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Hydrogen Bond Directed Aerobic Oxidation of Amines by Photoredox Catalysis

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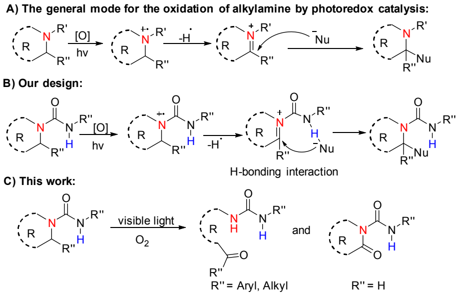
An application of H-bonding interactions for directing the α-C-H oxidation of amines to amides and amino-ketones catalyzed by an organic photocatalyst is reported. The high efficiency of this method is demonstrated by the aerobic oxidation of pyrrolidines, diarylamines and benzylamines bearing urea groups with high yields and wide substrate scope.

Efficient transformation of organic amines is an important strategy for the construction of nitrogenous and other functionalized compounds, such as Mannich-type reaction and cross-coupling reaction via the cleavage of C-N bond.[1] In particular, photoredox catalysis has emerged as an important tool for the efficient transformation of organic amines, and many literatures have been reported on the oxidation of alkylamines via visible-light-induced processes.[2] In general, the nitrogen-radical-cation will be firstly generated through photoredox catalysis, and then the imine is obtained after a proton's elimination, which will be attacked by a nucleophile (Scheme 1A). Although this catalytic mode is widely applied in large number of organic reactions, it still exists some challenging problems to be resolved at the moment, such as long reaction time and narrow substrate scope. Therefore, searching an efficient method for resolving these problems is highly desirable.

The introduction of efficient directing groups is an important strategy for improving regioselectivities and yields in organic reactions.[3] Meanwhile, H-bonding interaction present a vital role for the design of directing groups, which can bind together two different molecules in the transition states.[3g, 3h, 3j, 4] Inspired by these observations, we postulated that an amine protected as a urea may offer a H-bonding interaction for controlling nucleophiles as a result of directing the addition reaction of imines under photoredox conditions (Scheme 1B). Herein, we disclose a strategy involving a urea derived H-bond directed oxidation of amines to amides and amino-ketones (Scheme 1C).

Pyrrolidines are found in numerous natural products and bioactive molecules; these building blocks are easily accessible through a variety of reported procedures.[6] However, investigations devoted to the transformation of pyrrolidines to other useful molecules are limited.[7] Based on our previous successes,[8] the model reaction was first performed with **1a** and organic photosensitizer **I** ($E^{t}_{(S^*/S^{\bullet-})}$ = 2.3 V) with visible light irradiation under aerobic conditions. The reaction was found to proceed well and gave oxidation product **2a** in a 73% yield within 4 h (Table 1, entry 1). Control experiments were conducted to investigate the influence of various reaction parameters, as shown in Table 1. When the reactions were performed in the absence of light, photocatalyst or O_2, no products were yielded. These result illustrated that the reaction was oxidized by oxygen under visible light irradiation (entries 2-4). Moreover, **2a** was obtained in lower yields (entries 5 and 6) when the reaction was conducted in the presence of chloroform or 1,2-dichloroethane as the solvent. After that, careful screening of the reaction conditions was continued, but improved reaction outcomes were not obtained even using other photosensitizers.



Scheme 1. The generations of N-centered radical species and their applications.

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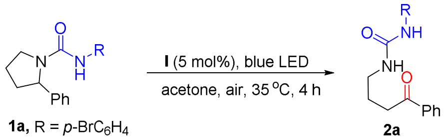
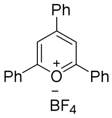
Table 1. Optimization of reaction conditions.[a]

