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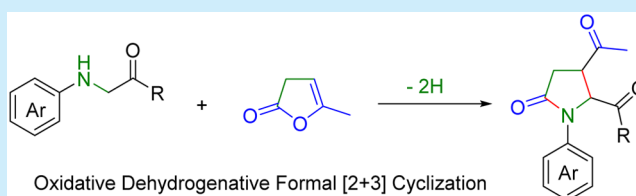
# Copper-Catalyzed Aerobic Oxidative Dehydrogenative Formal [2 + 3] Cyclization of Glycine Esters with $\alpha$ -Angelicalactone: Approach To Construct Polysubstituted Pyrrolidones

Congde Huo,\* Yong Yuan, Fengjuan Chen, Jing Tang, and Yajun Wang

Key Laboratory of Eco-Environment-Related Polymer Materials Ministry of Education, College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou, Gansu 730070, China

## S Supporting Information

**ABSTRACT:** A novel and efficient copper-catalyzed aerobic oxidative dehydrogenative formal [2 + 3] cyclization of glycine derivatives with  $\alpha$ -angelicalactone is described. A series of complex pyrrolidones were produced under mild and simple reaction conditions.



In the current century, oxidative dehydrogenative coupling reactions have emerged as a powerful tool for the construction of complex molecules from simple starting materials in an atom-economic and concise way.<sup>1,2</sup> Glycine is the simplest and cheapest natural amino acid on earth.  $\alpha$ -C–H functionalizations of glycine would provide a direct way to generate various  $\alpha$ -amino acid derivatives.<sup>3</sup> For this reason, the oxidative dehydrogenative  $\alpha$ -C–H functionalizations of glycine derivatives have gained significant attention since the pioneering work developed by Li et al. in 2008.<sup>4</sup> Coupling of glycine derivatives with quite a few nucleophiles such as ketones,  $\beta$ -ketoesters, malonates, 2-methylquinolines, allylstannanes, indoles, alkynes, and aryl boronic acids have been reported.<sup>5</sup> In 2011, an oxidative Povarov/aromatization tandem reaction of *N*-aryl glycine derivatives with electron-rich alkenes was first presented by Manchego et al.<sup>6</sup> Interesting progress has been achieved in this area since then. For example, our group developed the above-mentioned [4 + 2] tandem process under the auto-oxidation conditions in 2014.<sup>7</sup> The reaction was performed in the absence of any redox-active catalyst and chemical oxidant under mild conditions. This methodology was applied to the auto-oxidative coupling of glycine derivatives with indoles too. As stated above, the so far reported oxidative dehydrogenative reactions of glycine derivatives can be mainly classified into two categories: (1) direct oxidative dehydrogenative coupling of glycine derivatives with nucleophiles to prepare complex  $\alpha$ -amino acid derivatives; (2) oxidative dehydrogenative [4 + 2] cyclization of glycine derivatives with electron-rich multiple bonds to form substituted quinoline motifs. Therefore, the development of a new type of oxidative dehydrogenative reaction of glycine derivatives is highly desirable. In the past year, Xiao et al. reported a visible-light-induced aerobic oxidation/[3 + 2] cycloaddition/aromatization cascade reaction between glycine derivatives and isocyanides to construct substituted imidazoles (5-membered heterocycle with 2 N atoms).<sup>8</sup> Very recently, Liu et al. also developed a copper-catalyzed aerobic oxidation/[3 + 2]

cycloaddition/oxidative aromatization tandem reaction of glycine derivatives with ethyl diazoacetate to form 1,2,3-triazoles (5-membered heterocycle with 3 N atoms).<sup>9</sup> Polysubstituted pyrrolidones are valuable five-membered heterocycles and widely present in natural products and pharmaceutical drugs, which are associated with a broad spectrum of biological activities.<sup>10</sup> Therefore, exploration of new synthesis methods for these heterocycle skeletons from easily accessible starting materials with a simple operation is of great significance. Herein, in this letter, we detail a novel copper-catalyzed aerobic oxidative dehydrogenative formal [2 + 3] cyclization of glycine derivatives with  $\alpha$ -angelicalactone that provides an efficient access to complex pyrrolidones (5-membered heterocycle with 1 N atom) under mild and simple reaction conditions (Scheme 1).

