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A copper-catalysed amidation of aldehydes *via* *N*-hydroxysuccinimide ester formation†

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A copper-catalysed oxidative amidation of aldehydes *via* *N*-hydroxysuccinimide ester formation is reported. The methodology employed to prepare amides directly from aldehydes has a very wide scope, is high yielding, and does not need dry conditions. This cross-coupling reaction appears to be simple and makes use of cheap, abundant and easily available reagents.

Introduction

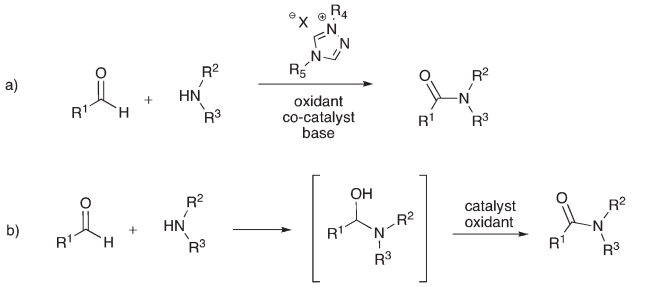
The amide functionality is one of the most significant functional groups present in many natural products, polymers, pharmaceuticals and synthetic intermediates. The classical route to amides is the acylation of an amine with a previously activated carboxylic acid (acid chlorides, mixed anhydrides, carbonic anhydrides or active esters) in the presence of a base.[1]

An elegant alternative approach is the one-pot oxidative amidation of aldehydes, which are readily available starting materials. This alternative process falls into two broad categories. In the first one, a functionalized aldehyde (formylcyclopropanes, α,β-unsaturated aldehydes,[2] α-haloaldehydes and epoxyaldehydes,[3] aromatic or allylic aldehydes[4]) is catalytically transformed into an active ester with an N-heterocyclic carbene (NHC) catalyst and a co-catalyst, which is then reacted with an amine (Scheme 1a).

In the second category, an aldehyde reacts with an amine forming a hemiaminal intermediate, which is subsequently oxidized to an amide, generally by the use of catalysts, such as Cu,[5] Rh,[6] Ru,[7] Pd,[8] Ni[9] and Fe (Scheme 1b).[10]

Nevertheless, the above mentioned methodologies often suffer from drawbacks derived from the steric attributes of the amine and the aldehyde, the use of expensive transition metal catalysts, the limited substrate scope and the utilization of co-reagents.

Therefore, the development of a new method for amide synthesis of general applicability remains an area of active research. The preparation of amides directly from aldehydes, through their transformation into activated esters, is a novel strategy recently investigated in order to alleviate substrate structural dependence. In this context, Yamamoto and co-workers have reported two pioneering examples of oxidative amidation of aldehydes *via* *N*-hydroxysuccinimide ester (NHS ester) formation using *N*-hydroxysuccinimide, O_2 and $Co(OAc)_2$,[11] and *N*-hydroxysuccinimide and hypervalent iodine reagents.[12] The first methodology worked only with sterically unhindered and electronically activated aldehydes and with a few unhindered aliphatic amines, while the second procedure worked only with primary and cyclic secondary aliphatic unhindered amines. The above-described procedures used preferentially the amine hydrochloride salt to limit the oxidation of the amine.



Scheme 1 (a) Amide formation from aldehydes *via* the N-heterocyclic carbene (NHC) catalyst. (b) Oxidative amidation of aldehydes to amides *via* hemiaminal formation.

Barbas III and co-workers[13] have also reported an innovative example of organocatalytic activation of aromatic aldehydes by a cross-coupling strategy to obtain aromatic amides.

Due to our interest in the use of iron- and copper-based catalysts for the synthesis of amides,[14] we tested the possibility of performing a metal catalysed one-pot amidation of aldehydes *via* NHS ester formation.[15]

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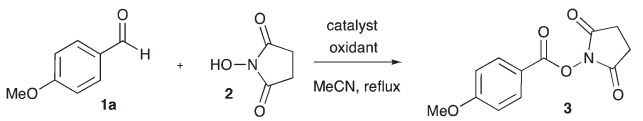
Results and discussion

We started our investigation by treating *p*-methoxybenzaldehyde **1a** with hydroxysuccinimide (NHS) **2**. An overview of the synthetic details is provided in Table 1. Using a catalytic amount of $FeCl_3$ as a catalyst and an aqueous solution of 70% *tert*-butyl hydrogen peroxide (TBHP) in water as an oxidant and in acetonitrile as a solvent, at reflux, the desired *p*-methoxybenzoate ester **3** was obtained in 35% yield[16] (Table 1, entry 1).

