Photochemistry

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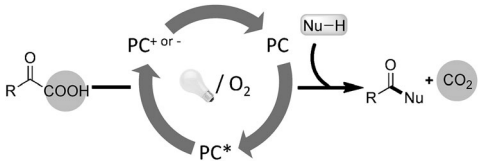
Visible-Light-Mediated Decarboxylation/Oxidative Amidation of α-Keto Acids with Amines under Mild Reaction Conditions Using O_2**

Jie Liu, Qiang Liu, Hong Yi, Chu Qin, Ruopeng Bai, Xiaotian Qi, Yu Lan, and Aiwen Lei**

Abstract: *Photochemistry has ushered in a new era in the development of chemistry, and photoredox catalysis has become a hot topic, especially over the last five years, with the combination of visible-light photoredox catalysis and radical reactions. A novel, simple, and efficient radical oxidative decarboxylative coupling with the assistant of the photocatalyst [Ru(phen)$_3$]Cl$_2$ is described. Various functional groups are well-tolerated in this reaction and thus provides a new approach to developing advanced methods for aerobic oxidative decarboxylation. The preliminary mechanistic studies revealed that: 1) an SET process between [Ru(phen)$_3$]$^{2+}$* and aniline play an important role; 2) O_2 activation might be the rate-determining step; and 3) the decarboxylation step is an irreversible and fast process.*

Decarboxylation of pyruvate, the simplest α-keto acid, popularly prevails in nearly all organisms.[1] At the first stage of cellular respiration in aerobic organisms, pyruvate reacts with coenzyme A (a thiol) to produce acetyl-CoA catalyzed by the pyruvate dehydrogenase complex.[1,2] This mild and efficient decarboxylative process is not only an important link between the metabolic pathways of glycolysis and the citric acid cycle, but also crucial for vital processes occurring in living organisms.[3] Inspired by nature's efficiency, it is desirable to develop a mild and efficient method to construct functional acyl compounds by decarboxylation of the α-keto acids. Though transition-metal-catalyzed decarboxylative coupling of carboxylic acids has become an important protocol to form C–C and C–heteroatom bonds in recent years,[4] decarboxylation of α-keto acids as acyl surrogates has received less attention.[5] Gooßen et al. firstly demonstrated a palladium-catalyzed decarboxylative acylation of aryl bromides with α-keto carboxylate salts as acyl anion equivalents to afford diaryl ketones at 170 °C.[5b] In addition, directing-group-assisted *ortho*-selective decarboxylative acylation of aromatic C–H bonds with α-keto acids has also been achieved using persulfates as oxidants.[5e,f,h,i] In spite of the significant progress offered by these reactions, there are still certain limitations including elevated temperature, superfluous usage of strong oxidants, and high catalyst loading. Thus, it is necessary to improve upon the harsh reaction conditions and develop a powerful synthetic method for oxidative decarboxylation of α-keto acids.

Recently, by taking advantage of visible light with the assistance of photocatalysts, a variety of efficient organic synthetic reactions have been realized under mild reaction conditions through a single-electron-transfer process.[6] Moreover, one impressive feature of visible-light photocatalysis is that O_2 can act as a terminal oxidant for catalyst reoxidation and afford an active superoxide radical anion.[7] Therefore, we envision that it is possible to accomplish visible-light-induced oxidative decarboxylation in the presence of O_2 as the oxidant (Scheme 1). The superoxide radical anion generated from the photoredox process can promote the decarboxylation process with subsequent nucleophilic attack to generate the final product. In this work, we choose amines as the nucleophiles, thus generating the corresponding amides. To the best of our knowledge, this is the first photocatalyzed aerobic oxidative decarboxylation of α-keto acids mediated by visible light, and it proceeds under very mild reaction conditions like the above-mentioned biological decarboxylation of pyruvate.



Scheme 1. Visible-light-mediated aerobic oxidative decarboxylation. PC = photocatalyst.