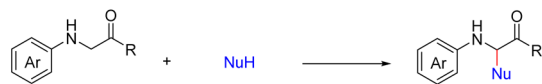
At the outset, glycine ester (**1a**) and  $\alpha$ -angelicalactone (**2**) were selected as the model substrates to optimize the reaction conditions, including the catalysts, oxidants, additives, reaction solvents, and the loadings of the catalyst and oxidant. We first compared different oxidants (Table 1, entries 1–6), and to our delight, it was found that the reaction afforded the desired product **3a** in high yields by employing CuCl<sub>2</sub> (5 mol %) as a catalyst and H<sub>2</sub>SO<sub>4</sub> (10M, 50 mol %) as an additive in acetonitrile at room temperature using air, O<sub>2</sub>, or TBHP as the oxidant after 24 h. **3a** was obtained as a pair of unseparable diastereoisomers (5:1). The diastereomeric ratio was determined by <sup>1</sup>H NMR spectroscopic analysis of the crude reaction mixtures, and the trans-isomer was identified as the major stereoisomer in accordance with the literature.<sup>11</sup> Air was chosen for the further reaction conditions screening due to the requirement of green chemistry.<sup>12</sup> A range of copper salts (Table 1, entries 8–11) were investigated, and all displayed lower effectiveness than CuCl<sub>2</sub>; iron salts (Table 1, entries 12, 13) showed almost no catalytic activity in this reaction. Notably, the use of CuCl gave similar

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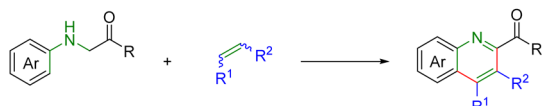
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## Scheme 1. Oxidative Dehydrogenative Reaction of Glycine Derivatives

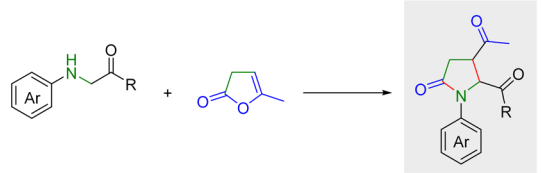
Since 2008, Oxidative Dehydrogenative Coupling of Glycine Derivatives



Since 2011, Oxidative Dehydrogenative [4+2] Cyclization of Glycine Derivatives



This work: Oxidative Dehydrogenative [2+3] Cyclization of Glycine Derivatives



results to  $\text{CuCl}_2$ , thus demonstrating that both  $\text{Cu(II)}$  and  $\text{Cu(I)}$  catalyst precursors were able to facilitate this transformation. It is possible that the conversion between  $\text{Cu(II)}$  and  $\text{Cu(I)}$  species might occur during this reaction process.<sup>13</sup> Afterward, the study of other usually used promoters (Table 1, entries 14–16) showed that triarylaminium salt, CAN, and DDQ could not give a superior yield. Reducing or increasing the amount of  $\text{CuCl}_2$  led to decreased yields (Table 1, entries 17, 18). A lower yield was also observed when the amount of  $\text{H}_2\text{SO}_4$  was decreased or increased (Table 1, entries 19, 20). Following this result, other Bronsted acids ( $\text{HCl}$ ,  $\text{HBr}$ ,  $\text{PTSA}$ ,  $\text{TFA}$ ,  $\text{TfOH}$ ) were tested as additives; however, no further increase of the yields was observed (Table 1, entries 21–25). A series of solvents were screened for the reaction (Table 1, entries 26–29), and MeCN proved to be the best choice for the transformation. Accordingly, the optimized conditions were as follows:  $\text{CuCl}_2$  (5 mol %),  $\text{H}_2\text{SO}_4$  (10 M, 50 mol %), acetonitrile as the solvent at room temperature under an air atmosphere.

