# Copper-Catalyzed Oxidative Amidation of Aldehydes with Amine Salts: Synthesis of Primary, Secondary, and Tertiary Amides

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Ⓢ *Supporting Information*
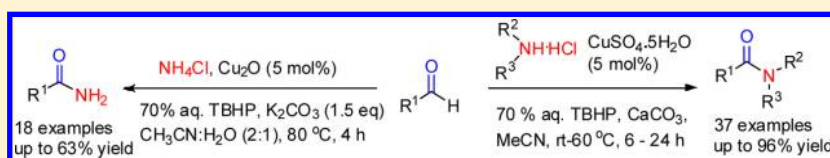
ABSTRACT: A practical method for the amidation of aldehydes with economic ammonium chloride or amine hydrochloride salts has been developed for the synthesis of a wide variety of amides by using inexpensive copper sulfate or copper(I) oxide as a catalyst and aqueous *tert*-butyl hydroperoxide as an oxidant. This amidation reaction is operationally straightforward and provides primary, secondary, and tertiary amides in good to excellent yields for most cases utilizing inexpensive and readily available reagents under mild conditions. In situ formation of amine salts from free amines extends the substrate scope of the reaction. Chiral amides are also synthesized from their corresponding chiral amines without detectable racemization. The practicality of this amide formation reaction has been demonstrated in an efficient synthesis of the antiarrhythmic drug *N*-acetylprocainamide.

■ INTRODUCTION

Amide bond formation is one of the most often used transformations in the synthesis of pharmaceuticals, fine chemicals, and polymers (Figure 1).[1] It is estimated that more than 25% of known drugs contain an amide group.[2] The most frequently used amide formations involve the reaction of an amine (including ammonia) with activated carboxylic acid derivatives[3] or coupling with carboxylic acids mediated by a coupling reagent.[4] These existing methods have several common drawbacks, such as poor atom-efficiency, use of

hazardous reagents, and generation of wastes that not only reduce process efficiency but also pose environmental problems. To address these challenging problems in amide synthesis, a plethora of novel amide formation reactions have been developed,[5] such as catalytic acylation of amines with carboxylic acid,[6] dehydrogenative amidation of alcohol,[7] amino carbonylation of haloarenes,[8] hydroamination of alkynes,[9] transamidation of primary amides,[10] and oxidative amidation of aldehydes.[11−21] Among these, oxidative amidation of aldehydes with amine salts (Scheme 1) is highly synthetically useful as both starting materials are readily available and less hazardous than those traditionally used such as acid halides.
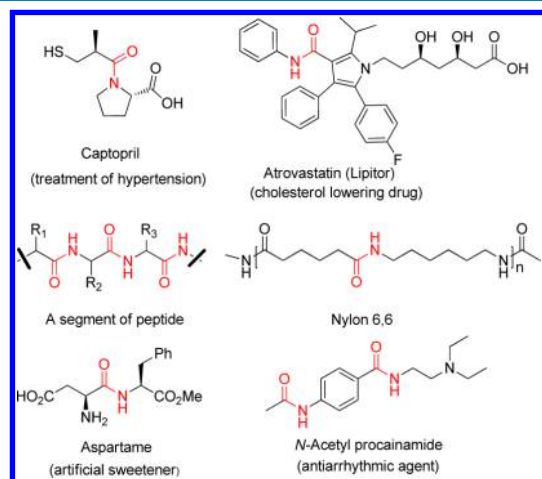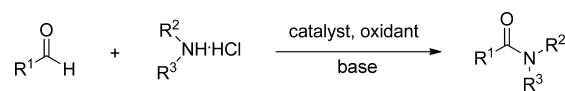
Scheme 1. Oxidative Amidation of Aldehydes with Amine Hydrochloride Salts

Oxidative amidation of aldehydes with amines was first reported by Nakagawa et al. in 1966 by using stoichiometric amounts of nickel peroxide as the oxidant.[11] Subsequently, several groups have developed new methods for the direct conversion of amides from aldehydes using iodine,[12] NBS,[13] manganese oxide,[14] 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone,[15] and TBHP[16] as oxidizing agents. More efficient catalytic

Figure 1. Examples of molecules containing an amide group.

methods using N-heterocyclic carbene (NHC),[17] copper/silver,[18] transition metals (Pd, Rh and Ru),[19] and lanthanides[20] have also been reported.
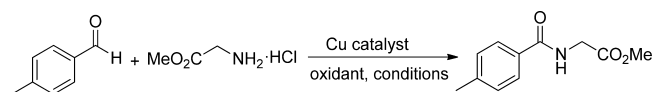
Among these methods, oxidative amidation of aldehydes with amine hydrochlorides using CuI−AgIO$_3$ as the catalyst and inexpensive aqueous tert-butyl hydroperoxide (T-Hydro) as the oxidant reported by Li et al.[18] is an attractive method for exploration. This pioneering work provides an efficient and greener method for amide formation. However, the reaction requires a dual catalyst system and has a narrower substrate scope, only applicable to the synthesis of secondary amides. Hence the search of a less costly and simpler catalyst system with broader subtract scope remains a challenge from a practicality point of view. As part of our ongoing effort to develop novel efficient methods for amide bond formation,[21] we report herein an improved oxidative amidation of aldehydes with amine salts for the synthesis of primary, secondary and tertiary amides, using inexpensive and readily available copper compounds as the catalysts.

■ RESULTS AND DISCUSSION

At the outset, a model reaction of 4-methylbenzaldehyde and glycine methyl ester hydrochloride to form methyl 2-(4-methylbenzamido)acetate was chosen to identify the catalytic system. With T-Hydro as the oxidant, a wide range of copper salts were screened for the reaction and most of them provided good to excellent yield of the amide (entries 1−9) with CuSO$_4$·5H$_2$O (86%, entry 9) performed slightly better over other catalysts. As CuSO$_4$·5H$_2$O is the least expensive among the copper catalyst studied and gave best conversion, it was selected for further optimization. Decreasing the reaction temperature from 80 to 40 °C or ambient temperature did not affect the reaction (entry 10−11), demonstrating the mildness and convenience of operation. With 1 mol % catalyst loading, the yield of amide decreased slightly to 74% (entry 12). Control experiments (entries 13−15) revealed that an oxidant (T-Hydro, entry 13), a copper catalyst (entry 14), and a base (entry 15) are all necessary for the amide formation. The effect of solvents was investigated, and it was found that acetonitrile is superior to other solvents (entries 16−20). Screening a range of bases revealed that CaCO$_3$ performed best among other bases including K$_2$CO$_3$, Na$_2$CO$_3$, and NaHCO$_3$ (not included in Table 1). Other oxidants including H$_2$O$_2$, NaOCl, NaO$_2$Cl, PhI(OAc)$_2$, TEMPO, Oxone, and air were also screened, but in all cases only 0−5% amide product formation was observed (not included in Table 1).