Initially, we started our evaluation of the reaction parameters employing benzoylformic acid (**1a**) and 4-methylaniline (**2a**) as model substrates. The combination of 1 mol% of [Ru(phen)$_3$]Cl$_2$ and 1.5 equivalents of 4-methylaniline, exposed to a 25 W household fluorescent lamp, in DMSO under the atmosphere of O_2 (balloon) for 36 hours gave the best yield of up to 85%. Other data illustrating the

[*] J. Liu,[+] Dr. Q. Liu,[+] H. Yi, C. Qin, R. Bai, X. Qi, Prof. Y. Lan, Prof. A. Lei
College of Chemistry and Molecular Sciences
Wuhan University, 430072, Wuhan (P. R. China)
E-mail: aiwenlei@whu.edu.cn
Prof. A. Lei
National Research Center for Carbohydrate Synthesis
Jiangxi Normal University
Nanchang 330022, Jiangxi, (P. R. China)
Prof. Y. Lan
School of Chemistry and Chemical Engineering
Chongqing University, 400030, Chongqing (P. R. China)
[+] These authors contributed equally to this work.

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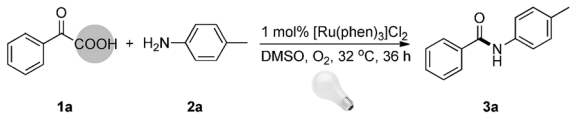
Table 1: Control experiments.[a]



Entry	Visible light	Photocatalyst	O_2	Yield [%][b]
1	+	+	+	85
2[c]	+	−	+	9
3[d]	−	+	+	trace
4[e]	+	+	−	n.d.

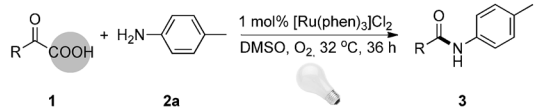
[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.375 mmol), photocatalyst (0.0025 mmol), DMSO (1 mL), irradiation with 25 W household light bulb, 32 °C, 36 h. [b] Yields determined by GC. [c] Reaction was carried out in the absence of catalyst. [d] Reaction was carried out in the dark. [e] Reaction was carried out under N_2. DMSO = dimethylsulfoxide; phen = 1,10-phenathorline; n.d. = not detected.

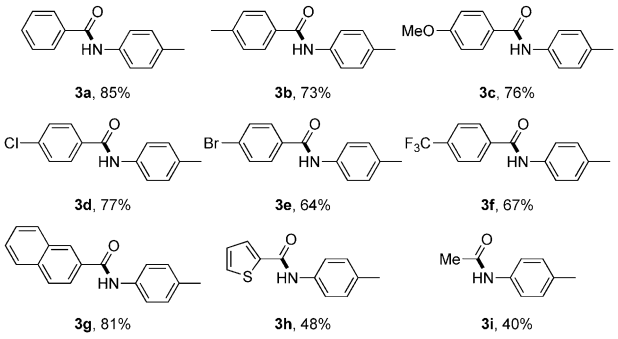
impact of different parameters on the efficiency of this reaction is shown in the Supporting Information (Table S2). Furthermore, a series of control experiments were examined. The reaction yield was only 9% without the assistance of a photocatalyst (Table 1, entry 2). Trace amounts of product were obtained in the absence of either visible light or oxygen (Table 1, entries 3 and 4), thus demonstrating that this decarboxylative process is promoted by both photocatalyst and oxygen, and mediated by visible light.

With the optimal reaction conditions in hand, we examined the scope of this reaction by testing the decarboxylative coupling of a variety of substituted α-keto acids with **2a** (Table 2). Our catalytic system was successfully amenable to a wide range of α-keto acids, and good to excellent yields were achieved with substrates bearing both electron-deficient (**3f**) and electron-rich (**3b** and **3c**) substituents. This transformation also showed satisfactory tolerance of halogen groups (**3d** and **3e**), which provide useful handles for further transformations through traditional cross-coupling reactions. In addition, α-keto acids with a naphthyl group (**3g**) also participated in this decarboxylative process with a high reactivity. Heterocyclic α-keto acid was found to be favored under this catalytic system to afford the corresponding product (**3h**) in moderate yield. It is noteworthy that an aliphatic α-keto acid was compatible with the reaction as well and gave moderate yield of the desired product (**3i**).

