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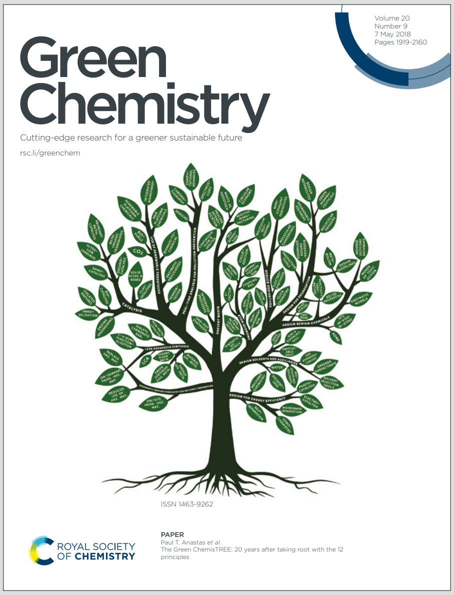

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Visible-Light-Induced Intermolecular [3+2] Alkenylation–Cyclization Strategy: Metal-Free Construction of Pyrrolo[2,1,5-*cd*]indolizine Rings

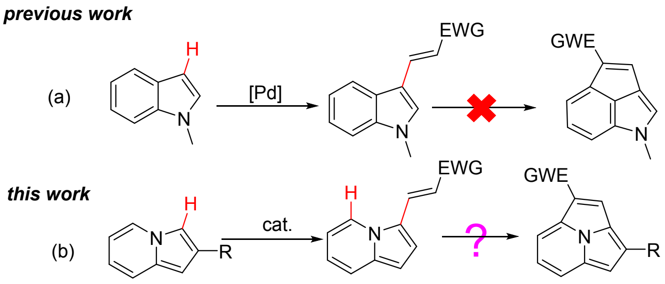
Yaofeng Liang,[a] Lili Teng,[a] Yajun Wang,[a] Qiuxing He*[a] and Hua Cao*[a]

Abstract: A simple and efficient visible-light-induced intermolecular [3+2] alkenylation–cyclization process has been developed. This reaction provided an unprecedented metal-free double C(sp2)–H bond oxidation coupling of indolizines with electron-deficient alkenes. Through this cascade reaction, a series of pyrrolo[2,1,5-*cd*]indolizine derivatives with a large π-system were synthesized. Furthermore, this approach features easily available starting materials, good functional group tolerance, step-economy, high efficiency and mild conditions.

The importance of developing convenient and straightforward strategies for the synthesis of fused indolizines[1] is well demonstrated by the extensive application[2] of these compounds as pharmaceuticals or agrochemicals in the chemical fields. In addition, they can be used as fluorescent molecular probes in cell functional studies,[3] as well as important fluorescent sensor and fluorescent materials in materials chemistry.[4] The synthesis of fused indolizines has been of intense interest for scientists over the past few decades.[5] Among these methods, transition-metal-catalyzed reactions are considered to be one of the most valuable and powerful tools for producing higher-value products in both fundamental and applied chemistry.[6] Many elegant and successful C(sp2)-H activations and transformations have been developed by using Pd,[7] Cu,[8] Ru[9] salts as the catalysis[10]. Although the tremendous strategies have been developed that allow for highly selective reactions, these reactions are unable to achieve secondary dehydrogenation coupling to synthesize fused indolizines (Scheme 1a). [11] The straightforward routes to improve their activity and widen the range of feedstocks remain a longstanding challenge for new practical applications.

Photocatalytic transformations are considered to be a promising alternative for the activation of C-H bonds under mild conditions.[12] They provide uniquely direct access to molecular structures that are often difficult to synthesize using other reaction types. The development of photocatalytic reaction is an attractive synthetic strategy in synthetic chemistry. Compared with transition metal catalysts, organic dyes are more excellent due to their low cost, versatility in synthesis, non-toxicity and environmental friendliness.[13]

Recently, we have developed efficient methods to construct heterocycles.[14] Herein, in continuation of our current focus in synthesizing fused indolizines via photocatalyzed alkenylation-cyclization, which were typically challenging to achieve straightforward using facile and simple methods.



