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Phenazinium Salt-Catalyzed Aerobic Oxidative Amidation of Aromatic Aldehydes

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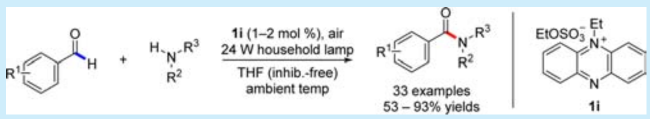
Supporting Information

ABSTRACT: Amides are prevalent in organic synthesis. Developing an efficient synthesis that avoids expensive oxidants and heating is highly desirable. Here the oxidative amidation of aromatic aldehydes is reported using an inexpensive metal-free visible light photocatalyst, phenazine ethosulfate, at low catalytic loading (1−2 mol %). The reaction proceeds at ambient temperature and uses air as the sole oxidant. The operationally easy procedure provides an economical, green, and mild alternative for the formation of amide bonds.



One of the most important chemical linkages is the amide bond, which forms the structural backbone of protein and peptides. The amide bond is also prevalent in natural products and biologically active compounds.[1] Tertiary benzamide-containing drugs[2a] possess a broad range of biological activities such as antirheumatic (CGI1746)[2b] and antiemetic (Aloxi) (Figure 1). Current amidation reactions

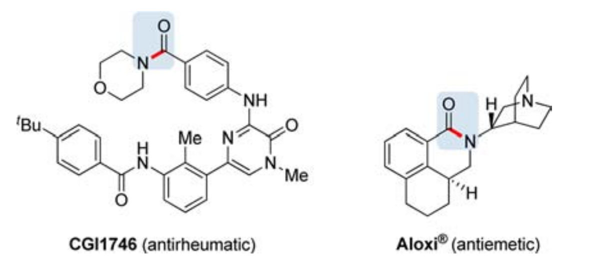
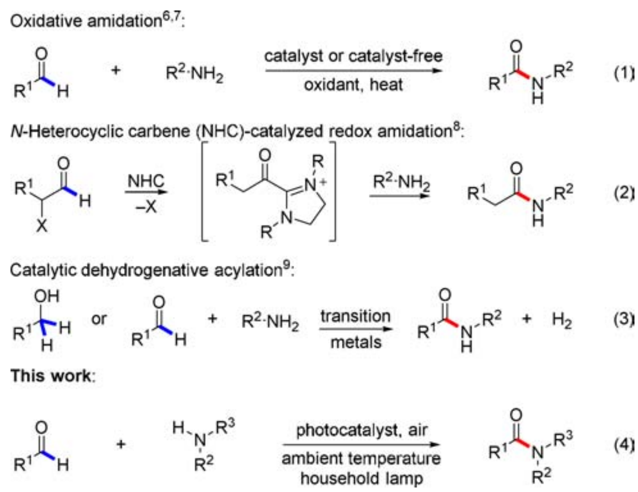


Figure 1. Biologically active tertiary benzamides.

generate huge amounts of byproducts and chemical wastes.[3] Despite the exceptional versatility these methods offer, the general consensus is to improve the atom economy of amidation reaction.[4]

There are tremendous efforts to improve amide bond synthesis.[5] The oxidative amidation of aldehydes provides a viable approach (eq 1).[6] In 2006, Li and co-workers reported an elegant system using Cu(I) and T-Hydro.[6b] Subsequently, several groups have developed catalyst-free methods using oxidants such as TBHP[6c] and, more recently, hydrogen peroxide.[6i,j] On the other hand, Barbas et al. developed the cross-coupling reaction of aldehydes with activating groups.[7]

An alternative approach to the activating group strategy is the use of *N*-heterocyclic carbene (NHC) catalysis to generate an active ester (eq 2).[8] Milstein et al. developed a dearomatized PNN pincer ruthenium complex for the catalytic dehydrogenative acylation, producing H_2 as the only byproduct (eq 3).[9]



Although there were many existing approaches to amide bond synthesis, the majority of them require oxidants, heating, or a combination of both. In some of these methods, expensive transition metals are used and an inert atmosphere is sometimes required. The development of an environmentally benign and mild method for this transformation is needed.