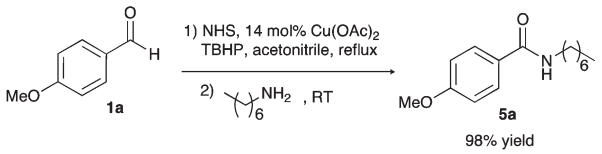
In order to optimize the reaction conditions various parameters, such as catalyst, oxidant and temperature were varied. We repeated the same reaction with the use of $Cu(OAc)_2{\cdot}H_2O$ instead of $FeCl_3{\cdot}6H_2O$, obtaining the product **3** with a significant improvement in yield (99%) and a considerable decrease of reaction time (Table 1, entry 2). When TBAI (nBu_4NI) was used as a catalyst, the reaction time increased considerably (12 h, Table 1, entry 3). Moreover, employing TBAI the reaction did not proceed on aliphatic aldehydes. Very poor results in terms of yield were observed when employing *tert*-butyl peroxybenzoate that gave 34% yield (Table 1, entry 4). No product formation was observed when using classical oxidants such as H_2O_2 and oxone (Table 1, entries 5 and 6). When the reaction was performed at room temperature the yield of ester **3** decreased (Table 1, entry 7). The use of TBHP in decane (Table 1, entry 8) gave the same result as that obtained by the use of aqueous TBHP. No product formation was observed when the reaction was performed without the oxidant (Table 1, entry 9) or without the catalyst (Table 1, entry 10). After the preparation of NHS ester was optimized, we investigated the possibility of performing a one-pot transformation of aldehydes into amides. Thus, when heptylamine was added to the reaction mixture of *p*-methoxybenzaldheyde and NHS,

Table 1 Screening of reaction conditions



Entry[a]	Catalyst	Oxidant	Time (h)	Yield[b] (%)
1	$FeCl_3{\cdot}6H_2O$	TBHP	8	35
2	$Cu(OAc)_2{\cdot}H_2O$	TBHP	1/2	99
3	nBu_4NI	TBHP	12	95
4	$Cu(OAc)_2{\cdot}H_2O$	TBPB	8	34
5	$Cu(OAc)_2{\cdot}H_2O$	H_2O_2[c]	8	—
6	$Cu(OAc)_2{\cdot}H_2O$	Oxone	8	—
7	$Cu(OAc)_2{\cdot}H_2O$	TBHP	8	25[d]
8	$Cu(OAc)_2{\cdot}H_2O$	TBHP[e]	1	98
9	$Cu(OAc)_2{\cdot}H_2O$	—[f]	8	—
10	—[g]	TBHP	8	—

[a] Reaction conditions: *p*-methoxybenzaldehyde **1a** (2 equiv.), *N*-hydroxysuccinimide **2** (1 equiv.), oxidant (2 equiv.), and catalyst (14 mol%) in acetonitrile at reflux. [b] Yields were calculated based on NHS. [c] 10% H_2O_2 in water. [d] Reaction performed at room temperature. [e] Reaction performed with 5.5 M TBHP in decane. [f] Reaction performed without TBHP. [g] Reaction performed without $Cu(OAc)_2{\cdot}H_2O$.