Scheme 1 Regioselective Oxidative Alkenylation of Different Heterocycles

In the preliminary study, we employed 2-phenylindolizine **1a** and methyl acrylate **2a** as the substrates to optimize this reaction. The results are indicated in Table 1. We were pleased to find that the desired product **3a** was formed in the presence of RB as a photosensitizer and 1 equiv. of TFA as an additive in MeCN at room temperature for 10 h under 20 W blue LED (entry 1). After that, different photocatalysts (entries 2-5), such as eosin Y, eosin B, rhodamine 6G and fluorescein were also investigated, and the results indicated that the use of other photocatalysts were also capable of promoting the reaction but with lower yields. The results encouraged us to improve the yield, we then tested other solvents (DMSO, DMF, CH_2Cl_2, Toluene, EtOH, Dioxane). It was found that only CH_2Cl_2 could provide target product **3a** in good yield (entry 8), and other solvents led to no or trace product. Subsequently, TsOH, benzoic acid, PivOH, and AcOH was respectively added in the reaction in place of TFA. However, those showed lower

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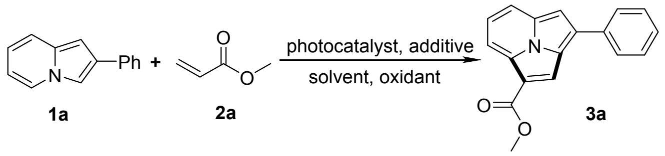
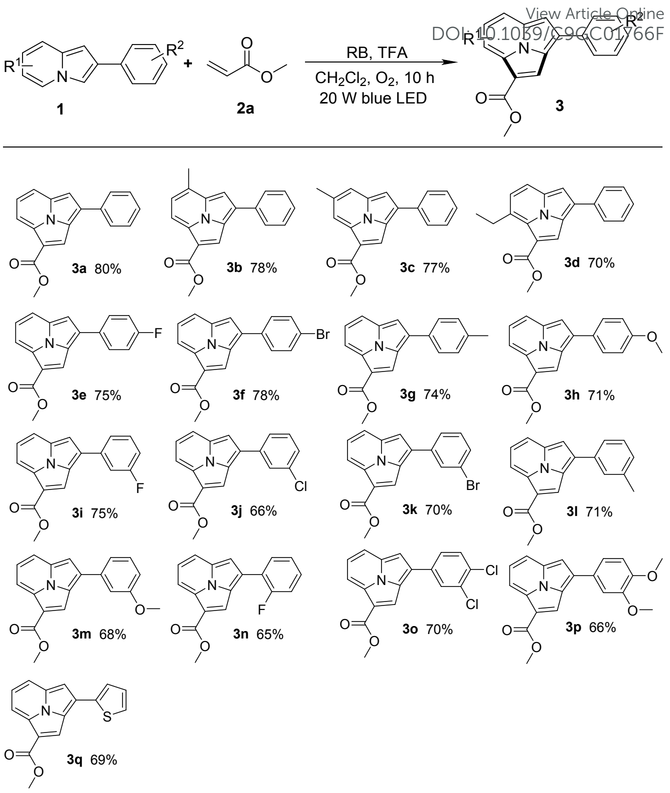
reactivity, and the cyclized product was obtained in poor yield (entries 12-15). The use of other stoichiometric oxidants such as TBHP and $K_2S_2O_8$ results in lower yields (entries 16-17). When the reaction was carried out in air, only a trace product **3a** was detected (entry 18). No product was formed without any photocatalyst (entry 19). In addition, this reaction does not occur in the dark as well as under an argon atmosphere (entries 20 and 21). Thus, these results led us to establish the optimized reaction conditions as follows: 3 mol% of RB and 1 equiv. of TFA, 2.0 mL of CH_2Cl_2 as solvent under O_2 atmosphere in the presence of 20 W blue LED for 10 hours.

Table 1 Optimization of the reaction conditions [a]



entry	photocatalyst	oxidant	additive	solvent	yield [b](%)
1	RB	O_2	TFA	MeCN	50
2	eosin Y	O_2	TFA	MeCN	43
3	eosin B	O_2	TFA	MeCN	39
4	rhodamine 6G	O_2	TFA	MeCN	48
5	fluorescein	O_2	TFA	MeCN	45
6	RB	O_2	TFA	DMSO	56
7	RB	O_2	TFA	DMF	54
8	**RB**	**O_2**	**TFA**	**CH_2Cl_2**	**80**
9	RB	O_2	TFA	Toluene	trace
10	RB	O_2	TFA	EtOH	25
11	RB	O_2	TFA	Dioxane	NR [c]
12	RB	O_2	TsOH	CH_2Cl_2	35
13	RB	O_2	Benzoic Acid	CH_2Cl_2	39
14	RB	O_2	PivOH	CH_2Cl_2	46
15	RB	O_2	AcOH	CH_2Cl_2	47
16	RB	TBHP	TFA	CH_2Cl_2	52
17	RB	$K_2S_2O_8$	TFA	CH_2Cl_2	53
18	RB	air	TFA	CH_2Cl_2	trace
19		O_2	TFA	CH_2Cl_2	NR
20 [d]	RB		TFA	CH_2Cl_2	NR
21 [e]	RB	O_2	TFA	CH_2Cl_2	NR

