Synthetic Methods

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Cross Coupling of Acyl and Aminyl Radicals: Direct Synthesis of Amides Catalyzed by Bu_4NI with TBHP as an Oxidant**

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Dedicated to Professor Christian Bruneau on the occasion of his 60th birthday

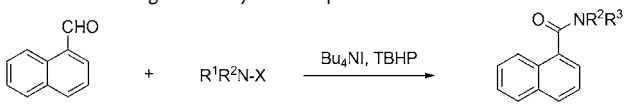
Amides are prevalent structural motifs that are found in biologically relevant molecules, such as proteins, as well as natural products, marketed drugs, and synthetic intermediates.[1] As a result, the synthesis of amides has attracted considerable interest and a number of methods have been devised. Conventionally, amides are synthesized by coupling a carboxylic acid or a carboxylic acid derivative with an amine.[1a,b,2,3] In addition, the aminocarbonylation of aryl halides has been developed for the chemoselective formation of amides.[4] Transition-metal-catalyzed oxidative coupling between alcohols and amines also offers elegant and direct access to amides.[5] Alternatively, the use of thioacids or thioesters as acylation reagents has emerged as a powerful method for amide synthesis.[6] Other attractive approaches include the hydration of nitriles,[7] rearrangement of oximes,[8] acylation of amines,[9] the modified Staudinger reaction,[10] carbonylation of alkenes[11] or alkynes,[12] amidation of nitriles,[13] or transition-metal-catalyzed C–C bond cleavage.[14] Although great progress has been achieved in this field, there still remains significant challenges for synthetic organic chemists in both academic and industrial teams worldwide.

Currently, the synthesis of amides relies heavily on ionic reactions. Undoubtedly, a radical process,[15] for example the coupling of acyl- and nitrogen-centered radicals, is a fundamentally different method for the formation of amide bonds. Recently, we developed a Bu_4NI-catalyzed *tert*-butyl perester synthesis,[16d] in which acyl radicals, which are generated in situ from aldehydes, could be trapped by 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO). Inspired by this success, we envisioned the coupling of a nitrogen-centered radical, instead of TEMPO, with the acyl radical to provide a method for amide synthesis.

To achieve this goal, an appropriate nitrogen-centered radical precursor that favors the formation of the amide bond was required. As shown in Table 1, a variety of amine derivatives, which include *N*-chlorosuccinimide (NCS), *N*-bromosuccinimide (NBS), *N*-iodosuccinimide (NIS), Chloramine-T, NH_2NH_2, and NH_2OH, were used as potential donors of nitrogen-centered radicals.[17] Unfortunately, no significant formation of the amide bond was detected in these reactions. When the reaction was performed in *N*,*N*-dimethylformamide (DMF), however, *N*,*N*-dimethyl-1-naphthamide (**3a**) was detected, which indicates that DMF is an effective source of aminyl radicals. The success of the reaction with DMF might be a consequence of the longer lifetime of aminyl radicals relative to amidyl radicals.[18] Through systematic screening of the reaction conditions, a stirred solution of 1-naphthaldehyde **1a**, DMF, Bu_4NI (20 mol%), and *tert*-butyl hydroperoxide (TBHP, 5.8 equiv) in 1,1,2-trichloroethane at 90°C for 24 h gave **3a** in 89% yield, with no formation of 1,2-diketones or *tert*-butyl peresters (Table 1, entry 7; for optimization of the reaction conditions, see Table S1 in the Supporting Information). A trace amount of hydrazine was formed in the transformation, which indicates that the aminyl radical was generated in situ from DMF. The high selectivity could be a result of the persistent radical effect (PRE).[19]

Further investigations on the mechanism were performed. A trace amount of carboxylic acid was detected in the reaction mixture. When 1-naphthoic acid (**4**) was used in the optimized conditions, no **3a** was detected (Scheme S1a in the Supporting Information). Furthermore, the use of *tert*-butyl perester **5** as reaction partner suppressed the amide synthesis

Table 1: Screening for aminyl radical precursors.[a]



1a 2 3

Entry	R^1R^2N-X	Yield [%][b]
1	NCS	<5
2	NBS	<5
3	NIS	<5
4	Chloramine-T	<5
5	NH_2NH_2	<5
6	NH_2OH	<5
7	DMF	89

[a] Reaction conditions: A mixture of 1-naphthaldehyde (**1a**, 0.5 mmol), amino radical precursors **2** (7.5 mmol), Bu_4NI (20 mol%), TBHP (2.9 mmol, 0.4 mL of a 70% aqueous solution) in 1,1,2-trichloroethane (2.0 mL) was stirred at 90°C for 24 h. [b] Yield of isolated product.