To understand the substrate scope of this reaction, a wide range of aldehydes and amine hydrochlorides were reacted under the optimized reaction conditions (Table 2). Good to excellent yields of secondary amides were obtained in most cases (3a−g). However, with sterically bulky tert-butyl amine hydrochloride a diminished yield was obtained (3j). Electron-donating or electron-withdrawing substituents on aldehydes produce good to excellent yields of secondary amides (3k−p), indicating that the reaction is not sensitive to electronic effects. Various functional groups such as ester, alcohol, and alkyl chlorides are well-suited for this reaction. Chiral amine salt derived from L-amino acids provided chiral amides in high yields (3d−f) without detectable racemization when compared with the HPLC chromatograms of the racemic compounds. Aliphatic (3q, r) and heteroaromatic (3s) aldehydes were less favored substrates, providing lower yields of amide products similar to the results reported by other groups.[18,20a] The

Table 1. Screening of Catalysts and Optimization of Reaction Conditions for Secondary Amide Formation[a]

entry	catalyst	base	oxidant	solvent	T (°C)	yield[b] (%)
1	Cu$_2$O	CaCO$_3$	TBHP	CH$_3$CN	80	84
2	CuCl	CaCO$_3$	TBHP	CH$_3$CN	80	75
3	CuCl$_2$·2H$_2$O	CaCO$_3$	TBHP	CH$_3$CN	80	70
4	CuBr	CaCO$_3$	TBHP	CH$_3$CN	80	66
5	CuOAc	CaCO$_3$	TBHP	CH$_3$CN	80	65
6	Cu(OAc)$_2$	CaCO$_3$	TBHP	CH$_3$CN	80	69
7	Cu(OTf)$_2$	CaCO$_3$	TBHP	CH$_3$CN	80	69
8	Cu powder	CaCO$_3$	TBHP	CH$_3$CN	80	82
9	CuSO$_4$·5H$_2$O	CaCO$_3$	TBHP	CH$_3$CN	80	86
10	CuSO$_4$·5H$_2$O	CaCO$_3$	TBHP	CH$_3$CN	40	86
11	CuSO$_4$·5H$_2$O	CaCO$_3$	TBHP	CH$_3$CN	rt	88
12	CuSO$_4$·5H$_2$O	CaCO$_3$	TBHP	CH$_3$CN	rt	74[c]
13	CuSO$_4$·5H$_2$O	CaCO$_3$	/	CH$_3$CN	rt	0
14	/	CaCO$_3$	TBHP	CH$_3$CN	rt	15
15	CuSO$_4$·5H$_2$O	/	TBHP	CH$_3$CN	rt	14
16	CuSO$_4$·5H$_2$O	CaCO$_3$	TBHP	DCM	rt	62
17	CuSO$_4$·5H$_2$O	CaCO$_3$	TBHP	DMF	rt	55
18	CuSO$_4$·5H$_2$O	CaCO$_3$	TBHP	THF	rt	40
19	CuSO$_4$·5H$_2$O	CaCO$_3$	TBHP	toluene	rt	53
20	CuSO$_4$·5H$_2$O	CaCO$_3$	TBHP	CH$_3$CN + H$_2$O	rt	36[d]

[a]The reaction was carried out with 4-methylbenzaldehyde (1.0 mmol), glycine methyl ester HCl salt (1.2 mmol), base (1.1 mmol), oxidant (70 wt% TBHP in water, 1.1 mmol), Cu catalyst (5 mol % unless otherwise mentioned), and solvent (0.2 mL) at the temperature indicated overnight. [b]Yields were determined by quantitative GC analysis using dodecane as an internal standard. [c]1 mol % of catalyst was used. [d]CH$_3$CN/H$_2$O = 1:1 (v/v), 0.2 mL.

reaction was applied successfully to the synthesis of an antiarrhythmic drug, N-acetylprocainamide (3t), from 4-acetamidobenzaldehyde and 2-diethylaminoethylamine hydrochloride salt generated in situ from the free amine.

Encouraged by the facile synthesis of secondary amides from primary amine salts, the scope of the reaction was extended to the formation of more challenging tertiary amides which were not previously accessible.[18] However, the reaction of benzaldehyde with sarcosine methyl ester hydrochloride (4f) gave only 60% yield of the desired amide (5f) after 24 h reaction at room temperature with unreacted starting materials being recovered (Table 3). It was suspected that the slower reaction rate could be due to the increased steric hindrance of secondary amine. We reoptimized the reaction conditions and delighted to find that the reaction carried out at 60 °C for 6 h afforded the desired amide in 92% yield (5f). Under these conditions, a range of tertiary amides were obtained in good to excellent yield (5a−q). Interestingly, electron-deficient aldehydes gave much improved yields (5j−m) than in the case of secondary amides. The broad applicability of this reaction was well demonstrated in its substrate scope for both secondary amine salts and aldehydes as well as good compatibility with various functional groups (5c−f, i−m). Similar to the case of secondary amide formation, chiral amide (5e) was obtained with methyl L-prolinate hydrochloride. Nevertheless, aliphatic aldehydes remained difficult substrates, giving tertiary amides in only moderate yields (5o−p). When methoxymethylamine

Table 2. CuSO$_4$-Catalyzed Synthesis of Secondary Amides from Aldehydes and Primary Amine Hydrochloride Salts[a]

Entry	Aldehyde	Amine salt	Amide product	Yield (%)[b]	Entry	Aldehyde	Amine salt	Amide product	Yield (%)[b]
1	1a	2a	3a	74	12	1c	2c	3l	63[e]
2	1a	2b	3b	86, 82[c]	13	1d	2c	3m	77
3	1a	2c	3c	83	14	1e	2c	3n	80
4	1a	2d	3d	96	15	1f	2c	3o	72
5	1a	2e	3e	88	16	1g	2c	3p	46
6	1a	2f	3f	86	17	1h	2c	3q	42
7	1a	2g	3g	92	18	1i	2c	3r	44
8	1a	2h	3h	50	19	1j	2c	3s	49
9	1a	2i	3i	49	20	1k	2k	3t	81[f]
10	1a	2j	3j	47[d]					
11	1b	2c	3k	83					

[a]Reactions were carried out with an aldehyde (1.0 mmol), primary amine hydrochloride salt (1.2 mmol), calcium carbonate (1.1 mmol), and TBHP (70 wt % in water, 1.1 mmol) in acetonitrile (0.2 mL) at room temperature under argon atmosphere. [b]Isolated yields. [c]Reaction was carried out by in situ HCl salt formation. [d]Reaction was carried out at 60 °C. [e]4-Methoxybenzoic acid (18%) was also isolated. [f]The salt 2k was formed in situ by reaction with concd HCl.

hydrochloride was used, Weinreb amide **5g** was obtained in moderate yield. As Weinreb amides which are versatile synthetic intermediates,[22] this novel method for their preparation warrants further exploration.

Given the prevalence of the primary amides in biological, pharmaceutical, synthetic, and polymer chemistry,[23] we sought to extend our facile and economic amidation method to primary amides using inexpensive ammonium chlorides as an ammonia source. However, our initial reaction of 4-methylbenzaldehyde with ammonium chloride using the previous conditions for tertiary amide formation was disappointing, with 4-methylbenzamide formed in only 18% yield (Table 4, entry 1). The major byproduct was identified as the corresponding carboxylic acid, which was formed by competitive oxidation reaction of the aldehyde. After screening a range of copper salts, including CuCl, CuCl$_2$·2H$_2$O, CuBr, Cu(OAc)$_2$, CuOAc, Cu$_2$O, Cu(OTf)$_2$, and CuI, copper(I)

oxide was found to be the most effective although the yield remained at ∼30%. We then realized that the low solubility of ammonium chloride in acetonitrile could be detrimental to the reaction. This was indeed proved to be a key factor because addition of water significantly improved the yield (entries 4 and 5). A ratio of acetonitrile/water = 2:1 was found to be the optimal solvent system for this reaction. With this encouraging improvement, a wide variety of inorganic and organic bases, including K$_2$CO$_3$, Cs$_2$CO$_3$, LiOH, Na$_2$CO$_3$, NaHCO$_3$, CaO, 1,8-diazabicycloundec-7-ene (DBU), and N, N-diisopropyle-thylamine (DIPEA), were screened (not included in Table 4), and K$_2$CO$_3$ was found most effective for this transformation (entry 6). Further optimization concluded that with 1.5 equiv of TBHP and at an elevated reaction temperature of 80 °C, 66% yield of the desired amide was obtained in only 4 h of reaction time (entry 7). A variety of ammonium sources including ammonium hydroxide (42%, entry 8), ammonium