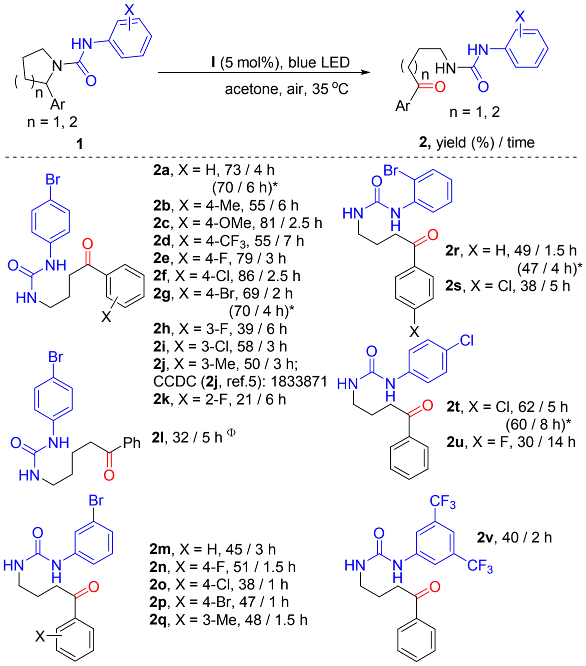


Entry	*variation from standard conditions*	yield
1	none	73% y
2	no light	NR
3	no photosensitizer	NR
4	in N_2	NR
5	$CHCl_3$ instead of acetone	43% y
6	$ClCH_2CH_2Cl$ instead of acetone	50% y
7	DMF instead of acetone	NR
8	THF instead of acetone	NR
9	Mes-AcrClO_4 instead of **I**	36% y
10	$[Ru(bpy)_3Cl_2]\cdot 6H_2O$ instead of **I**	NR
11	$[Ir(ppy)_2(dtbbpy)]PF_6$ instead of **I**	NR


I

[a]Unless otherwise noted, all the reactions were performed with **1a** (0.05 mmol) in the presence of a catalyst (5 mol%) in solvent (1 mL) for 4 h. Yields of **2a** are isolated yields. NR: no reaction.

Table 2. The scope of the reactions.[a]



[a]All reactions were performed on a 0.05 mmol scale under the optimized conditions. Yields of **2** are isolated yields. *The reactions were performed on a 0.20 mmol scale under the optimized conditions. [Φ]15 mol % **I** was used.

Under the optimized conditions, the scope of the reaction was then investigated by fine tuning the steric effects and electronic influences of the substituents (Table 2). *Para*-substituents on the benzene rings were well tolerated in the reactions regardless of their electron-withdrawing or electron-donating effects. Meanwhile, substrates with *meta*- or *ortho*-substituents, such as fluorine, chlorine and methyl, were examined in this reaction and afforded the corresponding products in moderate yields. In addition, a 32% yield of the desired product was obtained when the reactant derived from piperidine was exposed to the catalytic system. Subsequently, the urea with *meta*- and *ortho*- substituted bromine were investigated, and all the reactions proceeded smoothly and furnished the corresponding products. Moreover, *para*-substituted fluorine, chlorine and 3,5-CF_3 group were also investigated despite of moderate yields under the mild conditions. In addition, the ketonic carbonyl of **2a** was easily reduced by $NaBH_4$ in a 92% yield in a short time, and the hydrolyzation of **2a** to furnish the corresponding amino-ketone was also realized using aqueous H_2SO_4 (see Scheme S1). To expand the applications of this reaction, we continued to examine the direct oxidation of acyclic amines for preparing ketones by this strategy (Table 3).[9] We first examined substrates with alkyl groups such as ethyl and Bn, which successfully furnished the corresponding products in moderate yields. To our delight, substrates with aryl groups can be efficiently converted to diarylketones in excellent yields. For example, diphenylketone **4c** was obtained in an 88% yield by photoredox catalysis. For explaining the importance of the urea group, the oxidation reaction with diphenylmethanamine was carefully performed under the standard conditions. However, benzophenone (**4c**) was not obtained after stirring for 12 h, which indicated that the hydrogen bond was essential for the reaction. Then, the variations of the substrates by fine tuning the electronic and steric effects were investigated to expand the applications of this method. Introducing electron-withdrawing and electron-donating groups showed no influence on the reaction outcome, and *meta*- and *ortho*-substituted ketones (**4d, 4j** and **4l**) could be obtained in high yields. In addition, **4m** and **4n** were furnished in 32% and 61% yields, respectively. Notably, product **4q** could be easily converted to *fenofibrate* with 77% yield over two steps.

N-Acyl ureas are important structural motifs present in numerous bioactive compounds, and, the benzoyl ureas are often found in agrochemicals and insect growth regulators. Therefore, the development of novel methods for efficiently synthesizing these compounds is in high demand.[10] Herein, we proposed that this visible-light-induced method would be a desirable strategy for preparing benzoyl ureas. We found that the efficient oxidation of **5a** using Mes-AcrClO_4 ($E^{t}_{(S^*/S^{\bullet-})}$ = 2.06 V) can be achieved in a 80% yield (Table S1). In addition, the scope of the reaction was carefully explored by introducing different groups at the *para*-, *meta*- and *ortho*- sites of the benzene ring. As shown in Table 4, all substrates furnished the corresponding products in good to excellent yields via photoredox catalysis. In addition, four commercial insecticides were synthesized under these mild conditions, and *penfluron* could be carried on a gram-scale synthesis with 0.76 g (71% yield).

