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Aerobic Oxidative Amidation of Aromatic and Cinnamic Aldehydes with Secondary Amines by CuI/2-Pyridonate Catalytic System

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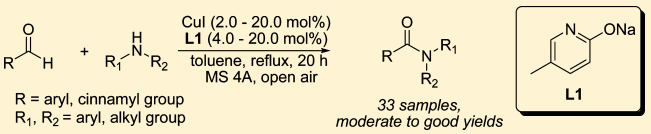
Supporting Information

ABSTRACT: A simple and convenient CuI/2-pyridonate catalytic system for the oxidative amidation of aldehydes with secondary amines has been developed. With this system, a variety of useful arylamides have been synthesized in moderate to good yields in the presence of small amount of copper catalyst and the pyridonate ligand, generating only water as a coproduct. Synthesis of cinnamamides was also achieved by the reactions of cinnamaldehydes with secondary amines in moderate yields. Air was successfully employed as a green oxidant in this catalytic system, achieving a safe and atom-efficient system for the synthesis of amides.



INTRODUCTION

Amides are a basic and highly important class of compounds with a variety of biological activities. Amide moiety can be found in a number of agrochemicals, pharmaceuticals, and polymeric materials.[1] One of the general methods for the synthesis of amides is the condensation of carboxylic acids with amines.[2] Such reactions usually require a high reaction temperature to avoid the formation of stable ammonium salts by the acid−base reaction.[2] The carbodiimide-mediated amidation is another general method for the synthesis of amides.[3] However, generation of a stoichiometric amount of urea derivatives as coproduct leads to the decrease of atom efficiency. Other methods for the synthesis of amides include the aminocarbonylation of haloarenes,[4] the Staudinger ligation,[5] the Schmidt reaction,[6] the Beckmann rearrangement,[7] and the cross-coupling of formamides with aryl/alkyl halides.[8] However, most of these methods generate a large amount of wasteful byproduct and suffer from low atom efficiency. Thus, a more environmentally friendly, safe and highly atom-efficient method for the synthesis of amides is still needed.

In recent years, transition metal (Ru, Rh, La, Pd, and Cu) catalyzed synthesis of amides by the oxidative coupling of alcohols[9] or aldehydes[9d,10−13] with amines have been reported. Although these catalytic systems provide a new route for the synthesis of amides, there are still some problems, such as the use of expensive noble transition metal,[9,10,12] the use of a large excess amount of a substrate,[11] or the need of explosive oxidant (hydrogen peroxide or TBHP),[12,13] remaining to be solved.

Meanwhile, we have recently reported the aerobic dehydrogenative oxidative homocoupling of azoles affording biazoles catalyzed by a copper(I)/2-pyridonate catalytic system.[14] In this system, air could be employed as a green oxidant for the oxidative homocoupling. Here, we report a simple and convenient aerobic oxidative amidation of aldehydes with secondary amines by a CuI/2-pyridonate catalytic system.

RESULTS AND DISCUSSION

First, we examined the oxidative coupling of benzaldehyde (**1a**) with piperidine (**2a**) to give 1-benzoylpiperidine (**3a**) under various conditions in order to find optimal conditions (Table 1). When the reaction of **1a** with **2a** was carried out in toluene under reflux (110 °C) in the presence of CuI (2.0 mol %), sodium 5-methyl-2-pyridonate (**L1**) (4.0 mol %), and molecular sieves 4A for 20 h under air, the formation of the desired amide product **3a** was isolated in 82% yield (entry 1). Employment of other Cu(I) and Cu(II) salts as the catalyst instead of CuI resulted in lower yields (entries 2−7). We also attempted the oxidative amidation of **1a** in other solvents such as *p*-xylene, mesitylene, diglyme, 1,4-dioxane and water. However, all of these reactions gave lower yields than that in toluene.[15]

Next, we examined the effect of ligand added to the reaction (entries 8−14). Sodium 2-pyridonate ligands having an electron-donating substituent on the pyridine ring gave better yields (entries 1, 8−11) than those having an electron-withdrawing substituent (entries 12 and 13). When sodium phenoxide (**L8**) was used instead of **L1**, the oxidative amidation of **1a** with **2a** proceeded in extremely low yield (entry 14), suggesting that the copper complex bearing a 2-pyridonate ligand would act as an important catalytically active species, which was first proposed in our previous report.[14]

When the reaction was carried out under an argon atmosphere, only a trace amount of **3a** could be obtained (entry 15). On the contrary, when the reaction was carried out under an oxygen atmosphere, 86% yield of **3a** was observed (entry 16), indicating that the oxygen in the air must be an important terminal oxidant. The reaction did not proceed well in the absence of CuI or 2-pyridonate ligand (entries 17 and 18). Reaction without the addition of molecular sieves resulted in low yield (entry 19). From the results shown above, we

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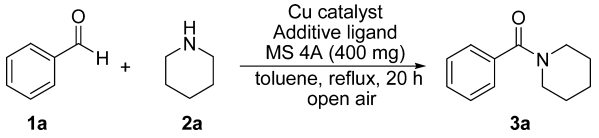
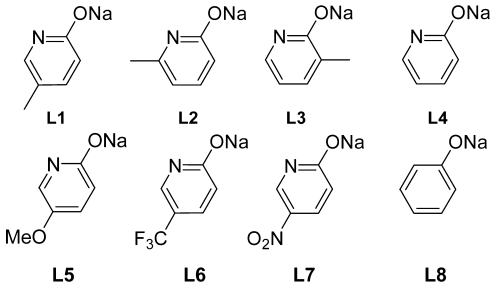
Table 1. Optimization of the Reaction Conditions in the Aerobic Oxidative Amidation of Benzaldehyde (1a) with Piperidine (2a)[a]