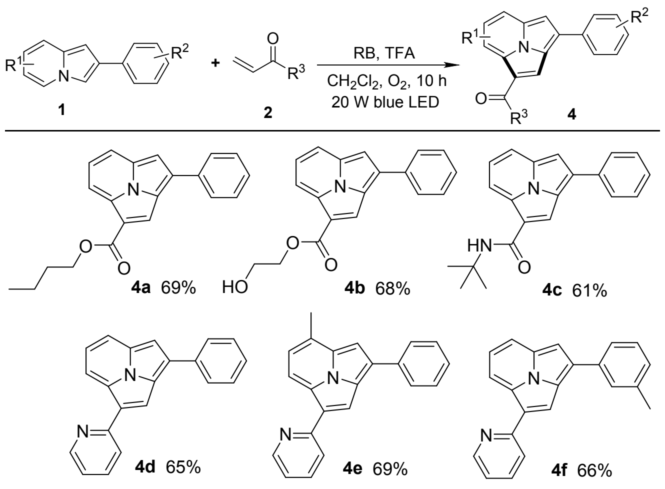
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), photocatalyst (3 mol %), oxidant (0.4 mmol), additives (0.2 mmol) and solvent (2 mL), carried out in a sealed tube (25 mL), and irradiation with a 20 W blue LED for 10 h.; [b] Determined by GC analysis. [c] No reaction. [d] Under a N_2 atmosphere. [e] In the dark.



[a] Isolated yield.

Scheme 2 Substrate Scope of Indolizine [a]

With the optimal reaction conditions in hand, a series of different indolizines coupled with methyl acrylate were employed to examine the generality of the current reaction (Scheme 2). For the most part, the reactions were worked very well under the optimized conditions and provided the corresponding compound (**3a-3q**) in moderate to good yields. A substituent on the indolizine ring, were well-tolerated and afforded the desired products (**3b-3d**) in 70-78% yields. Interestingly, electron-donating substituents (methyl or methoxy) and electron-withdrawing substituents (chloro, fluorine, bromine) substituted on the benzene ring did not affect the reactivity or regioselectivity and were effective to furnish the desired products (**3e-3p**) under the optimized system. Additionally, the reaction of 2-(thiophene-2-yl)indolizine with **2a** was also performed to give the corresponding product **3q** in 69% yield. The molecular structure of product **3g** was determined by X-ray crystallography (Figure 1).



[a] Isolated yield.

Scheme 3 Substrate Scope of other Electron-Deficient Alkene [a]

Next we further turned our attention to exploring the substrate scope of this [3+2] alkenylation–cyclization. A variety of electron-deficient alkene were also tested as the substrate (Scheme 3). The substrates, such as butyl acrylate **2b**, 2-hydroxyethyl acrylate **2c**, and *N*-(tert-butyl)acrylamide **2d** were employed and the desired products (**4a-4c**) were obtained in 61-69%. To our delight, 2-vinylpyridine **2e** participated in the reaction to give the products **4d** in 65% yield, which provided a new synthetic route to construct fused heterocyclic systems with pyridine ring. Then, the reactions of indolizines with **2e** performed very well and produced the corresponding products (**4e, 4f)** in 69 and 66% yields, respectively.

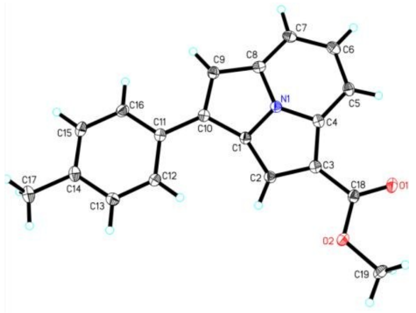
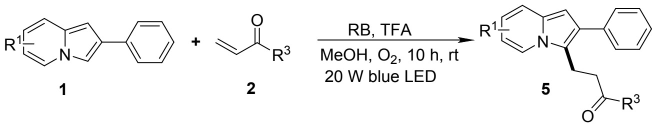


Figure 1 Crystal Structure of Compound **3g**

Interestingly, the C-3 alkylation product **5a** was formed via regioselective intramolecular addition process, when the solvent replaced CH_2Cl_2 with methanol. The extent of the reaction was also investigated as summarized in Scheme 4. The presence of a substituent either on the indolizine or the aromatic ring did not affect the reaction to give the desired products (**5a-d**) in good yields.