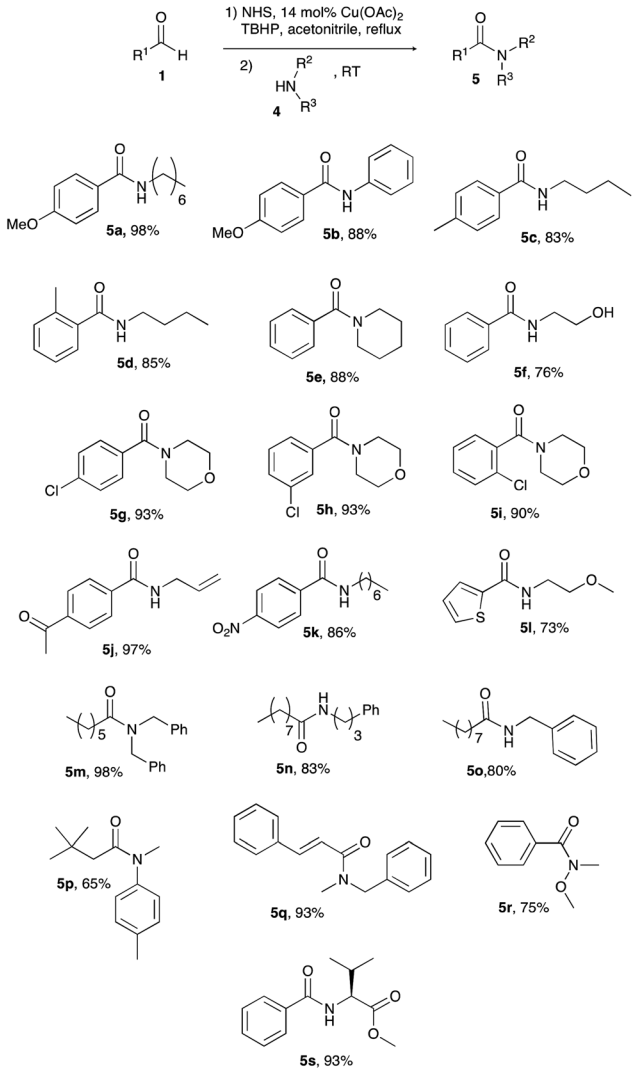


Scheme 2 One-pot synthesis of amides.

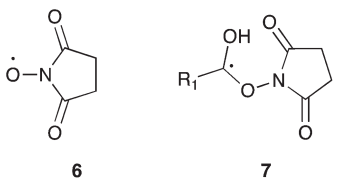
the desired amide **5a** was obtained in 30 min in very good yield (98%).[16] The free amine can be used directly and preparation of amine salt is not necessary. It is noteworthy that in these transformations, the *N*-hydroxysuccinimide used and the excess of aldehyde could be recovered unmodified (Scheme 2).

To investigate the scope of the one-pot methodology for the synthesis of amides, the procedure was tested with an array of commercially available aldehydes and amines. Aromatic aldehydes with a wide range of functional groups, both electron-donating groups, such as –OMe (Scheme 3, **5a** and **5b**) and *o*- and *p*-benzylic C–H (Scheme 3, **5c** and **5d**), and withdrawing groups, such as $–NO_2$ (Scheme 3, **5k**), were well tolerated providing the desired amides in excellent yields. Aromatic aldehydes with carbonyl substituents gave very good results too (Scheme 3, **5j**). The reaction carried out on aldehydes with halide substituents, in different *o*-, *m*- and *p*- positions on the aromatic ring, gave the corresponding amides in very high yields, which could be further transformed by traditional cross-coupling reactions (Scheme 3, **5g**, **5h** and **5i**). To verify the synthetic utility of the method, thiophene-2-carbaldehyde was subjected to optimized conditions, giving the desired heteroaryl amide (Scheme 3, **5l**) in good yield. When *trans*-cinnamaldehyde was employed, the corresponding unsaturated amide (Scheme 3, **5q**) was obtained without affecting the double bond. Aliphatic linear aldehydes provided the resulting aliphatic amides in good yields (Scheme 3, **5m**, **5n** and **5o**), and even aliphatic sterically hindered aldehydes (Scheme 3, **5p**) gave the corresponding amides in satisfactory yield. The reaction was tested with a series of secondary amines showing excellent tolerance. Both very sterically hindered acyclic (Scheme 3, **5m** and **5q**) and cyclic secondary amines (Scheme 3, **5e**, **5g**, **5h** and **5i**) were shown to be effective in this reaction. Furthermore, primary amines (Scheme 3, **5a**, **5c**, **5d**, **5k** and **5n**), even with unsaturation (Scheme 3, **5j**), gave the corresponding N-monosubstituted amides in very good yields. Less active primary (Scheme 3, **5b**) and secondary anilines (Scheme 3, **5p**) also provided good yields of amides. It is to be underlined that primary alcohols were compatible under the optimized reaction conditions (Scheme 3, **5f**). This procedure is suitable for preparing the synthetically useful Weinreb amide too (Scheme 3, **5r**). Finally, in this reaction, the optically pure L-valine methyl ester retained its optical purity (Scheme 3, **5s**).