1a 2a 3a

entry	catalyst (mol %)	additive ligand (mol %)	yield (%)[b]
1	CuI (2.0)	**L1** (4.0)	85 (82[c])
2	CuBr (2.0)	**L1** (4.0)	44
3	CuCl (2.0)	**L1** (4.0)	31
4	CuOAc (2.0)	**L1** (4.0)	12
5	Cu_2O (1.0)	**L1** (4.0)	8
6	$Cu(OAc)_2$ (2.0)	**L1** (4.0)	18
7	$CuCl_2$ (2.0)	**L1** (4.0)	36
8	CuI (2.0)	**L2** (4.0)	72
9	CuI (2.0)	**L3** (4.0)	68
10	CuI (2.0)	**L4** (4.0)	67
11	CuI (2.0)	**L5** (4.0)	85
12	CuI (2.0)	**L6** (4.0)	23
13	CuI (2.0)	**L7** (4.0)	15
14	CuI (2.0)	**L8** (4.0)	6
15[d]	CuI (2.0)	**L1** (4.0)	5
16[e]	CuI (2.0)	**L1** (4.0)	86
17		**L1** (4.0)	0
18	CuI (2.0)		10
19[f]	CuI (2.0)	**L1** (4.0)	40

[a]Reactions were carried out with **1a** (1.5 mmol), **2a** (1.0 mmol), Cu-catalysts (2.0 mol %), additive ligands (4.0 mol %) and molecular sieves 4A (400 mg) in toluene (4 mL) reflux at 110 °C under air for 20 h. [b]Yields were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [c]Isolated yield. [d]The reaction was carried out under argon atmosphere in a sealed reactor. [e]The reaction was carried out under oxygen atmosphere (1 atm). [f]The reaction was carried out without addition of molecular sieves 4A.



chose the reaction performed in the presence of CuI (2.0 mol %) and **L1** (4.0 mol %) in toluene reflux under air as the optimal conditions (entry 1).

Next, the oxidative couplings of various aldehydes with **2a** were conducted under the optimal conditions. The results are summarized in Table 2. The reaction of **1a** with **2a** gave **3a** in 82% isolated yield (entry 1). 4-phenylbenzaldehyde (**1b**) reacted with **2a** to give the amide product **3b** in 67% yield (entry 2). Introduction of electron-donating groups to the aromatic ring of the benzaldehyde resulted in relatively low yields (entries 3−7). Compared with the reactions of 4-methylbenzaldehyde (**1e**) and 3-methylbenzaldehyde (**1f**), the reaction of 2-methylbenzaldehyde (**1g**) resulted in a slightly lower yield, probably due to steric hindrance (entries 5−7).

On the other hand, reactions of benzaldehyde derivatives bearing an electron-withdrawing substituent (fluoro, chloro, bromo, trifluoromethyl, methoxycarbonyl, cyano, and nitro groups) at the aromatic ring proceeded to give corresponding amide products in better yields (entries 8−15) than those bearing an electron-donating substituent. Since the present reactions were performed in the absence of strong base, reactions of 4-fluoro, 4-chloro and 4-bromo benzaldehydes (**1h**−**1j**) with **2a** gave the corresponding amides (**3h**−**3j**) selectively, remaining halogen substituents intact (entries 8−10).[16]

The oxidative amidation of 2-naphthaldehyde (**1p**) with **2a** proceeded in moderate yield (entry 16). Reactions of heteroaromatic aldehydes required relatively higher catalyst loadings (10 mol %) to obtain good yields (entries 17−19). Reaction of terephthaldehyde (**1t**) bearing two formyl groups was also examined. As a result, the oxidative amidation took place only at one formyl group giving a monoamide product **3t** in 70% isolated yield.

We have also carried out the reactions of aliphatic aldehydes such as 1-octanal and pivalaldehyde with **2a**. However, the corresponding amides were not produced in spite of complete consumption of the aldehydes.

Next, the scope of amines was surveyed. The results are summarized in Table 3. A good yield of amide product **4b** was obtained in the reaction of **1a** with 4-phenylpiperidine (**2b**) (entry 1). Piperazine derivatives are important building blocks for the synthesis of biologically active compounds.[17] The reactions of **1a** with N-methyl-, N-benzyl-, and N-Boc-piperazines (**2c**, **2d**, and **2e**) afforded the corresponding amides (**4c**, **4d**, and **4d**) in good to moderate yields (entries 2−4).[18] Reaction of **1a** with morpholine (**2f**) also proceeded smoothly, giving the corresponding amide **4f** in good yield (entry 5). Seven-membered cyclic amine **2g** reacted with **1a** to give the corresponding amide product **4g** in 74% yield (entry 6). Amidation of **1a** with secondary acyclic amines was also examined. As shown in entries 7 and 8, the reaction of **1a** with N-methylbenzylamine (**2h**) and N-ethylbenzylamine (**2i**) afforded the corresponding amide products **4h** and **4i** in moderate yields, respectively. Furthermore, **1a** reacted with dibutylamine (**2j**) smoothly to give N,N′-dibutylbenzamide (**4j**) in 71% yield (entry 9).

The reactions of benzaldehyde with primary amines such as benzylamine and aniline were also examined. However, condensation reaction of aldehydes and amines occurred preferentially affording undesired imines as the products.

