

# Copper-Catalyzed Aerobic Oxidative Cross-Dehydrogenative Coupling of Amine and $\alpha$ -Carbonyl Aldehyde: A Practical and Efficient Approach to $\alpha$ -Ketoamides with Wide Substrate Scope

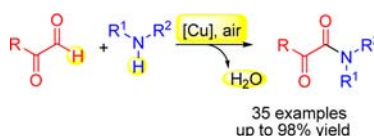
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## ABSTRACT



A copper-catalyzed aerobic oxidative cross-dehydrogenative coupling (CDC) of amine with  $\alpha$ -carbonyl aldehyde has been developed. Many types of amines are tolerant in this transformation leading to various  $\alpha$ -ketoamides compounds. Wide substrate scope, CDC strategy and using air as oxidant make this transformation highly efficient and practical. Molecular oxygen acts not only as the oxidant, but also as an initiator to trigger this catalytic process. Furthermore, mechanism studies show that carbonyl group of  $\alpha$ -carbonyl aldehyde plays a role as the directing group to facilitate this chemical process.

$\alpha$ -Ketoamides have attracted considerable attention not only because of their remarkable biological and pharmacological activity but also because of their wide application as useful precursors for a variety of functional group transformations.<sup>1</sup> Consequently, numerous synthetic methodologies for the construction of this important unit

have been developed in the past decades.<sup>2</sup> Recently, aerobic oxidative cross-dehydrogenative coupling (CDC) reactions have presented one of the most attractive and powerful strategies for C–C and C–X bond formation.<sup>3,4</sup> In the context of CDC strategy, three kinds of oxidative

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approaches to  $\alpha$ -ketoamides have been developed employing molecular oxygen<sup>5</sup> as the oxidant.<sup>6–8</sup>

Despite the environmentally benign character and the efficiency of these methods, the substrate scope still remains as a challenge: (1) *N*-Unsubstituted anilines are required in the reaction of amidation–diketonization of terminal alkynes (method 1, Scheme 1).<sup>6</sup> (2) Aliphatic amines do not work in the reaction of aryl acetaldehydes with anilines (method 2, Scheme 1).<sup>7</sup> (3) Only aliphatic secondary amines work in the coupling reaction of aryl methyl ketones with amines (method 3, Scheme 1).<sup>8</sup> Thus, many important  $\alpha$ -ketoamides could not be afforded by these methods.<sup>6–8</sup> Furthermore, pure molecular oxygen is required in all these three methods for high efficiency. Therefore, development of a more practical approach with broad substrate scope compatible with various amines is still attractive. Herein, we report a practical and efficient Cu-catalyzed CDC of  $\alpha$ -carbonyl aldehyde with a variety of amines using air as the oxidant (Scheme 1).

Interestingly, when CuBr was used as the catalyst, the cross-dehydrogenative coupling of 4-aminobenzonitrile (**1a**) with phenylglyoxal monohydrate (**2a**) afforded the desired *N*-(4-cyanophenyl)-2-oxo-2-phenylacetamide (**3aa**) in 81% yield (entry 1, Table S1). Other copper catalysts including Cu(II) salts gave low efficiencies (entries 1–3, Table S1, and Supporting Information). This reaction nearly did not work in the absence of Cu catalyst (entry 4, Table S1). The reactions gave low yields, respectively, in CH<sub>3</sub>CN, DMF, or other solvents (entries 1, 5, and 6,

**Scheme 1.** Methods of Synthesis of  $\alpha$ -Ketoamides

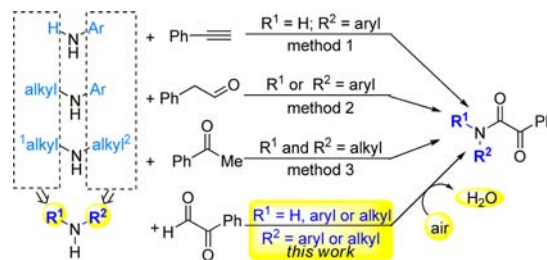


Table S1, and Supporting Information). Further studies indicated that base can promote this transformation (entries 1, 7, and 8, Table S1, and Supporting Information). Furthermore, some ligands could affect this transformation (entries 1 and 9–11, table S1, and Supporting Information). Among these ligands, 2,2'-bipyridine is the best for improving the yield of **3aa** to 91% (entries 9, Table S1).

