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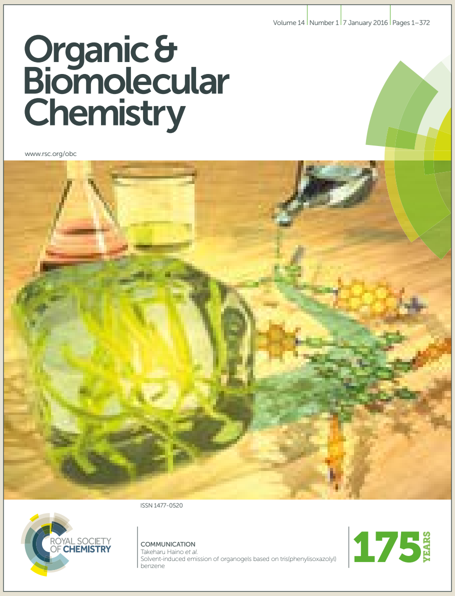

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# Merging visible-light photoredox and copper catalysis in catalytic aerobic oxidation of amines to nitriles

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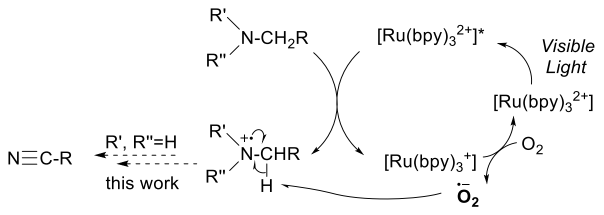
**Absract:** Visible-light-initiated homogeneous oxidative synthesis of nitriles from amines was accomplished through combined use of photoredox and copper catalysis. This transformation was performed at room temperature with $O_2$ as the oxidant.

Nitriles are versatile building blocks in the synthesis of natural products, pharmaceuticals, agricultural chemicals and dyes.[1] Development of new methods for the synthesis of aryl nitriles is of significant interest. From an environmental point of view, $O_2$ is considered as an appealing oxidant for sustainable oxidation chemistry. Obviously, molecular oxygen as oxidant has remarkable advantages, including its abundance, low cost, and benign by-products (usually $H_2O$). The development of catalytic aerobic oxidation methodologies would be highly desirable.[2] For example, our group[3] and others[4] developed copper catalyst systems to directly convert benzylic alcohols into aryl nitriles, where $NH_3$ was used as the nitrogen source and $O_2$ as the oxidant. When referred to amines as starting materials, aerobic oxidative synthesis of nitriles has been studied using heterogeneous catalysts such as $TiO_2$,[5a, 5b] $Nb_2O_5$,[5c] Au–Pd/$ZrO_2$,[5d] Au/$TiO_2$,[5e] $RuO_2{\cdot}xH_2O/TiO_2$,[5f] red Cu(0)/$NH_4Br$[5g] and Cu(0)/$Al_2O_3$[5h]. Recently, Stahl et al.[6] reported an efficient homogeneous copper catalyst system for aerobic oxidation of primary amines to the corresponding nitriles. Nitroxyl radical compound ABNO (9-azabicyclo[3.3.1]nonan-3-one-N-oxyl) and ligand 4,4'-$^tBu_2$bpy are critical for the transformation.

Visible-light-driven photoredox catalysis has become a powerful means to promote efficient organic transformations under remarkably mild conditions.[7] The latest progress in this area shows that merging visible photocatalysis and transition metal catalysis may enable the development of new synthetic strategys and improvement of the conditions of established organic reactions.[8] It is important to note that this concept can bridge the gap between visible-light photoredox catalysis and transition-metal catalysis such as nickel,[9] palladium,[10] gold,[11] and copper[12].

In the photoredox cycle, precedent mechanistic investigations of reductive quenching suggested that iminium ions were likely by-products in the reactions using tertiary amines as reductants (Scheme 1).[7,13] Inspired by this mechanism, we hypothesized that if primary amines were chosen as reductant, nitriles could be formed under photoredox conditions. Herein, as part of our ongoing efforts to develop method to synthesize nitriles, we disclose a homogeneous dual-catalysis combining visible-light photocatalysis and copper catalysis to accomplish efficient conversion amines into nitriles. To the best of our knowledge, this work demonstrates the first example of combined visible-light-induced photoredox catalysis and transition-metal catalysis in transformation of amines to nitriles. The catalytic system expands the toolbox for synthesis of nitriles through aerobic oxidation of amines. Moreover, this new reaction is not only convenient and environmentally benign, but also can be conducted under mild reaction conditions with high conversions.



