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Copper and N-Heterocyclic Carbene-Catalyzed Oxidative Amidation of Aldehydes with Amines

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Abstract A one-pot two-step oxidative process has been developed for the *tert*-butyl hydroperoxide mediated transformation of aldehydes and amines into amides catalyzed by copper(I) iodide and an N-heterocyclic carbene. The process is additive-free and does not require the amine to be transformed into its hydrochloride salts. The method is simple and practicable, has a broad substrate scope, and uses economical, feasible, and abundant reagents.

Keywords N-heterocyclic carbenes, copper catalysis, organocatalysis, aldehydes, amines, amides

The peptide or amide linkage has a high importance as it finds applications in many areas, such as pharmaceuticals, natural products, agrochemicals, biochemistry, and organic synthesis. It is also present in many natural and synthetic polymers, such as proteins, peptides, and polyamides.^{1,2} The most common approach to amide-bond synthesis involves acylating an amine in the presence of a base with an acid derivative such as an acid chloride, anhydride, or ester.³ This method has been widely used in the syntheses of pharmaceuticals. However, the method has several innate disadvantages in that it makes use of dangerous materials and produces stoichiometric amounts of waste byproducts.⁴ To circumvent these problems, alternative strategies such as the Staudinger reaction;⁵ the Beckmann rearrangement;⁶ the Schmidt reaction;⁷ direct amidation of inactivated carboxylic acids with amines;8 aminocarbonylation of alkanes,9 arenes, or haloarenes;10 amidation of thioacids with azides;¹¹ or amidation of aldehydes with N-chloroamines.^{11c}

Oxidative amidation of aldehydes with amines is desirable because of the ready availability and relatively high abundance of the starting materials, and because these are less hazardous than conventional acid halides.¹² In 1966, Nakagawa et al. reported the first oxidative amidation of aldehydes with amines by using nickel peroxide (Ni₂O₃) as an oxidant in stoichiometric amounts.¹³ Later, several reports were published describing novel methods for the direct conversion of aldehydes and amines into amides by employing such oxidants as N-bromosuccinimide (NBS), iodine, MnO₂, or *tert*-butyl hydroperoxide (TBHP).¹⁴ In addition, inexpensive metals such as Fe or Cu have been actively employed in amide syntheses.^{15,16} However, all the reported methods are limited by the need to use the amine as a salt, and consequently have narrow substrate scopes (Scheme 1). In this context, the use of systems based on N-heterocyclic carbenes and metals appears to circumvent this limitation by facilitating the direct conversion of hemiaminal intermediates into amides.¹⁷

In recent years, NHCs have undoubtedly become popular as ligands. The unique stereoelectronic modularity associated with NHCs and their complexes with various metals have raised their importance as catalytically active species for a wide variety of organic transformations.^{18,19} Many amidation reactions employing NHCs have been reported,





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demonstrating their roles as organocatalysts or as ligands.^{17b,20} Metal-catalyst-assisted amidation reactions featuring NHCs and such transition metals such as Ru,²¹ Rh,²² Ag,²³ or Pd²⁴ have drawn significant attention. Among these, Ru-NHC catalysts have been most actively used in the oxidative formation of amides from aldehydes or alcohols and amines.25

Because of our interest in using cheaper metal along with NHCs for the synthesis of amides, we recently developed an amidation reaction catalyzed by an Fe complex and an NHC.²⁶ Here, we report our attempts to develop a onepot two-step oxidative pathway for amide synthesis from aldehydes and amines through hemiaminal formation by using TBHP with CuI and an NHC (Figure 1) as catalysts in the absence of any additives.

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Pleasingly, our initial coupling reaction of benzaldehyde (2a) (2.5 mmol) with morpholine (2a) (2.5 mmol), catalyzed by CuBr (10 mol%) and NHC precursor 1a (10 mol%), with NaH (10 mol%) as a base and TBHP (3 equiv) as the oxidant in acetonitrile (3 mL) under an inert atmosphere at 90 °C for 20 hours resulted in the formation of the amide product 4-benzoylmorpholine (4a) in 54% yield (Table 1, entry 1). The same reaction did not complete when performed at

Table 1 Investigation of the Effects of Various NHC Precursors, Catalysts, Oxidants and Solvents on the Amidation Reaction^a



