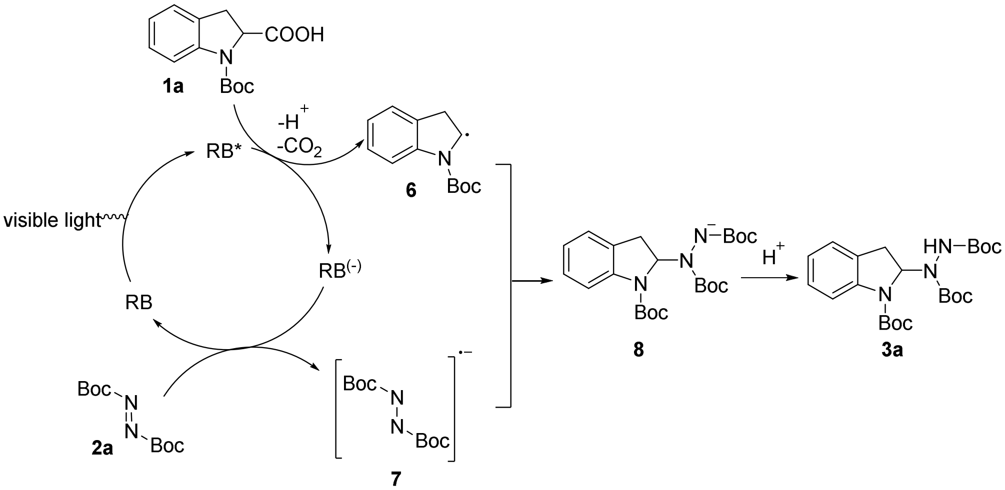

Scheme 4. Possible mechanism in the presence of Rose Bengal.

Finally, based on current literature[51-53], a plausible reaction pathway in the presence of Rose Bengal is proposed in **Scheme 4**. Upon light absorption, Rose Bengal (RB) accepts a photon from the visible light to generate excited state RB*. Subsequent single-electron oxidation of *N*-Boc-indoline-2-carboxylic acid (**1a**) by the visible-light-excited photocatalyst generates the reduced $RB^{(-)}$ and α-aminoalkyl radical **6**, and CO_2 is extruded. Then the reduction of the azodicarboxylate ester (**2a**) by $RB^{(-)}$ affords radical anion (**7**). Intermediate **8** is generated by the radical-radical coupling of **6** and **7**, and the α-aminated product (**3a**) is obtained by the protonation of **8**.

Conclusion

In summary, we have developed a visible light-mediated decarboxylative amination of *N*-protected indoline-2-carboxylic acid and azodicarboxylate esters. This reaction can be expanded to other cyclic system that incorporates α-oxy group and *N*-Boc-tetrahydroisoquinoline carboxylic acids. 13 new amination products were prepared with yields of up to 72%. The reaction was catalyzed by Rose Bengal as a metal-free photocatalyst under mild conditions. This process provides a general method for the amination of indolines at the C-2 position.

General procedure for the decarboxylative amination

A round-bottom flask was charged with Rose Bengal (1 mol%), acids **1** (0.4 mmol) and azodicarboxylate esters **2** (0.2 mmol), to which CH_3CN (0.5 mL) was introduced. The resultant

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mixture was stirred at rt under irradiation of 23 W fluorescent bulb for the specified reaction time and monitored by TLC. The crude mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/ ethyl acetate10:1-3:1) to give the products.

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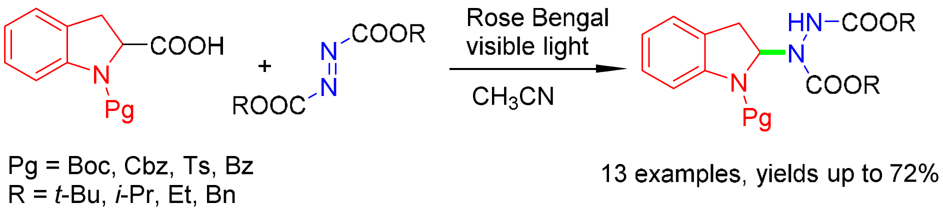
Graphical abstract



A visible-light-induced decarboxylative amination of *N*-protected indoline-2-carboxylic acids and azodicarboxylate esters catalyzed by Rose Bengal has been developed.