Furthermore, the reactivity of different amines was also investigated (Table 3). Anilines bearing electron-neutral and election-rich groups at the *para* and *ortho* positions underwent this decarboxylation process smoothly to afford the desired products (**3j–o**) in moderate to good yields. In addition, this reaction was applicable to aliphatic amines and gave good yields in the presence of 5–10 equivalents amines (**3p** and **3q**). Propargylamine was compatible in this transformation, albeit in lower yield (**3r**).

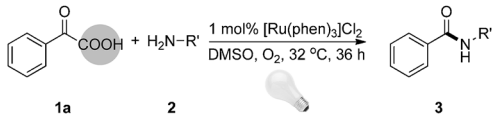
Table 2: Scope of the substituted α-keto acids **1** for visible-light-mediated decarboxylation with **2a**.[a]

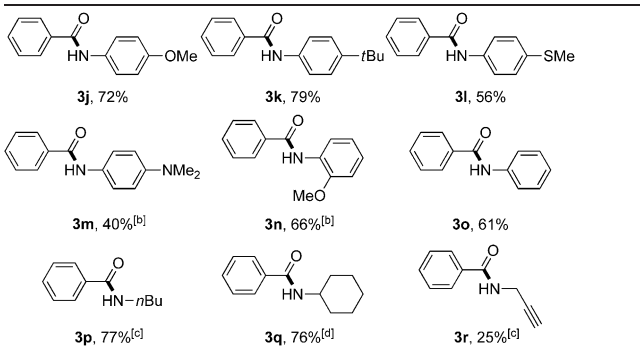




[a] Reaction conditions: **1** (0.5 mmol), **2a** (0.75 mmol), photocatalyst (0.005 mmol), DMSO (2 mL), irradiation with 25 W household light bulb, 32 °C, 36 h. Yields of isolated products.

Table 3: Scope of the substituted amines **2** for visible-light-mediated decarboxylation with **1a**.[a]



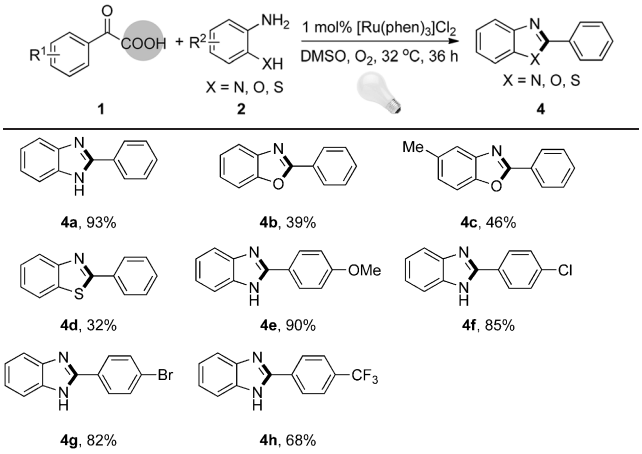


[a] Reaction conditions: **1a** (0.5 mmol), **2** (0.75 mmol), photocatalyst (0.005 mmol), DMSO (2 mL), irradiation with 25 W household light bulb, 32 °C, 36 h. Yields of isolated products. [b] 1.0 mmol **2** was added. [c] 2.5 mmol **2** was added. [d] 5 mmol **2** was added.

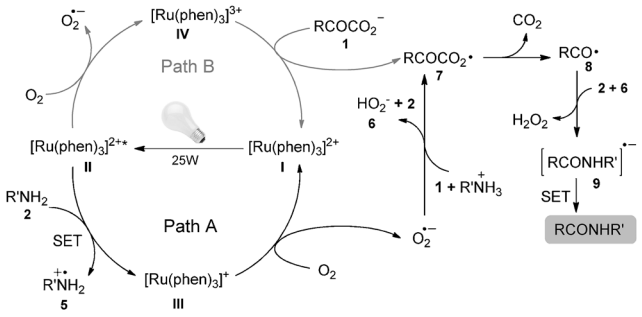
This method can be further applied to construct heterocyclic compounds such as benzimidazole, benzoxazole, and benzothiazole when the *ortho* positions of the anilines were bore NH_2, OH, and SH groups, respectively (Table 4). It is known that these heterocyclic skeletons can be found in numerous pharmaceutical agents with a diverse spectrum of biological properties.[8] This method provides a novel and straightforward procedure for the synthesis of these nitrogen heterocycles under very mild reaction conditions.