**Scheme 1** Concept of visible-light-induced aerobic oxidation of amine to nitrile.

Initially, we attempted to perform the reaction by treating benzylamine **1a** with $O_2$ as the oxidant at room temperature. As shown in Table 1, with $Ru(bpy)_3Cl_2$ as catalyst, aerobic oxidation to benzonitrile **2a** was not detected (entry 1). Slightly increased yield was observed when catalytic amount of $LiOBu^t$ was

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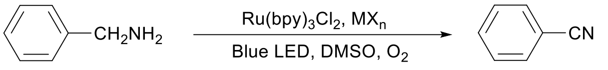
introduced (entry 2)[6]. We systematically evaluated different transition metal catalysts in the photocatalytic oxidation of benzylamine (entries 3-8). It was found that yields of product **2a** could be improved to 20-29% when palladium and cobalt were used (entries 3-5). However, oxidation yields were low when nickel and iron were added (entries 6-7). To our great satisfaction, we observed dramatic improvement when copper catalyst was used (entry 8).

**Table 1**. Cooperative interactions of photocatalyst with transition metal catalysts in oxidation amines to nitriles [a]



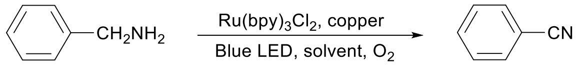
**1a** **2a**

| Entry | Photocatalyst | Transition metal catalyst | **2a**/%[b] |
|---|---|---|---|
| 1 | $Ru(bpy)_3Cl_2 \cdot 6H_2O$ | - | 0[c] |
| 2 | $Ru(bpy)_3Cl_2 \cdot 6H_2O$ | - | 5 |
| 3 | $Ru(bpy)_3Cl_2 \cdot 6H_2O$ | $PdCl_2$ | 22 |
| 4 | $Ru(bpy)_3Cl_2 \cdot 6H_2O$ | $Pd(OAc)_2$ | 20 |
| 5 | $Ru(bpy)_3Cl_2 \cdot 6H_2O$ | $CoCl_2$ | 29 |
| 6 | $Ru(bpy)_3Cl_2 \cdot 6H_2O$ | $NiCl_2$ | 12 |
| 7 | $Ru(bpy)_3Cl_2 \cdot 6H_2O$ | $FeCl_3$ | 10 |
| 8 | $Ru(bpy)_3Cl_2 \cdot 6H_2O$ | CuCl | 68 |

[a] Reaction conditions: benzyl amine **1a** 0.2 mmol, transition metal catalyst 10 mol%, $Ru(bpy)_3Cl_2 \cdot 6H_2O$ 2 mol%, $LiOBu^t$ 20 mol%, DMSO 1.6 mL, room temperature, time 18 h. [b] GC yield. [c] $LiOBu^t$ is free.

Next, different copper salts were evaluated in the photocatalyzed oxidation of benzylamine (Table 2, entries 1-7). It was found that yield of product **2a** is 67-77% when cuprous salts were used, while cupric salts gave lower yields. For instance, CuBr, when combined with $Ru(bpy)_3Cl_2$, resulted in the oxidation product in 77% yield (entry 2). However, $CuBr_2$ only gave 29% product (entry 4). Gratifyingly, the result of $Cu(OAc)_2$ is good, and 71% yield was obtained (entry 7). We speculated that the counter anion influenced the catalytic activity. Noteworthily, if the photocatalyst of $Ru(bpy)_3Cl_2$ was removed, we did not obtain the designed product (entry 8). Also, when no light was used to irradiate the reaction, the oxidation product could not be obtained (entry 9). Moreover, catalytic amount of $LiOBu^t$ seems to be essential to achieve a high yield, and 18% yield was produced in the absence of $LiOBu^t$ (entry 10). Then, we evaluated different solvents for cooperative catalysis. DMF gave comparative yield 75% (entry 11), but only 5% of product was produced in MeCN (entry 12). Finally, the concentration of reaction mixture slightly influenced the results, and the yield can be improved to 82% in 1.2mL of DMSO (entry 13).