Entry	Catalyst	NHC precursor	Oxidant	Solvent	Time (h)	Temp (°C)	Yield ^b (%)
1	CuBr	1a	TBHP	CH ₃ CN	20	90	54
2	CuBr	1b	ТВНР	CH ₃ CN	20	90	22
3	CuBr	1c	TBHP	CH ₃ CN	5	90	17
4	CuBr	1d	ТВНР	CH₃CN	24	90	20
5	CuBr	1e	TBHP	CH₃CN	24	90	26
6	CuBr	1f	TBHP	CH ₃ CN	24	90	12
7	Cul	1a	TBHP	CH ₃ CN	6	90	87
8	Cul	1b	TBHP	CH ₃ CN	20	90	34
9	Cul	1c	TBHP	CH ₃ CN	18	90	29
10	Cul	1d	TBHP	CH ₃ CN	10	90	70
11	Cul	1e	TBHP	CH ₃ CN	8	90	63
12	Cul	1f	TBHP	CH ₃ CN	18	90	11
13	CuSO ₄	1a	TBHP	CH ₃ CN	24	90	8
14	Cu powder	1a	ТВНР	CH₃CN	24	90	trace
15	CuCl	1a	TBHP	CH₃CN	24	90	61
16	Cul	1a	-	CH₃CN	24	90	-
17	Cul	1a	Oxone	CH₃CN	24	90	-
18	Cul	1a	air	CH₃CN	24	90	-
19	Cul	1a	H_2O_2	CH ₃ CN	24	90	54
20	Cul	1a	TBHP	THF	24	100	32
21	Cul	1a	TBHP	toluene	24	110	40
22	Cul	1a	TBHP	EtOH	24	90	29
23	Cul	1a	TBHP	1,4-dioxane	24	90	trace

^a Reaction conditions: 1a (2.5 mmol), 2a (2.5 mmol), TBHP (3 equiv), catalyst (10 mol%), NHC precursor (10 mol%), NaH (10 mol%), solvent (3 mL). ^b Isolated yield after column chromatography.

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room temperature or at ambient temperature, demonstrating the importance of reflux conditions. For catalyst formation, the NHC precursor, NaH base, and CuBr were agitated vigorously under a N_2 atmosphere for 30 minutes before the introduction of other reagents. The successful formation of the amide product after the initial experiment showed that the Cu(I) metal center along with the NHC are capable of promoting the oxidative amidation of aldehydes with amines by TBHP to form amides. For additional optimization studies, we chose benzaldehyde (**2a**) and morpholine (**3a**) as typical substrates (Table 1). We began by analyzing the effects of various NHC precursors **1** on the product formation. Several commercially available NHC precursors **1a**–**f** were subjected to the above reaction conditions (Table 1, entries 1–6), and NHC precursor **1a** emerged as the most suitable precursor, giving amide product **4a** in 54% yield (entry 1). Next, we directed our attention to the choice of a suitable copper catalyst for this conversion. We found that

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Scheme 2 Scope of the reaction. *Reagents and conditions*: **2** (2.5 mmol), **3** (2.5 mmol), TBHP (3 equiv), Cul (10 mol%), NHC precursor **1a** (10 mol%), NHC in mol%), CH₃CN (3 mL). Isolated yields after column chromatography are reported.

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copper(I) iodide (CuI) together with NHC precursor **1a** catalyzed this reaction most efficiently within a timeframe of six hours, giving amide **4a** in 87% yield (entry 7). Among the other copper catalysts examined (entries 13–15), CuCl gave a 61% yield of product **4a**, whereas $CuSO_4$ and Cu powder gave only an 8% yield and a trace of product **4a**, respectively, even after a prolonged reaction time. We therefore concluded that CuI is the optimal catalytic species for this reaction.

We next examined the choice of oxidant for more-precise optimization. We noticed that in the absence of any oxidant, a zero yield of the amide product **3a** was obtained (Table 1, entry 16). Similarly, oxidations carried out in the presence of air or Oxone resulted in no yield of **3a** (entries 17 and 18), whereas H_2O_2 as oxidant showed a slightly better performance, producing a 54% of product **3a** (entry 19). TBHP is therefore as the oxidant of choice for the oxidative procedure. We also studied the effects of various polar and nonpolar solvents on the amidation reaction, keeping all other parameters the same. We observed that the acetonitrile was a better solvent than the other solvents screened (entries 20–23).

Having determined the optimal conditions [aldehyde (2.5 mmol), amine (2.5 mmol), CuI (10 mol%), NHC precursor **1a** (10 mol%), NaH (10 mol%), TBHP (3 equiv), CH₃CN (3 mL), reflux, 6 h], we examined the substrate scope and limitations of our developed method. A broad range of commercially available aldehydes and amines were checked (Scheme 2). A range of substituted aromatic aldehydes **2** bearing electron-donating, electron-withdrawing, or neutral groups smoothly gave the corresponding amides **4b**-h, **4v**, and **4w** in good to excellent yields (Scheme 2). However aromatic aldehydes such as 1-naphthaldehyde did not undergo amidation, possibly due to the bulkiness of the reacting species. However, long-chain and sterically hindered aliphatic aldehydes gave good yields of the corresponding amidation products **4n**, **4q**, **4s**, **4x**, and **4y**.