Cinnamamides are very important and useful compounds, which can be used as an herbicide,[1a] insecticide[1b,c] and antioxidant.[1f] Thus, we intended to extend our aerobic oxidative catalytic system to the synthesis of cinnamamides. The results are summarized in Table 4. At first, we carried out the oxidative amidation of cinnamaldehyde (**1u**) with piperidine (**2a**) under the optimal conditions determined in Table 1. Unfortunately, the desired amide product **5a** was not formed, although the complete consumption of **1u** was observed, probably because of the oxidative decomposition of **1u** at relatively high temperature. Then, we tried to carry out the oxidative coupling at a lower temperature (100 °C) with increasing the amount of **1u** to 2.0 mmol and the catalyst loading to 20 mol %. As a result, 77% yield of the corresponding cinnamamide **5a** was successfully obtained (entry 1). Reaction of 4-fluorocinnamaldehyde (**1v**) with **2a** proceeded at a relatively lower temperature (90 °C), affording **5b** in lower yield (entry 2).[19] Reaction of 4-methoxycinnamaldehyde (**1w**) with **2a** was carried out with the addition of

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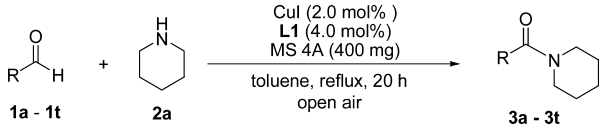
Table 2. Cu(I)-catalyzed Aerobic Oxidative Amidation of Aromatic and Heteroaromatic Aldehydes with Piperidine (2a)

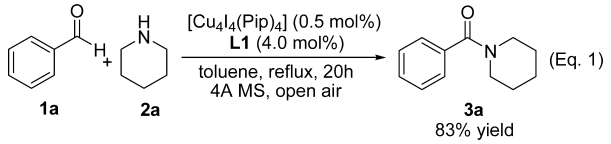


Entry	Aldehydes	Products	Yield (%)[b]	Entry	Aldehydes	Products	Yield (%)[b]
1	1a	3a	82	11	1k	3k	88
2	1b	3b	67	12	1l	3l	86
3	1c	3c	60	13	1m	3m	79
4	1d	3d	66	14	1n	3n	82
5	1e	3e	77	15	1o	3o	74
6	1f	3f	60	16	1p	3p	61
7	1g	3g	39	17[c]	1q	3q	83
8	1h	3h	88	18[c]	1r	3r	80
9	1i	3i	80	19[c]	1s	3s	76
10	1j	3j	75	20	1t	3t	70

[a]The reactions were carried out with various aldehydes (**1a**−**1t**) (1.5 mmol), **2a** (1.0 mmol), CuI (2.0 mol %), **L1** (4.0 mol %) and molecular sieves (400 mg) in toluene (4 mL) reflux at 110 °C under air for 20 h. [b]Isolated yield. [c]The reactions were carried out with CuI (10.0 mol %) and **L1** (10.0 mol %).

ligand **L5** instead of **L1** to give **5c** in 66% yield (entry 3). Reaction of **1u** with morpholine (**2f**) proceeded smoothly at 100 °C to give the corresponding cinnamamide **5d** in 67% yield (entry 4).

To isolate and characterize the catalytically active copper species, a stoichiometric reaction of CuI with **2a** was carried out. When an excess amount of **2a** was added to a suspension of CuI in THF at room temperature, a soluble copper(I) complex was formed immediately. The structure of this copper(I) complex was determined by X-ray diffraction analysis, revealing that the copper(I) complex is a tetranuclear structure of $[Cu_4(\mu_3\text{-}I)_4(Pip)_4]$ (**6**) in which copper centers are bridged by iodine atoms.[20,21] Catalytic reaction of **1a** with **2a** by using **6** as a catalyst in the presence of additive ligand **L1** gave **3a** in 83% yield (eq 1), suggesting that the copper complex **6** would be a precatalyst (a plausible mechanism for the present CuI/2-pyridonate catalytic system is proposed in the Supporting Information).



CONCLUSION

In conclusion, we have developed a simple and convenient method for the synthesis of amides. A variety of amides, which have useful applications in the areas of agrochemicals, pharmaceuticals and polymetric materials, were synthesized in moderate to good yields generating only water as a coproduct

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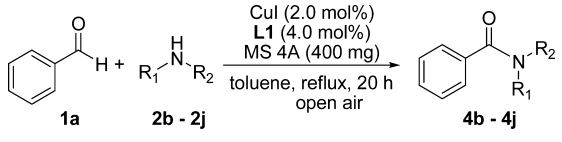
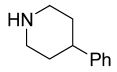
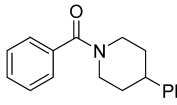
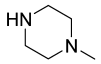
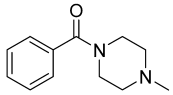
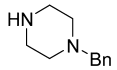
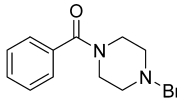
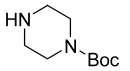
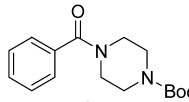
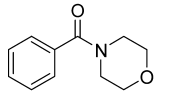
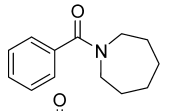
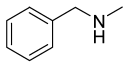
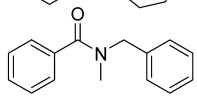
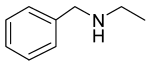
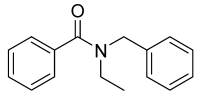
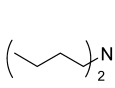
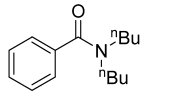
Table 3. Cu(I)-catalyzed Aerobic Oxidative Amidation of Benzaldehyde (1a) with Various Secondary Amines[a]



Entry	Amines		Products		Yield (%)[b]
1		2b		4b	82
2		2c		4c	74
3		2d		4d	63
4		2e		4e	51
5		2f		4f	75
6		2g		4g	74
7		2h		4h	68
8		2i		4i	42
9		2j		4j	71

[a]The reactions were carried out with **1a** (1.5 mmol), secondary amines (**2b**−**2j**) (1.0 mmol), CuI (2.0 mol %), **L1** (4.0 mol %) and molecular sieves 4A (400 mg) in toluene (4 mL) reflux at 110 °C under air for 20 h. [b]Isolated yield.