**Table 2**. Optimization of the cooperative catalysis of $Ru(bpy)_3Cl_2$ and copper in the aerobic oxidation of amine to nitrile reaction [a]



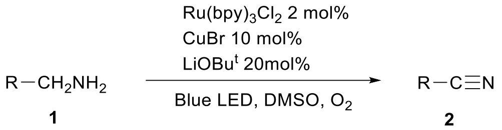
**1a** **2a**

| Entry | Photocatalyst | Copper catalyst | Solvent | **2a**/%[b] |
|---|---|---|---|---|
| 1 | $Ru(bpy)_3Cl_2 \cdot 6H_2O$ | CuI | DMSO | 67 |
| 2 | $Ru(bpy)_3Cl_2 \cdot 6H_2O$ | CuBr | DMSO | 77 |
| 3 | $Ru(bpy)_3Cl_2 \cdot 6H_2O$ | CuCl | DMSO | 68 |
| 4 | $Ru(bpy)_3Cl_2 \cdot 6H_2O$ | $CuBr_2$ | DMSO | 29 |
| 5 | $Ru(bpy)_3Cl_2 \cdot 6H_2O$ | $CuCl_2$ | DMSO | 17 |
| 6 | $Ru(bpy)_3Cl_2 \cdot 6H_2O$ | $Cu(NO_3)_2$ | DMSO | 42 |
| 7 | $Ru(bpy)_3Cl_2 \cdot 6H_2O$ | $Cu(OAc)_2$ | DMSO | 71 |
| 8 | - | CuBr | DMSO | 0 |
| 9 | $Ru(bpy)_3Cl_2 \cdot 6H_2O$ | CuBr | DMSO | 0[c] |
| 10 | $Ru(bpy)_3Cl_2 \cdot 6H_2O$ | CuBr | DMSO | 18[d] |
| 11 | $Ru(bpy)_3Cl_2 \cdot 6H_2O$ | CuBr | DMF | 75 |
| 12 | $Ru(bpy)_3Cl_2 \cdot 6H_2O$ | CuBr | MeCN | 5 |
| 13 | $Ru(bpy)_3Cl_2 \cdot 6H_2O$ | CuBr | DMSO | **82**[e], 73[f] |

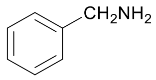
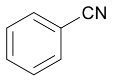
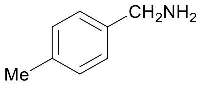
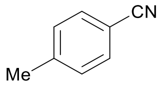
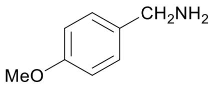
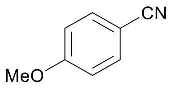
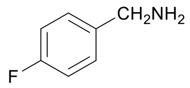
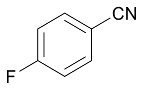
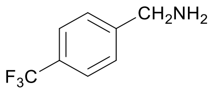
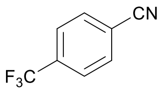
[a] Reaction conditions: benzyl amine **1** 0.2 mmol, copper catalyst 10 mol%, $Ru(bpy)_3Cl_2 \cdot 6H_2O$ 2 mol%, $LiOBu^t$ 20 mol%, solvent 1.6 mL, room temperature, time 18 h. [b] GC yield. [c] No light and the ambient is dark. [d] $LiOBu^t$ is free. [e] the volume of solvent is 1.2mL. [f] the volume of solvent is 1.0 mL.

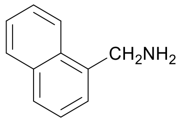
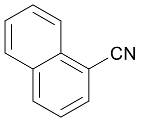
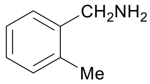
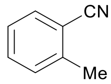
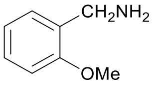
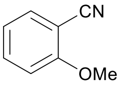
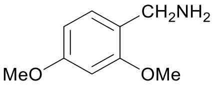
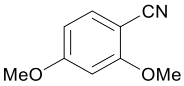
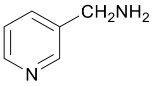
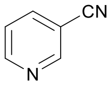
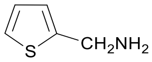
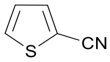
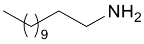
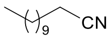
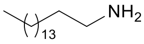
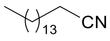
The above results show that $Ru(bpy)_3Cl_2/CuBr/LiOBu^t/DMSO$ is an efficient combination for the synthesis of nitriles from amines. Using the optimized conditions, we next explored the scope and generality of the process (Table 3). It was found that benzylic amines carrying electron-donating and electron-withdrawing groups could be smoothly converted into the desired products with good to excellent isolated yields (up to 95%, entries 1–5). Benzylic amines carrying an ortho-substituent were also found to readily participate in the reaction (83–94%, entries 6–9). Electron-donating and electron-withdrawing groups, ranging from −OMe to $-CF_3$ groups, were well tolerated in the reactions. The catalyst is also tolerant of molecules containing heteroatoms such as nitrogen and sulfur. Heteroatom-containing amines reacted smoothly to afford the corresponding nitriles in moderate yields (50–63%, entries 10, 11). In addition, aliphatic amines also could be converted into nitriles under the standard conditions, and good yields were obtained by increasing the reaction time (entries 12, 13).

