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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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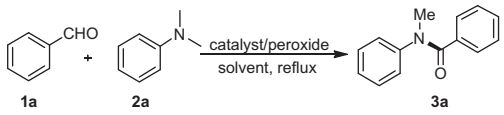
Table 1
Optimization of the reaction conditions[a]



Entry	Catalyst	Oxidant (equiv)	Solvent	Yield[b] (%)
1	nBu$_4$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	nBu$_4$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	nBu$_4$NI	DTBP (4)	CH_3CN	N.D
10[c]	nBu$_4$NI	H2O2 (4)	CH_3CN	N.D
11[d]	nBu$_4$NI	TBHP (4)	CH_3CN	92
12[e]	nBu$_4$NI	TBHP (4)	CH_3CN	<20
13	***n*Bu$_4$NI**	**TBHP (4)**	**EtOAc**	**98**
14[f]	nBu$_4$NI	TBHP (4)	EtOAc	74
15[g]	nBu$_4$NI	TBHP (4)	EtOAc	47

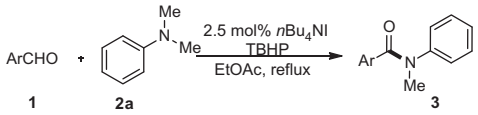
[a] Reaction conditions: **1a** (2.5 mmol), **2a** (0.5 mmol), catalyst (0.0125 mmol), oxidant, solvent (3 mL), 90 °C, 24 h, TBHP: *tert*-Butyl hydroperoxide 70% in water.
[b] Isolated yield.
[c] H_2O_2 30% in water.
[d] TBHP (5.5 M in decane).
[e] 70 °C.
[f] Compound **2a** (1.0 mmol).
[g] Compound **1a** (0.5 mmol).

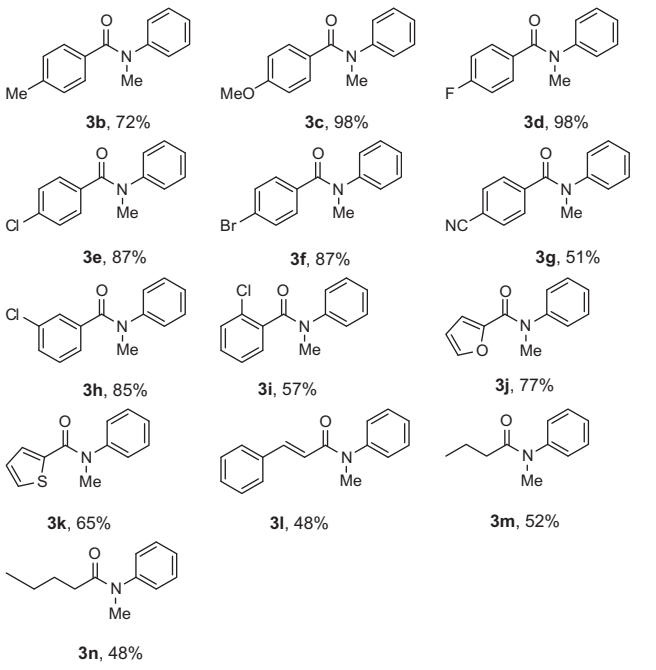
aldehyde decrement went against the model reaction (Table 1, entries 12–15). It is worth noting that the yield of the amidation performed in ethyl acetate was slightly higher than that obtained with CH_3CN as the solvent (Table 1, entry 13).

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

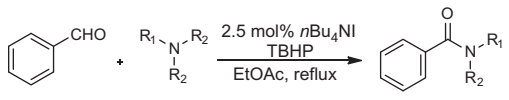
Table 2
Substrate scope of aldehydes[a,b]