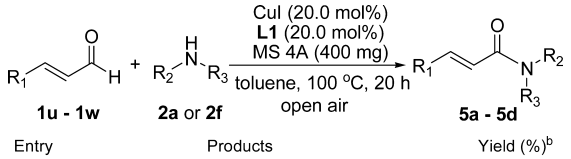
by a new catalytic system composed of CuI/2-pyridonate. Air was successfully employed as a green oxidant in this catalytic system, which greatly improved the safety of the synthesis and is beneficial from an atom-economical viewpoint.

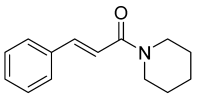
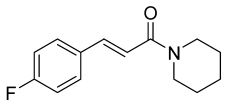
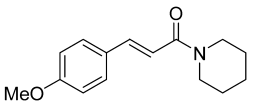
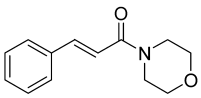
EXPERIMENTAL SECTION

General. All reactions and manipulations were carried out by means of standard Schlenk techniques. The column chromatography was carried out by using silica gel. ^{1}H NMR (500 MHz) and ^{13}C (125 MHz) were performed on a 500 MHz spectrometer. Solvents were dried by standard procedures and distilled prior to use. *N*-Benzylpiperazine (**2d**)[22] and *N*-*tert*-butoxycarbonylpiperazine (**2e**)[23] were prepared according to the literature method. All other reagents are commercially available and were used without further purification.

Preparation of 2-Pyridonate Ligands. To an oven-dried, argon purged flask were added hydroxypyridine derivatives (1.0 mmol), sodium ethoxide (1.0 mmol), and ethanol (2.5 mL). The mixture was stirred at room temperature for 2 h. Then the solvent was removed and the residue was dried in vacuo to give **L1**−**L8** as a colorless or pale-yellow powder.

Table 4. Cu(I)-catalyzed Aerobic Oxidative Amidation of Cinnamaldehydes with Secondary Amines[a]



Entry	Products		Yield (%)[b]
1		5a	77
2[c]		5b	44
3[d]		5c	66
4		5d	67

[a]The reactions were carried out with cinnamaldehydes (**1u**−**1w**) (2.0 mmol), secondary amines (**2a** or **2f**) (1.0 mmol), CuI (20.0 mol %), **L1** (20.0 mol %) and molecular sieves 4A (400 mg) in toluene (4 mL) at 100 °C under air for 20 h. [b]Isolated yield. [c]The reaction was carried out in toluene at 90 °C. [d]The reaction was carried out with **1w** (3.0 mmol), **2a** (1.0 mmol), CuI (20.0 mmol %) and **L5** (20.0 mmol %) and molecular sieves 4A (400 mg) in toluene (4 mL) at 100 °C under air for 20 h.

Procedure for the Cu(I)-catalyzed Aerobic Oxidative Amidation of Benzaldehyde (1a) with Piperidine (2a) Shown in Table 1. To an oven-dried, argon purged two-necked flask were added additive ligands (**L1**−**L8**) (0.04 mmol, 4.0 mol %), Cu-catalysts (0.02 mmol, 2.0 mol %), molecular sieves 4A (400 mg), **1a** (1.5 mmol), toluene (4 mL), and **2a** (1.0 mmol). The flask was sealed and preheated at 110 °C under argon for about 1 min and then the mixture was stirred at 110 °C under open air for 20 h. The mixture was cooled to room temperature. After the solvent was removed in vacuo, the residue was diluted with dichloromethane (10 mL) and filtered through a pad of Celite. Dichloromethane was removed in vacuo and 1,3,5-trimethoxybenzene was added as an internal standard for ^{1}H NMR analysis. The yield of 1-benzoyl-piperidine (**3a**) was calculated by ^{1}H NMR analysis in chloroform-d.

Procedure for the Cu(I)-catalyzed Aerobic Oxidative Amidation of Various Aldehydes with Secondary Amines Shown in Tables 2 and 3. To an oven-dried, argon purged flask were added sodium 5-methyl-2-pyridonate (**L1**) (0.04 mmol, 2.0 mol %), CuI (0.02 mmol, 2.0 mol %), molecular sieves 4A (400 mg), aldehydes (**1a**−**1t**) (1.5 mmol), toluene (4 mL), and secondary amines (**2a**−**2j**) (1.0 mmol). The flask was sealed and preheated at 110 °C under argon for about 1 min and then the mixture was stirred at 110 °C under open air for 20 h. The mixture was cooled to room temperature. After the solvent was removed in vacuo, the residue was diluted with dichloromethane (10 mL) and filtered through a pad of Celite. The filtrate was concentrated by evaporation and purified by a silica gel column chromatography (eluent: ethyl acetate/hexane).

Procedure for the Cu(I)-catalyzed aerobic oxidative amidation of cinnamaldehydes with secondary amines shown in Table 4. To an oven-dried, argon purged flask were added sodium 5-methyl-2-pyridonate (**L1**) (0.2 mmol, 20.0 mol %), CuI (0.2 mmol, 20.0 mol %), molecular sieves 4A (400 mg), cinnamaldehydes (**1u** - **1w**) (2.0 mmol), toluene (4 mL), and secondary amines (**2a** or **2f**) (1.0 mmol). The flask was sealed and preheated under argon for about 1 min and then the mixture was stirred at 100 °C under open air for 20 h. The mixture was cooled to room temperature. After the solvent was

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removed in vacuo, the residue was diluted with dichloromethane (10 mL) and filtered through a pad of Celite. The filtrate was concentrated by evaporation and purified by a silica gel column chromatography (eluent: ethyl acetate/hexane). Evaporation of the collected product followed by the Kugelrohr distillation gave the pure product.