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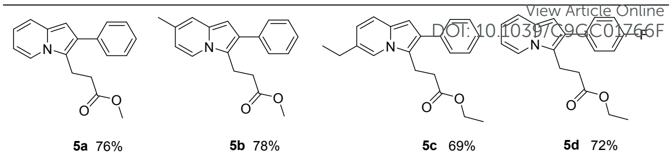

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), RB (3 mol %), TFA (0.2 mmol), MeOH (2 mL), irradiation with a 20 W blue LED for 10 h. Isolated yield.

Scheme 4 Synthesis of 3-substituted Indolizines [a]

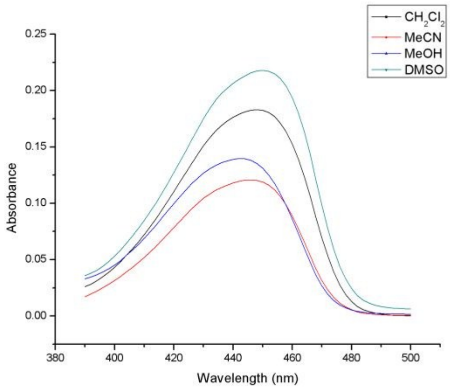

Figure 2 Absorption spectra of compound **4d**

Table 2 Spectroscopic Data of Compound **4d** in Different Solvent

solvent	CH_2Cl_2	MeCN	MeOH	DMSO
λ_{abs} [a] (nm)	452	446	442	450
λ_{em} [b] (nm)	477	475	472	480

[a] Longest wavelength absorption maximum. [b] Excited at the longest wavelength absorption maximum

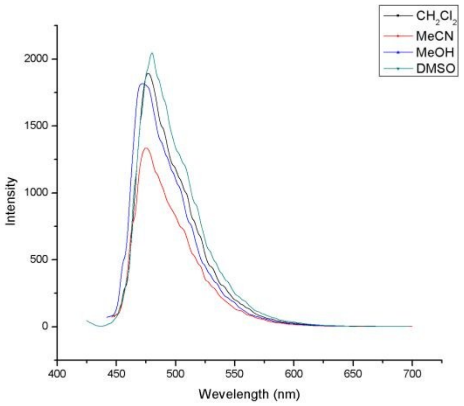

Figure 3 Emission Spectra of Compound **4d**

In case of 6-phenyl-8-(pyridin-2-yl)cyclopenta[hi]indolizine **4d**, we examined the influence of solvents for its photophysical property in air at 25 °C. These data are summarized in Table 2, Figure 2 and Figure 3. Here, the compound **4d** equilibrated CH_2Cl_2, MeCN, MeOH, and DMSO all have absorption (λ_{abs}) in the deep blue region (442-452 nm), and have their emission (λ_{em}) in the sky blue region (472-480 nm). It is also shown that **4d** has the highest absorption intensity and fluorescence emission intensity when using DMSO as solvent.

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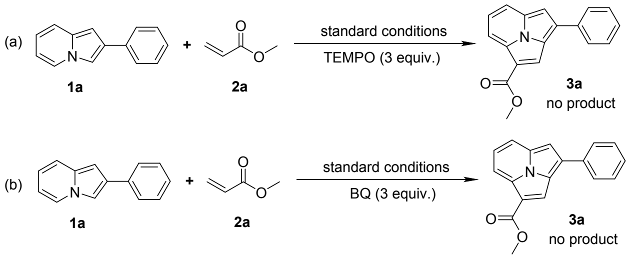


Scheme 5 Control Experiments

To gain some insight into the mechanism for the metal-free double C-H bonds oxidative coupling of functionalization of indolizines with acrylate derivatives, several control experiments were designed and conducted (Scheme 5). No target product was observed and the substrate **1a** was recovered, when the reactions of **1a** with **2a** were carried out in the presence of radical scavengeeither 2,2,6,6- tetramethyl-1-piperidinyloxy (TEMPO) or benzoquinone (BQ). The results indicated that a radial pathway might be involved in this transformation.