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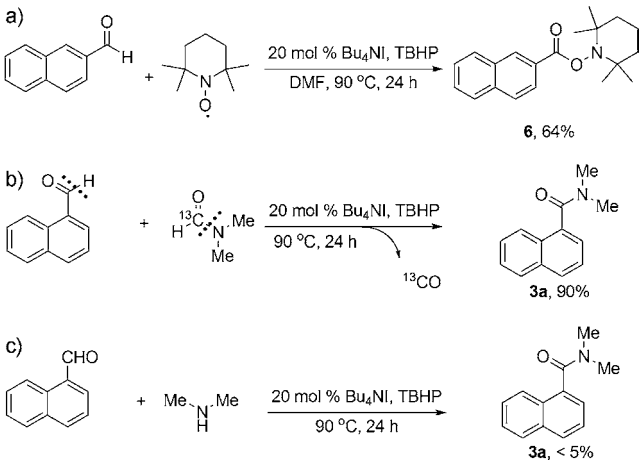
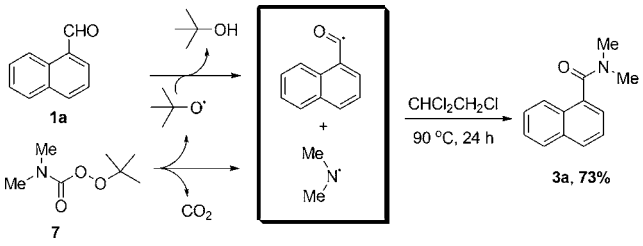
(Scheme S1b in the Supporting Information). Based on these two results, both the carboxylic acid and *tert*-butyl perester can be excluded as reaction intermediates. Recently, hypervalent iodine reagents have attracted much interest owing to their efficiency and the mild reaction conditions under which they can be used.[20] It was possible that a hypervalent iodine reagent might be formed in situ from Bu_4NI and TBHP, which would then serve as the oxidant in the transformation. However, both $PhI(OAc)_2$ and 2-iodoxybenzoic acid (IBX) completely suppressed the reaction (Scheme S1c in the Supporting Information).

As anticipated, the TEMPO adduct **6** was formed instead of the amide in 64% yield under the optimized conditions (Scheme 1a). A ^{13}C-isotope labeling experiment proved that the carbonyl group comes from the aldehyde, not from the DMF (Scheme 1b). Based on these results, the acyl radical is initially generated by hydrogen abstraction from the aldehydes, and then serves as the acylation reagent in the amide synthesis. Whereas both the functionalization of the C–H bond in aldehydes[21,22] and the decarbonylation of DMF[23] have been well-documented, combining them into one reaction under metal-free conditions has remained virtually unexplored.



Scheme 1. Investigations into the reaction mechanism.

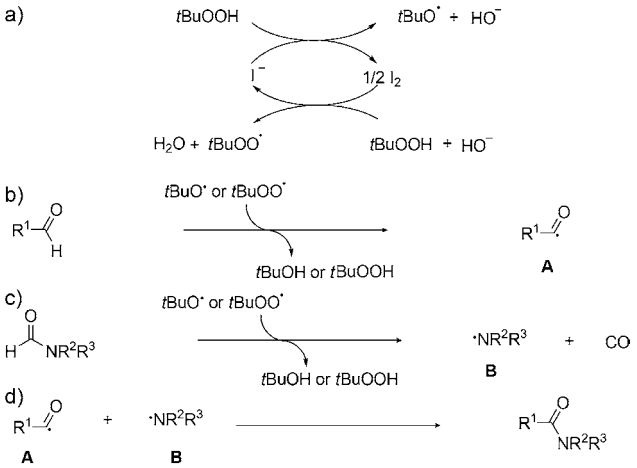
The acylation of amines has proved to be a reliable method for the construction of amide bonds.[9] Nucleophilic addition of an amine to an aldehyde and oxidation of the resulting carbinolamine was proposed as a mechanism. Our reaction would involve dimethylamine that is generated in situ from DMF. To rule out this pathway, dimethylamine was used instead of DMF under otherwise the same conditions (Scheme 1c), and only trace amount of amide **3a** was detected. *Tert*-butyl dimethylcarbamoperoxoate (**7**) decomposes to form an aminyl radical, a *tert*-butoxyl radical, and CO_2 when heated.[24] Thus, it is logical to assume that the aminyl radical, which is generated in situ from **7**, could couple with an acyl radical to generate an amide bond. To confirm this hypothesis, *tert*-butyl dimethylcarbamoperoxoate **7** was prepared and subjected to the amide synthesis reaction. As anticipated, amide **3a** was generated in 73% yield



Scheme 2. Trapping the aminyl radical.