Preparation of Copper Complex $[Cu_4(\mu_3\text{-}I)_4(Pip)_4]$ (6):[20] To an oven-dried, argon purged flask were added CuI (1.0 mmol) and THF (5 mL). Then, an excess of **2a** (1.0 mL) was added dropwise to the suspension. The mixture was stirred at room temperature for 1 h. The suspension turned clear and the color of the solution turned light violet. Concentration of the solution in vacuo to 2.5 mL followed by the slow diffusion of hexane into the concentrated solution in a glass tube gave colorless single crystals of **6**, which are suitable for X-ray diffraction analysis (193.3 mg, 70% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.00 (br, 16H), 1.85−1.60 (br, 24H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 49.4 (br), 27.5 (br), 24.3. Anal.Calcd. for $C_{20}H_{44}Cu_4N_4I_4$: C, 21.79; H, 4.02; N, 5.08. Found: C, 21.71; H, 3.90; N, 5.15.

Procedure for the $[Cu_4(\mu_3\text{-}I)_4(Pip)_4]$-catalyzed Aerboic Oxidative Amidation of Benzaldehyde with Piperidine Shown in eq 1. To an oven-dried, argon purged two-necked flask were added additive ligand **L1** (0.04 mmol, 4.0 mol %), the complex **6** (0.005 mmol, 0.5 mol %), molecular sieves 4A (400 mg), **1a** (1.5 mmol), toluene (4 mL), and **2a** (1.0 mmol). The flask was sealed and preheated at 110 °C under argon for about 1 min and then the mixture was stirred at 110 °C under open air for 20 h. The mixture was cooled to room temperature. After the solvent was removed in vacuo, the residue was diluted with dichloromethane (10 mL) and filtered through a pad of Celite. Dichloromethane was removed in vacuo and 1,3,5-trimethoxybenzene was then added as an internal standard for ^{1}H NMR analysis. The yield of 1-benzoyl-piperidine (**3a**) was calculated by ^{1}H NMR analysis in chloroform-d.

1-Benzoylpiperidine (3a).[24] Purification was performed by column chromatography on silica gel eluting with EtOAc/Hexane = 1:3 to give **3a** as a pale yellow oil, 154.1 mg, 82% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39 (s, 5H), 3.71 (br s, 2H), 3.34 (br s, 2H), 1.68 (br s, 4H), 1.52 (br s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.2, 136.5, 129.3, 128.3, 126.9, 48.6, 43.0, 26.5, 25.6, 24.5.

1-(4-Phenylbenzoyl)piperidine (3b).[25] Purification was performed by column chromatography on silica gel eluting with EtOAc/Hexane = 1:1 to give **3b** as a pale yellow solid, 178.4 mg, 67% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.62−7.58 (m, 4H), 7.48−7.43 (m, 4H), 7.36 (t, J = 7.5 Hz, 1H), 3.73 (br s, 2H), 3.41 (br s, 2H), 1.69 (br s, 4H), 1.54 (br s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.2, 142.4, 140.5, 135.4, 129.0, 127.8, 127.5, 127.2, 49.0, 43.3, 26.7, 25.8, 24.7.

1-(4-Methoxybenzoyl)piperidine (3c).[24] Purification was performed by column chromatography on silica gel eluting with EtOAc/Hexane = 1:1 to give **3c** as a pale yellow oil, 130.5 mg, 60% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35 (d, J = 8.0 Hz, 2H), 6.88 (d, J = 8.0 Hz, 2H), 3.81 (s, 3H), 3.67 (br s, 2H), 3.40 (br s, 2H), 1.66 (br s, 4H), 1.58 (br s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.4, 160.6, 129.0, 128.7, 113.7, 55.5, 49.1, 43.5, 26.2, 24.8.

1-(4-*tert*-Butylbenzoyl)piperidine (3d). Purification was performed by column chromatography on silica gel eluting with EtOAc/Hexane = 1:1 to give **3c** as a pale yellow solid, m.p.: 75.1−75.7 °C, 162.9 mg, 66% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 3.71 (br s, 2H), 3.38 (br s, 2H), 1.68 (br s, 4H), 1.52 (br s, 2H), 1.32 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.6, 152.7, 133.7, 126.8, 125.4, 48.9, 43.2, 34.9, 31.5, 26.7, 25.8, 24.8. Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 77.92; H, 9.82; N, 5.97.

1-(4-Methylbenzoyl)piperidine (3e).[26] Purification was performed by column chromatography on silica gel eluting with EtOAc/Hexane = 1:3 to give **3e** as a pale yellow oil, 157.4 mg, 77% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.29 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 3.70 (br s, 2H), 3.36 (br s, 2H), 2.37 (s, 3H), 1.67 (br s, 4H), 1.52 (br s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.6, 139.5, 133.7, 129.1, 127.0, 48.9, 43.3, 26.7, 25.9, 24.8, 21.5.

1-(3-Methylbenzoyl)piperidine (3f).[27] Purification was performed by column chromatography on silica gel eluting with EtOAc/Hexane = 1:1 to give **3f** as a pale yellow oil, 119.1 mg, 60% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.26 (t, J = 7.5 Hz, 1H), 7.2 (s, 1H), 7.19 (d, J = 7.5 Hz, 1H), 7.15 (d, J = 7.5 Hz, 1H), 3.70 (br s, 2H), 3.33 (br s, 2H), 2.36 (s, 3H), 1.67 (br s, 4H), 1.50 (br s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.5, 138.3, 136.5, 130.1, 128.2, 127.4, 123.7, 48.8, 43.1, 26.6, 25.7, 24.6, 21.4.

1-(2-Methylbenzoyl)piperidine (3g).[26] Purification was performed by column chromatography on silica gel eluting with EtOAc/Hexane = 1:3 to give **3g** as a pale yellow oil, 80.1 mg, 39% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.26−7.14 (m, 4H), 3.80 (br s, 1H), 3.70 (br s, 1H), 3.17 (br s, 2H), 2.31 (s, 3H), 1.66 (br s, 1H), 1.45 (br s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.0, 136.9, 134.1, 130.4, 128.7, 125.9, 125.7, 48.0, 42.5, 26.7, 25.8, 24.7, 19.1.