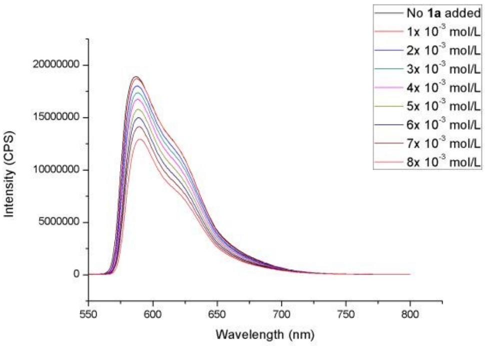


Figure 4 The quenching of RB fluorescence emission with **1a**

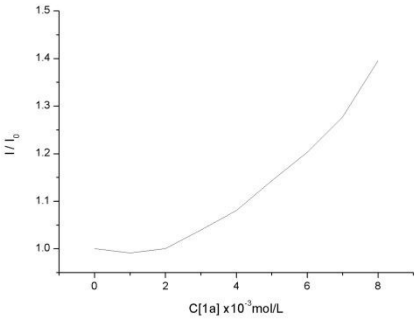
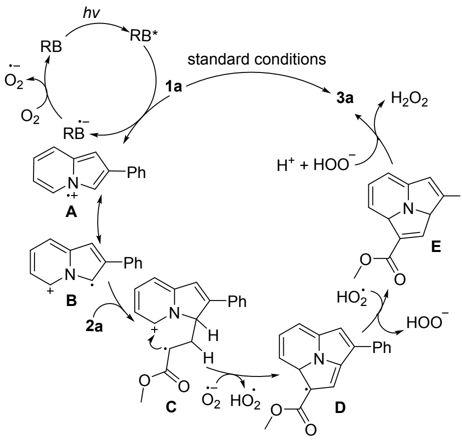


Figure 5 Stern-Volmer plot. I_0 is the inherent fluorescence intensity of RB. *I* is the fluorescence intensity of RB in the presence of **1a**.

In order to further verify the process of energy transfer in photocatalytic reaction, the fluorescence quenching experiment of RB and **1a** were investigated. In the blank experiment, the emission spectra of 1×10^{-4} mol/L RB were collected. Subsequently, the effect of **1a** at different concentrations on the fluorescence intensity of RB catalyst were determined. According to the results and the corresponding Stern-Volmer plots (Figure 4 and 5), it is shown that the fluorescence emission of RB is quenched by **1a** obviously because the fluorescence emission intensity of RB decreases with the increase of **1a**. Therefore, we deduced that **1a** was the energy receptor of the activated RB in this reaction.

Based on the above observations and the literature reports[13], a plausible reaction mechanism has been proposed in Scheme 6. Under visible light irradiation, the ground state of RB is converted to its excited state RB*. Then, **1a** could interact with excited state to give the radical intermediate **A** and $RB^{\bullet-}$ which is combined with oxygen to produce both superoxide radical anion ($O_2^{\bullet-}$) and RB to complete the photoredox cycle. The intermediate **A** is easily transferred to key radical resonance structure **B**. The intermolecular addition of radical **B** to **2a** furnishes the radical intermediate **C** which undergoes sequential dehydrogenation oxidation by the superoxide anion radical to give intermediate **E**. Finally, electron transfer from intermediate **E** affords product **3a** along with H_2O_2.



Scheme 6 Plausible Mechanistic Pathway

Conclusions

In summary, we have developed a metal-free, visible-light induced intermolecular [3+2] alkenylation–cyclization strategy. A broad range of pyrrolo[2,1,5-*cd*]indolizine derivatives are conveniently synthesized in moderate to good yields with good functional group tolerance, thus providing a green intermolecular [3+2] annulation reactions. Notably, synthesis of challenging 6-phenyl-8-(pyridin-2-yl)cyclopenta[*hi*]indolizine was also accomplished and its photophysical properties were investigated. Further work expanding the utility of these system to other types of coupling reaction is ongoing and will be reported in the near future.

Conflicts of interest

There are no conflicts to declare.

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TOC Graphic

Visible-Light-Induced Intermolecular [3+2] Alkenylation–Cyclization Strategy: Metal-Free Construction of Pyrrolo[2,1,5-*cd*]indolizine Rings

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An intermolecular [3+2] alkenylation–cyclization of indolizines with electron-deficient alkenes was developed using rose bengal as an organo photocatalyst.

- **metal-free**
- **organo photocatalysis**
- **O_2 as oxidant**
- **mild conditions**

23 examples
61-80 % yield