In order to drive reactions, we need a sustainable and renewable source of energy. To this aspect, the ubiquitous sunlight serves as an ideal source.[10] Simultaneous works from the Macmillan and Yoon groups, and later the Stephenson group, demonstrated the use of visible light photoredox catalysis in organic synthesis.[11] Subsequently this field has experienced rapid expansions, and visible light can be utilized efficiently.[12]

On the other hand, we are intrigued by reports from several groups that hydrogen peroxide serves an excellent oxidant for

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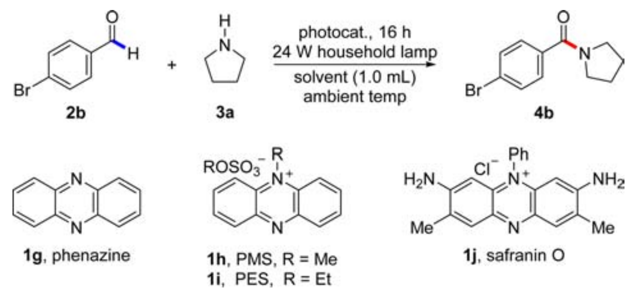
the oxidative amidation of aldehydes.[6i,j] However, air is an ideal oxidant.[6h,k] In oxidative visible light photocatalysis, air is often used as a terminal oxidant and the mechanism is well-known.[13] Herein we disclose the oxidative amidation of aldehydes promoted by visible light photocatalysis (eq 4).

We commenced our studies with photocatalyst identification on the oxidative amidation of aldehyde **2b** with pyrrolidine **3a** (Table 1). A 24 W compact fluorescent lamp (CFL) was used

Table 1. Reaction Optimization[a,b]



entry	photocat. (mol %)	solvent	yield (%)	entry	photocat. (mol %)	solvent	yield (%)
1	none	MeCN	7	9	**1h** (5)	MeCN	58
2	**1a** (5) Ru(bpy)$_3$Cl$_2$	MeCN	22	10	**1i** (5)	MeCN	64
3	**1b** (5) Ir(ppy)$_3$	MeCN	30	11	**1j** (5)	MeCN	62
4	**1c** (5) pyrene	MeCN	47	12	**1i** (5)	THF (with inhib.)	65
5	**1d** (5) TPP	MeCN	58	13	**1i** (1)	THF (with inhib.)	74
6	**1e** (5) eosin Y	MeCN	28	14	**1i** (1)	THF (inhib.-free)	81
7	**1f** (5) rose bengal	MeCN	44	15[c]	**1i** (1)	THF (inhib.-free)	11
8	**1g** (5)	MeCN	37	16[d]	**1i** (1)	THF (inhib.-free)	5

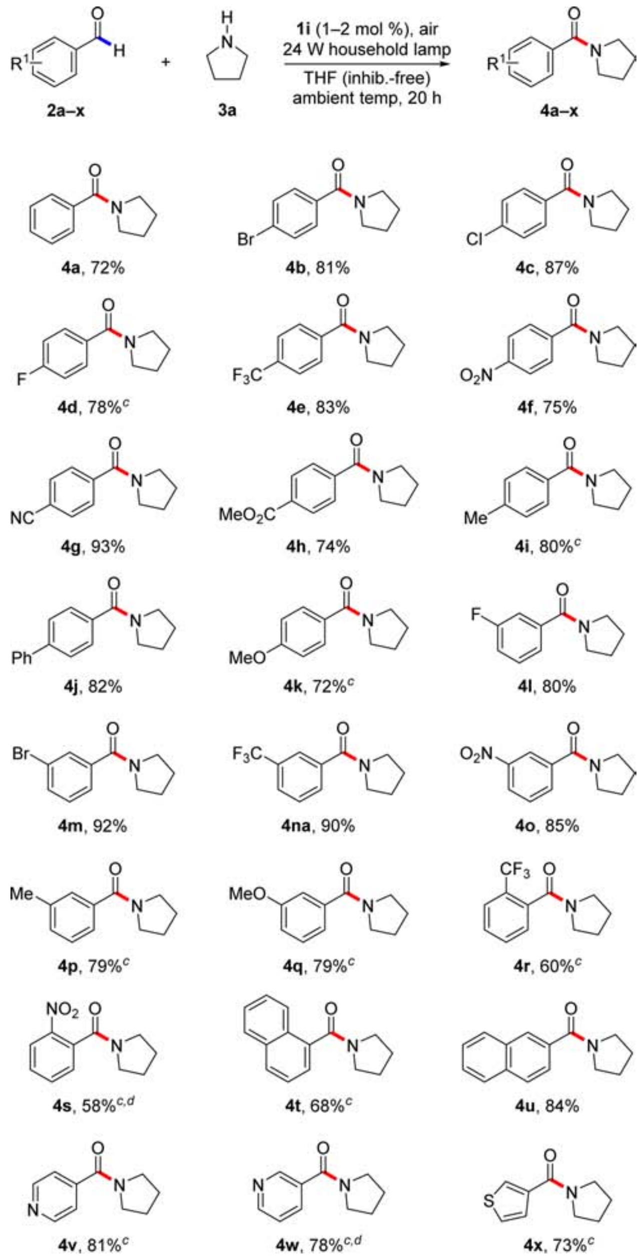
[a]Unless otherwise noted, the reaction conditions were as followed: Aldehyde **2b** (0.10 mmol), photocatalyst **1**, amine **3a**, solvent (1.0 mL), 24 W CFL, 16 h. [b]Yield determined by ^{1}H NMR analysis of unpurified reaction mixture using CH_2Br_2 as the internal standard. [c]Reaction was purged and refilled with argon. [d]Reaction was shielded from a light source. Abbreviations: PMS, phenazine methosulfate; PES, phenazine ethosulfate; Me, methyl; Et, ethyl; bpy, 2,2′-bipyridyl; ppy, 2-phenylpyridinyl; TPP, *meso*-tetraphenylporphyrin; THF, tetrahydrofuran.