1-(4-Fluorobenzoyl)piperidine (3h).[24] Purification was performed by column chromatography on silica gel eluting with EtOAc/Hexane = 1:3 to give **3h** as a colorless solid, 182.0 mg, 88% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41−7.39 (m, 2H), 7.10−7.07 (m, 2H), 3.70 (br s, 2H), 3.36 (br s, 2H), 1.69 (br s, 4H), 1.53 (br s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.6, 164.4, 162.4, 132.6, 132.6, 129.3, 129.2, 115.7, 115.5, 49.1, 43.5, 26.7, 25.8, 24.7.

1-(4-Chlorobenzoyl)piperidine (3i).[24] Purification was performed by column chromatography on silica gel eluting with EtOAc/Hexane = 1:3 to give **3i** as a pale yellow solid, 178.9 mg, 80% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H), 3.70 (br s, 2H), 3.33 (br s, 2H), 1.68 (br s, 4H), 1.52 (br s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.3, 135.5, 134.9, 128.8, 128.5, 48.9, 43.3, 26.6, 25.7, 24.6.

1-(4-Bromobenzoyl)piperidine (3j).[28] Purification was performed by column chromatography on silica gel eluting with EtOAc/Hexane = 1:3 to give **p10** as a pale yellow solid, 201.8 mg, 75% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.54 (d, J = 8.5 Hz, 2H), 7.27 (d, J = 8.5 Hz, 2H), 3.69 (br s, 2H), 3.32 (br s, 2H), 1.68 (br s, 4H), 1.52 (br s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.4, 135.4, 131.8, 128.7, 123.7, 48.9, 43.3, 26.7, 25.7, 24.7.

1-(4-Trifluoromethylbenzoyl)piperidine (3k).[27] Purification was performed by column chromatography on silica gel eluting with EtOAc/Hexane = 1:3 to give **3k** as a pale yellow solid, 228.5 mg, 88% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.67 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.0 Hz, 2H), 3.73 (br s, 2H), 3.30 (br s, 2H), 1.70 (br s, 4H), 1.52 (br s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.9, 140.2, 131.4 (q, J = 32.6 Hz), 127.3, 125.7, 123.7 (q, J = 272.3 Hz), 48.8, 43.3, 26.7, 25.7, 24.6.

1-(4-Methoxycarobonylbenzoyl)piperidine (3l).[28] Purification was performed by column chromatography on silica gel eluting with EtOAc/Hexane = 1:3 to give **3l** as a pale yellow solid, 211.7 mg, 86% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.08 (d, J = 10.0 Hz, 2H), 7.46 (d, J = 10.0 Hz, 2H), 3.94 (s, 3H), 3.73 (br s, 2H), 3.30 (br s, 2H), 1.69 (br s, 4H), 1.52 (br s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.2, 166.4, 140.9, 130.8, 129.8, 126.8, 52.3, 48.7, 43.1, 26.5, 25.6, 24.5.

1-(4-Cyanobenzoyl)piperidine (3m). Purification was performed by column chromatography on silica gel eluting with EtOAc/Hexane = 1:1 to give **3m** as a pale yellow solid, m.p.: 95.3−96.0 °C, 171.7 mg, 79% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.71 (d, J = 8.5 Hz, 2H), 7.50 (d, J = 8.5 Hz, 2H), 3.72 (br s, 2H), 3.29 (br s, 2H), 1.70 (br s, 4H), 1.53 (br s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.3, 141.0, 132.5, 127.6, 118.3, 113.3, 48.7, 43.3, 26.6, 25.6, 24.5. Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.89; H, 6.36; N, 12.99.

1-(4-Nitrobenzoyl)piperidine (3n).[29] Purification was performed by column chromatography on silica gel eluting with EtOAc/Hexane = 1:1 to give **3n** as a pale yellow solid, 192.1 mg, 82% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.27 (d, J = 8.0 Hz, 2H), 7.56 (d, J = 8.0 Hz, 2H), 3.73 (br s, 2H), 3.29 (br s, 2H), 1.71 (br s, 4H), 1.54 (br s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.0, 148.3, 142.8, 127.9, 124.0, 48.8, 43.3, 26.6, 25.6, 24.5.

1-(3-Nitrobenzoyl)piperidine (3o). Purification was performed by column chromatography on silica gel eluting with EtOAc/Hexane = 1:1 to give **3o** as a pale yellow solid, m.p.: 81.0−81.7 °C, 179.6 mg, 74% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.29−8.27 (m, 2H), 7.74 (d, J = 8.0 Hz, 1H), 7.62 (t, J = 7.5 Hz, 1H), 3.74 (br s, 2H), 3.34 (br

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s, 2H), 1.72 (br s, 4H), 1.56 (br s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.7, 148.2, 138.2, 133.1, 129.9, 124.4, 122.2, 49.0, 43.5, 26.7, 25.6, 24.6. Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.35; H, 5.99; N, 11.92.

1-(2-Naphthalenecarbonyl)piperidine (3p).[28] Purification was performed by column chromatography on silica gel eluting with EtOAc/Hexane = 1:1 to give **3p** as a pale yellow solid, 148.3 mg, 61% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.89−7.86 (m, 4H), 7.53−7.48 (m, 3H), 3.76 (br s, 2H), 3.39 (br s, 2H), 1.70 (br s, 4H), 1.53 (br s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.5, 134.0, 133.7, 132.9, 128.5, 128.3, 127.9, 127.0, 126.7, 126.6, 124.4, 49.0, 43.4, 26.7, 25.8, 24.8.