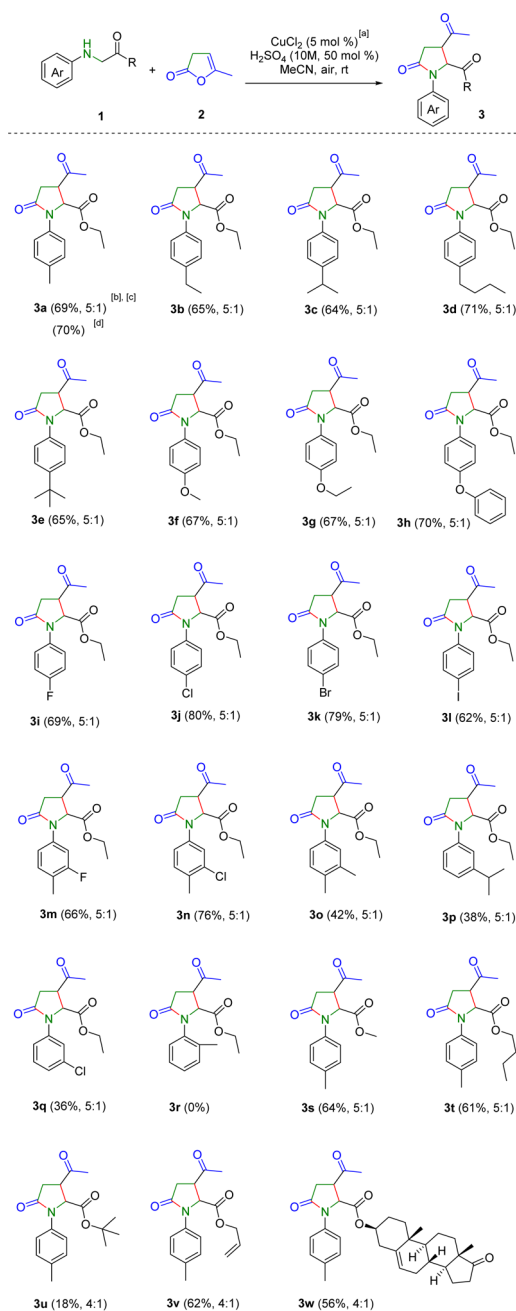
With the best reaction conditions established, the scope and generality of the copper-catalyzed aerobic oxidative dehydrogenative formal [2 + 3] cyclization reaction is illustrated in Scheme 2. Gratefully, our method was successfully amenable to a wide range

Table 1. Screening of Reaction Conditions<sup>a</sup>

entry	solvent	catalyst	additive	oxidant	3aa (yield %) <sup>b</sup>
1 <sup>c</sup>	$\text{CH}_3\text{CN}$	$\text{CuCl}_2$ (5 mol %)	$\text{H}_2\text{SO}_4$ (10 M, 50 mol %)	DDQ (1.0 equiv)	trace
2 <sup>c</sup>	$\text{CH}_3\text{CN}$	$\text{CuCl}_2$ (5 mol %)	$\text{H}_2\text{SO}_4$ (10 M, 50 mol %)	TBPH (1.0 equiv)	64
3 <sup>c</sup>	$\text{CH}_3\text{CN}$	$\text{CuCl}_2$ (5 mol %)	$\text{H}_2\text{SO}_4$ (10 M, 50 mol %)	DTBP (1.0 equiv)	trace
4 <sup>c</sup>	$\text{CH}_3\text{CN}$	$\text{CuCl}_2$ (5 mol %)	$\text{H}_2\text{SO}_4$ (10 M, 50 mol %)	TBPB (1.0 equiv)	38
5 <sup>d</sup>	$\text{CH}_3\text{CN}$	$\text{CuCl}_2$ (5 mol %)	$\text{H}_2\text{SO}_4$ (10 M, 50 mol %)	$\text{O}_2$	68
6	$\text{CH}_3\text{CN}$	$\text{CuCl}_2$ (5 mol %)	$\text{H}_2\text{SO}_4$ (10 M, 50 mol %)	air	69
7	$\text{CH}_3\text{CN}$	$\text{CuCl}_2$ (5 mol %)	$\text{H}_2\text{SO}_4$ (10 M, 50 mol %)	Ar	—
8	$\text{CH}_3\text{CN}$	$\text{CuCl}$ (5 mol %)	$\text{H}_2\text{SO}_4$ (10 M, 50 mol %)	air	65
9	$\text{CH}_3\text{CN}$	$\text{CuBr}_2$ (5 mol %)	$\text{H}_2\text{SO}_4$ (10 M, 50 mol %)	air	36
10	$\text{CH}_3\text{CN}$	$\text{Cu(OAc)}_2$ (5 mol %)	$\text{H}_2\text{SO}_4$ (10 M, 50 mol %)	air	35
11	$\text{CH}_3\text{CN}$	$\text{Cu(OTf)}_2$ (5 mol %)	$\text{H}_2\text{SO}_4$ (10 M, 50 mol %)	air	32
12	$\text{CH}_3\text{CN}$	$\text{FeCl}_3$ (5 mol %)	$\text{H}_2\text{SO}_4$ (10 M, 50 mol %)	air	trace
13	$\text{CH}_3\text{CN}$	$\text{FeCl}_2$ (5 mol %)	$\text{H}_2\text{SO}_4$ (10 M, 50 mol %)	air	trace
14	$\text{CH}_3\text{CN}$	TBPA (5 mol %)	$\text{H}_2\text{SO}_4$ (10 M, 50 mol %)	air	40
15	$\text{CH}_3\text{CN}$	CAN (100 mol %)	$\text{H}_2\text{SO}_4$ (10 M, 50 mol %)	air	33
16	$\text{CH}_3\text{CN}$	DDQ (100 mol %)	$\text{H}_2\text{SO}_4$ (10 M, 50 mol %)	air	trace
17	$\text{CH}_3\text{CN}$	$\text{CuCl}_2$ (1 mol %)	$\text{H}_2\text{SO}_4$ (10 M, 50 mol %)	air	56
18	$\text{CH}_3\text{CN}$	$\text{CuCl}_2$ (10 mol %)	$\text{H}_2\text{SO}_4$ (10 M, 50 mol %)	air	49
19	$\text{CH}_3\text{CN}$	$\text{CuCl}_2$ (5 mol %)	$\text{H}_2\text{SO}_4$ (10 M, 40 mol %)	air	67
20	$\text{CH}_3\text{CN}$	$\text{CuCl}_2$ (5 mol %)	$\text{H}_2\text{SO}_4$ (10 M, 60 mol %)	air	66
21	$\text{CH}_3\text{CN}$	$\text{CuCl}_2$ (5 mol %)	$\text{HCl}$ (conc, 100 mol %)	air	38
22	$\text{CH}_3\text{CN}$	$\text{CuCl}_2$ (5 mol %)	$\text{HBr}$ (conc, 100 mol %)	air	9
23	$\text{CH}_3\text{CN}$	$\text{CuCl}_2$ (5 mol %)	$\text{PTSA}$ (100 mol %)	air	60
24	$\text{CH}_3\text{CN}$	$\text{CuCl}_2$ (5 mol %)	$\text{TFA}$ (100 mol %)	air	42
25	$\text{CH}_3\text{CN}$	$\text{CuCl}_2$ (5 mol %)	$\text{TfOH}$ (100 mol %)	air	24
26	$\text{CH}_2\text{Cl}_2$	$\text{CuCl}_2$ (5 mol %)	$\text{H}_2\text{SO}_4$ (10 M, 50 mol %)	air	29
27	THF	$\text{CuCl}_2$ (5 mol %)	$\text{H}_2\text{SO}_4$ (10 M, 50 mol %)	air	trace
28	toluene	$\text{CuCl}_2$ (5 mol %)	$\text{H}_2\text{SO}_4$ (10 M, 50 mol %)	air	trace
29	$\text{H}_2\text{O}$	$\text{CuCl}_2$ (5 mol %)	$\text{H}_2\text{SO}_4$ (10 M, 50 mol %)	air	—