Table 3. CuSO$_4$-Catalyzed Synthesis of Tertiary Amides from Aldehydes and Secondary Amine Hydrochloride Salts[a]

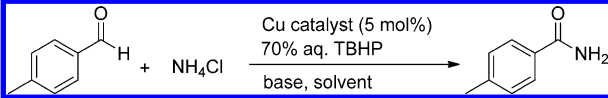| Entry	Aldehyde	Amine salt	Amide	Yield (%)[b]	Entry	Aldehyde	Amine salt	Amide	Yield (%)[b]
1	1a	4a	5a	67	10	1d	4f	5j	74
2	1a	4b	5b	65	11	1e	4f	5k	75
3	1a	4c	5c	70	12	1l	4f	5l	71
4	1a	4d	5d	78	13	1g	4f	5m	69
5	1a	4e	5e	82	14	1m	4f	5n	61
6	1a	4f	5f	60[c] 92	15	1h	4f	5o	53
7	1a	4g	5g	42	16	1i	4f	5p	43
8	1b	4f	5h	77	17	1j	4f	5q	69
9	1c	4f	5i	60[d]					

[a]The reactions were carried out with an aldehyde (1.0 mmol), a secondary amine hydrochloride salt (1.2 mmol), calcium carbonate (1.1 mmol), and TBHP (70 wt % in water, 1.1 mmol) in acetonitrile (0.2 mL) at 60 °C for 6 h under argon atmosphere. [b]Isolated yields. [c]Reaction was carried out at room temperature for 24 h. [d]Formation of 4-methoxybenzoic acid (20%) was observed.

carbonate (54%, entry 9), ammonium sulfate (52%, entry 10), and ammonium acetate (44%, entry 11) were also screened, and ammonium chloride used initially was found to be the best. Increasing the amount of ammonium chloride (2.5 equiv) did not improve the yield any further (67%, entry 12).

With the optimized reaction conditions, the amidation reaction of a variety of aromatic, unsaturated, and hetero-aromatic aldehydes with ammonium chloride were performed. The corresponding primary amides were obtained in moderate to good yields (Table 5). In general, electron-neutral and -rich substrates (**6a**, **6b**, **6c**, and **6e**) gave better yields than electron-deficient ones (**6i−o**). Substituents at different positions of the phenyl ring affected the yield of the amide to some extent, such that substituents present at the *para* (**6b**, **6e**) and *meta* positions (**6c**) were more reactive than those at the *ortho* position (**6d**, **6f**). The lower reactivity of *ortho*-substituted substrates may be attributed to steric factors. The steric sensitivities of the reaction is also observed with 1-naphthaldehyde, which is less reactive than 2-naphthaldehyde. All electron-deficient aldehydes gave moderate yields of the primary amides (**6i−n**). Conjugated aldehydes such as

cinnamaldehyde also afforded moderate yield of the primary amide (**6q**). Functional groups such as ester, cyano, and halogens are tolerant under the reaction conditions. Using ^{15}NH$_4$Cl as a convenient nitrogen isotope labeling reagent, the synthesis of a ^{15}N-isotope labeled primary amide (**6r**) was successfully demonstrated. This provides a facile access to ^{15}N-isotope-labeled primary amides which are valuable for chemical, biological, and medical studies.[24]

The mechanism of this copper-catalyzed oxidative amidation can be assumed to be similar to what has been proposed by Li et al.[18] and that of the iron-catalyzed reaction suggested by us,[21] i.e., the reaction proceeds via a hemiaminal intermediate that is oxidized to amide via a free-radical mechanism (Scheme 2). The free-radical nature of the reaction is confirmed by the addition of 2,6-di-*tert*-butyl-4-methylphenol (BHT, 1 equiv) which completely inhibited the formation of the amide product. Similar to the case of iron-catalyzed amidation reaction, it was found that the use of amines salts is necessary to avoid *N*-oxidation of free amines by TBHP[25] while the use of insoluble

Table 4. Catalyst Screening and Condition Optimization for the Primary Amide Formation[a]

entry	catalyst	solvent	base	T (°C)	time (h)	yield[b] (%)
1	CuSO$_4$·5H$_2$O	ACN	CaCO$_3$	60	6	18
2	Cu$_2$O	ACN	CaCO$_3$	60	6	32
3	Cu$_2$O	ACN	CaCO$_3$	40	24	31
4	Cu$_2$O	ACN + H$_2$O (10:1)	CaCO$_3$	40	24	45
5	Cu$_2$O	ACN + H$_2$O (2:1)	CaCO$_3$	40	24	51
6	Cu$_2$O	ACN + H$_2$O (2:1)	K$_2$CO$_3$	40	24	54
7	Cu$_2$O	ACN + H$_2$O (2:1)	K$_2$CO$_3$	80	4	66[c]
8	Cu$_2$O	ACN + H$_2$O (2:1)	K$_2$CO$_3$	80	4	42[d]
9	Cu$_2$O	ACN + H$_2$O (2:1)	K$_2$CO$_3$	80	4	54[e]
10	Cu$_2$O	ACN + H$_2$O (2:1)	K$_2$CO$_3$	80	4	52[f]
11	Cu$_2$O	ACN + H$_2$O (2:1)	K$_2$CO$_3$	80	4	44[g]
12	Cu$_2$O	ACN + H$_2$O (2:1)	K$_2$CO$_3$	80	4	67[h]

[a]The reactions were carried out with 4-methylbenzaldehyde (1.0 equiv), a copper catalyst (5 mol %), ammonium chloride (1.8 equiv), a base (1.1 equiv), and TBHP (70 wt % in water, 1.1 equiv) in 0.2 mL of acetonitrile with or without water at 80 °C for 6–24 h in a closed vessel, unless otherwise noted. [b]Yields were determined by quantitative GC analysis with dodecane as an internal standard. [c]1.5 equiv of TBHP was used. [d]Ammonium hydroxide was used. [e]Ammonium carbonate was used. [f]Ammonium sulfate was used. [g]Ammonium acetate was used. [h]2.5 equiv of ammonium chloride was used with 1.5 equiv of TBHP and 1.5 equiv of K$_2$CO$_3$. ACN = acetonitrile.
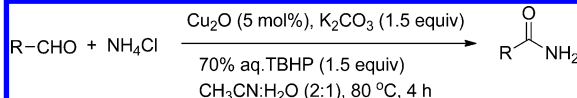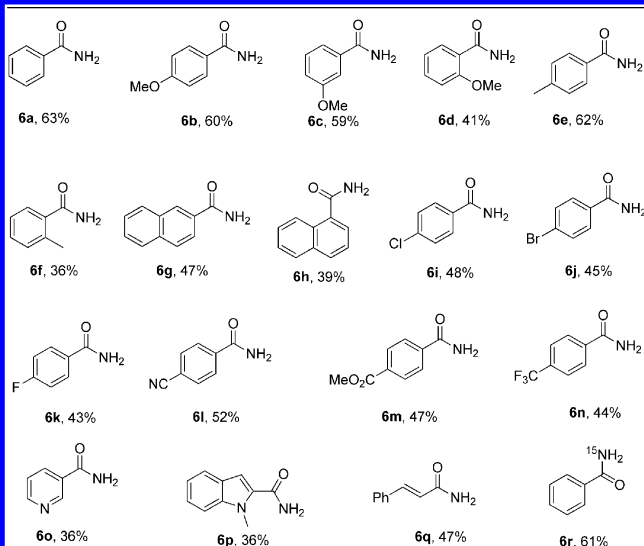
CaCO$_3$ as the base enables slow formation of the amine and thus minimizes the undesired amine oxidation reactions.