1-(4-Pyridinecarbonyl)piperidine (3q).[30] Purification was performed by column chromatography on silica gel eluting with EtOAc 100% to give **3q** as a pale yellow oil, 158.5 mg, 83% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.70 (s, 2H), 7.29 (d, J = 5.0 Hz, 2H), 3.71 (t, J = 5.0 Hz, 2H), 3.29 (t, J = 5.0 Hz, 2H), 1.69 (br s, 4H), 1.52 (br s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.4, 150.1, 144.0, 121.0, 48.3, 42.8, 26.3, 25.3, 24.2.

1-(3-Pyridinecarbonyl)piperidine (3r).[30] Purification was performed by column chromatography on silica gel eluting with EtOAc 100% to give **3r** as a pale yellow oil, 155.1 mg, 80% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.66 (s, 2H), 7.75 (d, J = 9.5 Hz, 2H), 7.37−7.34 (m, 2H), 3.73 (br s, 2H), 3.36 (br s, 2H), 1.70 (br s, 4H), 1.55 (br s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.8, 150.6, 147.8, 134.9, 132.3, 123.6, 48.9, 43.3, 26.7, 25.6, 24.5.

1-(2-Pyridinecarbonyl)piperidine (3s).[31] Purification was performed by column chromatography on silica gel eluting with EtOAc 100% to give **3s** as a pale yellow oil, 146.1 mg, 76% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.60 (d, J = 4.5 Hz, 1H), 7.80−7.77 (m, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.33 (t, J = 6.0 Hz, 1H), 3.75 (s, 2H), 3.43 (t, J = 5.5 Hz, 2H), 1.69 (br s, 4H), 1.57 (br s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.8, 154.9, 148.6, 137.1, 124.3, 123.4, 48.4, 43.4, 26.6, 25.7, 24.7.

1-(4-Formylcarbonyl)piperidine (3t).[32] Purification was performed by column chromatography on silica gel eluting with EtOAc/Hexane = 1:1 to give **3t** as a pale yellow oil, 152.8 mg, 70% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.05 (s, 1H), 7.93 (d, J = 8.5 Hz, 2H), 7.50 (d, J = 8.5 Hz, 2H), 3.73 (br s, 2H), 3.43 (br s, 2H), 1.70 (br s, 4H), 1.53 (br s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 191.7, 169.0, 142.4, 136.8, 130.1, 127.5, 48.8, 43.2, 26.7, 25.7, 24.6.

1-Benzoyl-4-phenylpiperidine (4b). Purification was performed by column chromatography on silica gel eluting with EtOAc/Hexane = 1:1 to give **4b** as a pale yellow solid, m.p.: 80.0−80.8 °C, 217.7 mg, 82% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.42 (m, 5H), 7.32 (t, J = 7.5 Hz, 2H), 7.20 (d, J = 7.0 Hz, 3H), 4.89 (br s, 1H), 3.88 (br s, 1H), 3.13 (br s, 1H), 2.86 (br s, 1H), 2.78 (br t, J = 8.5 Hz, 1H), 1.98 (br s, 1H), 1.79 (br s, 2H), 1.64 (br s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.5, 145.2, 136.4, 129.6, 128.7, 128.6, 127.0, 126.8, 126.6, 48.5, 42.9, 34.1, 33.0. Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.18; H, 7.24; N, 5.23.

1-Benzoyl-4-methylpiperazine (4c).[33] Purification was performed by column chromatography on silica gel eluting with EtOAc/Hexane = 5:1 to give **4c** as pale yellow oil, 143.0 mg, 70% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41 (s, 5H), 3.83 (br s, 2H), 3.48 (br s, 2H), 2.53 (br s, 2H), 2.40 (br s, 2H), 2.35 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.4, 135.9, 129.7, 128.5, 127.1, 55.4, 54.8, 47.7, 46.1, 42.1.

1-Benzoyl-4-benzylpiperazine (4d).[34] Purification was performed by column chromatography on silica gel eluting with EtOAc (100%) to give **4d** as pale yellow oil, 182.2 mg, 63% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39 (s, 5H), 7.33−7.31 (m, 5H), 3.80 (brs, 2H), 3.54 (s, 2H), 3.42 (brs, 2H), 2.54 (brs, 2H), 2.38 (brs, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.4, 137.7, 136.0, 129.7, 129.2, 128.6, 128.5, 127.4, 127.2, 63.0, 53.5, 52.9, 47.9, 42.3.

1-Benzoyl-4-*tert*-butoxylcarbonylpiperazine (4e). Purification was performed by column chromatography on silica gel eluting with EtOAc/Hexane = 1:1 to give **4e** as pale yellow solid, mp 107.0−107.6 °C, 146.8 mg, 51% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.44−7.39 (m, 5H), 3.75 (br, 2H), 3.52 (br, 2H), 3.40 (br, 2H), 1.47 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.8, 154.7, 135.7, 130.1, 128.7, 127.2, 80.1, 47.7, 43.9 (br), 42.2, 28.5. Anal. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.65. Found: C, 65.91; H, 7.74; N, 9.85

1-Benzoylmorpholine (4f).[24] Purification was performed by column chromatography on silica gel eluting with EtOAc/Hexane = 1:1 to give **4f** as a pale yellow solid, 136.3 mg, 75% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.42 (s, 5H), 3.76−3.46 (br, 8H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.5, 135.5, 130.0, 128.7, 127.2, 67.0, 48.4, 42.8.

