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

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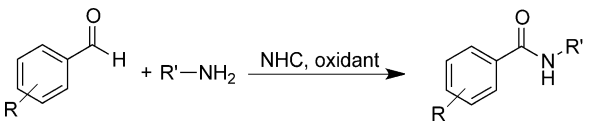
Abstract: The N-heterocyclic carbene (NHC)-catalyzed oxidative amidation of aromatic aldehydes with amines in the presence of *N*-bromosuccinimide (NBS) as an oxidant has been developed for the synthesis of amides. This amidation strategy is tolerant to both the electronic and the steric nature of the aryl aldehydes employed. The present methodology was extended to chiral amino acid derivatives to generate the corresponding amides in good yields and excellent *ee* values (>98%).

Keywords: amides; N-heterocyclic carbenes; organic catalysis; oxidation; oxidative amidation

Amides are ubiquitous structural motifs found in various natural products that have immense importance in the chemical as well as the pharmaceutical industry[1a] and exhibit a wide array of biological activities.[1b] Classical methods for the synthesis of amides include acylation of amines with carboxylic acid derivatives including acid chlorides, anhydrides and activated esters.[2] However, these methods have the innate drawbacks of generating a stoichiometric amount of by-product and employing hazardous reagents. An alternative method for the synthesis of amides is oxidative amidation, which is quite attractive from atom economy and green chemistry points of view. Here, an equivalent amount of aldehyde and amine were coupled together. Up to date, oxidative amidation was performed by employing homogeneous/heterogeneous catalysis which uses expensive and/or toxic transition metal catalysts such as Mn, Al, Ru, Rh, Pd, Cu, Fe, Au and Ag salts.[3–6] A modified approach involving the use of an organocatalyst was also found to be effective to carry out this transformation.

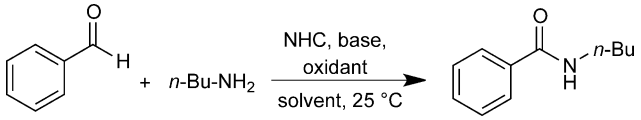
Over the past few years, a large number of synthetically important transformations have been developed in the presence of N-heterocyclic carbene (NHC)-based organocatalysts.[7] Unlike phosphine ligands, NHCs are found to be very stable under oxidative conditions and can even act as a stabilising ligand in Pd-catalyzed oxidation reactions.[8] A considerable number of oxidative transformations have also been developed in the presence of NHC-coordinated metal complexes.[9] Similarly, oxidative NHC catalysis was employed for several transformations: oxidation of aldehydes to esters,[10] amidation and azidation of aldehydes,[11] β-activation of saturated aldehydes,[12] α-functionalization of simple aldehydes,[13] oxidative cleavage of cyclic 1,2-diketones,[14] oxidation of aromatic aldehydes to aryl esters using boronic acids,[15] oxidation of non-activated aldehydes to acids,[16] redox esterification of enals and ynals,[17] and oxo-acyloxylation of alkenes with aromatic aldehydes.[18] In addition, a recent review on NHC catalysis under oxidative conditions gives a detailed account of the application of NHCs as organocatalysts for various oxidative processes and their applications in cascade reaction, enantioselective transformations, and in natural product synthesis.[19]

Amide bond formation of α-functionalized aldehydes with amines catalyzed by NHC has been reported previously.[20] However, to the best of our knowledge, the NHC-catalyzed amidation of simple aryl aldehydes with primary amines has not been explored. Herein, we present the oxidative amidation of aryl aldehydes with aliphatic primary/secondary amines catalyzed by an imidazolium-based NHC, in the presence of *N*-bromosuccinimide (NBS) as the terminal oxidant [Eq. (1)].