In order to find experimental evidence for the reaction mechanism, we carried out a series of electron spin resonance (ESR) experiments under various reaction conditions. In our system, we did not find any clear ESR signal corresponding



Scheme 3 One-pot synthesis of amides: investigation of aldehydes and amines scope of the reaction.



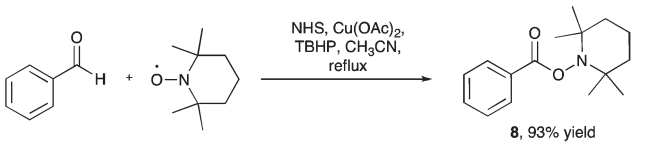
Scheme 4 Succinimide *N*-oxy (SINO) radicals and hemiaminal radicals.

either to succinimide *N*-oxy (SINO) radicals or to hemiaminal radicals (Scheme 4).[17]

However, the radicals may still be present in our system, but the radical reaction is too fast to follow using conventional spectrophotometry.[18]

When we introduced the radical scavenger TEMPO into the reaction, the product **8** was obtained in good yield (Scheme 5).

This result supports the involvement of radical species (either acyl or acetal radicals) in the reaction mechanism.



Scheme 5 Experiment to evaluate the reaction mechanism.

Investigations on the reaction mechanism are currently underway in our group.

Conclusions

In conclusion, a copper-catalysed oxidative amidation of aldehydes was developed. The methodology was employed to prepare amides directly from aldehydes, both aliphatic, aromatic and vinylic, and primary and secondary amines, anilines, amino acids and amino alcohols. The procedure reported herein has a wide scope, is high yielding, does not need dry conditions and uses cheap and easily available reagents.

Experimental section

All reagents and solvents were obtained from commercial sources. All the reactions were carried out under an N_2 atmosphere using standard techniques. Column chromatography was generally performed on silica gel (pore size 60 Å and particle size 40–63 μm) and reactions were monitored by thin-layer chromatography (TLC) analysis performed with Merck Kieselgel 60 F254 plates and visualized using UV light at 254 nm and $KMnO_4$ staining. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker Avance III 400 spectrometer (400 MHz or 100 MHz, respectively) with $CDCl_3$ as a solvent and recorded in ppm relative to the internal standard tetramethylsilane. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; q, quartet; br, broad. The coupling constants, *J*, are reported in hertz (Hz). Melting points were determined in open capillary tubes and are uncorrected. High resolution mass spectroscopy data of the product were collected on a Waters Micromass GCT instrument.

Procedure for the preparation of 2,5-dioxopyrrolidin-1-yl 4-methoxybenzoate (3)

TBHP (6 mmol, 0.8 mL of a 70 wt% solution in water) was added to a mixture of *p*-methoxybenzaldehyde (6 mmol), *N*-hydroxysuccinimide (3 mmol), and $Cu(OAc)_2{\cdot}H_2O$ (0.42 mmol, 0.08 g) in 15 mL of acetonitrile under an argon atmosphere. The reaction mixture was heated in an oil bath at reflux for 40 min (the reaction was monitored by TLC until the disappearance of *N*-hydroxysuccinimide). Then the mixture was cooled to room temperature and was quenched with 50 mL of a saturated solution of Na_2SO_3 and extracted three times with 20 mL of diethyl ether. The combined organic phases were

dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography to provide compound **3** (0.73 g, 99%). White solid, mp 142–145 °C.[19] Purified by flash chromatography (v/v petroleum ether–Et_2O = 3/2), R_f = 0.13; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 7.1 Hz, 2H), 6.99 (d, J = 8.1 Hz, 2H), 3.91 (s, 3H), 2.92 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 164.9, 161.5, 132.9, 117.1, 114.2, 55.6, 25.7. Analysis of the spectroscopic data matched the reported data.[19]

