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nBu$_4$NI-catalyzed oxidative amidation of aldehydes with tertiary amines

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ABSTRACT

An efficient oxidative coupling protocol for amide formation has been developed. Various tertiary amines and aromatic aldehydes were oxidized to their corresponding tertiary amides in moderate to good yields in the presence of a simple nBu$_4$NI-catalyst.

Amide functionalities are among the most important motifs in natural products, polymers, agrochemicals, and pharmaceuticals.[1] Acylation of amines with activated carboxylic acid derivatives is a common strategy. [1c,g,2] However, due to the lability of activated carboxylic acid derivatives, novel chemical approaches to amide formation are therefore being developed. Examples include the metal-catalyzed aminocarbonylation,[3] modified Staudinger reaction,[4] acid-promoted Schmidt reaction[5] and Beckmann rearrangements,[5b,6] coupling of carboxylic acids with isocyanide,[7] and oxidation of imines to amides via an oxaziridine.[8] Finally, the direct utilization of the acyl C–H of aldehydes under oxidative conditions with amines can also serve as an attractive entry into amides.[9,10] Although these approaches of amidation of aldehydes are very interesting from the points of view of the atom economy and green chemistry, most of the reactions are catalyzed by expensive transition-metal catalyst.

In 2010, Ishihara and co-workers reported a new class of iodine-based oxidation catalysts which were used to catalyze the highly enatioselective intramolecular cycloetherification of ketophenols.[11] Recently, an nBu$_4$NI catalyzed direct oxidative amidation of aldehydes with *N*,*N*-disubstituted formamides or sulfonimides was reported by Wan and Barbas.[12] A careful comparison presents that the reaction mechanisms are similar until the last step and the differences are displayed due to different nitrogen group sources. Based on these researches, we assumed that tertiary amines could replace the two former kinds of nitrogen group sources in the similar 'nBu$_4$NI-Oxidant' radical catalytic system. Additionally, there are some facts to support the above hypothesis: (1) various types of transformation of tertiary amines by oxidation have been widely explored, and the iron-catalyzed oxidative amidation of tertiary amines with aldehydes has been developed by Li.[13] (2) Wang and co-workers developed a nBu$_4$NI-catalyzed C3-formylation of indoles. The amines which were generated from oxidative dealkylation of secondary or tertiary amines in situ were by-products of the formylation, but they could also be the substrates of amidation.[14] (3) Meanwhile, tertiary amines are easily prepared in laboratories and they are also widely discovered in nature, which is meaningful in biology and chemistry. Herein, we reported a new procedure for oxidative amidation of aldehydes using tertiary amines as nitrogen sources, which were catalyzed by nBu$_4$NI through the cleavage of C–N bond.[15]

Initially, we chose benzaldehyde **1a** and *N*,*N*-dimethylaniline **2a** as model substrates to optimize the reaction conditions. Some screening results are summarized in Table 1. nBu$_4$NI was found to be the best catalyst (Table 1, entries 1–4). Increasing the amount of *tert*-butyl hydrogen peroxide (TBHP) gave product **3a** in 92% isolated yield (Table 1, entry 5). When KI or NaI was used as catalyst instead of nBu$_4$NI with 4 equiv of TBHP, the reaction also proceeded to obtain **3a** in up to 70% (Table 1, entries 6 and 7), but the reaction was unsuccessful without catalysts (Table 1, entry 8), which indicated that the use of iodide (I^-) ion in combination with excess co-oxidant is essential to this reaction. Then other oxidants were also examined. Di-*tert*-butyl peroxide (DTBP) and H_2O_2 were ineffective and anhydrous TBHP was as excellent as 70% aqueous TBHP (Table 1, entries 9–11). Further optimization studies were sequentially performed, such as solvent, temperature, and the amount of aldehyde. Remarkably, temperature reduction and

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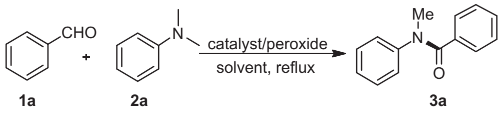
Table 1
Optimization of the reaction conditions[a]