(1)

Table 1. Optimization of the reaction conditions for the NHC-catalyzed oxidative amidation of aldehydes.[a]



Entry	NHC pre-catalyst	Base	Oxidant	Solvent	Yield [%][b]
1	**A**	Et_3N	NBS	CH_3CN	63
2	***B***	***Et_3N***	***NBS***	***CH_3CN***	***75***
3	**C**	Et_3N	NBS	CH_3CN	53
4	**D**	Et_3N	NBS	CH_3CN	51
5	**E**	Et_3N	NBS	CH_3CN	45
6	**F**	Et_3N	NBS	CH_3CN	42
7	**G**	Et_3N	NBS	CH_3CN	38
8	**B**	Et_3N	NBS	CH_3CN	56[c]
9	**B**	Et_3N	H_2O_2	CH_3CN	26
10	**B**	Et_3N	TBHP	CH_3CN	<5
11	**B**	Et_3N	BQ[d]	CH_3CN	–
12	**B**	Et_3N	AQ[e]	CH_3CN	–
13	**B**	Et_3N	NQ[f]	CH_3CN	32
14	**B**	Et_3N	NCS	CH_3CN	43
15	**B**	K_2CO_3	NBS	CH_3CN	–
16	**B**	Cs_2CO_3	NBS	CH_3CN	–
17	**B**	NaH	NBS	CH_3CN	48
18	**B**	*t*-BuOK	NBS	CH_3CN	52
19	**B**	DEAD	NBS	CH_3CN	73
20	**B**	Et_3N	NBS	MeOH	61
21	**B**	Et_3N	NBS	DCM	<5
22	**B**	Et_3N	NBS	toluene	<5
23	**B**	Et_3N	NBS	DMF	<5

[a] *Reaction conditions*: benzaldehyde (1 mmol), *n*-butylamine (1.2 mmol), NHC pre-catalyst (10 mol%), base (10 mol%), oxidant (3 mmol) in CH_3CN (3 mL) at 25 °C for 18 h.
[b] Isolated yield.
[c] **B** (5 mol%), Et_3N (5 mol%) for 24 h.
[d] BQ = benzoquinone.
[e] AQ = anthraquinone.
[f] NQ = naphthaquinone.

For our initial optimization studies, benzaldehyde and *n*-butylamine were taken as model substrates for the oxidative amidation (Table 1). By varying different NHC-salts from **A** to **G** as pre-catalysts (Figure 1), we found out that both **A** and **B** gave better results than the other pre-catalysts, and the yield was optimal with **B** (entries 1–7). When the reaction was performed with 5 mol% of **B**, the yield of the desired product decreased significantly from 75% to 56% (entry 8). Once the pre-catalyst was fixed, we tested different oxidants for this transformation (entries 9–14). The yield obtained was found to be low with H_2O_2 and TBHP as terminal oxidant (entries 9 and 10). When quinones were used as oxidants, except for naphthaquinone, the reaction failed miserably (entries 11–13). The yield decreased considerably

