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Catalyst-Free Singlet Oxygen-Promoted Decarboxylative Amidation of α-Keto Acids with Free Amines

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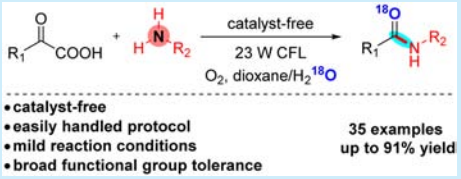
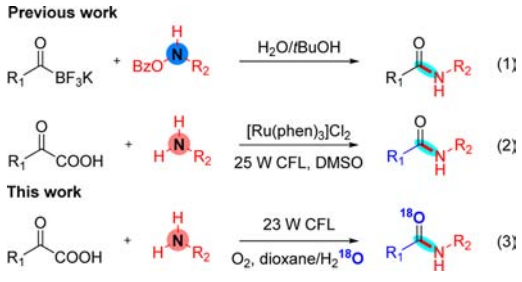
Supporting Information

ABSTRACT: A novel catalyst-free decarboxylative amidation of α-keto acids with amines under mild conditions has been developed. Advantages of the new protocol include avoidance of metal catalysts and high levels of functional group tolerance. In addition, the reaction can be scaled up and shows high chemoselectivity. Preliminary mechanistic studies suggest that singlet oxygen, generated from oxygen under irradiation, is the key promoter for this catalyst-free transformation.



Amides are ubiquitous organic functional groups, especially as components of natural products and pharmaceuticals.[1] The most prevalent strategy for preparing amides is the interconversion of amines with carboxylic acids or carboxylic acid derivatives, but due to the need to protect other functional groups fully, the lability of activated carboxylic acid derivatives and the low chemoselectivity makes a new generation of bond-forming reactions using acyl anion equivant increasingly attractive.[2,3] The development of new amide linkage methods using stable acyl synthon equivalents has received considerable attention. In 2012, Bode reported that O-benzoyl hydroxylamines underwent rapid amide formation in aqueous solvents without the need for reagents or catalysts (Scheme 1, eq 1).[3] An

Scheme 1. Recent Amide Linkage Methods Using Stable Acyl Synthon Equivalents



effective aryl donor, potassium acyltrifluoroborate, has been reported in the literature. The reactions are chemoselective, high yielding, and operationally simple and provide a green method for synthesis of amides.

Recently, α-keto acids have emerged as a new acyl anion reagent.[4] Significant progress has been made in the development of photoredox catalysis,[5] and photocatalysis has been widely applied in organic synthesis because of the mild and green conditions.[6] Decarboxylative acylation for construction of $C_{sp}2-C_{sp}$ bonds, $C_{sp}2-C_{sp}2$ bonds, and $C_{sp}2-C_{sp}3$ bonds in photochemistry has attracted considerable attention, such as Wang's,[7,10] Chen's,[8] MacMillan's,[9] and Fu's work.[11] Although decarboxylative coupling of α-keto acids has been proven to be a powerful method for forming C−C bonds, oxidative coupling of α-keto acids with amines for forming C−N bonds has been less explored, especially with weakly nucleophilic aromatic amines. In 2014, Lei et al. disclosed decarboxylative amidation by employing $[Ru(phen)_3]Cl_2$ as the photocatalyst (Scheme 1, eq 2).[12] In contrast to Bode's work, Lei developed a new photoredox process for synthesis of amides. Herein, we found that α-keto acids could react with amines in the presence of O_2 and H_2O and underwent a decarboxylative oxidation process to produce amides (Scheme 1, eq 3). The reaction can proceed smoothly without adding any photocatalyst.

Mechanistic investigations revealed that, in contrast to a previous report,[12] this reaction proceeds through an α-imino acid[13] intermediate, and the key enabler of this catalyst-free process is attributed to the involvement of singlet oxygen, generated under irradiation under our reaction conditions. This reaction provides an easy-to-handle protocol for production of amides and also demonstrates a new application of decarboxylative carbon−heteroatom coupling reactions promoted by photoexcited singlet oxygen.