■ CONCLUSION

In conclusion, we have identified inexpensive CuSO$_4$·5H$_2$O as a catalyst for the efficient oxidative amidation of aldehydes with amine hydrochloride salts for the synthesis of secondary and tertiary amides. Furthermore, we have, for the first time, achieved the formation of primary amides by oxidative amidation of aldehydes with inexpensive ammonium chloride by using Cu$_2$O as a catalyst. These novel cost-effective amide formation reactions provide practical alternatives for the synthesis of amides under mild conditions.

■ EXPERIMENTAL SECTION

General Considerations. All reactions were carried out in oven-dried glassware under an inert atmosphere of dry argon or nitrogen. All aldehydes and amine hydrochloride salts were obtained from commercial sources and used as received. ^{1}H/^{13}C NMR spectra were measured at 400/100 MHz, respectively, in CDCl$_3$ unless otherwise stated, using either TMS or the undeuterated solvent residual signal as the reference. Chemical shifts are given in ppm, and J values are given in hertz. Optical rotations were measured using an automatic digital polarimeter. Mass spectra were obtained by the electrospray ionization time-of-flight (ESI-TOF) mass spectrometry. Anhydrous solvents were used for moisture-sensitive reactions. GC yields were obtained using

Table 5. Cu$_2$O-Catalyzed Synthesis of Primary Amides from Aldehydes and Ammonium Chloride[a,b]

[a]The reactions were carried out with an aldehyde (1.0 equiv), ammonium chloride (1.8 equiv), potassium carbonate (1.1 equiv), and TBHP (70 wt %in water, 1.5 equiv) in 0.2 mL of acetonitrile and 0.1 mL of water at 80 °C for 4 h in a closed vessel. [b]Isolated yields.

Scheme 2. Proposed Mechanism for Cu-Catalyzed Oxidative Amidation of Aldehydes with Amine Salts
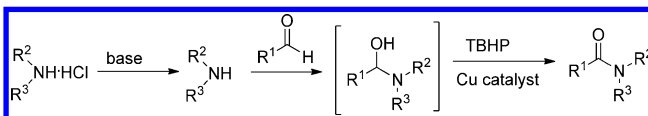
dodecane as an internal standard. Flash column chromatography purification of compounds was carried out by gradient elution using ethyl acetate (EA) in light petroleum ether (PE) unless otherwise stated. Enantiomeric excess for chiral amide products was determined by HPLC analysis using a chiral HPLC column and a UV detector.

General Procedure for the Oxidative Amidation of Aldehydes with Primary Amine Hydrochloride Salts. To a mixture of CuSO$_4$·5H$_2$O (12.5 mg, 0.05 mmol, 5.0 mol %), primary amine hydrochloride salt **2** (1.2 mmol, 1.2 equiv), and CaCO$_3$ (110 mg, 1.1 mmol, 1.1 equiv) in acetonitrile (0.2 mL) were added aldehyde **1** (1 mmol, 1 equiv) and TBHP (70 wt % in H$_2$O, 0.16 mL, 1.1 mmol, 1.1 equiv) under argon atmosphere at room temperature. The reaction vessel was capped and allowed to stir at room temperature overnight. The volatiles were removed under reduced pressure, and the crude product was purified by flash chromatography on silica gel by gradient elution with ethyl acetate in petroleum ether to obtain the amide product **3**. All secondary amides were identified by full spectroscopic characterization and comparison with literature or analogous literature data.

N-Ethylbenzamide (3a).[21] White solid; 111 mg, 74% yield. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.80–7.76 (m, 2H), 7.53–7.48 (m, 1H), 7.47–7.41 (m, 2H), 6.15 (brs, 1H), 3.51 (qd, J = 7.3, 5.7 Hz, 2H), 1.28 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 167.5, 134.8, 131.3, 128.5, 126.8, 34.9, 14.9.

N-Benzylbenzamide (3b).[21] White solid; 181 mg, 86% yield. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.79 (dd, J = 5.3, 3.3 Hz, 2H), 7.54–7.47 (m, 1H), 7.47–7.39 (m, 2H), 7.39–7.32 (m, 4H), 7.32–7.27 (m, 1H), 6.42 (brs, 1H), 4.65 (d, J = 5.7 Hz, 2H). ^{13}C NMR (100 MHz,

CDCl$_3$): δ 167.5, 138.3, 134.6, 131.7, 128.9, 128.7, 128.1, 127.8, 127.1, 44.3.

N-Benzoylglycine Methyl Ester (3c).[21] White solid; 161 mg, 83% yield. ^{1}H NMR (400 MHz, CD$_3$OD): δ 7.86−7.84 (m, 2H), 7.57−7.54 (m, 1H), 7.52−7.45 (m, 2H), 4.12 (s, 2H), 3.75 (s, 3H). ^{13}C NMR (100 MHz, CD$_3$OD): δ 171.9, 170.5, 135.0, 133.0, 129.6, 128.4, 52.6, 42.4.

N-Benzoyl L-phenylalanine Methyl Ester (3d).[21] White solid; 285 mg, 96% yield. [α]$^{25}_D$ = +98.1 (c 1, CHCl$_3$) [lit.[21] [α]$^{24}_D$ = +96.8 (c 1, CHCl$_3$)]. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.79−7.70 (m, 2H), 7.56−7.48 (m, 1H), 7.48−7.40 (m, 2H), 7.33−7.26 (m, 3H), 7.17 (dd, J = 7.8, 1.5 Hz, 2H), 6.60 (d, J = 7.1 Hz, 1H), 5.08 (dt, J = 7.5, 5.7 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 3.28 (qd, J = 13.8, 5.7 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 171.8, 166.9, 136.1, 134.2, 131.9, 129.6, 128.8, 128.7, 127.3, 127.1, 61.8, 53.7, 38.1, 14.3.

N-Benzoyl-L-valine Methyl Ester (3e).[21] White solid; 206 mg, 88% yield. [α]$^{25}_D$ = +42.7 (c 1, CHCl$_3$) [lit.[21] [α]$^{24}_D$ = +43.0 (c 1, CHCl$_3$)]. HPLC (column: Chiracel AD-H, n-hexane/IPA 90/10 (v/v), flow rate: 0.5 mL/min) t_R 18.837 min, ee = 99%. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.80 (dd, J = 8.3, 1.1 Hz, 2H), 7.62−7.37 (m, 3H), 6.64 (d, J = 7.5 Hz, 1H), 4.78 (dd, J = 8.6, 4.9 Hz, 1H), 3.77 (s, 3H), 2.27 (qd, J = 11.9, 6.9 Hz, 1H), 1.00 (dd, J = 9.1, 6.9 Hz, 6H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 172.8, 167.4, 134.3, 131.8, 128.7, 127.2, 57.6, 52.3, 31.8, 19.1, 18.1.

N-Benzoyl-D/L-valine Methyl Ester.[21] White solid; 208 mg, 89% yield. HPLC (column: Chiracel AD-H, n-hexane/IPA 90/10 (v/v), flow rate: 0.5 mL/min) t_{R-D} 14.669, t_{R-L} 18.799 min, ee = 0%. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.80 (dd, J = 8.3, 1.1 Hz, 2H), 7.62−7.37 (m, 3H), 6.64 (d, J = 7.5 Hz, 1H), 4.78 (dd, J = 8.6, 4.9 Hz, 1H), 3.77 (s, 3H), 2.27 (qd, J = 11.9, 6.9 Hz, 1H), 1.00 (dd, J = 9.1, 6.9 Hz, 6H).