Under these optimized conditions, the scope of substituted amines (**1**) was investigated (Scheme 2). Both electron-rich and electron-deficient anilines could be smoothly transformed into the desired products (**3aa–qa**, Scheme 2). Furthermore, substituents at different positions of the arene group (*para*-, *meta*-, and *ortho*-position) did not affect the efficiency (**3aa–ca**, Scheme 2). Halo-substituted aryl acetaldehydes survived well leading to halo-substituted products (**3fa–ha** and **3ja–la**, Scheme 2). It is noteworthy that *N*-substituted anilines such as *N*-methyl-, *N*-ethyl-, and *N*-phenylaniline could be smoothly transformed into the desired products (**3oa–qa**, Scheme 2). Furthermore, aliphatic secondary amines also worked well to afford the desired products in good to excellent yields (**3ra–ua**, Scheme 2). Using pure oxygen as oxidant, *N*-substituted anilines and aliphatic secondary amines afforded higher yields of desired products than under air conditions (**3oa**, **3pa**, and **3ra**). Notably, the scope of substituted amines could expand to the aliphatic primary amine, which could not be achieved by the reported three aerobic oxidative approaches (Scheme 1). For example, **1v** coupling with **2a** could produce the desired product (**3va**) in 34% yield (Scheme 2).

The scope of the Cu-catalyzed aerobic oxidative dehydrogenative functionalization was further expanded to a variety of substituted  $\alpha$ -carbonyl aldehydes **2** (Table 1). Both anilines (**1a**) and aliphatic amines (**1r**) reacted with aldehyde (**2**), respectively, leading to good to excellent yields of desired products (**3aa–ag** and **3ra–rf**, Table 1). Furthermore, aryl  $\alpha$ -carbonyl aldehyde with both electron-donating and electron-withdrawing groups did not affect the efficiency of this transformation (Table 1).

$\alpha$ -Ketoamides are ubiquitous structural motifs that can be found in many drugs and bioactive compounds.<sup>1</sup> The present method, which affords  $\alpha$ -ketoamides with wide substrate scope, provides a green and easily practical protocol for the construction of biologically active compounds from simple and readily available starting

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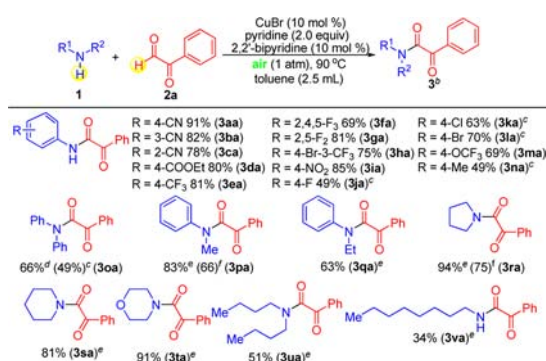
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**Scheme 2.** Cu-Catalyzed Aerobic Oxidative Cross-Dehydrogenative Coupling of Different Amine (**1**) with **2a**<sup>a</sup>

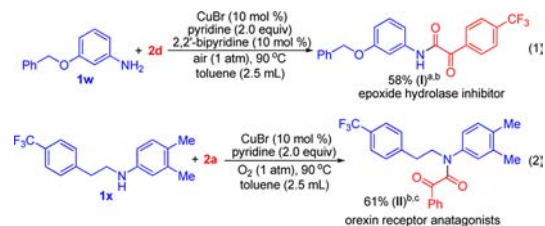


<sup>a</sup>Standard reaction conditions: see entry 9, Table S1. <sup>b</sup>Isolated yields. <sup>c</sup>The reactions were carried in out the absence of ligand. <sup>d</sup>The reactions were carried in the absence of ligand using O<sub>2</sub> (1 atm) as the oxidant. <sup>e</sup>**1** (0.375 mmol), **2a** (0.25 mmol) were employed in the absence of ligand using O<sub>2</sub> (1 atm) as the oxidant. <sup>f</sup>**1** (0.375 mmol), **2a** (0.25 mmol) were employed in the absence of ligand using air (1 atm) as the oxidant.

materials. For example, **I**, which is reported as an epoxide hydrolase inhibitor (1, Scheme 3),<sup>1a</sup> can be easily synthesized from **1w** and **2d** in 58% yields (1, Scheme 3). Furthermore, **II**, which is reported as an orexin receptor antagonist (2, Scheme 3),<sup>1b</sup> can be easily synthesized from simple **1x** and **2a** in 61% yields (2, Scheme 3).