General procedure for the preparation of amides 5a–q

TBHP (6 mmol, 0.8 mL of a 70 wt% solution in water) was added to a mixture of aldehyde (6 mmol), *N*-hydroxysuccinimide (3 mmol), and $Cu(OAc)_2{\cdot}H_2O$ (0.42 mmol, 0.08 g) in 15 mL of acetonitrile under an argon atmosphere. The reaction mixture was heated in an oil bath at reflux for 40 min (the reaction was monitored by TLC until the disappearance of *N*-hydroxysuccinimide). Then the mixture was cooled to room temperature. An amine (8 mmol) was added to the mixture in one portion. After 30 min (the reaction was monitored by TLC until the disappearance of NHS ester), the reaction mixture was quenched with 50 mL of a saturated solution of Na_2SO_3 and extracted three times with 20 mL of diethyl ether. The combined organic phases were washed with a 1 M solution of $KHSO_4$ and then dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography to provide the desired amide.

***N*-Heptyl-4-methoxybenzamide (5a).** 0.73 g, 98%. Pale yellow oil. Purified by flash chromatography (v/v petroleum ether–AcOEt = 4/1.5), R_f = 0.31; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.9 Hz, 2H), 6.89 (d, J = 8.9 Hz, 2H), 6.42 (br s, 1H), 3.82 (s, 3H), 3.40 (q, J = 5.9 Hz, 2H), 1.62–1.55 (m, 2H), 1.35–1.26 (m, 8H), 0.88 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 161.9, 128.7, 127.1, 113.6, 55.3, 40.1, 31.7, 29.7, 29.0, 27.0, 22.6, 14.0; HRMS (EI) ([M^+]) calcd for $C_{15}H_{23}NO_2$: 2 491 729, found: 2 491 725.

4-Methoxy-*N*-phenylbenzamide (5b). 0.68 g, 88%. White solid, mp 172–175 °C.[20] Purified by flash chromatography (v/v petroleum ether–AcOEt = 3.7/1.3), R_f = 0.33; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.8 Hz, 2H), 7.74 (br s, 1H), 7.65 (d, J = 8.7 Hz, 2H), 7.39 (t, J = 7.8 Hz, 2H), 7.17 (t, J = 7.4 Hz, 1H), 7.00 (d, J = 8.9 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 162.5, 138.1, 129.1, 128.9, 127.1, 124.3, 120.1, 114.0, 55.5. Analysis of the spectroscopic data matched the reported data.[20]

***N*-Butyl-4-methylbenzamide (5c).** 0.47 g, 83%. White solid, mp 53–55 °C.[21] Purified by flash chromatography (v/v petroleum ether–AcOEt = 4/1), R_f = 0.17; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.2 Hz, 2H), 7.18 (d, J = 8.2 Hz, 2H), 6.59 (br s, 1H), 3.40 (q, J = 5.8 Hz, 2H), 2.63 (s, 3H), 1.60–1.53 (m, 2H), 1.42–1.32 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 141.5, 132.0, 129.1, 126.9, 39.8, 31.8, 21.4, 20.2, 13.8. Analysis of the spectroscopic data matched the reported data.[21]

***N*-Butyl-2-methylbenzamide (5d).** 0.49 g, 85%. Pale yellow oil. Purified by flash chromatography (v/v petroleum ether–AcOEt = 4/1), R_f = 0.21; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.28 (m 2H), 7.22–7.17 (m, 2H), 5.88 (br s, 1H), 3.42 (q, J = 6.3 Hz, 2H), 2.44 (s, 3H), 1.63–1.55 (m, 2H), 1.47–1.37 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 136.8, 135.7, 130.8, 129.5, 126.6, 125.5, 39.5, 31.7, 20.1, 19.6, 13.8. Analysis of the spectroscopic data matched the reported data.[14a]

Phenyl(piperidin-1-yl)methanone (5e). 0.49 g, 88%. Colourless oil. Purified by flash chromatography (v/v petroleum ether–AcOEt = 3.5/1.5), R_f = 0.18; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (m, 5H), 3.55 (br s, 2H), 3.18 (br s, 2H), 1.51–1.35 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 136.4, 129.2, 128.2, 126.6, 48.6, 42.9, 26.4, 25.5, 24.4. Analysis of the spectroscopic data matched the reported data.[22]