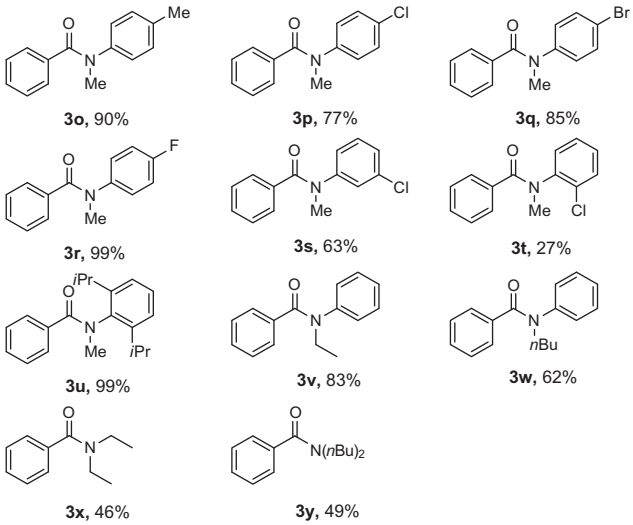




[a] General conditions: **1** (2.5 mmol), **2a** (0.5 mmol), nBu$_4$NI (0.0125 mmol), TBHP (2 mmol), EtOAc (3 mL), 90 °C, 24 h. TBHP: *tert*-Butyl hydroperoxide 70% in water.
[b] Isolated yields.

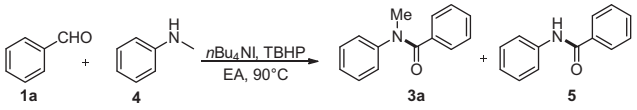
Table 3
Substrate scope of tertiary amines[a,b]





[a] General conditions: **1a** (2.5 mmol), **2** (0.5 mmol), nBu$_4$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 4
Reaction between benzaldehyde and *N*-methylaniline[a]



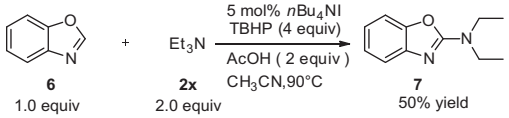
Entry	nBu$_4$NI (mol %)	TBHP (equiv)	Yield of **3a**[b] (%)	Yield of **5**[b] (%)
1	2.5	4	65	15
2	10	4	70	27
3	20	4	59	22
4	2.5	2	69	20
5	2.5	6	47	Trace

[a] Reaction conditions: **1a** (2.5 mmol), **2a** (0.5 mmol), nBu$_4$NI, TBHP, EtOAc (3 ml), 90 °C, 24 h, TBHP: *tert*-Butyl hydroperoxide 70% in water.
[b] Isolated yield.

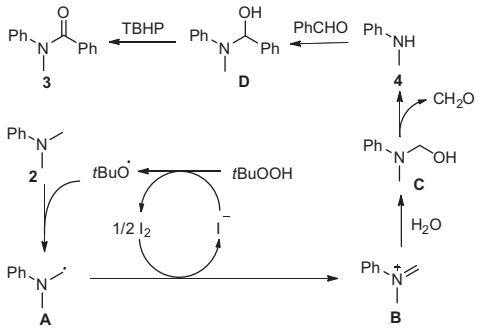
amidation with benzaldehyde to yield **3r** gracefully. So far, the fluoro group has been completely tolerated in both aldehyde and amine. To investigate the steric effect, substituents on the different positions of aniline or benzaldehyde were screened (**3d**, **3h**, **3i**, **3p**, **3s**, and **3t**). The results showed an obvious yield decrease when the substituent was moved from *para*-position to *ortho*-position. Meanwhile, two bulky isopropyls were introduced into the *ortho*-position of *N,N*-dimethylaniline to examine the effect of a larger steric hindrance. Surprisingly, the desired hindered amide product **3u** was isolated in 99% yield. Combining these two results, a conclusion is drawn that the steric hindrance impact is minor, while the electronic effect of the functional groups attached to the arene ring is outstanding. At last, other N-substituted amines also underwent the reaction smoothly by oxidative dealkylation. Not only aromatic amines but also aliphatic amines such as triethylamine and tributylamine were used in the amidation reactions catalyzed by nBu$_4$NI to obtain **3x** and **3y** in moderate yields .