Entry	Catalyst	Oxidant (equiv)	Solvent	Yield[b] (%)
1	$n\text{Bu}_4\text{NI}$	TBHP (2)	CH_3CN	38
2	I2	TBHP (2)	CH_3CN	Trace
3	PhI	TBHP (2)	CH_3CN	N.D
4	NaI	TBHP (2)	CH_3CN	27
5	$n\text{Bu}_4\text{NI}$	TBHP (4)	CH_3CN	92
6	KI	TBHP (4)	CH_3CN	73
7	NaI	TBHP (4)	CH_3CN	70
8		TBHP (4)	CH_3CN	N.D
9	$n\text{Bu}_4\text{NI}$	DTBP (4)	CH_3CN	N.D
10[c]	$n\text{Bu}_4\text{NI}$	H2O2 (4)	CH_3CN	N.D
11[d]	$n\text{Bu}_4\text{NI}$	TBHP (4)	CH_3CN	92
12[e]	$n\text{Bu}_4\text{NI}$	TBHP (4)	CH_3CN	<20
13	$\mathbf{n\text{Bu}_4\text{NI}}$	**TBHP (4)**	**EtOAc**	**98**
14[f]	$n\text{Bu}_4\text{NI}$	TBHP (4)	EtOAc	74
15[g]	$n\text{Bu}_4\text{NI}$	TBHP (4)	EtOAc	47

[a] Reaction conditions: **1a** (2.5 mmol), **2a** (0.5 mmol), catalyst (0.0125 mmol), oxidant, solvent (3 mL), 90 °C, 24 h, TBHP: *tert*-Butyl hydroperoxide 70% in water.

[b] Isolated yield.

[c] H_2O_2 30% in water.

[d] TBHP (5.5 M in decane).

[e] 70 °C.

[f] Compound **2a** (1.0 mmol).

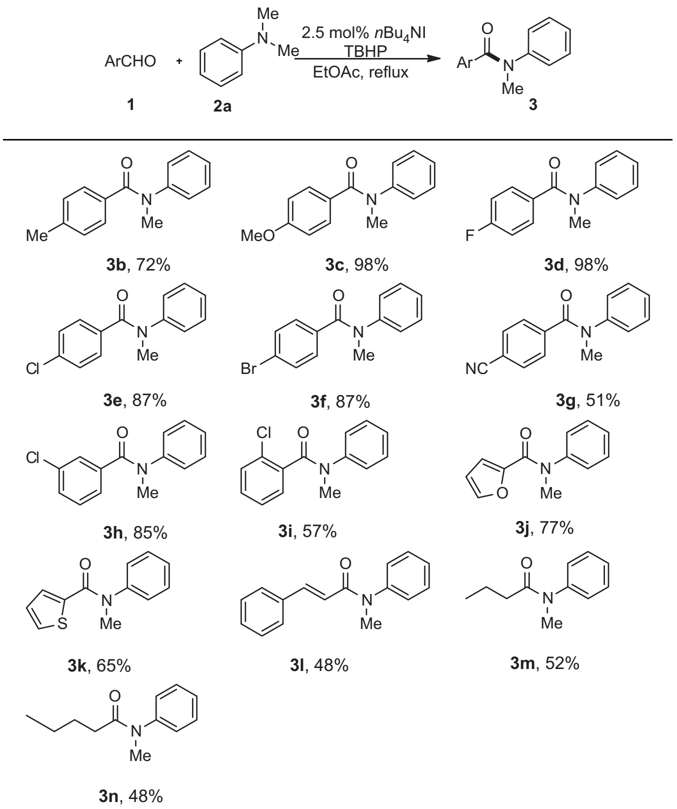
[g] Compound **1a** (0.5 mmol).

aldehyde decrement went against the model reaction (Table 1, entries 12–15). It is worth noting that the yield of the amidation performed in ethyl acetate was slightly higher than that obtained with CH_3CN as the solvent (Table 1, entry 13).