In the case of the amine, secondary cyclic amines such as morpholine and piperidine gave good yields of the corresponding amide products 4a-c and 4q. Benzylamines and variously substituted aldehydes also gave satisfactory yields of products 4d-f, 4h, 4m, 4s-v, and 4y. [2-(2-Thienyl)ethyl]amine underwent appreciable amidation with 2,4-difluorobenzaldehyde to give product 4x in 78% yield. However, it is worth mentioning that aromatic amines such as anilines gave quite low yields of the corresponding amides 4g, 4j, 4k, 4o, and 4r. Substituted anilines containing either electron-donating or electron-withdrawing groups gave lower yields of amides than did simple anilines (4k, 4o, and 4r). From this, it can be inferred that amidation of aldehydes with anilines is controlled by steric factors rather than by electronic factors. Aliphatic primary amines gave better yields of the corresponding products 4i, 4n, 4p, and 4w than did an aliphatic secondary amine (product 4l).

To gain an understanding of the catalytic activity, we carried out some control experiments (Scheme 3). The reaction of benzaldehyde (2a) with benzylamine (3d) under

the optimized reaction conditions in the absence of oxidant TBHP gave the imine (Schiff base) product **5**, whereas in the presence of TBHP, the amide product **4d** was obtained.



From the above results, we inferred that the oxidative amidation reaction must proceed via a hemiaminal intermediate formed by coupling of the aldehyde and amine, rather than via an ester. The oxidant TBHP is therefore responsible for oxidizing the hemiaminal intermediate to an amide. Based on these experimental outcomes, a plausible mechanism for the reaction is proposed (Scheme 4). The copper–NHC catalyst coordinates to the aldehyde, which reacts with the amine to form the hemiaminal intermediate **B**. This reacts with oxidant TBHP to give the transition state **C**. Subsequent β -H abstraction results in the formation of the amide and *tert*-butanol. Finally, the catalytic cycle is completed by the reaction of the labile halide ion with the NHC–Cu–O radical, with release of molecular oxygen.





In conclusion, a new copper(I) iodide/NHC-catalyzed oxidative amidation of aldehydes with amines has been developed.²⁷ The method is unique among such approaches in that it does not require a large excess of starting materials, the presence of additives, or prior conversion of the amine into its hydrochloride salt for conversion into amides. The method has a wide substrate scope, is high yielding, and uses an inexpensive Cu catalyst and readily available reagents. Further research on the nature of the main catalytic

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species and on the mechanism of the reaction is in progress in our research laboratory.

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Supporting Information

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 (27) Amides 3a-y; General Procedure
- An oven-dried Schlenk tube was charged with a solution of NHC precursor **1a** (10 mol%) and CuI (10 mol%) in CH₃CN (3 mL) under N₂. NaH (10 mol%) was added, and the resulting mixture was stirred vigorously for about 20–30 min and then the appropriate aldehyde (2.5mmol) and amine (2.5mmol) were added to the flask together with TBHP (3 equiv). The mixture was refluxed for 6 h in an oil bath then cooled to r.t., filtered through a Celite pad, and washed with H₂O. The organic portion was extracted with EtOAc, dried (Na₂SO₄), and purified by column chromatography (silica gel, EtOAc–hexane).

2,6-Difluoro-*N*-[2-(2-thienyl)ethyl]benzamide (4x)

White solid; yield: 521 mg (78%); mp 152–153 °C. ¹H NMR (400 MHz, CDCl₃): δ = 7.36–7.28 (m, 1 H), 7.15 (dt, *J* = 5.1, 1.2 Hz, 1 H), 6.96–6.83 (m, 4 H), 6.19 (br s, 1 H), 3.71 (q, *J* = 6.3 Hz, 2 H), 3.14 (t, *J* = 6.7 Hz, 2 H). ¹³C NMR (101 MHz, CDCl₃): δ = 161.32, 160.55, 141.04, 131.65, 127.22, 125.75, 124.20, 114.36, 111.95, 41.51, 29.85. LC-MS: *m*/z [M + H]⁺ calcd for C₁₃H₁₂F₂NOS: 268.0512; found: 268.0509.

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