N-Benzoyl-L-leucine Methyl Ester (3f).[26] White solid; 214 mg, 86% yield. [α]$^{25}_D$ = +25.3 (c 1.3, CHCl$_3$) [lit.[26] [α]$^{19}_D$ = +39.9 (c 1, CHCl$_3$)]. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.80−7.77(m, 2H), 7.49−7.46 (m, 1H), 7.42−7.39 9 m, 2H), 6.62 (d, J = 7.9 Hz, 1H), 4.88−4.83 (m, 1H), 1.82−1.64 (m, 3H), 0.96 (dd, J = 7.2, 6.3 Hz, 6H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 173.8, 167.2, 134.1, 131.8, 128.7, 127.2, 52.4, 51.3, 42.0, 25.1, 22.9, 22.2. HRMS (ESI): m/z = 272.1260 [M + Na]$^+$, calcd for C$_{14}$H$_{19}$NNaO$_3$ 272.1263.

N-(2-Chloroethyl)benzamide (3g).[21] White solid; 168 mg, 92% yield; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.83−7.74 (m, 2H), 7.56−7.48 (m, 1H), 7.49−7.39 (m, 2H), 6.62 (br s, 1H), 3.85−3.77 (m, 2H), 3.73 (dd, J = 8.1, 3.1 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 167.8, 134.3, 131.9, 128.8, 127.1, 44.3, 41.8.

N-(5-Hydroxypentyl)benzamide (3h).[27] White solid; 104 mg, 50% yield. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.86−7.71 (m, 2H), 7.49−7.45 (m, 1H), 7.44−7.33 (m, 2H), 6.46 (br s, 1H), 3.64 (t, J = 6.3 Hz, 2H), 3.50−3.30 (m, 2H), 2.18 (br s, 1H), 1.76−1.54 (m, 4H), 1.54−1.35 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 167.9, 134.7, 131.5, 128.6, 127.0, 62.6, 40.0, 32.2, 29.5, 23.2. HRMS (ESI): m/z = 230.1153 [M + Na]$^+$, calcd for C$_{12}$H$_{17}$NNaO$_2$ 230.1157.

N-(trans-4-Hydroxycyclohexyl)benzamides (3i).[21] White solid; 107 mg, 49% yield. ^{1}H NMR (400 MHz, CD$_3$OD): δ 7.80−7.77 (m, 2H), 7.53−7.50 (m, 1H), 7.49−7.41 (m, 2H), 3.88−3.82 (m, 1H), 3.57−3.55 (m, 1H), 2.00 (d, J = 10.0 Hz, 4H), 1.50−1.36 (m, 4H). ^{13}C NMR (100 MHz, CD$_3$OD): δ 169.8, 136.0, 132.5, 129.5, 128.3, 70.5, 49.9, 35.1, 31.5.

N-tert-Butylbenzamide (3j).[21] White solid; 84 mg, 47% yield. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.74−7.67 (m, 2H), 7.48−7.42 (m, 1H), 7.41−7.34 (m, 2H), 5.98 (br s, 1H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 167.0, 136.1, 131.1, 128.5, 126.8, 51.7, 29.0.

N-(4-Methylbenzoyl)glycine Methyl Ester (3k).[21] White solid; 172 mg, 83% yield. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.71 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 7.9 Hz, 2H), 6.61 (br s, 1H), 4.25 (d, J = 5.0 Hz, 2H), 3.80 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): I 170.6, 167.3, 142.3, 130.8, 129.3, 127.1, 52.5, 41.7, 21.5.

N-(4-Methoxybenzoyl)glycine Methyl Ester (3l).[21] White solid; 141 mg, 63% yield; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.82−7.74 (m, 2H), 6.97−6.88 (m, 2H), 6.61 (br s, 1H), 4.23 (d, J = 5.1 Hz, 2H), 3.85 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.7, 166.9, 162.4, 128.9, 125.9, 113.8, 77.3, 77.0, 76.7, 55.4, 52.4, 41.7.

N-(4-Chlorobenzoyl)glycine Methyl Ester (3m).[21] White solid: 176 mg, 77% yield. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.78−7.72 (m, 2H), 7.46−7.39 (m, 2H), 6.64 (br s, 1H), 4.24 (d, J = 5.0 Hz, 2H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 170.4, 166.3, 138.1, 132.0, 128.9, 128.5, 52.5, 41.7.

N-(4-Bromobenzoyl)glycine Methyl Ester (3n).[21] White solid; 218 mg, 80% yield. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.70−7.64 (m, 2H), 7.60−7.55 (m, 2H), 6.67 (brs, 1H), 4.23 (d, J = 5.1 Hz, 2H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 170.5, 166.6, 132.6, 132.0, 128.8, 126.7, 52.6, 41.9.

Methyl 4-((2-Methoxy-2-oxoethyl)carbamoyl)benzoate (3o).[21] White solid; 181 mg, 72% yield. ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.16−8.07 (m, 2H), 7.93−7.82 (m, 2H), 6.68 (s, 1H), 4.27 (d, J = 5.0 Hz, 2H), 3.95 (s, 3H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 170.32, 166.52, 166.21, 137.56, 133.09, 129.91, 127.14, 52.57, 52.40, 41.80.

N-(4-Cyanobenzoyl)glycine Methyl Ester (3p).[21] White solid; 116 mg, 46% yield. Mp: 157−161 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.95−7.87 (m, 2H), 7.79−7.71 (m, 2H), 6.72 (br s, 1H), 4.25 (d, J = 5.0 Hz, 2H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 170.2, 165.6, 137.6, 132.5, 127.8, 117.9, 115.5, 52.6, 41.8. HRMS (ESI): m/z = 241.0591 [M + Na]$^+$, calcd for C$_{11}$H$_{10}$N$_2$NaO$_3$ 241.0589.

N-Cyclohexanoylglycine Methyl Ester (3q).[21] White solid; 84 mg, 42% yield. ^{1}H NMR (400 MHz, CDCl$_3$): δ 5.98 (br s, 1H), 4.03 (d, J = 5.1 Hz, 2H), 3.75 (s, 3H), 2.15 (tt, J = 11.7, 3.5 Hz, 1H), 1.89−1.86 (m, 2H), 1.80−1.74 (m, 2H), 1.69−1.60 (m, 2H), 1.44 (qd, J = 12.2, 2.9 Hz, 2H), 1.34−1.17 (m, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 176.3, 170.8, 52.5, 45.3, 41.2, 29.7, 25.9, 25.8.

N-Hexanoylglycine Methyl Ester (3r).[21] Pale yellow liquid; 83 mg, 44% yield. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.01 (br s, 1H), 4.04 (d, J = 5.2 Hz, 2H), 3.75 (s, 3H), 2.23 (t, J = 7.4 Hz, 2H), 1.64 (qd, J = 7.4, 2.1 Hz, 2H), 1.35−1.24 (m, 4H), 0.88 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 173.5, 170.7, 52.4, 41.3, 36.5, 31.5, 25.4, 22.5, 14.0.

Methyl 2-(1-Methyl-1H-indole-3-carboxamido)acetate (3s).[21] White solid; 121 mg, 49% yield. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.65 (d, J = 8.0 Hz, 1H), 7.40−7.30 (m, 2H), 7.16 (ddd, J = 7.9, 6.8, 1.1 Hz, 1H), 6.95 (s, 1H), 6.68 (br s, 1H), 4.24 (d, J = 5.2 Hz, 2H), 4.04 (s, 3H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 170.4, 162.5, 139.2, 131.1, 126.0, 124.3, 122.0, 120.6, 110.2, 104.5, 52.5, 41.3, 31.5.