***N*-(2-Hydroxyethyl)benzamide (5f).** 0.41 g, 76%. White solid, mp 57–59 °C.[23] Purified by flash chromatography (AcOEt), R_f = 0.21; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 7.5 Hz, 2H), 7.53–7.41 (m, 3H), 6.88 (br s, 1H), 3.87–3.82 (m, 2H), 3.65–3.61 (m, 2H), 3.17 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 134.0, 131.6, 128.5, 127.0, 61.7, 42.8. Analysis of the spectroscopic data matched the reported data.[23]

(4-Chlorophenyl)(morpholino)methanone (5g). 0.63 g, 93%. White solid, mp 74–75 °C.[24] Purified by flash chromatography (v/v petroleum ether–AcOEt = 4/3), R_f = 0.33; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.36 (m, 4H), 3.72–3.49 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 136.0, 133.6, 128.9, 128.7, 66.8, 48.1, 42.6. Analysis of the spectroscopic data matched the reported data.[22]

(3-Chlorophenyl)(morpholino)methanone (5h). 0.63 g, 93%. Colourless oil. Purified by flash chromatography (v/v petroleum ether–AcOEt = 5/3), R_f = 0.31; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.42 (m, 2H), 7.38 (t, J = 7.4 Hz, 1H), 7.31–7.28 (m, 2H), 3.77–3.46 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 137.0, 134.7, 130.0, 129.9, 127.3, 125.1, 66.8, 48.2, 42.6. Analysis of the spectroscopic data matched the reported data.[24]

(2-Chlorophenyl)(morpholino)methanone (5i). 0.61 g, 90%. White solid, mp 72–73 °C.[22] Purified by flash chromatography (v/v petroleum ether–AcOEt = 2/3), R_f = 0.34; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.28 (m, 4H), 3.93–3.87 (m, 1H), 3.81–3.78 (m, 3H), 3.74–3.69 (m, 1H), 3.64–3.58 (m, 1H), 3.34–3.28 (m, 1H), 3.26–3.19 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 135.3, 130.3, 130.2, 129.7, 127.8, 127.3, 66.8, 66.7, 47.1, 42.1 (some signals are overlapping). Analysis of the spectroscopic data matched the reported data.[25]

***N*-Allyl-4-ethanoylbenzamide (5j).** 0.59 g, 97%. Pale yellow solid, mp 108–110 °C. Purified by flash chromatography (v/v petroleum ether–AcOEt = 2/3), R_f = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.6 Hz, 2H), 7.88 (d, J = 8.6 Hz, 2H), 6.64 (br s, 1H), 5.99–5.89 (m, 1H), 5.29–5.18 (m, 1H), 4.11–4.08 (m, 3H), 2.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 166.4, 139.1, 138.4, 133.8, 128.5, 127.3, 116.9, 42.6, 26.8; HRMS (EI) ([M^+]) Calcd for $C_{12}H_{13}NO_2$: 2 030 946, found: 2 030 943.

***N*-Heptyl-4-nitrobenzamide (5k).** 0.68 g, 86%. Pale yellow solid, mp 78–81 °C. Purified by flash chromatography (v/v petroleum ether–AcOEt = 4/1), R_f = 0.23; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 8.8 Hz, 2H), 7.94 (d, J = 8.8 Hz, 2H), 6.18 (br s, 1H), 3.5 (q, J = 7.1 Hz, 2H), 1.69–1.60 (m, 4H), 1.42–1.31 (m, 6H), 0.91 (t J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 149.5, 140.4, 128.0, 123.8, 40.5, 31.7, 29.5, 28.9, 26.9, 22.5, 14.1. HRMS (EI) ([M^+]) Calcd for $C_{14}H_{20}N_2O_3$: 2 641 474, found: 2 641 472.

***N*-(2-Methoxyethyl)thiophene-2-carboxamide (5l).** 0.41 g, 73%. White solid, mp 84–87 °C. Purified by flash chromatography (v/v petroleum ether–AcOEt = 1/4), R_f = 0.41; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.51 (m, 1H), 7.49–7.47 (m, 1H), 7.09–7.06 8m, 1H), 6.50 (br s, 1H), 3.65–3.61 (m, 2H), 3.57–3.55 (m, 2H), 3.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 138.9, 129.9, 127.9, 127.5, 71.1, 58.8, 39.6; HRMS (EI) ([M^+]) Calcd for $C_8H_{11}NO_2S$: 1 850 510, found: 1 850 512.