Using the optimized reaction conditions shown in Table 1, entry 13, we subsequently explored the reaction scope by using substituted aromatic aldehydes **1** and *N*,*N*-dimethylaniline (**2a**) (Table 2).[16] The reaction of **2a** was compatible with a variety of functional groups and gave the corresponding products **3a–3n** in the range of 48–98%. The results indicated that both electron-rich and electron-deficient benzaldehyde could be successfully transformed into their corresponding products in moderate to good yields. Specifically, excellent yields were obtained for reactions with 4-halogen-substituted aldehydes, especially for 4-fluoro-*N*-methyl-*N*-phenylbenzamide **3d**. On the other hand, strong electron-withdrawing groups such as CN and NO_2 induced lower reaction efficiency. Though several attempts were made, only 51% product yield was obtained when 4-formylbenzonitrile was coupled with *N*,*N*-dimethylaniline **2a**. However, 73% substrate 4-formylbenzonitrile was recycled. Subsequently, 4-nitrobenzaldehyde was absolutely inefficient with *N*,*N*-dimethylaniline for amide synthesis, but trace methylation product 4-nitroacetophenone was detected by GC–MS. It is easy to understand this methylation reaction based on our introduction of oxidative dealkylation of amines. Besides, reactants with heteroaromatic groups such as furyl and thienyl also afforded the desired products **3j** and **3k** in excellent yields. As for **3l**, the result that less product was produced maybe result from that the double bond in cinnamaldehyde could be oxidized under the optimized conditions.[17] Except for aromatic aldehydes, aliphatic aldehydes were examined, and **3m** and **3n** were obtained in moderate yields.

Next, different substrates with tertiary amines were tested for this amidation with benzaldehyde **1a**. As shown in Table 3 and 4-substituted-*N*,*N*-dimethylaniline gave the corresponding amides **3o–3y** in good to excellent yields. It is particularly attractive that 4-fluoro-*N*,*N*-dimethylaniline also proceeded to oxidative

Table 2
Substrate scope of aldehydes[a,b]

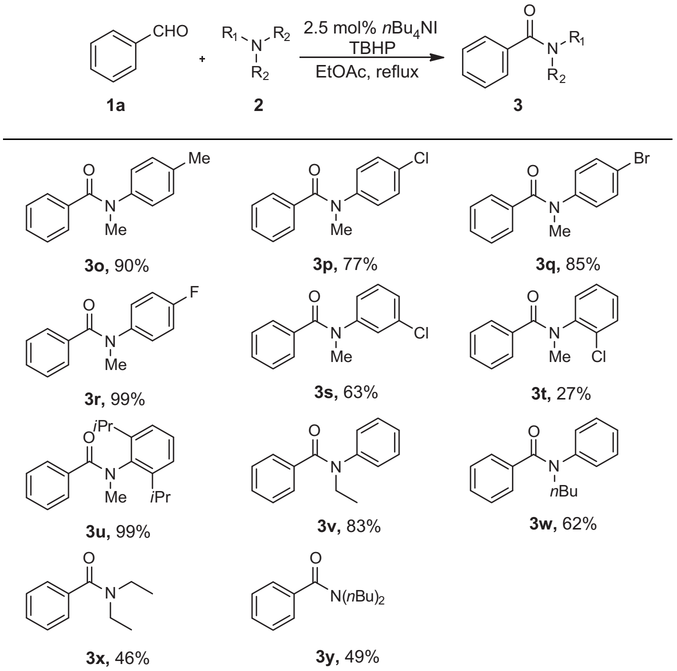


3b, 72% **3c**, 98% **3d**, 98%
3e, 87% **3f**, 87% **3g**, 51%
3h, 85% **3i**, 57% **3j**, 77%
3k, 65% **3l**, 48% **3m**, 52%
3n, 48%

[a] General conditions: **1** (2.5 mmol), **2a** (0.5 mmol), $n\text{Bu}_4\text{NI}$ (0.0125 mmol), TBHP (2 mmol), EtOAc (3 mL), 90 °C, 24 h. TBHP: *tert*-Butyl hydroperoxide 70% in water.

[b] Isolated yields.

Table 3
Substrate scope of tertiary amines[a,b]



3o, 90% **3p**, 77% **3q**, 85%
3r, 99% **3s**, 63% **3t**, 27%
3u, 99% **3v**, 83% **3w**, 62%
3x, 46% **3y**, 49%

[a] General conditions: **1a** (2.5 mmol), **2** (0.5 mmol), $n\text{Bu}_4\text{NI}$ (0.0125 mmol), TBHP (2 mmol), EtOAc (3 mL), 90 °C, 24 h. TBHP: *tert*-Butyl hydroperoxide 70% in water.

[b] Isolated yields.