We started our investigation with benzoylformic acid (**1a**) and 4-methylaniline (**2a**) as the standard substrates in the presence of O_2 exposed to two 23 W household bulbs at room temperature (Table 1). First, based on Bode's work,[14] we were pleased to find that a solution of these two reactants in dimethylformamide (DMF) produced the desired amide product in 26% yield (entry 1). The screening of solvents showed that 1,4-dioxane/H_2O (5:1, v:v) was the optimal solvent (entries 2−9). Changing the ratio of **1a** and **2a** from 1.0/1.5 to 1.5/1.0 resulted in a 75% GC yield (in 68% isolated yield, entry 10). Further studies showed that the yield of **3a** was slightly decreased with the addition of a base or an acid (entries 11−13). Finally, extending the reaction time to 48 h

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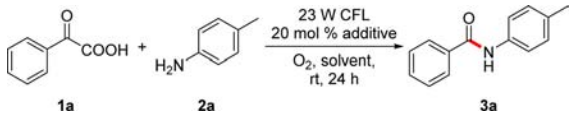
Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

entry	solvent	additive	yield[c] (%)
1	DMF		26
2	*t*BuOH		15
3	1-Butanol		4
4	CH_3OH		8
5	CH_3CN		trace
6	DMSO		20
7	dioxane		45
8	DCM		2
9	dioxane/H_2O[b]		67
10[d]	dioxane/H_2O[b]		75 (68)
11	dioxane/H_2O[b]	Et_3N	45
12	dioxane/H_2O[b]	CH_3COONa	56
13	dioxane/H_2O[b]	CH_3COOH	63
14[d,e]	**dioxane/H_2O**[b]		**87 (80)**
15[d,f]	dioxane/H_2O[b]		trace
16[d,g]	dioxane/H_2O[b]		nd

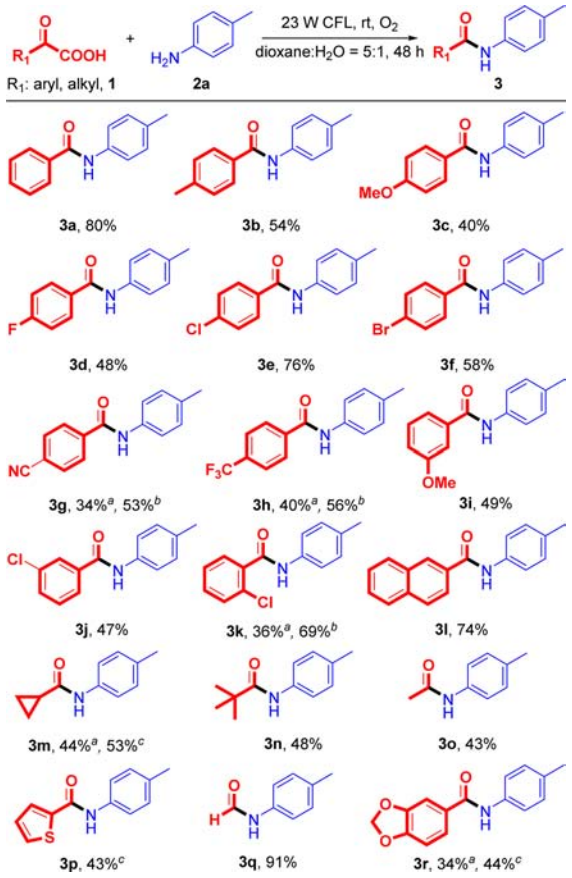
[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.375 mmol), irradiation with two 23 W household light bulbs in solvent (3 mL) at room temperature for 24 h under O_2 atmosphere, unless otherwise noted. [b]The ratio is 5:1 (v:v). [c]GC yields. The number in parentheses is the isolated yield. [d]**1a** (0.375 mmol), **2a** (0.25 mmol). [e]48 h. [f]Reaction was carried out in the dark for 48 h. [g]Reaction was carried out under N_2 for 48 h. DMF = dimethylformamide; DMSO = dimethyl sulfoxide; DCM = dichloromethane; n.d. = not detected. CFL = compact fluorescent light.

resulted in an optimal yield of **3a** (80% isolated yield, entry 14). In addition, two control experiments indicated that visible light and O_2 were necessary for the success of this reaction (entries 15 and 16).