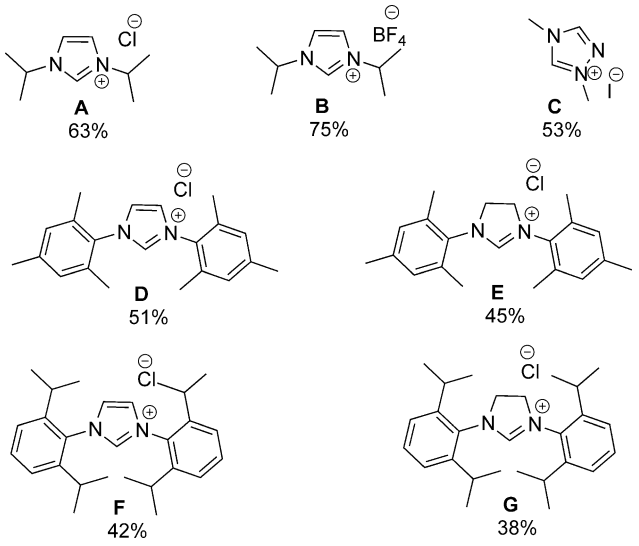
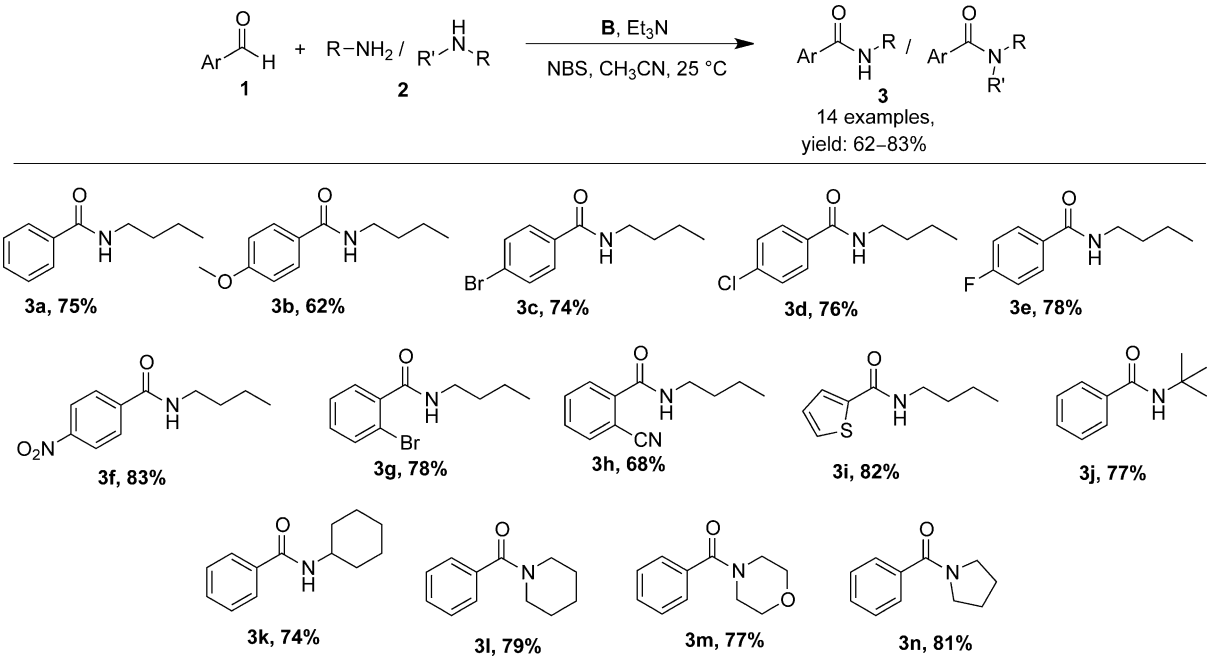


Figure 1. Structures of different NHCs employed for the oxidative amidation.

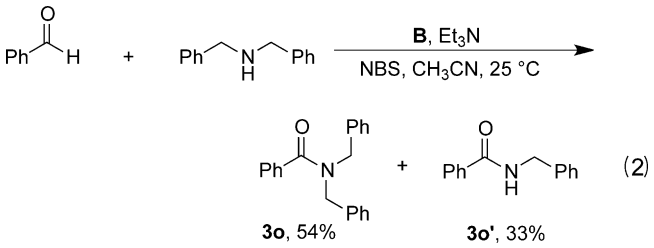
on changing the oxidant from NBS to its halogen counterpart NCS (entries 2 and 14). Then, variation of bases for this oxidative amidation was performed (entries 15–19). With inorganic bases like K_2CO_3 and Cs_2CO_3, the reaction does not yield the desired product, but on employing a strong base like NaH, a 48% yield of the desired amide was observed (entries 15–17). It was observed that organic bases gave better results than inorganic bases (entries 2 and 19). Even though Et_3N and diethyl azodicarboxylate (DEAD) gave comparable yields, Et_3N was used for further studies due to its wide availability and cost effectiveness. Different solvents were screened for this oxidative amidation and acetonitrile proved to be the best solvent (entries 2, 20–23).