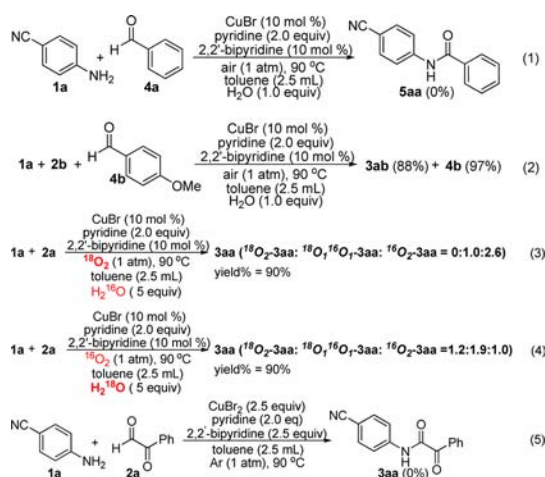
Aldehydes are desirable starting materials in amide synthesis due to their ready availability and nontoxic nature.<sup>9</sup> In the past 10 years, catalytic systems to effect this transformation have been substantially developed into useful organic reactions.<sup>9</sup> However, under the standard reaction conditions, 4-aminobenzonitrile (**1a**) and benzaldehyde (**4a**) did not afford the desired product 4-cyanophenyl benzoate **5aa** (eq 1), which illustrates that this new method underwent different reaction process in contrast to previous reported C–N coupling of aldehydes.<sup>10</sup> Furthermore, the reaction of **1a** with **2b** in the presence of 4-methoxybenzaldehyde (**4b**) produced **3ab** in 88% yield with 97% of **4b** recovery (eq 2). The above results

**Scheme 3.** Construction of Some Bioactive Compounds



<sup>a</sup>Standard reaction conditions: see entry 9, Table S1. <sup>b</sup>Isolated yields. <sup>c</sup>**1x** (0.375 mmol), **2a** (0.25 mmol), CuBr (0.025 mmol), pyridine (0.5 mmol), toluene (2.5 mL), 60 °C, O<sub>2</sub> (1 atm), 12 h.

demonstrate that the α-carbonyl group of α-carbonyl aldehyde plays the role of a directing group to facilitate this chemical process.



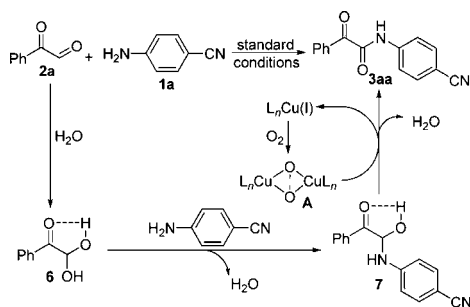
The transformation of **1a** and **2a** in the presence of <sup>18</sup>O<sub>2</sub> (1 atm) and 1.25 mmol of H<sub>2</sub><sup>16</sup>O generated **3aa** in 90% yield (<sup>18</sup>O-<sup>16</sup>O-**3aa**:<sup>16</sup>O<sub>2</sub>-**3aa** = 1.0:2.6; <sup>18</sup>O<sub>2</sub>-**3aa** was not detected in the reaction system) (eq 3). When the reaction of **1a** and **2a** in the presence of <sup>16</sup>O<sub>2</sub> (1 atm) and

**Table 1.** Cu-Catalyzed Aerobic Oxidative Cross-Dehydrogenative Coupling of **1a** and **1r** with Different Aldehydes **2a**<sup>a</sup>

entry	<b>1</b>	R <sup>3</sup>	yield of <b>3</b> <sup>b</sup> (%)	entry	<b>1</b>	R <sup>3</sup>	yield of <b>3</b> <sup>b</sup> (%)
1	<b>1a</b>	C <sub>6</sub> H <sub>5</sub> – ( <b>2a</b> )	91 ( <b>3aa</b> )	8	<b>1r</b>	C <sub>6</sub> H <sub>5</sub> – ( <b>2a</b> )	94 ( <b>3ra</b> ) <sup>c</sup>
2	<b>1a</b>	4-OMeC <sub>6</sub> H <sub>4</sub> – ( <b>2b</b> )	89 ( <b>3ab</b> )	9	<b>1r</b>	4-OMeC <sub>6</sub> H <sub>4</sub> – ( <b>2b</b> )	93 ( <b>3rb</b> ) <sup>c</sup>
3	<b>1a</b>	3,4,5-(OMe) <sub>3</sub> C <sub>6</sub> H <sub>2</sub> – ( <b>2c</b> )	94 ( <b>3ac</b> )	10	<b>1r</b>	3,4,5-(OMe) <sub>3</sub> C <sub>6</sub> H– ( <b>2c</b> )	90 ( <b>3rc</b> ) <sup>c</sup>
4	<b>1a</b>	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> – ( <b>2d</b> )	65 ( <b>3ad</b> )	11	<b>1r</b>	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> – ( <b>2d</b> )	81 ( <b>3rd</b> ) <sup>c</sup>
5	<b>1a</b>	4-FC <sub>6</sub> H <sub>4</sub> – ( <b>2e</b> )	63 ( <b>3ae</b> )	12	<b>1r</b>	4-FC <sub>6</sub> H <sub>4</sub> – ( <b>2e</b> )	98 ( <b>3re</b> ) <sup>c</sup>
6	<b>1a</b>	3-FC <sub>6</sub> H <sub>4</sub> – ( <b>2f</b> )	61 ( <b>3af</b> )	13	<b>1r</b>	3-FC <sub>6</sub> H <sub>4</sub> – ( <b>2f</b> )	97 ( <b>3rf</b> ) <sup>c</sup>
7	<b>1a</b>	2,4-F <sub>2</sub> C <sub>6</sub> H <sub>3</sub> – ( <b>2g</b> )	98 ( <b>3ag</b> )				