The optimized reaction conditions were applied to the decarboxylative amidation of a variety of α-keto acids (**1**) with modest to good yields (Scheme 2). The present reaction can tolerate electron-donating groups (**3b**, **3c**, **3i**) well and electron-withdrawing groups (**3g**, **3h**). Notably, this reaction also showed satisfactory tolerance of halogens (**3d**, **3e**, **3f**, **3j**, **3k**), which provide available protocols for cross-coupling reactions. In addition, a 2-naphthyl-substituted substrate worked well to deliver the product in 74% yield (**3l**). However, an acetal-substituted substrate resulted in slightly lower yields (**3r**). Furthermore, aliphatic α-keto acids and heterocyclic α-keto acid were also compatible with this reaction (**3m**−**o** and **3p**). Notably, 2-oxoacetic acid produced the corresponding amide product (**3q**) in 91% yield.

The scope of amines was next investigated in reaction with benzoylformic acid, as shown in Scheme 3. The reaction can tolerate electron-donating groups such as *tert*-butyl (**3u**), isopropyl (**3v**), and methoxy (**3t**, **3ac**, **3ae**) well as well as electron-neutral groups (**3s**). To our delight, halide groups were also found to be well compatible with the amidation reaction (**3w**, **3x**, **3ad**, 47−71% yield). Anilines containing electron-withdrawing groups such as acetyl (**3y**, 58%) and trifluoromethyl (**3z**, 40%) groups reacted efficiently. In addition, aniline with an unprotected carboxyl group in the para position gives the desired amide (**3ab**) in 60% yield, illustrating that carboxyl functional groups are tolerated and the reaction can avoid dehydration condensation of 4-aminobenzoic acid itself. In addition, 4-

Scheme 2. Scope of α-Keto Acids[a]



[a]Reaction conditions: **1** (0.375 mmol), **2a** (0.25 mmol), 1,4-dioxane/H_2O (2.5:0.5 v/v) irradiation with two 23 W household light bulbs at room temperature for 48 h under O_2 atmosphere, unless otherwise noted. Yield of isolated product. [b]**1** (0.5 mmol), **2a** (0.25 mmol), *tert*-butyl hydroperoxide (TBHP, 0.5 mmol). [c]**1** (0.5 mmol), **2a** (0.25 mmol).

morpholinoaniline could also afford the corresponding product **3af** in 43% yield. Furthermore, reaction with benzylamine was achieved in the presence of 2 equiv of *tert*-butyl hydroperoxide (TBHP), but in lower yield (**3ag**). Encouraged by the results, we proceeded to employ this decarboxylative amidation of benzoylformic acids with the secondary amine pyrrolidine, and the reaction gave the desired product **3ah** in moderate yield under the modified conditions.

We next focused our attention on the synthetic application of the *N*-(*p*-tolyl)benzamide product (Scheme 4). A gram-scale reaction between benzoylformic acid (2.25 g) and 4-methylaniline (1.07 g) provided the *N*-(*p*-tolyl)benzamide (1.34 g) in 64% yield.

Note that the present reaction permits a compatible reaction profile. Under the reaction conditions described in this study, a chemoselective amidation of 2-oxopentanedioic acid with 4-methylaniline in the presence of an unprotected carboxyl group could be accomplished in 60% yield without **4a′** and **4a″** (Scheme 5a). When the reaction of pyruvic acid with 4-aminophenols was performed, we were pleased to find that the amino group in 4-aminophenols was selectively acetylated, affording 4-acetamidophenol **4b**, without hydroxyl acetylated product **4b′** (Scheme 5b).