<sup>a</sup>Reaction conditions: **1a** (1.0 mmol), **2** (2.0 mmol), solvent (20 mL), rt, air, 24 h. <sup>b</sup>Isolated yields of the isolated products. <sup>c</sup>Under an Ar atmosphere. <sup>d</sup> $\text{O}_2$  balloon.

### Scheme 2. Copper-Catalyzed Aerobic Oxidative Dehydrogenative Formal [2 + 3] Cyclization Reaction of Glycine Esters with $\alpha$ -Angelicalactone<sup>a</sup>



<sup>a</sup>Reaction conditions: **1** (1 mmol), **2** (2 mmol), CuCl<sub>2</sub> (5 mol %), H<sub>2</sub>SO<sub>4</sub> (10 M, 50 mol %), MeCN (20 mL), air, rt, 5–24 h. <sup>b</sup>Yield of the isolated product. <sup>c</sup>Diastereomeric ratio. <sup>d</sup>Gram scale.

of glycine esters. It was observed that the desired *N*-aryl pyrrolidones were obtained in good to high yields with both electron-donating and -withdrawing groups on the *para*-position of the phenyl ring of **1** (Scheme 2, **3a–3l**). *meta*-Substituted and polysubstituted glycine esters also delivered the corresponding products in moderate to good yields (Scheme 2, **3m–3q**). This transformation showed satisfactory tolerance of all kinds of halogen atoms (Scheme 2, **3i–3n**, **3q**), which provide useful handles for further transformations. Organic molecules bearing a F atom could also have a significant effect on their

pharmacological properties. Subsequently, substrates with different ester groups were investigated, and the reaction proceeded smoothly to afford the desired products in high yields (Scheme 2, **3a**, **3s–3w**). The allyl group was tolerated in this transformation. It is worth noting that **1w** derived from (+)-dehydroisoandrosterone (DHEA) was also a suitable substrate for the reaction under the standard conditions, affording the desired product **3w** in 56% isolated yield (Scheme 2, **3w**). This product may have potential utilities in pharmaceutical chemistry. To demonstrate the efficiency and practicality of this transformation, a scaled up reaction was performed. Gram-scale synthesis of ethyl 3-acetyl-5-oxo-1-(*p*-tolyl)pyrrolidine-2-carboxylate (**3a**) was achieved in 70% yield.