N-Acetylprocainamide (3t).[21] Pale yellow solid; 225 mg, 81% yield. ^{1}H NMR (400 MHz, CD$_3$OD): δ 7.83−7.75 (m, 2H), 7.65 (d, J = 8.8 Hz, 2H), 3.53−3.45 (m, 2H), 2.71 (dd, J = 7.7, 6.6 Hz, 2H), 2.65 (q, J = 7.2 Hz, 4H), 2.14 (s, 3H), 1.09 (t, J = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, CD$_3$OD): δ 171.8, 169.5, 143.2, 130.6, 129.1, 120.3, 52.6, 48.2, 38.3, 23.9, 11.6.

General Procedure for the Oxidative Amidation of Aldehydes with Secondary Amine Hydrochloride Salts. To a mixture of CuSO$_4$·5H$_2$O (12.5 mg, 0.05 mmol, 5.0 mol %), secondary amine hydrochloride salt **4** (1.2 mmol, 1.2 equiv), and CaCO$_3$ (110 mg, 1.1 mmol, 1.1 equiv) in acetonitrile (0.2 mL) were added aldehyde **1** (1 mmol, 1 equiv) and TBHP (70 wt % in H$_2$O, 0.16 mL, 1.1 mmol, 1.1 equiv) under argon atmosphere at room temperature. The reaction vessel was capped and allowed to stir at 60 °C for 6 h. The volatiles were removed under reduced pressure and the crude product was purified by flash chromatography on silica gel by gradient elution with ethyl acetate in petroleum ether to obtain the amide product **5**. All tertiary amides were identified by full spectroscopic characterization and comparison with literature or analogous literature data.

N,N-Dimethylbenzamide (5a).[21] Colorless liquid; 100 mg, 67% yield. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.44−7.36 (m, 5H), 3.10 (br s, 3H), 2.98 (br s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 171.6, 136.4, 129.5, 128.3, 127.0, 39.6, 35.3. HRMS (ESI): m/z = 172.0740 [M + Na]$^+$, calcd for C$_9$H$_{11}$NNaO 172.0738.

N,N-Diethylbenzamide (5b).[21] Colorless liquid; 115 mg, 65% yield. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.46−7.30 (m, 5H), 3.40 (br s, 4H), 1.17 (br s, 6H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 171.3, 137.3, 129.1, 128.4, 126.3, 43.21, 39.20, 14.11, 12.93.

1-Benzoylpiperidin-4-one (5c).[28] Colorless liquid: 134 mg, 70% yield. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.95–6.95 (m, 15H), 3.85 (br s, 4H), 2.50 (br s, 4H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 206.7, 171.1, 135.3, 130.4, 128.8, 127.1, 59.5, 41.3. HRMS (ESI): m/z = 226.0829 [M + Na]$^+$, calcd for C$_{12}$H$_{13}$NNaO$_2$ 226.0844.

N-Benzoylmorpholine (5d).[21] Colorless liquid; 150 mg, 78% yield. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.05 (s, 5H), 3.78–3.27 (br s, 8H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 170.5, 135.5, 130.0, 128.7, 127.2, 67.0, 48.2, 42.5.

N-Benzoyl-L-proline Methyl Ester (5e).[21] Colorless liquid: 192 mg, 82% yield as a 4:1 mixture of rotamers. [α]$^{25}_D$ = −102.6 (c 1, CHCl$_3$) [lit.[21] [α]$^{24}_D$ = −103.4 (c 1, CHCl$_3$)]. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.60–7.55 (m, 1.6H), 7.41 (dt, J = 6.8, 5.2 Hz, 3.4H), 4.70 (dd, J = 8.3, 5.2 Hz, 0.8H), 4.35 (d, J = 6.7 Hz, 0.2H), 3.80 (s, 3H), 3.69–3.63 (m, 1H), 3.62–3.49 (m, 1H), 2.36–2.31 (m, 1H), 2.14–1.81 (m, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 172.8, 169.7, 136.2, 130.2, 128.4, 128.2, 127.3, 126.5, 61.4, 59.1, 52.2, 49.9, 46.5, 31.5, 29.4, 25.4, 22.7.

N-Benzoylsarcosine Methyl Ester (5f).[21] Colorless liquid; 191 mg, 92% yield in a 2:1 mixture of rotamers. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.47–7.42 (m, 5H), 4.29 (s, 1.3H), 4.00 (s, 0.7H), 3.79 (s, 2H), 3.75 (s, 1H), 3.12 (s, 1H), 3.04 (s, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 172.2, 169.6, 135.6, 130.0, 128.7, 128.5, 127.3, 126.7, 53.3, 52.3, 49.2, 38.8, 34.4.

N-Methoxy-N-methylbenzamide (5g).[21] Colorless liquid; 69 mg, 42% yield. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.70–7.62 (m, 2H), 7.47–7.36 (m, 3H), 3.55 (s, 3H), 3.35 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 170.0, 134.2, 130.5, 128.1, 128.0, 61.0, 33.8.

N-(4-Methylbenzoyl)sarcosine Methyl Ester (5h).[21] Colorless liquid; 170 mg, 77% yield as a 2:1 mixture of rotamers. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.37 (br s, 2H), 7.21 (d, J = 6.4 Hz, 2H), 4.27 (s, 1.3H), 4.01 (s, 0.7H), 3.78 (s, 3H), 3.06 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 172.2, 169.6, 140.0, 132.5, 129.2, 129.0, 127.3, 126.7, 53.3, 52.1, 49.1, 41.7, 38.7, 34.3, 21.4.

N-(4-Methoxybenzoyl)sarcosine Methyl Ester (5i).[21] Colorless liquid; 142 mg, 60% yield as a mixture of rotamers. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.42 (br s, 2H), 6.89 (d, J = 8.4 Hz, 2H), 4.21 (brs, 2H), 3.81 (s, 3H), 3.75 (s, 3H), 3.07 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 171.9, 170.6, 169.7, 167.0, 162.3, 160.9, 129.2, 129.0, 128.7, 127.5, 126.0, 113.7, 55.3,53.3, 52.1, 49.3, 41.6, 38.9, 34.5.

N-(4-Chlorobenzoyl)sarcosine Methyl Ester (5j).[21] Colorless liquid; 179 mg, 74% yield as a 2:1 mixture of rotamers. ^{1}H NMR (400 MHz, CD$_3$OD): δ 7.53–7.48 (m, 3.33H), 7.37 (d, J = 8.1 Hz, 0.67H), 4.30 (s, 1.33H), 4.10 (s, 0.67H), 3.80 (s, 2H), 3.74 (s, 1H), 3.11 (s, 1H), 3.07 (s, 2H). ^{13}C NMR (100 MHz, CD$_3$OD): δ 173.7, 173.3, 171.2, 171.0, 140.1, 137.3, 137.2, 135.5, 135.2, 132.3, 130.0, 129.9, 129.7, 129.4, 54.0, 52.9, 52.7, 50.2, 39.3, 34.9. .

N-(4-Bromobenzoyl)sarcosine Methyl Ester (5k).[21] Colorless liquid; 215 mg, 75% yield as a 2:1 mixture of rotamers. ^{1}H NMR (400 MHz, CD$_3$OD): δ 7.66–7.60 (m, 2H), 7.40 (d, J = 8.3 Hz, 1.33H), 7.28 (d, J = 8.1 Hz, 0.67H), 4.28 (s, 1.33H), 4.07 (s, 0.67H), 3.78 (s, 2H), 3.72 (s, 1H), 3.09 (s, 1H), 3.04 (s, 2H). ^{13}C NMR (100 MHz, CD$_3$OD): δ 171.8, 171.4, 169.3, 169.1, 134.1, 133.8, 131.2, 131.1, 130.9, 130.6, 128.4, 128.2, 127.7, 126.8, 123.6, 123.4, 52.1, 51.1, 50.9, 48.4, 37.5, 33.1.