***N*,*N*-Dibenzylheptanamide (5m).** 0.91 g, 98%. Colourless oil. Purified by flash chromatography (v/v petroleum ether–AcOEt = 3.5/1.5), R_f = 0.20; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.19 (m, 10H), 4.64 (s, 2H), 4.48 (s, 2H), 2.45 (d, J = 7.4 Hz, 2H), 1.78–1.71 (m, 2H), 1.40–1.28 (m, 6H), 0.91 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 137.6, 136.7, 128.9, 128.6, 128.3, 127.6, 127.3, 126.4, 49.9, 48.1, 33.3, 31.6, 29.1, 25.4, 22.5, 14.1. Analysis of the spectroscopic data matched the reported data.[14a,b]

***N*-(3-Phenylpropyl)nonanamide (5n).** 0.68 g, 83%. White solid, mp 49–52 °C. Purified by flash chromatography (v/v petroleum ether–AcOEt = 3.5/1.5), R_f = 0.29; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.19 (m, 5H), 5.39 (br s, 1H), 3.32 (q, J = 5.9 Hz, 2H), 2.68 (t, J = 7.8 Hz, 2H), 2.14 (t, J = 7.4 Hz, 2H), 1.91–1.83 (m, 2H), 1.66–1.57 (m, 2H), 1.28 (m, 10H), 0.90 (m, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 141.5, 128.5, 128.3, 126.0, 39.2, 36.9, 33.4, 31.9, 31.3, 29.6, 29.5, 29.3, 25.8, 22.7, 14.2. HRMS (EI) ([M^+]) calcd for $C_{18}H_{29}NO$: 2 752 249, found: 2 752 247.

***N*-Benzylnonanamide (5o).** 0.59 g, 80%. White solid, mp 70–73 °C.[26] Purified by flash chromatography (v/v petroleum ether–AcOEt = 3.8/1.2), R_f = 0.38; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H), 5.69 (br s, 1H), 4.47 (d, J = 5.7 Hz, 2H), 2.23 (t, J = 7.4 Hz, 2H), 1.69–1.64 (m, 2H), 1.37–1.29 (m, 10H), 0.90 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 138.4, 128.7, 127.8, 127.5, 43.6, 36.9, 31.8, 29.3, 29.3, 29.1, 25.8, 22.6, 14.1. Analysis of the spectroscopic data matched the reported data.[26]

***N*,3,3-Trimethyl-*N*-*p*-tolylbutanamide (5p).** 0.43 g, 65%. Pale yellow oil. Purified by flash chromatography (v/v petroleum ether–AcOEt = 4.5/0.5), R_f = 0.14; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 7.9 Hz, 2H), 7.04 (d, J = 8.1 Hz, 2H), 3.24 (s, 3H), 2.39 (s, 3H), 2.05 (s, 2H), 0.97 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 142.2, 137.3, 130.2, 127.3, 45.4, 37.4, 31.4, 29.9, 21.1; HRMS (EI) ([M^+]) calcd for $C_{14}H_{21}NO$: 2 191 623, found: 2 191 626.

***N*-Benzyl-*N*-methyl-3-phenylprop-2-enamide (5q).** 0.71 g, 93%. Pale yellow oil. Purified by flash chromatography (v/v petroleum ether–AcOEt = 3.5/1.5), R_f = 0.28; ^{1}H NMR (400 MHz, $CDCl_3$) δ (mixture of rotamers) **5q′**: 7.78 (d, J = 15.6 Hz 1H, H-3), 7.54 (d, J = 6.6 Hz, 2H), 7.20–7.41 (m, 8H), 6.90 (d, J = 15.6 Hz, H-2), 4.71 (s, 2H), 3.09 (s, 3H), **5q″**: 7.80 (d, J = 15.6 Hz, 1H, H-3), 7.46 (d, J = 5.4 Hz, 2H), 7.20–7.41 (m, 8H), 6.96 (d, J = 15.6 Hz, H-2), 4.75 (s, 2H), 3.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 166.4, 142.8, 137.1, 135.0, 136.4, 129.4, 129.4, 128.7, 128.5, 128.5, 128.4, 127.8, 127.6, 127.6, 127.1, 126.2, 117.1, 53.2, 51.0, 34.7, 34.1 (some signals are overlapping). Analysis of the spectroscopic data matched the reported data.[27]