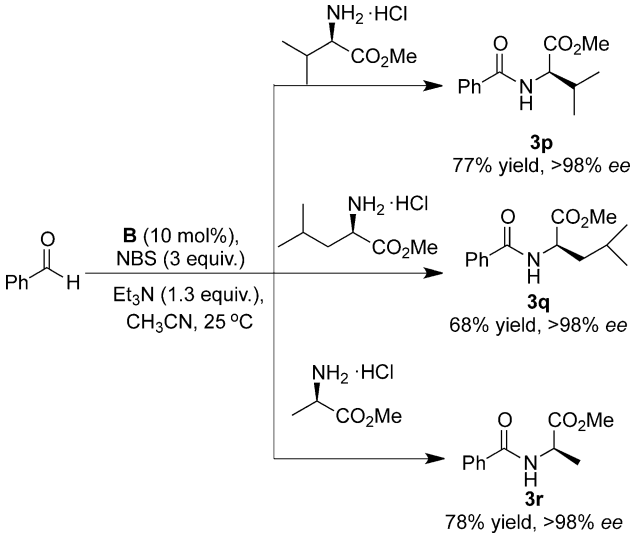
To demonstrate the synthetic utility of this amidation process, various aldehydes and amines were tested under the optimized reaction conditions (Scheme 1). The reaction was tolerant to the electronic nature of the aryl aldehydes as both electron-withdrawing and electron-donating substituted aldehydes worked well to deliver the corresponding products in moderate to good yields (**3a–3f**). Generally, when electron-withdrawing substituents are present in the benzene ring, the yields are better compared to their electron-donating counterparts. The steric factors had minimal effect on this transformation, as 2-substituted aryl aldehydes gave their corresponding products in good yields, for example, 2-bromo- and 2-cyanobenzaldehydes gave 78% and 68% yields of the corresponding amides, respectively (**3g** and **3h**). Moreover, the heteroaromatic thiophene-2-carboxaldehyde gave the corresponding amide in a good yield of 82% (**3i**). Then variation of the primary amines was performed and the yields obtained are comparable with those of



Scheme 1. Scope of the oxidative amidation *via* NHC catalysis. *Reaction conditions:* aldehyde (1 mmol), amine (1.2 mmol.), NHC pre-catalyst **B** (10 mol%), base (10 mol%), NBS (3 mmol) in CH_3CN (3 mL), 25 °C, 18 h. Isolated yields reported.

n-butylamine, when *tert*-butylamine and cyclohexylamine were taken as coupling partners (**3j** and **3k**). When cyclic secondary amines like piperidine, morpholine and pyrrolidine were taken, the desired products were observed in good yields of 79%, 77%, and 81%, respectively (**3l–3n**). When an acylic secondary amine such as dibenzylamine was used for the amidation process along with the expected amide (**3o**, 54%), *N*-benzylbenzamide (**3o′**, 33%) was obtained as a side product, due to benzylic C–H oxidation [Eq. (2)].





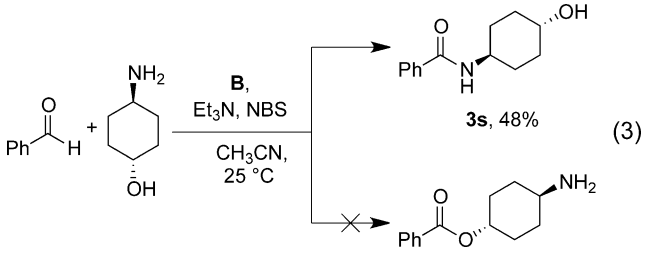
Scheme 2. Oxidative amidation of benzaldehyde with chiral amino acid derivatives.[21]

The scope of this oxidative amidation was extended to chiral amino acid derivatives. When the reaction of benzaldehyde with L-valine methyl ester hydrochloride was performed under the optimized conditions, the corresponding amide was obtained in 77% yield with >98% enantioselectivity.

Similarly, reactions with other amino acid derivatives like L-leucine and L-alanine methyl ester hydrochlorides gave the corresponding amides in moderate yields with excellent enantioselectivities (Scheme 2). The reaction of benzaldehyde with L-phenylglycine methyl ester hydrochloride resulted in a poor yield of the corresponding amide (34%) with partial racemization (92% *ee*).

To probe the reaction mechanism, several background reactions were performed. The reaction of benzaldehyde with *n*-butylamine resulted in the for-