N-(4-Nitrobenzoyl)sarcosine Methyl Ester (5l).[21] Colorless liquid; 179 mg, 71% yield as a 7:3 mixture of rotamers. ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.29–8.20 (m, 2H), 7.65 (d, J = 8.5 Hz, 1.4H), 7.58 (d, J = 8.2 Hz, 0.6H), 4.30 (s, 1.4H), 3.93 (s, 0.6H), 3.81 (s, 2H), 3.75 (s, 1H), 3.14 (s, 1H), 3.02 (s, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 169.9, 169.0, 148.6, 141.5, 135.0, 131.2, 128.2, 127.8, 124.0, 123.8, 123.6, 52.8, 52.6, 52.4, 49.0, 38.5, 34.5.

N-(4-Cyanobenzoyl)sarcosine Methyl Ester (5m).[21] Colorless liquid; 161 mg, 69% yield as a 7:3 mixture of rotamers; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.69 (dd, J = 14.9, 8.2 Hz, 2H), 7.56 (d, J = 8.2 Hz, 1.4H), 7.48 (d, J = 8.1 Hz, 0.6H), 4.26 (s, 1.4H), 3.91 (s, 0.6H), 3.77 (s, 2H), 3.72 (s, 1H), 3.10 (s, 1H), 2.99 (s, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 170.1, 169.2, 169.1, 140.1, 139.8, 132.6, 132.4, 127.9, 127.4, 118.2, 113.7, 52.9, 52.7, 52.5, 49.0, 38.6, 34.5.

N-(3,4,5-Trimethoxybenzoyl)sarcosine Methyl Ester (5n).[21] Colorless liquid; 182 mg, 61% yield as a 3:2 mixture of rotamers. ^{1}H NMR

(400 MHz, CDCl$_3$): δ 6.67 (br s, 2H), 4.24 (s, 1.2H), 4.01 (s, 0.8H), 3.92–3.79 (m, 9H), 3.79–3.71 (m, 3H), 3.07 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 172.0, 169.6, 153.4, 139.5, 130.9, 104.7, 104.1, 61.0, 56.4, 56.4, 53.4, 53.3, 52.5, 52.3, 49.2, 38.9, 34.5.

N-Cyclohexanoylsarcosine Methyl Ester (5o).[21] Colorless liquid; 113 mg, 53% yield as a 4.1 mixture of rotamers. ^{1}H NMR (400 MHz, CDCl$_3$): δ 4.08 (s, 1.6 H), 4.07 (s, 0.4H) 3.77 (s, 0.6H), 3.70 (s, 2.4H), 3.09 (s, 2.4H), 2.94 (s, 0.6H), 2.54 (tt, J = 11.4, 3.1 Hz, 0.8H), 2.34–2.22 (m, 0.2H), 1.77–1.64(m, 5H), 1.56–1.41 (m, 2H), 1.36–1.17 (m, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 176.9, 170.1, 52.1, 51.5, 49.5, 42.7, 40.8, 40.6, 36.5, 35.1, 29.5, 29.1, 29.0, 25.9, 25.9, 25.5.

N-Hexanoylsarcosine Methyl Ester (5p).[21] Colorless liquid; 86 mg, 43% yield as a 4:1 mixture of rotamers. ^{1}H NMR (400 MHz, CDCl$_3$): δ 4.11 (s, 1.6H), 4.04 (s, 0.4H), 3.76 (s, 0.6H), 3.71 (s, 2.4H), 3.06 (s, 2.4H), 2.96 (s, 0.6H), 2.42–2.31 (t, J = 7.5 Hz, 1.6H), 2.21 (t, J = 7.5 Hz, 0.4H), 1.72–1.56 (m, 2H), 1.32 (dd, J = 8.6, 5.6 Hz, 4H), 0.95–0.83 (m, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 174.1, 173.6, 170.1, 169.7, 52.5, 52.1, 51.7, 49.4, 36.7, 35.0, 33.2, 33.0, 31.7, 24.9, 24.7, 22.6, 14.1.

Methyl 2-(N,1-Dimethyl-1H-indole-3-carboxamido)acetate (5q).[21] Colorless liquid; 179 mg, 69% yield. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.63 (d, J = 7.9 Hz, 1H), 7.37 (d, J = 8.2 Hz, 1H), 7.33–7.27 (m, 1H), 7.18–7.12 (m, 1H), 6.71 (br s, 1H), 4.32 (s, 2H), 3.85 (s, 3H), 3.79 (s, 3H), 3.23 (br s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 169.5, 165.2, 138.3, 138.0, 131.3, 126.4, 125.2, 123.5, 121.6, 120.3, 109.9, 104.2, 53.4, 52.3, 49.1, 38.7, 34.4, 31.1.

General Procedure for the Conversion of Aldehydes to Primary Amides. To a mixture of Cu$_2$O (7 mg, 0.05 mmol, 5.0 mol %), NH$_4$Cl (134 mg, 2.5 mmol, 2.5 equiv) and K$_2$CO$_3$ (207 mg, 1.5 mmol, 1.5 equiv) in acetonitrile (0.2 mL) and water (0.1 mL) were added an aldehyde **1** (1 mmol, 1 equiv) and TBHP (70 wt % in H$_2$O, 0.22 mL, 1.5 equiv) under argon atmosphere at room temperature. The reaction vessel was capped and allowed to stir for 4 h at 80 °C. The reaction mixture was then concentrated and purified by silica gel column chromatography (EtOAc/petroleum ether) to provide the corresponding primary amide **6**. The amides were identified by full spectroscopic characterization and comparison with literature data.

Benzamide (6a).[29] White solid; 76 mg, 62% yield. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.81 (d, J = 7.2 Hz, 2H), 7.53–7.50 (m, 1H), 7.44–7.41 (m, 2H), 6.30 (brs, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 169.9, 133.5, 132.1, 128.7, 127.5. HRMS (ESI): m/z =144.0424 [M + Na]$^+$, calcd for C$_7$H$_7$NNaO 144.0425.

p-Methoxybenzamide (6b).[29] White solid; 91 mg, 60% yield. ^{1}H NMR (400 MHz, acetone-d$_6$): δ 7.94–7.90 (m, 2H), 7.38 (brs, 1H), 6.98–6.95 (m, 2H), 6.65 (brs, 1H), 3.84 (s, 3H). ^{13}C NMR (100 MHz, acetone-d$_6$): δ 168.7, 163.1, 130.2, 127.6, 114.2, 55.7. HRMS (ESI): m/z =174.0528 [M + Na]$^+$, calcd for C$_8$H$_9$NNaO$_2$ 174.0531.

m-Methoxybenzamide (6c).[29] White solid; 89 mg, 59% yield. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.44–7.42 (m, 1H), 7.35–7.31 (m, 2H), 7.07–7.05 (m, 1H), 6.08 (brs, 2H), 3.85 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ= 169.5, 160.0, 134.9, 129.7, 119.3, 118.4, 112.7, 55.6. HRMS (ESI): m/z =152.0710 [M + H]$^+$, calcd for C$_8$H$_{10}$NO$_2$ 152.0712.

o-Methoxybenzamide (6d).[29] White solid; 62 mg, 41% yield. ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.21 (dd, J = 7.8, 1.8 Hz, 1H), 7.72 (brs, 1H), 7.48–7.41 (m, 1H), 7.07 (m, 1H), 6.99 (d, J = 8.3 Hz, 1H), 6.06 (brs, 1H), 3.96 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 167.2, 157.9, 133.5, 132.7, 121.4, 120.9, 111.5, 56.1. HRMS (ESI): m/z =174.0525 [M + Na]$^+$, calcd for C$_8$H$_9$NNaO$_2$ 174.0531.

p-Methylbenzamide (6e).[29] White solid; 84 mg, 62% yield. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.71 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 8.3 Hz, 2H), 6.02 (brs, 2H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 169.4, 142.7, 130.6, 129.4, 127.5, 21.6. HRMS (ESI): m/z =136.0761 [M + H]$^+$, calcd for C$_8$H$_{10}$NO: 136.0762.

o-Methylbenzamide (6f).[29] White solid; 49 mg, 36% yield. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.45 (d, J = 7.6 Hz, 1H), 7.35–7.34 (m, 1H), 7.23 (m, 2H), 5.79 (brs, 2H), 2.50 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 171.9, 136.4, 135.0, 131.2, 130.4, 126.9, 125.7, 20.0. HRMS (ESI): m/z =136.0761 [M + H]$^+$, calcd for C$_8$H$_{10}$NO 136.0762.

