Photocatalytic decarboxylative coupling between αoxocarboxylicacids and alkenes

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Photocatalytic decarboxylative cross-coupling which achieves the derivatization of widespread organic acids has become a hot topic in organic synthesis. As special acids, α -oxocarboxylicacids show the great potential in running decarboxylation to construct ketone derivatives. In this article, we have developed a photocatalytic decarboxylative cross-coupling of α -oxocarboxylicacids and olefins to the synthesis of diverse aryl ketones. Various alkenes and α -oxocarboxylicacids were compatible, generating the desired products in up to 90% yield. Preliminary mechanism studies suggest that a free radical pathway is involved in this process.

photocatalysis, decarboxylative coupling

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Aryl ketones are vital structural building blocks in a huge variety of molecules, including natural products, pharmaceutical drugs, photosensitizer and organic materials [1]. Additionally, aryl ketones are important intermediates for the further transformation to other useful molecular fragment [2]. The development of efficient methods for the synthesis of aryl ketones constitutes a continuing hot research area in synthetic chemistry. To the best of our knowledge, various methods have been reported to the synthesis of aryl ketones [3], like Friedel-Crafts acylation [4], transition-metal catalyzed cross-coupling and so on [5]. However these protocols suffer from poor selectivity, low atomic economy, use of rare metal catalysts, pre-synthesized organometallic reagents and toxic CO gas. Recently transition-metal catalyzed radical cross-couplings of easily available aldehydes and olefins have shown the potential in solving these problems above [6]. Due to the inert aldehyde C–H bonds, peroxides and harsh reaction conditions are always necessary for this transformation. Hence, exploiting efficient and mild catalysis to access aryl ketones is still significant and appealing.

As we know, α -oxocarboxylic acids which are widely used in organic synthesis could be easily oxidized and decarboxylated to give acyl radical [7]. So it is interesting and meaningful to use α -oxocarboxylic acids instead of aldehydes in the radical cross-coupling to the synthesis of aryl ketones. During the past decades, photocatalytic reaction has shown its great potential in mild cross-coupling and attracted more and more attention. In 2014, our group [8] has reported the first example of visible-light-mediated decarboxylation/ oxidative amidation of α -keto acids with amines under mild reaction conditions using O₂ as the terminal oxidant. After that, there are several works reporting the photocatalytic decarboxylative cross-coupling of α -keto acids [9]. But it still remains rare. Herein we have developed a mild photocatalytic decarboxylative cross-coupling of olefins and α -

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keto acids to access various aryl ketones (Scheme 1).

We initiated our investigation with the model reaction of ethene-1,1-divldibenzene (1a) and 2-oxo-2-phenylacetic acid (2a) utilizing 2 mol% Ir(ppy)₂(dtbbpy)PF₆ as photocatalyst, 2 equiv. K₃PO₄ as base under the irradiation of 3 W blue LED in toluene for 12 h. To our delight, the desired product 1,3,3-triphenylpropan-1-one (3a) was obtained in 51% yield (Table 1, entry 1). The screening of various solvents indicated that tetrahydrofuran (THF) was the best solvent in this reaction (Table 1, entries 2–5). Then, different bases were tested, showing that K₃PO₄ gave the highest yield. While no product was achieved with NEt₃ as the base (Table 1, entries 6–8). Encouraged by the above results, next, we tried to change the ratio of 1a/2a. When increasing the amount of 2a to 1.5 and 2.0 equiv., the yield of 3a was consequently increased to 70% and 80%, respectively (Table 1, entries 9, 10). Control experiments showed that photocatalyst, base and visible light were all essential to this reaction (Table 1, entries 11–13).

With the optimized reaction conditions in hand, we tested



Scheme 1 Retrosynthetic analysis of ketones.