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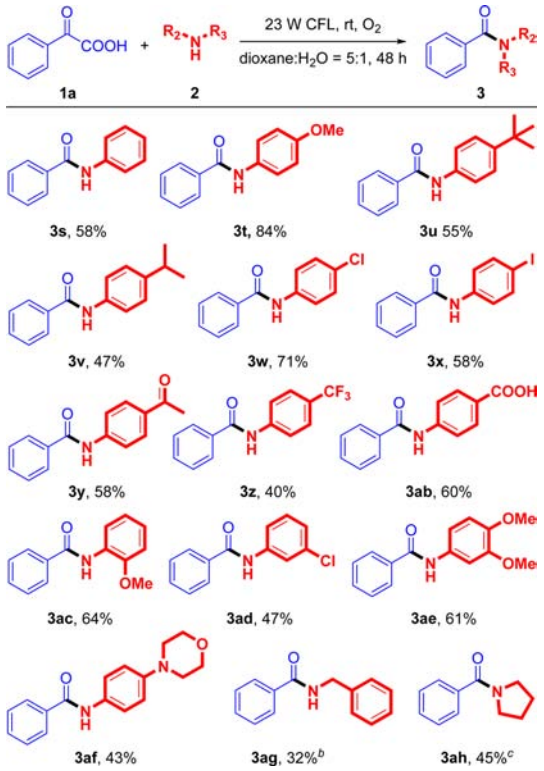
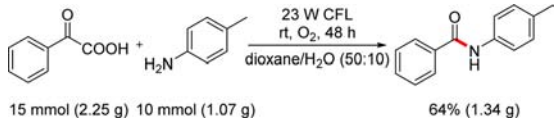
Scheme 3. Scope of Amines[a]

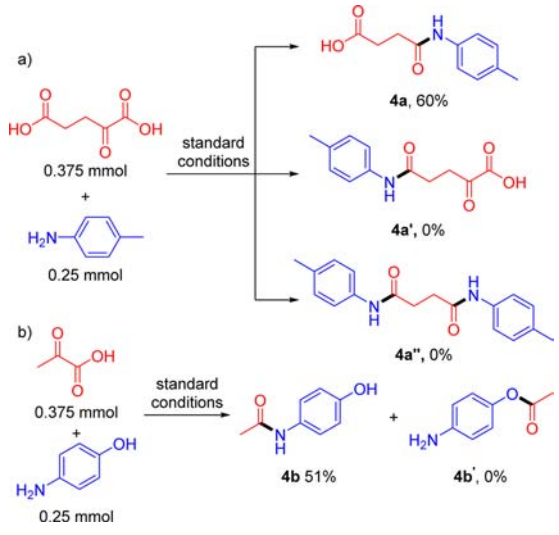


[a]Reaction conditions: **1a** (0.375 mmol), **2** (0.25 mmol), 1,4-dioxane/H_2O (2.5:0.5, v-v) irradiation with two 23 W household light bulbs at room temperature for 48 h under O_2 atmosphere, unless otherwise noted. Yield of isolated product. [b]2 equiv (0.5 mmol) of **TBHP** was added. [c]**1a** (0.25 mmol) and **2** (2.5 mmol) were added in 1,4-dioxane (3 mL).