We proposed two pathways for the mechanism (Scheme 2, Path A and B): irradiation of **I** with visible light leads to the excited compound **II** by metal-to-ligand charge transfer (MLCT),[9] and is initially quenched by an amine to form **III** by a reductive quenching mechanism (Path A).[10] Then O_2 undergoes a single-electron-transfer (SET) process to render the superoxide radical anion and regenerate **I**. The superoxide radical anion then abstracts an electron from **1** to generate the intermediates **6** and **7**. Then **7** undergoes decarboxylation to

Table 4: Scope of the *ortho*-substituted aniline **2** for visible-light-mediated decarboxylation with **1**.[a]



[a] Reaction conditions: **1** (0.5 mmol), **2** (0.75 mmol), photocatalyst (0.005 mmol), DMSO (2 mL), irradiation with 25 W household light bulb, 32 °C, 36 h. Yields of isolated products.



Scheme 2. Proposed mechanism.

generate the acyl radical **8**, which may subsequently react with an amine to deliver the amide radical anion **9**[11] in the presence of **6**, as the base, and then undergo SET to give the desired product amide. Alternatively, in Path B, **II** can form **IV** in the presence of O_2 by an oxidative quenching process[7b,12] and subsequently **IV** abstracts an electron from **1** to give **7** and regenerate **I** to finish the catalytic cycle. Then intermediate **7** follows the same process as described for Path A.

To confirm the possible pathway of this transformation, electron paramagnetic resonance (EPR) was applied to study the photocatalytic reaction (Figure 1).[7h,k,13] No EPR signal was observed when **2a** alone was tested under irradiation of visible light (Figure 1A), similar to the mixture of **2a** and $[Ru(phen)_3]Cl_2$ in the absence of visible light (Figure 1B). However, some strong signals were detected upon irradiation of the mixture of **2a** and $[Ru(phen)_3]Cl_2$ (Figure 1C). When **1a** was added to the mixture of **2a** and $[Ru(phen)_3]Cl_2$ under irradiation by visible light (Figure 1D), the EPR spectrum displayed resonance character similar to that of a $[Ru(bpy)_3]^+$ species.[14] On the basis of these results, we speculate that: 1) electron transfer may occur directly between the $[Ru(phen)_3]^{2+*}$ and amines according to Figure 1C; 2) the EPR signals in the Figure 1C may consist of two components:

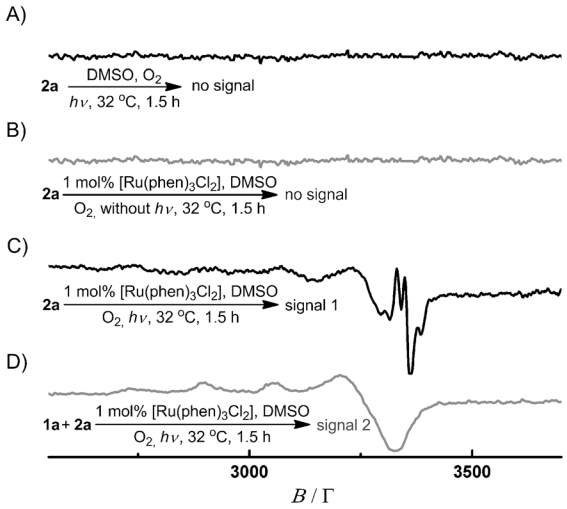
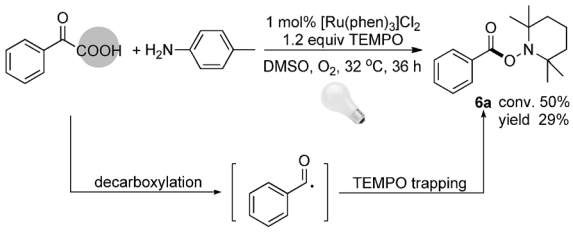


Figure 1. EPR spectra (X band, 9.4 GHz, 160 K).