To elucidate the mechanism of the reaction, we carried out control experiments (Scheme 2). First, the influences of urea in the optimized reaction were determined by changing the substituents on the pyrrolidines (Scheme 2a). No desired product was obtained by this method if no protecting group was

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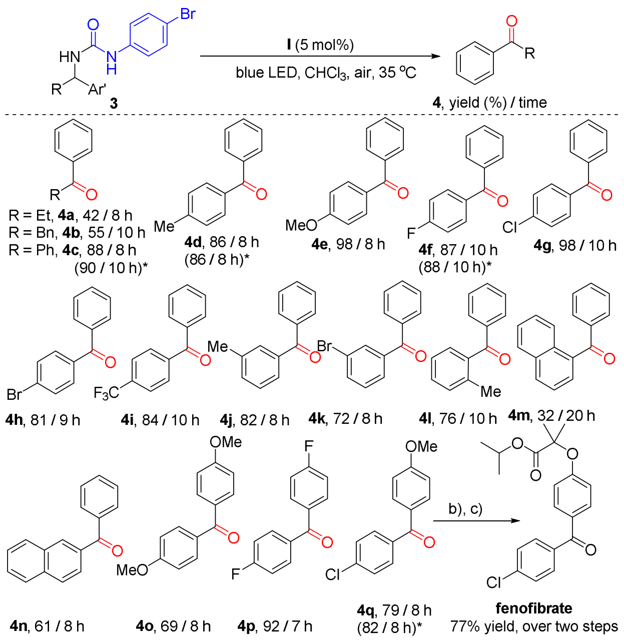
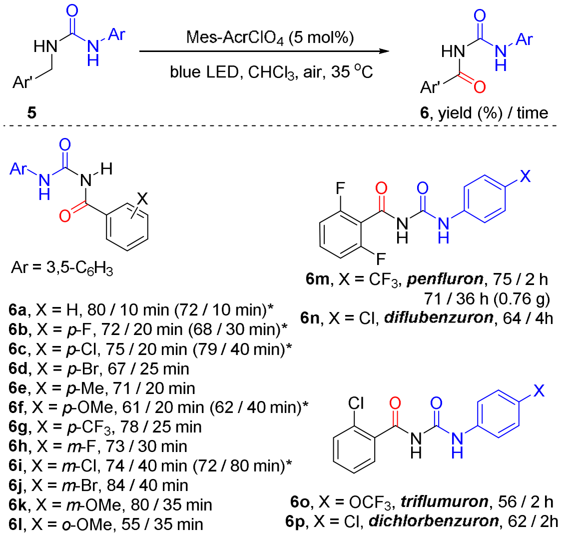
Table 3. Substrate scope for the oxidation of benzylamines by photoredox catalysis.[a]



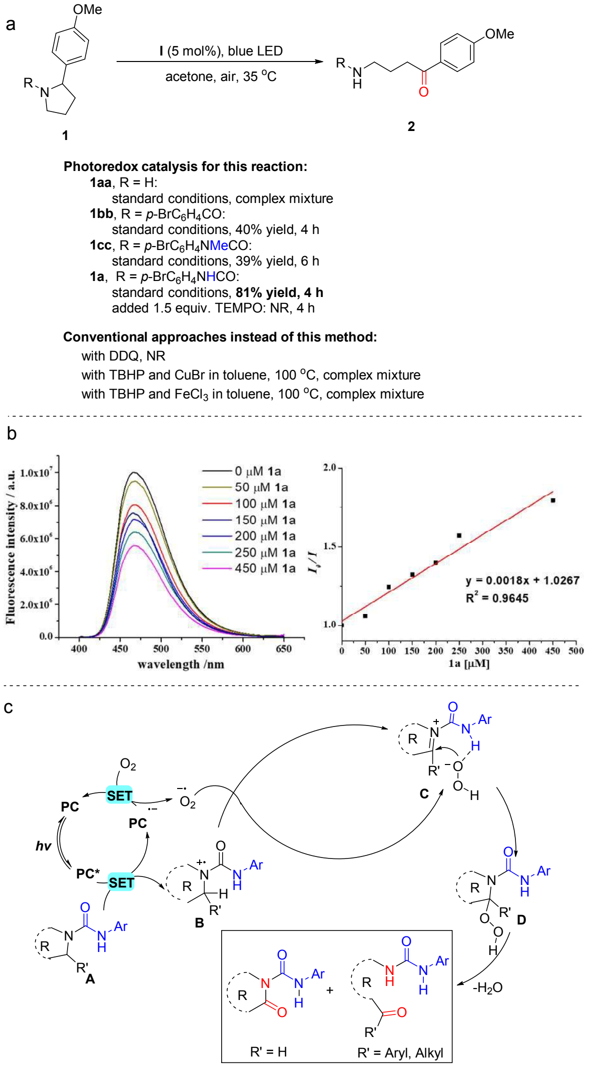
[a]All reactions were performed on a 0.05 mmol scale under the optimized conditions. *The reactions were performed on a 0.30 mmol scale under the optimized conditions. Yields of **4** are isolated yields. (b) BBr_3, THF, H_2O; (c) isopropyl 2-bromo-2-methylpropanoate, $KHCO_3$, isopropanol, reflux.