To clarify the possible reaction pathway, the reaction between benzaldehyde and *N*-methylaniline was optimized. To our delight, two kinds of products **3a** and **5** were formed in good yields and this is sufficient evidence toward the direct acylation of N–H under our catalytic system. Logically, the minor product **5** should be obtained by oxidative amidation of benzaldehyde **1a** with phenylamine which was generated from demethylation of *N*-methylaniline **4**. This does accord with Reddy's report about oxidative amidation of aldehydes with primary amines catalyzed by KI-TBHP in 2008.[10b] Generally, catalyst loading and the quantity of oxidant have a significant effect on the yield of these two amides. An excellent overall yield of **3a** and **5** was achieved in the presence of 4 equiv of TBHP by using 10% nBu$_4$NI as catalyst (Table 4, entry 2). The ratio between **3a** and **5** was steady except entry 5 in which TBHP was increased to 6 equiv.

With the proven fact that the secondary amines generated in situ from tertiary amines have been utilized effectively in hand, we exploited other reactants which could combine these 'slow'-releasing amines. In our previous study, we have reported iron-catalyzed direct amination of benzoxazole **6** using secondary amines as nitrogen sources.[18] Meanwhile, iodine- or nBu$_4$NI-catalyzed benzoxazole **6** C–H amination with amines was also presented by Prabhu and Nachtsheim respectively.[19] Based on these developments, we envisioned that what if the tertiary amines might substitute for secondary amines to react with benzoxazole **6**. Disappointedly, we did not isolate the desired product when benzoxazole **6** was mixed into *N,N*-dimethylaniline **2a** under our optimized conditions. This result was coincident with previous reports that phenylamine was inert in the oxidative amination of benzoxazole. However, triethylamine **2x** could react smoothly with benzoxazole **6** with a 50% yield using a slightly different condition



Scheme 1. Amination of benzoxazole with tertiary triethylamine.



Scheme 2. Proposed reaction mechanism.

(Scheme 1). To the best of our knowledge, the nBu$_4$NI-catalyzed direct amination of benzoxazole **6** using tertiary amines as nitrogen sources has never been reported.

A tentative mechanism for the oxidative amidation of aldehydes with tertiary amines as nitrogen sources is proposed in Scheme 2. Initially, a reaction between an iodide (I^-) ion and TBHP provides a *tert*-butyloxy radical and iodine (I_2).[12b] The generated radical abstracts a hydrogen atom from the C–H bond adjacent to a nitrogen atom to afford radical **A**, followed by oxidation to afford iminium ion **B**. Subsequently, hydrolysis of **B** through **C** affords secondary amine **4**. Theoretically, a further hydrogen abstraction and one-electron oxidation is feasible, such as the reaction in Table 4. In fact, once it is produced, amine **4** immediately combines with aldehyde which is in large excess relative to the 'slow'-releasing amine. Finally, the desired amide product **3** is obtained after an oxidation process of the intermediate **D**.

In conclusion, we have developed a novel amidation reaction of aromatic aldehydes with tertiary amines in the absence of metal. A variety of aldehydes and tertiary amines could be used to obtain the related amides in moderate to excellent yields, and only cheap and nontoxic nBu$_4$NI was used as the catalyst. Further investigation on the reaction is ongoing in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.09.018.

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15. During prepare this manuscript, Qu et al. reported a nBu$_4$NI-catalyzed unexpected amide bond formation between aldehydes and aromatic tertiary amines. See: Mai, W.-P.; Song, G.; Yuan, J.-W.; Yang, L.-R.; Sun, G.-C.; Xiao, Y.-M.; Mao, P.; Qu, L.-B. *RSC Adv.* **2013**, *3*, 3869–3872.
16. *General procedure for amides:* amine (0.5 mmol) and aldehyde (2.5 mmol) were added to a tube with a mixture of nBu$_4$NI (4.6 mg, 0.0125 mmol) and EtOAc (3.0 mL) at room temperature. Then *tert*-butyl hydroperoxide (TBHP in water, 70 wt%) was dropped into the mixture. The resulting mixture was stirred at 90 °C for 24 h. The temperature of the reaction was cooled to room temperature. The resulting reaction solution was concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel with ethyl acetate/petroleum ether (1:10) as an eluent to afford the amide product.
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