$[Ru(phen)_3]^+$ and an organic radical. When **1a** was added, this organic radical may be consumed and only $[Ru(phen)_3]^+$ remained. Therefore, from the EPR experiments, Path A (Scheme 2) is the more favored and serves as a feasible reaction pathway for aryl amines.[15] In addition, $[Ru(phen)_3]^+$, the stable species detected by EPR, is the resting state of photocatalyst in this transformation, thus indicating that O_2 activation by $[Ru(phen)_3]^+$ was possibly involved in the rate-determining step.

Moreover, to investigate the decarboxylation of α-keto acids, cyclic voltammetry (CV) experiments were carried out. As shown in the Figure 2A, in the presence of PhCOCOOK in DMSO, an obvious oxidative peak was detected. According to the Figure 2C, this oxidative peak can be attributed to the oxidation of PhCOCOOK. However, the corresponding reductive peak was not observed (Figure 2A) even when the scan rate was increased (Figure 2B). This irreversible process may result from instability of the oxidation product of PhCOCOOK. So from the results of the CV experiments, we may confirm that $PhCOCOO^-$ can experience an oxidative process to form $PhCOCOO^{\bullet}$, with subsequent fast and irreversible decarboxylation with the generation of the $PhCO^{\bullet}$ intermediate.[12b] (for detailed CV experiments, see Figure S7 in the Supporting Information).

To further confirm the existence of the radical intermediate **8**, a radical-trapping experiment was carried out (Scheme 3). The addition of TEMPO profoundly suppressed the reaction and afforded the addition product, **6a**, of the



Scheme 3. Radical-trapping experiment. TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy.

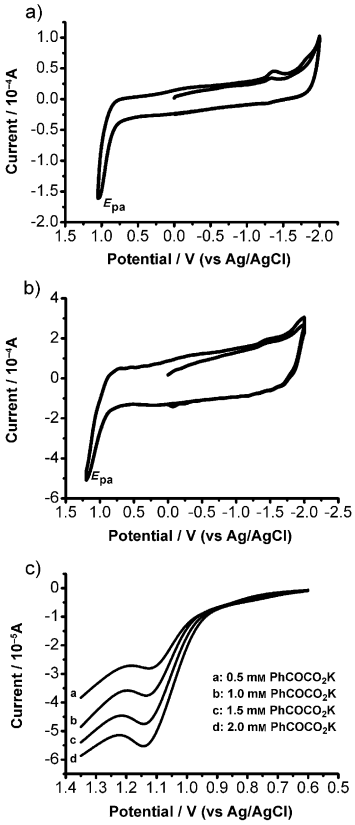


Figure 2. Cyclic voltammetry of PhCOCOOK in DMSO, NBu_4BF_4 (0.1 M) under nitrogen. A) At a scan rate of $\nu = 0.5\ V s^{-1}$ at a steady glassy carbon disk electrode. B) At a scan rate of $\nu = 5.0\ V s^{-1}$ at a steady glassy carbon disk electrode. C) Different concentration of PhCOCOOK at a scan rate of $\nu = 0.5\ V s^{-1}$ at a rotating electrode.

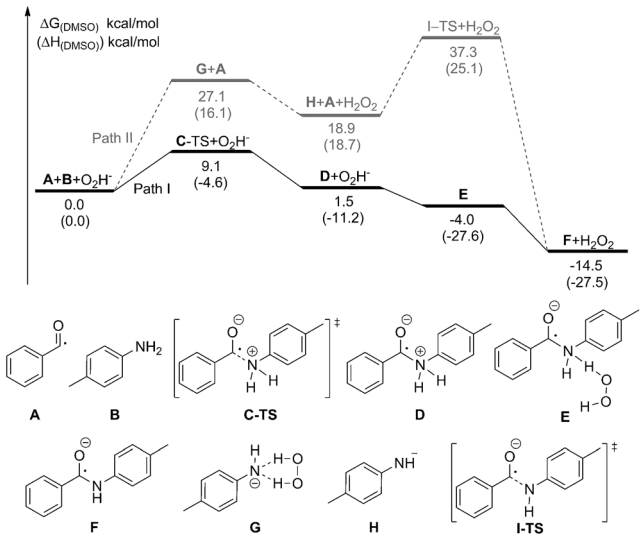


Figure 3. Free-energy profile for the formation of **F**. The values are calculated (M06-2X) free energies in DMSO solvent.