 Table 1
 Optimization of reaction conditions^{a)}

, ↓		2 mol% photocatalyst 2 equiv K ₃ PO ₄		\bigcirc
	C + C GH	THF, N ₂ , 16 3 W blue LE	ih ED	
1a	2a			3a
Entry	Photocatalyst	Solvent	Base	Yield $(\%)^{b)}$
1	Ir(ppy) ₂ (dtbbpy)PF ₆	Tol	K_3PO_4	51
2	Ir(ppy) ₂ (dtbbpy)PF ₆	Dioxane	K_3PO_4	56
3	Ir(ppy) ₂ (dtbbpy)PF ₆	CH ₃ CN	K_3PO_4	45
4	Ir(ppy) ₂ (dtbbpy)PF ₆	DMF	K_3PO_4	30
5	Ir(ppy) ₂ (dtbbpy)PF ₆	THF	K_3PO_4	57
6	Ir(ppy) ₂ (dtbbpy)PF ₆	THF	Na ₂ CO ₃	55
7	Ir(ppy) ₂ (dtbbpy)PF ₆	THF	$NH_3 \bullet H_2O$	20
8	Ir(ppy) ₂ (dtbbpy)PF ₆	THF	NEt ₃	n.d.
9 ^{c)}	Ir(ppy) ₂ (dtbbpy)PF ₆	THF	K_3PO_4	70
10 ^{d)}	Ir(ppy) ₂ (dtbbpy)PF ₆	THF	K_3PO_4	80
11 ^{e)}	_	THF	K_3PO_4	n.d.
12 ^{f)}	Ir(ppy) ₂ (dtbbpy)PF ₆	THF	_	n.d.
13 ^{g)}	Ir(ppy) ₂ (dtbbpy)PF ₆	THF	K_3PO_4	n.d.

a) Reactions conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), photocatalyst (2 mol%), base (2 equiv.), solvent (3 mL), 3 W blue LED, rt, 16 h. b) Isolated yield. c) 0.3 mmol **2a** was used. d) 0.4 mmol **2a** was used. e) without photocatalyst. f) without base. g) without light. n.d.=not detected.

the photocatalytic decarboxylative coupling reaction between **2a** and different alkenes (Scheme 2). Firstly, various 1,1-diphenylethene derivatives were tested, giving the corresponding decarboxylative coupling products in good to excellent yields (**3a–3c**). Halogens like F, Cl, Br were also well tolerated in this reaction, providing the opportunities for further functionalizations. Substrate with CF₃ could run this reaction smoothly to afford the desired product. When 2-(1phenylvinyl)naphthalene was utilized as the substrate, 78% yield was obtained (**3j**). To our delight, styrenes were also suitable substrates for this reaction. 86% yield was obtained when 3-vinylpyridine was used as the substrate (**3l**). Styrenes with halogens or electron-rich group in the benzene ring run the reaction smoothly to give the desired products (**3m–3q** and **3k**).

To further explore the scope and generality of this protocol, different α -keto acids were tested, and the results were listed in Scheme 2. α -Oxocarboxylicacids with methyl groups on the para site of benzene ring could smoothly be transferred to the desired products in good yields (**3r** and **3s**). Halogen substituents such as F (**3t**), could also be well tolerated in this reaction, generating the desired aryl ketones in 82% yield. To show the potential application of this synthetic protocol, the scale-up reaction was conducted, affording the corresponding product in 78% yield (Scheme 3).

To investigate the possible radical mechanism of the pre-



Scheme 2 Photocatalytic decarboxylative coupling between α -oxocarboxylicacids and alkenes. All the reaction were performed with **1a** (0.2 mmol), **2a** (0.4 mmol), Ir(ppy)₂(dtbbpy)PF₆ (2 mol%), K₃PO₄ (2 equiv.) and THF (3 mL), at 3 W blue LED, room temperature under N₂ for 16 h (see Supporting Information online for the detailed experimental procedure). Isolated yield.



Scheme 3 Scale-up reaction.



Scheme 4 Scale-up reaction.

sent transformation, a radical-trapping experiment was carried out. TEMPO, a radical-trapping reagent, was added into the reaction (Supporting Information online). The formation of desired product was suppressed, thus revealing that the initial steps of the transformation probably were caused by a radical process. On the basis of the experimental results and previous works, a plausible mechanism was proposed (Scheme 4). Firstly, excited state of photocatalyst Ir(III)* was firstly formed by the irradiation of blue LED. Then, this reactive catalyst species oxidative decarboxylize 2-oxo-2phenylacetic acid to generate benzoyl radical I while affording the low-valent Ir(II) simultaneously. The acyl radical can be trapped by the alkene to generate the radical II which could be oxidized by Ir(II) to give cation intermediate III and regenerate Ir(III). Finally, the cation intermediate would go protonation to obtain the desired product.

In conclusion, we developed a new photocatalytic decarboxylative coupling of α -oxocarboxylicacids and alkenes, giving the ketones as the products. Various alkenes and α oxocarboxylicacids were well tolerated, giving up to 90% yield. Moreover, gram-scale synthesis and functional group transformation further show the usefulness of this protocol, which provided straightforward and effective strategies for the synthesis of some natural products.

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

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