as the visible light source. In the absence of a photocatalyst, no product was obtained (Table 1, entry 1). Among the 17 photocatalysts that we had tested, we were delighted to find that photocatalyst **1i** gave the highest yield of 64% (see SI, Table S1). Common photocatalysts (Table 1, entries 2, 6, and 7) gave poor yields.

Lowering the catalytic loading from 5 to 1 mol % improved the yield (Table 1, entry 13). This was likely due to the decrease in the color intensity of the solution, and hence more light was able to pass through it. Finally the best result was obtained using inhibitor-free THF (Table 1, entry 14). The reaction slowed down under argon (Table 1, entry 15) or when shielded from light (Table 1, entry 16).

Under these optimized conditions, an array of synthetically useful aldehydes **2a–x** reacted with pyrrolidine **3a** in the presence of photocatalyst **1i** (Scheme 1). Generally, the phenazinium salt-catalyzed oxidative amidation reaction under visible light irradiation afforded the desired amides **4a–x** in good to excellent yields.

Scheme 1. Scope of Aromatic Aldehydes[a,b]



[a]Unless otherwise noted, the reaction conditions were as followed: Aldehyde **2** (0.12 mmol), photocatalyst **1i** (1 mol %), amine **3a**, THF (inhib.-free, 1.2 mL), 24 W CFL, 20 h. [b] Isolated yield. [c] Additional photocatalyst (1 mol %) was added during the course of reaction. [d] Reaction was conducted under O_2.

The aromatic aldehydes containing electron withdrawing groups reacted more efficiently than those with electron donating groups. Notably, we were pleased to find that the aromatic ester of amide **4h** remained intact due to the mild temperature of our reaction conditions. Due to crowding near the reaction center, *ortho*-substituted amides worked albeit with moderate yields. Aliphatic aldehydes such as cyclopropanecarboxaldehyde gave a desired amide product (22% yield, eq S2) along with other unidentified side products, presumably

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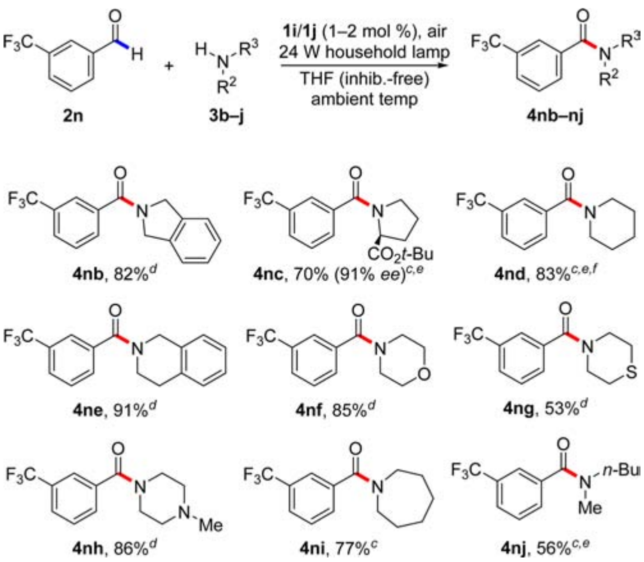
due to the formation of enamines.[6i] Pivaldehyde was too sterically hindered to react. On the other hand, primary aliphatic and aromatic amines generated imines as the major product under our reaction conditions.

Next, a diversity of amines possessing various ring sizes was examined (Scheme 2). Five- and seven-membered cyclic amines reacted with aldehyde **2n** smoothly to give amides in good yields. Initially, we experienced lower reactivity with six-membered cyclic amines. Later photocatalyst **1j** was discovered to exhibit better performance than photocatalyst **1i** for these substrates. Finally challenging acyclic amine **3j** proceeded in 56% yield.