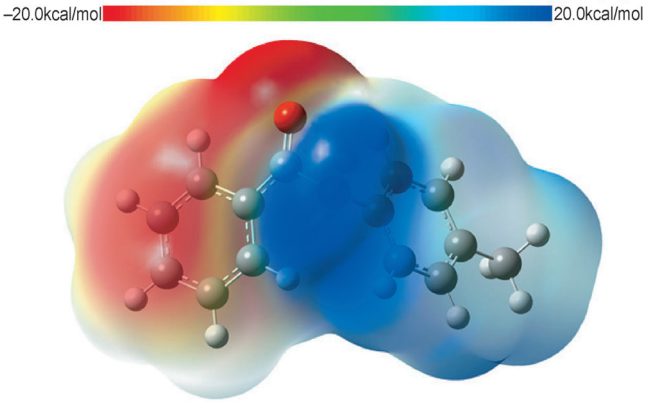


Figure 4. The electrostatic potential of **D**.

TEMPO and acyl radical, thus suggesting that **8** was a possible intermediate in this transformation.[16]

Furthermore, the density functional theory M06-2X method with a standard 6-311 + G(d) basis set was employed to investigate the reaction mechanism for the addition of **B** to **A** and the formation of the complex **F**. As depicted in Figure 3, **A**, **B**, and O_2H^- is set to zero in the free-energy profile, and two competitive pathways for the formation of **F** are computed. In Path-I, the nucleophilic addition of **B** to **A** takes place via the transition-state **C-TS** with only a 9.1 kcal mol^{-1} barrier. The natural population analysis of **D** indicates that **D** has a dipole character, in which positive and negative charge is located on the nitrogen and oxygen atoms, respectively (Figure 4).[17] Subsequently, **D** combines with O_2H^- through intermolecular hydrogen bonds, thus forming the intermediate **E** exothermically (4.0 kcal mol^{-1}). Release of H_2O_2 gives the amide radical anion **F** as the product and is exothermic by 10.5 kcal mol^{-1}, thus indicating that Path-I is thermodynamically favorable. Meanwhile, the addition of an amide anion to an acyl radical has also been considered in Path-II. However, the calculated result shows that the amide anion is unstable because the formation of the amide anions **G** and **H** is endothermic by 27.1 kcal mol^{-1} and 18.9 kcal mol^{-1}, respectively. Therefore, the overall barrier of amide anion addition towards an acyl radical via the transition state **I-TS** is as high as 37.3 kcal mol^{-1}, which is 28.2 kcal mol^{-1} higher than that of Path-I. The theoretical study indicates that **F** can be formed by the nucleophilic attack of **B** with the radical **A**. The formation of **F** is exothermic by 14.5 kcal mol^{-1}, with a barrier of only 9.1 kcal mol^{-1}.

In conclusion, we have disclosed the first example of visible-light-mediated decarboxylation/oxidative amidation of α-keto acids with amines under mild reaction conditions using O_2 as the terminal oxidant. This transformation provides a new approach to developing an advanced method of oxidative decarboxylation. The preliminary mechanism studies were investigated step by step and revealed that: 1) an SET process between $[Ru(phen)_3]^{2+*}$ and aniline played an important role; 2) O_2 activation might be the rate-determining step; 3) decarboxylation was an irreversible and fast process. The application of this powerful strategy to other oxidative decarboxylation reactions with various nucleophiles and further mechanistic investigations are underway in our laboratory.

Experimental Section

General procedure for visible-light-mediated aerobic oxidative decarboxylation of α-keto acids with amines: A dried Schlenk tube equipped with a stir bar was loaded with α-keto acid (0.5 mmol), amine (0.75 mmol), $[Ru(phen)_3]Cl_2$ (0.005 mmol, 1 mol%), and DMSO (2 mL) under an atmosphere of O_2. The tube was then stirred under visible light (with a 25 W fluorescent household light bulb (distance app. 10 cm) 32 °C) for 36 h. After completion of the reaction, it was quenched by water and extracted with ethyl acetate (3 × 10 mL). The organic layers were combined and the pure product was obtained by flash column chromatography on silica gel.

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[17] For a colorful figure see Figure S9.