Scheme 4. Gram-Scale Reaction

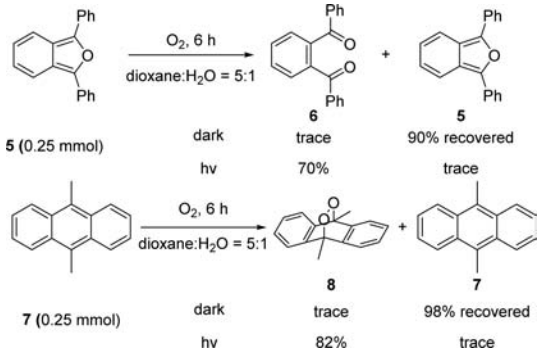


Scheme 5. Chemoselectivity Profile in Amidation



From the two control experiments (Table 1, entries 15 and 16), we know that visible light and O_2 are necessary for the success of this reaction. However, we wondered about the key enabling factor featuring this catalyst-free process. One possibility is that singlet oxygen is produced and is responsible for the oxidative procedure coupling process under our standard conditions.[15] We carried out control experiments trying to verify the presence of photoexcited singlet oxygen. Trapping experiments using 1,3-diphenylisobenzofuran **5**[16,17] and 9,10-dimethylanthracene **7**[18,19] under the standard conditions afforded **6**, a dicarbonyl compound formed through an endoperoxide, and the endoperoxide product **8** formed through [4 + 2] cycloaddition involving $^1O_2$, while the corresponding oxidation products **6** and **8** were not detected in the dark (Scheme 6). These trapping

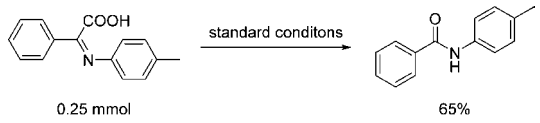
Scheme 6. Trapping Experiments of $^1O_2$



experiments of $^1O_2$ and the quenching experiments of $^1O_2$ by 1,4-diazabicyclo[2.2.2]octane (DABCO)[20] (see the Supporting Information) clearly indicate that $^1O_2$ is produced from O_2 under irradiation in our reaction system.

According to Gooßen's work,[21] 2-phenyl-2-(*p*-tolylimino)-acetic acid was successfully obtained and converted to the amide product **3a** in 65% yield under the standard conditions (Scheme 7).

Scheme 7. Transformation of the Key Intermediate α-Imino Acid



Based on the mechanistic investigations above, a possible pathway for this decarboxylative amidation process is proposed (Scheme 8). We reasoned that mixing α-keto acid **1** with primary amine **2** first leads to condensation via the hemiaminal to α-iminoacids **9**.[21] Then singlet oxygen, generated from oxygen under illumination in our reaction system, abstracts an electron from α-imino acids **9** to generate **10** and **11**, which next undergo decarboxylation to deliver *N*-arylimidoyl radicals[22] (**12**) followed by subsequently reacting with water to give enol compounds **13**. Compound **13** undergoes tautomerization to afford amides.[3,14] The mechanism involving hydrolysis of **12** by water was further supported by an $H_2{}^{18}O$ labeling experiment, in which ^{18}O was detected in the final amide product (see the Supporting Information).

In summary, a novel catalyst-free oxidative decarboxylativeamidation of α-keto acids with free amines under mild conditions

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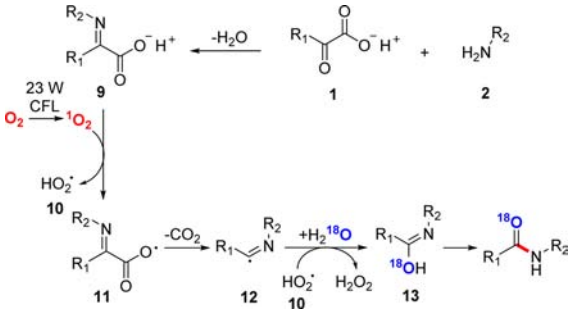
Scheme 8. Proposed Mechanism



has been developed. This new reaction affords amides in modest to good yields tolerating various substituents. Mechanistic studies revealed that this reaction proceeds through oxidative decarboxyltion of α-imino acids followed by hydrolysis, and singlet oxygen being generated under irradiation is the key promoter. Related oxidative decarboxylative cross-coupling reactions promoted by photoexcited singlet oxygen are currently under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01296.

Experimental procedures and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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