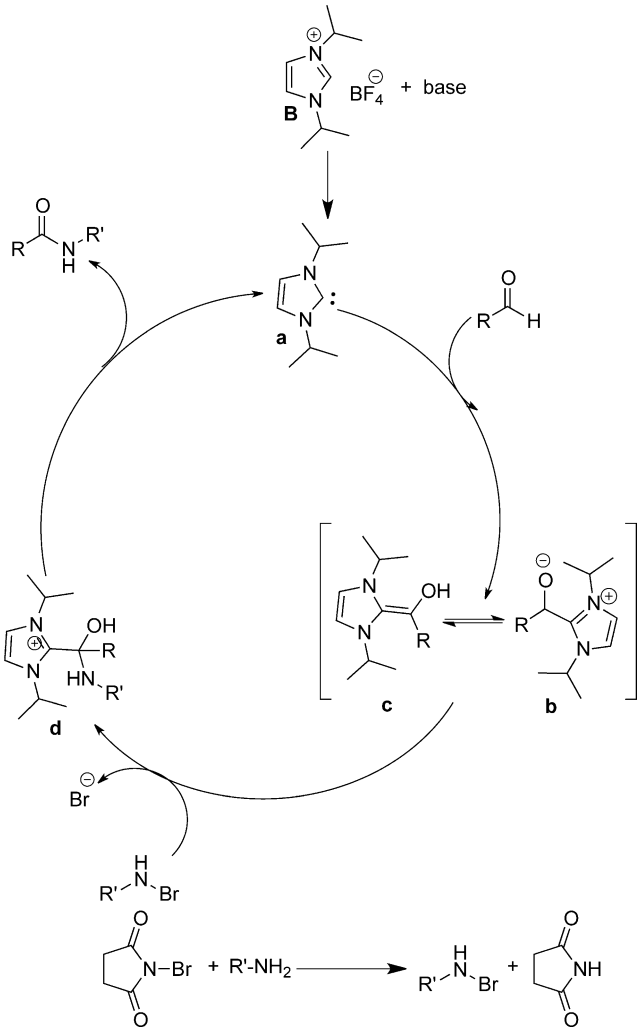
mation of imine which could be observed by ^{1}H NMR of the crude reaction mixture. With this imine, when NHC pre-catalyst **B** was added along with base followed by the addition of NBS, we could not observe the formation of the desired amide. Similarly, when benzoic acid was used as coupling partner, instead of aldehyde, the corresponding amide was not detected. These two test reactions suggest that neither imine nor acid can be the reaction intermediate. Reaction in the absence of either NHC or oxidant did not yield the desired product. This shows that the presence of both NHC and NBS is essential for this oxidative transformation. To arrive at the possible reaction pathway, *trans*-4-aminocyclohexanol was coupled with benzaldehyde under the optimized reaction conditions. Grimme and Studer et al. reported the regioselective formation of esters with the same substrates employing *N,N′*-dimethylimidazolium iodide as an NHC precursor for oxidative esterification.[22] They proposed that the reaction proceeds *via* an acylazolium ion intermediate. But under the present reaction conditions, we observed the regioselective formation of the amide [Eq. (3)]. The *N*-bromination of amines employing NBS has been reported previously.[23] Based on these reports, we anticipate that the bromination of amine employing NBS might have occurred under the reaction conditions, resulting in the formation of an *N*-bromoamine which may act as the key intermediate for this oxidative amidation.



(3)

Based on these reactions, we propose a plausible mechanism as shown in Scheme 3. The initial step is the generation of free carbene **a** from imidazolium salt precursor **B** on treatment with base. The carbene reacts with the aldehyde to generate intermediate **b**,[24] which rearranges to generate the Breslow intermediate **c**.[25] The amine reacts with NBS to give an *N*-bromoamine which further reacts with Breslow intermediate **c** to generate the aminal intermediate **d**.[26] Intermediate **d** undergoes further oxidation to yield the desired amide along with regeneration of the free carbene, thus making this reaction catalytic.

In conclusion, a simple and straightforward method for the synthesis of the amides by oxidative coupling between aldehydes and amines was achieved using oxidative NHC catalysis. The scope of the reaction includes heterocyclic, sterically hindered 2-substituted aldehydes and chiral amino acid derivatives, which are important intermediates in pharmaceuticals and synthetic organic chemistry.



Scheme 3. Plausible mechanism for the oxidative amidation of aldehydes with amines.

Experimental Section

General Procedure for the Synthesis of Amides from Aldehyde and Amine

A mixture of NHC (10 mol%) and base (10 mol%) in 3 mL of CH_3CN was stirred at 25 °C for 30 min. To this mixture, aldehyde (1.0 mmol) and amine (1.2 mmol) were added followed by NBS (3 mmol), and stirring was continued at 25 °C for 18 h. After the completion of the reaction, the solvent was evaporated to dryness. Then the reaction mixture was washed with $Na_2S_2O_3$ solution and extracted with ethyl acetate and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded the crude product, which was purified by column chromatography using hexane/ethyl acetate mixtures and was analyzed by ^{1}H NMR and ^{13}C NMR.

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