Table 4. Substrate scope for the oxidation of benzylamines by photoredox catalysis.[a]



[a]All reactions were performed on a 0.05 mmol scale under the optimized conditions. *The reactions were performed on a 0.20 mmol scale under the optimized conditions. Yields of **6** are isolated yields.

used (**1aa**). Meanwhile, when the urea group was replaced with *p*-BrC_6H_4CO (**1bb**), the desired product was obtained in only a 40% yield. If the acidic N-H bond of urea was protected with methyl group (**1cc**), only 39% yield was obtained. Therefore, H-binding interactions play an important role in this reaction. Furthermore, if TEMPO was added into the system, no reaction was observed despite increasing the reaction time. To illustrate the importance of this method, conventional approaches for the oxidation amines using DDQ and TBHP were subsequently examined,[11] but no products were furnished under these conditions. In addition, the Stern-Volmer quenching experiments were also carried out to get further information on the reaction mechanism. As shown in Scheme 2b, the excited state of the photocatalyst **I** was efficiently quenched by **1a**. According to these results and previous works,[12] a plausible pathway was proposed (Scheme 2c). First, amine **A** is oxidized to an intermediate **B** by the excited photoredox catalyst under visible light, and then a proton is abstracted by the $O_2^{\bullet-}$ to generate intermediate **C**. After the addition reaction between **C** and HO_2^- assisted by H-binding interaction, the addition product **D** is generated, which is then converted to the product after removal of H_2O.



Scheme 2. Mechanistic research. (a) Control experiments; (b) Catalyst quenching experiment; (c) The possible reaction pathway. DDQ: 2,3-dicyano-5,6-dichlorobenzoquinone; TBHP: *tert*-Butyl hydroperoxide.

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In summary, we have developed a hydrogen-bond directed aerobic oxidation reactions by photoredox catalysis and successfully applied this method to the transformation of C-N bonds. Moreover, pyrrolidines-derived substrates and benzylamines bearing urea groups could be efficiently oxidized under aerobic conditions to furnish the corresponding ketones and benzoyl ureas in excellent yields. The excellent yields and broad substrate scope illustrated the efficiency of this strategy for achieving novel reactions by photoredox catalysis.

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Conflicts of interest

The authors declare no competing financial interest.

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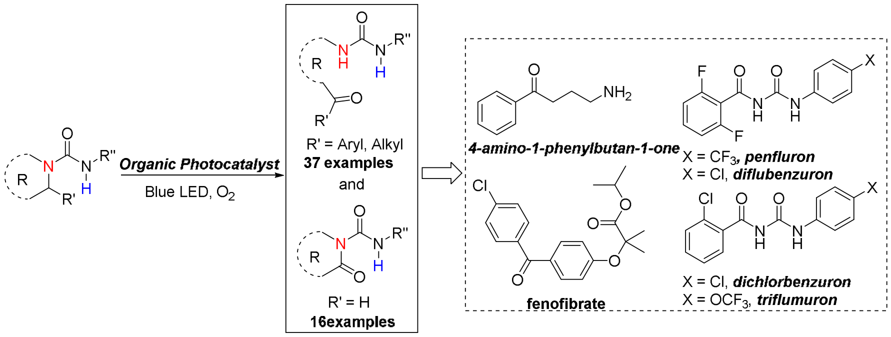
Hydrogen Bond Directed Aerobic Oxidation of Amines by Photoredox Catalysis

Hongyu Wang,†,* Yunquan Man,† Kaiye Wang, Xiuyan Wan, Lili Tong, Na Li and Bo Tang*



An application of H-bonding interactions for directing the α-C-H oxidation of amines to amides and amino-ketones catalyzed by an organic photocatalyst with high yields and wide substrate scope is reported.