1-Benzoylhexahydroazepine (4g). Purification was performed by column chromatography on silica gel eluting with EtOAc/Hexane = 1:3 to give **4f** as a pale yellow oil, 143.6 mg, 74% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37 (s, 5H), 3.68 (t, J = 5.8 Hz, 2H), 3.36 (t, J = 5.8 Hz, 2H), 1.85−1.81 (m, 2H), 1.65 - 1.58 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.6, 137.4, 129.1, 128.4, 126.4, 49.7, 46.3, 29.5, 27.9, 27.3, 26.5. Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.55; H, 8.56; N, 6.86

***N*-Benzyl-*N*-methyl-benzamide (4h).**[24] Purification was performed by column chromatography on silica gel eluting with EtOAc/Hexane = 1:3 to give **4i** as a pale yellow oil, 157.3 mg, 68% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.46−7.29 (m, 9H), 7.17 (s, 1H), 4.76 (br s, 1H), 4.51 (br s, 1H), 3.03 (br s, 1.5H), 2.86 (br s, 1.5H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.5, 171.7, 137.2, 136.7, 136.4, 129.7, 129.0, 128.8, 128.5, 128.3, 127.6, 127.1, 126.9, 55.3, 50.9, 37.1, 33.3.

***N*-Benzyl-*N*-ethyl-benzamide (4i).**[36] Purification was performed by column chromatography on silica gel eluting with EtOAc/Hexane = 1:3 to give **4j** as a pale yellow oil, 101.0 mg, 42% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.43−7.19 (m, 10H), 4.78 (br s, 1H), 4.51 (br s, 1H), 3.52 (br s, 1H), 3.21 (br s, 1H), 1.21 (br s, 1.5H), 1.07 (br s, 1.5H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.1, 137.6, 137.1, 136.9, 136.7, 129.5, 128.8, 128.6, 128.2, 128.0, 127.5, 126.9, 126.7, 126.5, 52.2, 47.0, 42.9, 39.7, 13.8, 12.3.

***N,N*-Dibutylbenzamide (4j).**[7] Purification was performed by column chromatography on silica gel eluting with EtOAc/Hexane = 1:3 to give **4j** as a pale yellow oil, 161.4 mg, 71% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36 (m, 5H), 3.49 (br s, 2H), 3.18 (br s, 2H), 1.65 (br s, 2H), 1.48 (br s, 2H), 1.41 (br s, 2H), 1.14 (br s, 2H), 0.98 (br s, 3H), 0.78 (br s, 3H) . ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.8, 137.5, 129.1, 128.4, 126.6, 48.9, 44.6, 30.9, 29.8, 20.4, 19.8, 14.1, 13.7.

1-Cinnamoylpiperidine (5a).[28] Purification was performed by column chromatography on silica gel eluting with EtOAc/Hexane = 1:1. Evaporation of the collected product followed by the Kugelrohr distillation (200 °C, 1.0 mmHg) gave the pure product **5a** as a pale yellow solid, 167.0 mg, 77% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.45 (d, J = 15.5 Hz, 2H), 7.52 (d, J = 6.0 Hz, 2H), 7.39−7.34 (m, 3H), 6.91 (d, J = 15.5 Hz, 2H), 3.67 (brs, 2H), 3.59 (brs, 2H), 1.69−1.62 (br, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.5, 142.3, 135.6, 129.5, 128.9, 127.8, 117.9, 47.2, 43.5, 26.9, 25.8, 24.8.

1-(*p*-Fluoro-cinnamoyl)piperidine (5b).[36] Purification was performed by column chromatography on silica gel eluting with EtOAc/Hexane = 1:1. Evaporation of the collected product followed by the Kugelrohr distillation (200 °C, 1.0 mmHg) gave the pure product **5b** as a pale yellow solid, 102.8 mg, 44% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.60 (d, J = 15.5 Hz, 2H), 7.51 (t, J = 7.0 Hz, 2H), 7.08−7.03 (t, J = 7.3 Hz, 2H), 3.67(brs, 2H), 3.58 (brs, 2H), 1.69−1.60 (br, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.3, 164.5, 162.5, 141.0, 131.8, 129.6, 129.5, 117.6, 116.0, 115.8, 47.1, 43.5, 26.9, 25.7, 24.7.

1-Methoxycinnamoylpiperidine (5c).[37] Purification was performed by column chromatography on silica gel eluting with EtOAc/Hexane = 1:1 gave **5c** as a pale yellow oil, 169.1 mg, 66% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.60 (d, J = 15.5 Hz, 2H), 7.48 (m, 2H), 7.08−6.88 (m, 2H), 6.77 (d, J = 15.5 Hz, 2H), 3.83 (s, 3H), 3.66 (brs, 2H), 3.58 (brs, 2H), 1.69−1.58 (br, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.7, 160.8, 141.9, 129.3, 128.4, 115.4, 114.3, 55.4, 47.1, 43.4, 26.8, 25.7, 24.8.

1-Cinnamoylmorpholine (5d).[38] Purification was performed by column chromatography on silica gel eluting with EtOAc/Hexane = 1:1 gave **5d** as a pale yellow solid, 154.3 mg, 71% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.70 (d, J = 15.5 Hz, 2H), 7.53−7.51 (m, 2H), 7.40−7.33 (m, 2H), 6.85 (d, J = 15.5 Hz, 2H), 3.73−3.67 (br, 8H).

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^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.7, 143.3, 135.2, 129.9, 128.9, 127.9, 116.7, 67.0, 46.3, 42.6.

X-ray Structure Analysis of Copper Complex 6. Diffraction data for **6** were obtained with a Rigaku RAXIS RAPID instrument. Reflection data were corrected for Lorentz and polarization effects. Empirical absorption corrections were applied. The structures was solved by direct method[39,40] and refined anisotropically for non-hydrogen atoms by full-matrix least-squares calculations. Atomic scattering factors and anomalous dispersion terms were taken from the literature.[41] Hydrogen atoms were located on the idealized positions. The calculations were performed using the program system CrystalStructure.[42,43] ORTEP drawing of **6** is shown in Figure S1 (Supporting Information). The crystal data and details are shown in a CIF file.

■ ASSOCIATED CONTENT

Supporting Information

Table of optimization of reaction solvent, copies of ^1H and ^{13}C NMR spectra of all products, X-ray structural details of **6**. 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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