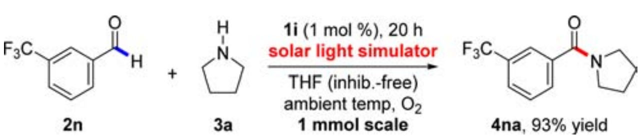
Scheme 2. Scope of Various Secondary Amines[a,b]



[a]Unless otherwise noted, the reaction conditions were as followed: Aldehyde **2n** (0.12 mmol), photocatalyst **1i** or **1j** (1 mol %), amine **3**, THF (inhib.-free, 1.2 mL), 24 W CFL, 20 h. [b] Isolated yield. [c] Photocatalyst **1i** was used. [d] Photocatalyst **1j** was used. [e] Additional photocatalyst (1 mol %) was added during the reaction. [f] Reaction was conducted under O_2.

To demonstrate the scalability and practicality of this newly developed reaction, it was performed at 1 mmol scale under the irradiation of a solar light simulator (Scheme 3). Remarkably, an excellent yield of 93% was achieved using a 1 mol % catalyst loading. However, the catalyst was not recyclable, as it did not survive under reaction conditions.

Scheme 3. Scalable Oxidative Amidation using Solar Light Simulator



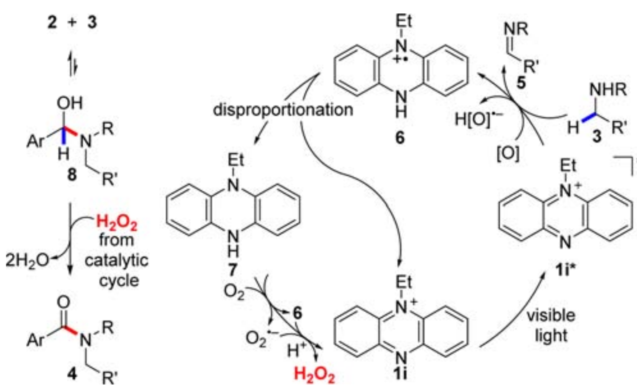
In order to obtain information on the reaction pathway, mechanistic studies were conducted. The participating role of the catalyst on the hydrogen abstraction step was intriguing. By comparing the initial reaction rate of aldehyde **2a** to that of aldehyde **2a**-d_1 under similar reaction conditions, a kinetic isotope effect (KIE) of 1.5 was observed (Figure S2). This result suggested that the C−H bond breaking step was the rate-determining step.

A Hammett plot analysis revealed a linear correlation with a small but positive ρ value of 0.23 (Figure S8). This indicated that the abstracted hydrogen was gaining positive charge. No cyclopropane ring-opening product was detected (eq S2). Hence radical hydrogen abstraction was excluded from the reaction pathway. When H_2O_2 was added, there was no observed accelerating effect of the photocatalyst with visible light irradiation (eq S1); interestingly, the reaction yield doubled when light was excluded. This seemed to suggest that photocatalyst **1i** was reduced after light excitation. Thus, its catalytic ability was lost as the cationic charge disappeared.

Next the interaction between photocatalyst **1i** and amine was probed. The maximum absorbance of photocatalyst **1i** shifted from 364 to 573 nm in the presence of amine **3a** (Figure S11). A large charge-transfer band was observed, indicating the formation of an electron donor−acceptor complex. Accordingly fluorescence quenching experiments of photocatalyst **1i** with amine **3a** revealed a linear concentration-dependent correlation (Figure S13). This implied that the amine acted as a reductive quencher.[13b] Furthermore, the reaction was inhibited by TEMPO and BHT, which were radical scavengers (eqs S4–6).[6b]

On the basis of the above-mentioned observations, a plausible mechanism was proposed (Scheme 4). A single electron was transferred from amine **3** to the excited state of photocatalyst **1i*** to give phenazyl radical **6**. Further oxidation of the aminyl radical intermediate gave imine **5** (eq S3). Phenazinium salts are a well-known electron acceptor in enzymatic assays.[14] Many studies have proven the existence of radical **6**.[15] It was shown to be unstable in a basic environment and would disproportionate to give the doubly reduced hydrophenazine **7**.[15a,e] Photocatalyst **1i** was then regenerated by the oxidation of hydrophenazine **7** with O_2 in sequential steps. Various groups have discussed this step in detail.[16] Subsequently H_2O_2 oxidized the hemiaminal **8** to amide **4**. The formation of the H_2O byproduct was observed in ^1H NMR when the reaction was conducted in THF-d_8 (see SI).

Scheme 4. Plausible Mechanism



In conclusion, we have developed a phenazinium salt-catalyzed aerobic oxidative amidation of aromatic aldehyde derivatives at a low catalytic loading. Importantly, our new protocol uses air as an oxidant and obviates the need for expensive reagents. The phenazinium cation is proposed to undergo an overall two-electron reduction to hydrophenazine under visible light irradiation. We believe this process will

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provide an attractive alternative for the synthesis of benzamide bonds. More studies were needed to disambiguate the mechanistic details of this reaction. Efforts to expand the scope of this transformation are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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