General procedure for the preparation of amides (5r–s)

TBHP (6 mmol, 0.8 mL of a 70 wt% solution in water) was added to a mixture of aldehyde (6 mmol), *N*-hydroxysuccinimide (3 mmol), and $Cu(OAc)_2{\cdot}H_2O$ (0.42 mmol, 0.08 g) in 15 mL of acetonitrile under an argon atmosphere. The reaction mixture was heated in an oil bath at reflux for 40 min (the reaction was monitored by TLC until the disappearance of *N*-hydroxysuccinimide). Then the mixture was cooled to room temperature. An amine hydrochloride (8 mmol) and triethylamine (8 mmol) were added to the mixture. After 30 min (the reaction was monitored by TLC until the disappearance of NHS ester), the reaction mixture was quenched with 50 mL of a saturated solution of Na_2SO_3 and extracted three times with 20 mL of diethyl ether. The combined organic phases were washed with a 1 M solution of $KHSO_4$ and then dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography to provide the desired amide.

***N*-Methoxy-*N*-methylbenzamide (5r).** 0.37 g, 75%. Colourless oil. Purified by flash chromatography (v/v petroleum ether–AcOEt = 3/2), R_f = 0.27; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (dd, J = 6.8, 1.6 Hz, 1H), 7.49–7.39 (m, 3H), 3.57 (s, 3H), 3.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 134.1, 130.5, 128.1, 127.9, 61.1, 33.8. Analysis of the spectroscopic data matched the reported data.[28]

***N*-Benzoyl-L-valine methyl ester (5s).** 0.65 g, 93%. White solid, mp 84–87 °C. $[\alpha]_D^{25}$ +42.8 (c 1 in $CHCl_3$). HPLC (column: Chiralpak IA, *n*-hexane–IPA 90/10 (v/v), flow rate 0.5 mL min^{-1}), t_R 19.414, ee = 99%. Purified by flash chromatography (v/v petroleum ether–AcOEt = 4/1), R_f = 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 7.3 Hz, 2H), 7.54–7.43 (m 3H), 6.68 (br s, 1H), 4.79 (dd, J = 8.5, 4.9 Hz, 1H), 3.78 (s, 3H), 2.29 (m, 1H), 1.00 (dd, J = 9.1, 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 167.2, 134.1, 131.6, 128.5, 126.9, 57.3, 52.2, 31.6, 18.9, 17.9. Analysis of the spectroscopic data matched the reported data.[29]

Preparation of 2,2,6,6-tetramethylpiperidin-1-yl benzoate (8)

TBHP (6 mmol, 0.8 mL of a 70 wt% solution in water) was added to a mixture of benzaldehyde (6 mmol), *N*-hydroxysuccinimide (1.5 mmol), 2,2,6,6-tetramethyl-1-piperidinyloxy (1.5 mmol), and $Cu(OAc)_2{\cdot}H_2O$ (0.42 mmol, 0.08 g) in 15 mL of acetonitrile under an argon atmosphere. The reaction mixture was heated in an oil bath at reflux for 50 min. Then the mixture was cooled at room temperature and was quenched

with 50 mL of a saturated solution of Na_2SO_3 and extracted three times with 20 mL of diethyl ether. The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (v/v diethyl ether–petroleum ether = 1/6), R_f = 0.3, to provide the product **6** (0.36 g, 93%). Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ : 8.09 (d, J = 7.11 Hz, 2H), 7.59 (t, J = 7.93 Hz, 1H), 7.47 (t, J = 7.32 Hz, 2H) 1.84–1.60 (m, 6H), 1.30 (s, 6H), 1.15 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ : 166.3; 132.8; 129.7; 129.5; 128.4; 60.4; 39.1; 31.9; 20.9; 17.1. Analysis of the spectroscopic data matched the reported data.[14a,b]

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