To investigate the details of the mechanism for this copper catalyzed aerobic oxidative dehydrogenative formal [2 + 3] cyclization of glycine derivatives with  $\alpha$ -angelicalactone, a series of control experiments were carried out (Table 2). First of all, the

Table 2. Control Experiments

substrates	conditions	products
	CuCl <sub>2</sub> (5 mol %) H <sub>2</sub> SO <sub>4</sub> (50 mol %) air, MeCN, rt, 24 h	CuCl <sub>2</sub> (5 mol %) air, MeCN, rt, 24 h
<b>1a</b>	dimer (11%)	imine <b>4</b> (8%) + dimer (trace)
<b>1a</b> + <b>2</b>	<b>3a</b> (69%)	substrates decomposed
<b>1a</b> + <b>2</b>	<b>3a</b> (51%)	substrates decomposed
<b>4</b> + <b>2</b>		<b>3a</b> (44%)

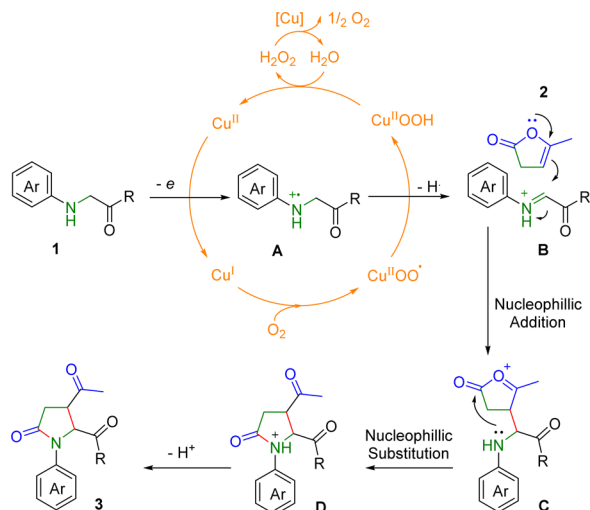
reaction of **1a** in the absence of  $\alpha$ -angelicalactone (**2**) under the standard reaction conditions was investigated. Dimers of **1a** were achieved in low yield. These results indicate that an imine should be an important intermediate in this reaction. Second, in the reaction of **1a** with **2**, compared with the reaction under the standard optimized conditions, glycine ester **1a** was decomposed completely in the absence of H<sub>2</sub>SO<sub>4</sub>. On the other hand, no reaction could be observed in the absence of a copper catalyst. However, in the reaction of imine **4** with **2**, similar yields were achieved with or without a copper catalyst. These results indicate that CuCl<sub>2</sub> is envisioned as an important catalyst for the oxidation of glycine derivatives to generate imine intermediates under aerobic conditions. H<sub>2</sub>SO<sub>4</sub> was utilized as a proton donor to improve the electrophilicity of the imine intermediate and facilitate the following nucleophilic procedures between an imine and  $\alpha$ -angelicalactone. Finally, a radical-trapping experiment was carried out by employing TEMPO as the radical scavenger. Only a trace amount of designed product **3a** was obtained when 1 equiv of TEMPO was added in the reaction of **1a** with **2**. These results suggest that this transformation might proceed through a radical pathway.

Based on the experimental data and precedent literature, a plausible mechanism for this reaction is proposed. The glycine ester **1a** was first oxidized to generate the imine intermediate **A** under copper catalyzed aerobic conditions. The iminium ion intermediate **B** could then be formed through a protonation process from intermediate **A** by H<sub>2</sub>SO<sub>4</sub>. Subsequently, nucleophilic addition of activated intermediate **B** with  $\alpha$ -angelicalactone occurred to give intermediate **C**. Finally, an



intramolecular nucleophilic substitution and the following deprotonation led to product **3a** (Scheme 3).

Scheme 3. Proposed Mechanism of **1a** and **2**



In conclusion, we have achieved a straightforward and efficient copper-catalyzed aerobic oxidative dehydrogenative formal [2 + 3] cyclization of glycine derivatives with  $\alpha$ -angelicalactone. The reaction provides a convenient method for the synthesis of biologically significant multisubstituted pyrrolidone derivatives in an atom-economic manner from easily available starting materials under mild and simple reaction conditions. Further studies on expanding this strategy are currently underway.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01985.

Experimental details, compound characterization, and NMR spectra (PDF)

## ■ AUTHOR INFORMATION

### Corresponding Author

\*E-mail: huocongde1978@hotmail.com.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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