**Table 3.** Substrates scope of the visible-light-induced aerobic oxidation of amine to nitrile reaction [a]



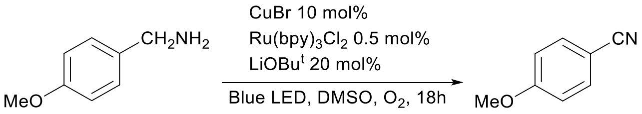
**1** **2**

| Entry | 1 | 2 | Yield/% [b] |
|---|---|---|---|
| 1 |  **1a** |  **2a** | 78 |
| 2 |  **1b** |  **2b** | 77 |
| 3 |  **1c** |  **2c** | 95 [c] |
| 4 |  **1d** |  **2d** | 45(65)[d] |
| 5 |  **1e** |  **2e** | 66(85)[d] |

| | | | |
|---|---|---|---|
| 6 |  **1f** |  **2f** | 83 |
| 7 |  **1g** |  **2g** | 73(94)[d] |
| 8 |  **1h** |  **2h** | 93 [c] |
| 9 |  **1i** |  **2i** | 88 |
| 10 |  **1j** |  **2j** | 63 |
| 11 |  **1k** |  **2k** | 50[d,e] |
| 12 |  **1l** |  **2l** | 61[e] |
| 13 |  **1m** |  **2m** | 64[e] |

[a] reaction conditions: amine **1** 0.5 mmol, CuBr 10 mol%, $Ru(bpy)_3Cl_2{\cdot}6H_2O$ 2 mol%, $LiOBu^t$ 20 mol%, DMSO 3.0 mL, room temperature, time 18 h. [b] Isolated yield. [c] Volume of DMSO = 1 mL. [d] GC yield. [e] Reaction time = 36 h.

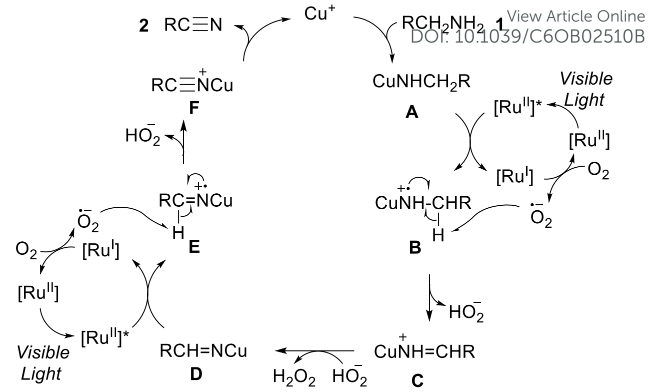
The new amine oxidation method was effective on a larger scale (Scheme 2): amine **1c** underwent efficient oxidation on a 10 mmol scale, resulting in an 86% isolated yield of the nitrile, even with decreased photocatalyst loading (0.5 mol %).



**1c**, 10mmol, 1.37g **2c**, 86%, 1.14g

**Scheme 2** Gram-scale synthesis of nitrile

While a precise reaction mechanism awaits further study, a plausible catalytic cycle is proposed in Scheme 3. Initially, the copper(I) catalyst underwent ligand exchange to generate copper amide **A**.[12c,12d] Reductive quenching of $^*[Ru(bpy)_3]^{2+}$ by the amide **A** gave intermediate **B** and $[Ru(bpy)_3]^+$ which reduce molecular oxygen to the superoxide radical anion.[13] Then, the superoxide radical anion abstracts a hydrogen atom from the radial cation **B** to form intermediate **C**.[13a,13b] The iminium ion **C** was neutralized by a hydrogen peroxide anion to produce copper amide **D**. The second reductive quenching cycle happened to convert intermediate **D** into radial cation **E**. The hydrogen atom of imine radial cation **E** was grabbed by a superoxide radical anion to form intermediate **F**, which furnished the desired product nitrile **1** and a copper(I) salt.



**Scheme 3** Plausible reaction mechanism.

## Conclusions

To summarize, in the present study we developed a visible-light-initiated homogeneous oxidative synthesis of nitriles from amines. Through the combination of photoredox and copper catalysis, the conversion of amines into nitriles was realized with $O_2$ as the oxidant. This new protocol combines copper with photoredox in a single reaction system and shows great substrate tolerance providing efficient access to a variety of nitriles in a highly concise fashion. Further studies on the mechanism of this visible-light mediated process is underway.

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