Naphthalene-2-carboxamide (6g).[29] White solid; 81 mg, 47% yield. ^{1}H NMR (400 MHz, CD$_3$OD): δ 8.45 (s, 1H) 8.02–7.97 (m, 1H) 7.96–7.91 (m, 3H), 7.63–7.55 (m, 2H). ^{13}C NMR (100 MHz, CD$_3$OD): δ 171.0, 134.9, 132.6, 130.7, 128.6, 127.8, 127.7, 127.4, 127.3, 126.3, 123.6. HRMS (ESI): m/z =194.0579 [M + Na]$^+$, calcd for C$_{11}$H$_9$NNaO 194.0582.

Naphthalene-1-carboxamide (6h).[29] White solid; 67 mg, 39% yield. ^{1}H NMR (400 MHz, CD$_3$OD): δ 8.32–8.26 (m, 1H), 7.98 (d, J = 8.3 Hz, 1H), 7.92 (dd, J = 7.2, 2.2 Hz, 1H), 7.68 (dd, J = 7.0, 1.0 Hz, 1H), 7.59–7.48 (m, 3H). ^{13}C NMR (100 MHz, CD$_3$OD): δ 175.1, 135.2, 131.7, 131.3, 129.4, 127.9, 127.4, 126.4, 125.9. HRMS (ESI): m/z =194.0583 [M + Na]$^+$, calcd for C$_{11}$H$_9$NNaO 194.0582.

p-Chlorobenzamide (6i).[29] White solid; 75 mg, 48% yield. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.76 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 8.5 Hz, 2H), 6.07 (brs, 1H), 5.76 (brs, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 168.3, 138.5, 131.7, 129.0, 128.9. HRMS (ESI): m/z =178.0032 [M + Na]$^+$, calcd for C$_7$H$_6$ClNNaO 178.0036.

p-Bromobenzamide (6j).[29] White solid; 90 mg, 45% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.03 (brs, 1H), 7.81 (d, J = 9.1 Hz, 2H), 7.66 (d, J = 9.1 Hz, 2H), 7.43 (brs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.8, 133.4, 131.2, 129.6, 125.0. HRMS (ESI): m/z =221.9527 [M + Na]$^+$, calcd for C$_7$H$_6$BrNNaO 221.9530.

p-Fluorobenzamide (6k).[29] White solid; 60 mg, 43% yield. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.96–7.71 (m, 2H), 7.22–7.02 (m, 2H), 5.95 (brs, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 168.1, 166.3, 163.8, 129.8, 129.7, 115.8, 115.6. HRMS (ESI): m/z =162.0323 [M + Na]$^+$, calcd for C$_7$H$_6$FNNaO 162.0331.

p-Cyanobenzamide (6l).[29] White solid; 76 mg, 52% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ8.19 (brs, 1H), 8.02 (d, J = 8.5 Hz, 2H), 7.94 (d, J = 8.5 Hz, 2H), 7.64 (brs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.4, 138.3, 132.3, 128.2, 118.3, 113.6. HRMS (ESI): m/z =169.0365 [M + Na]$^+$, calcd for C$_8$H$_6$N$_2$NaO 169.0378.

Methyl 4-carbamoylbenzoate (6m).[29] White solid; 84 mg, 47% yield. ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.12 (d, J = 8.5 Hz, 2H), 7.87 (d, J = 8.5 Hz, 2H), 6.13 (brs, 1H), 5.72 (brs, 1H), 3.95 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 168.2, 166.2, 137.1, 133.3, 129.9, 127.4, 52.4. HRMS (ESI): m/z =202.0478 [M + Na]$^+$, calcd for C$_9$H$_9$NNaO$_3$ 202.0480.

4-(Trifluoromethyl)benzamides (6n).[29] White solid; 84 mg, 44% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.18 (brs, 1H), 8.06 (d, J = 8.1 Hz, 2H), 7.82 (d, J = 8.2 Hz, 2H), 7.59 (brs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.7, 138.1, 131.3, 131.0, 130.7, 128.3, 125.3, 125.2, 125.2, 125.1, 122.6. HRMS (ESI): m/z =212.0299 [M + Na]$^+$, calcd for C$_8$H$_6$F$_3$NNaO 212.0299.

3-Pyridinecarboxamide (6o).[29] White solid; 44 mg, 36% yield. ^{1}H NMR (400 MHz, CD$_3$OD and CDCl$_3$): δ 8.99 (s, 1H), 8.71–8.58 (m, 1H), 8.27–8.18 (m, 1H), 7.52–7.34 (m, 1H). ^{13}C NMR (100 MHz, CD$_3$OD and CDCl$_3$): δ 168.8, 152.1, 148.7, 136.6, 130.2, 124.2. HRMS (ESI): m/z =145.0374 [M + Na]$^+$, calcd for C$_6$H$_6$N$_2$NaO 145.0378.

1-Methyl-1H-indole-2-carboxamide (6p).[29] White solid; 63 mg, 36% yield. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.64 (d, J = 8 Hz, 1H), 7.38–7.32 (m, 2H), 7.16 (t, J = 7.9 Hz), 6.93 (s, 1H), 5.94 (brs, 1H), 4.08 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 164.5, 139.4, 130.7, 126.1, 124.6, 122.1, 120.7, 110.4, 105.3, 31.7. HRMS (ESI): m/z =197.0689 [M + Na]$^+$, calcd for C$_{10}$H$_{10}$N$_2$NaO 197.0691.

Cinnamamide (6q).[29] White solid; 69 mg, 47% yield. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.65 (d, J = 15.7 Hz, 1H), 7.52–7.50 (m, 2H), 7.38–7.36 (m, 3H), 6.47 (d, J = 15.7 Hz, 1H), 5.79 (brs, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 168.0, 142.7, 134.6, 130.1, 129.0, 128.1, 119.6. HRMS (ESI): m/z =170.0570 [M + Na]$^+$, calcd for C$_9$H$_9$NNaO 170.0582.

[15]N-Benzamide (6r). White solid; 74 mg, 61% yield. Mp: 125–128 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.86–7.78 (m, 2H), 7.56–7.50 (m, 1H), 7.48–7.42 (m, 2H), 6.18 (brs, 1H), 5.97 (brs, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 169.6 (d, J = 15.4 Hz), 133.5 (d, J = 8.3 Hz), 132.2, 128.8, 127.5. HRMS (ESI): m/z =145.0388 [M + Na]$^+$, calcd for C$_7$H$_7$^{15}NNaO 145.0396.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of amide products and HPLC chromatograms of racemic and chiral compounds. 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.

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