<sup>a</sup>Standard reaction conditions: see entry 9, Table S1. <sup>b</sup>Isolated yields. <sup>c</sup>**1** (0.375 mmol) and **2a** (0.25 mmol) were employed in the absence of ligand using O<sub>2</sub> (1 atm) as the oxidant.

#### Scheme 4. Proposed Mechanism for Direct Transformation



1.25 mmol  $\text{H}_2^{18}\text{O}$ , **3aa** was obtained in 90% yield ( $^{18}\text{O}_2\text{-3aa}:\text{}^{18}\text{O}^{16}\text{O-3aa}:\text{}^{16}\text{O}_2\text{-3aa} = 1.2:1.9:1.0$ ) (eq 4). It should be noted that the  $\alpha$ -ketone at ketoamide **3** is very active and undergoes oxygen exchange via hemiketal with water. In contrast, the carbonyl of amide hardly exchanges with water. Therefore, the above results indicate that the oxygen atom of the  $\alpha$ -ketoamide originated from substrate **2** and/or  $\text{H}_2\text{O}$  (for details, see the Supporting Information). Furthermore, the desired product **3aa** was not detected when the reaction of **1a** and **2a** was

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carried out under Ar, even employing 2.5 equiv of  $\text{CuBr}_2$  (eq 5). This result shows that molecular oxygen plays a role not only as the oxidant but also as an initiator to trigger this catalytic process. Encouraged by the growing amount of information about Cu(I)–dioxygen reactivity,<sup>11</sup> we hypothesized that a  $(\mu-\eta^2:\eta^2\text{-peroxy})$ -dicopper(II) complex **A** (Scheme 4) might be the active catalytic species, which was produced in situ through the reaction of Ln–Cu(I) complex with  $\text{O}_2$  on the basis of the previous reports.<sup>11</sup>

On the basis of the above results, a plausible mechanism for the copper-catalyzed aerobic oxidative cross-dehydrogenative coupling is illustrated in Scheme 3. Phenylglyoxal **2a** reacts with  $\text{H}_2\text{O}$  to form phenylglyoxal monohydrate **6**.<sup>12</sup> Facilitated by the carbonyl group of  $\alpha$ -carbonyl aldehyde, the addition of amine to aryl glyoxal gave hemiaminal intermediate **7**.<sup>10</sup> At the same time, Cu(I) salt was initially chelated with ligand and oxidized by dioxygen to form the more active  $(\mu-\eta^2:\eta^2\text{-peroxy})$ -dicopper(II) complex **A**.<sup>11</sup> Subsequently, intermediate **7** was oxidized by copper complex to produce  $\alpha$ -ketoamide **3aa**.<sup>13</sup>

In conclusion, we have demonstrated a novel copper-catalyzed aerobic oxidative cross-dehydrogenative coupling (CDC) of amine with  $\alpha$ -carbonyl aldehyde. This method provides an efficient approach to  $\alpha$ -ketoamides compounds, which are ubiquitous structural units in a number of biologically active compounds. Wide substrate scope, CDC strategy, and use of air as oxidant are the advantages of this highly efficient and practical method. Molecular oxygen acts not only as the oxidant but also as an initiator to trigger this catalytic process. Furthermore, mechanism studies show that the carbonyl group of  $\alpha$ -carbonyl aldehyde plays a role as a directing group to facilitate this chemical process.

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**Supporting Information Available.** Experimental details and NMR spectra analysis of the products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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The authors declare no competing financial interest.