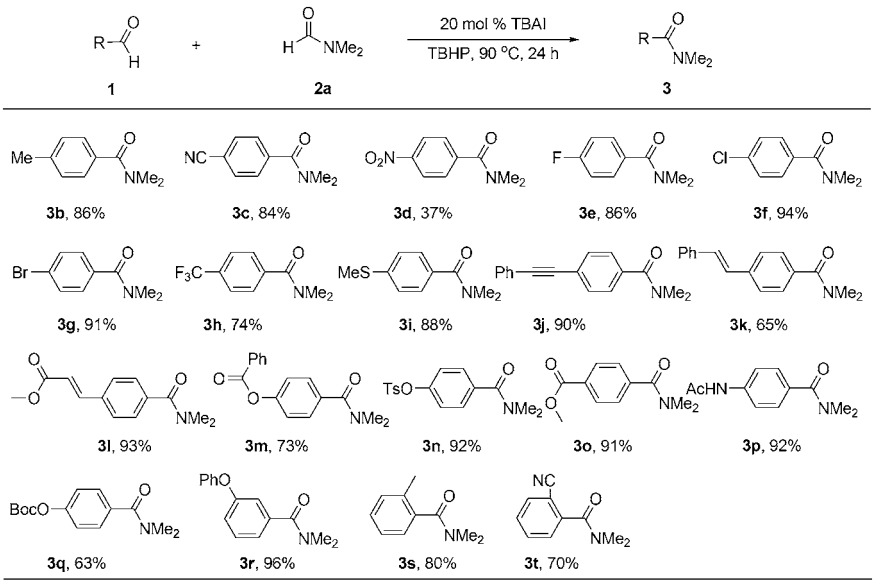
(Scheme 2). This result strongly suggests that an aminyl radical, not an amine, was the intermediate in the transformation. DMF has previously been employed as the amide source for aminocarbonylation of aryl halides;[4g–i] however, the expense of the transition-metal catalysts and the hazards of $POCl_3$ or other strong bases limit their applications. To the best of our knowledge, the use of DMF as a source of an aminyl radical has not been reported before.

On the basis of these results and previous publications, a plausible catalytic cycle is presented in Scheme 3. In the first step, the *tert*-butoxyl and *tert*-butylperoxyl radicals form catalytically (Scheme 3a).[25] These radicals then abstract hydrogen from the aldehyde and DMF to generate acyl radical **A**[16d,26] and aminyl radical **B**,[17] respectively (Scheme 3b and c). Finally, the acyl radical **A** and aminyl radical **B** couple to form the desired amide (Scheme 3d).



Scheme 3. Proposed reaction mechanism.

A variety of substituted aryl aldehydes were subjected to the optimized conditions, and representative results are summarized in Scheme 4. The results indicate that aldehydes with electron-withdrawing or electron-donating groups were well tolerated and provided the corresponding amides in moderate to excellent yields. Generally, aldehydes bearing electron-withdrawing substituents gave the correct products but with decreased yields. For example, when 4-nitrobenzaldehyde was coupled with DMF, the effect of the electron-withdrawing group was noticeable, and the reaction produced **3d** in low yield. Steric effects also influence the reaction. Slightly decreased but acceptable yields were achieved for

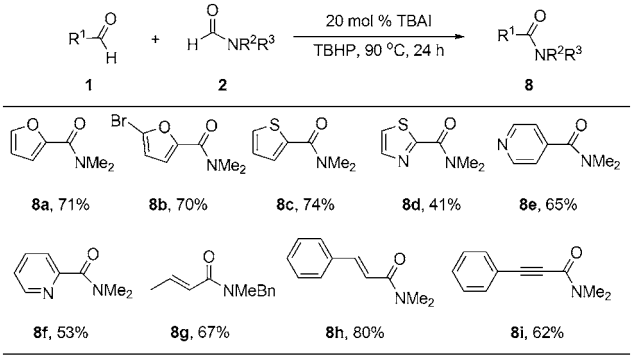


Scheme 4. Scope of the reaction with aryl aldehydes.

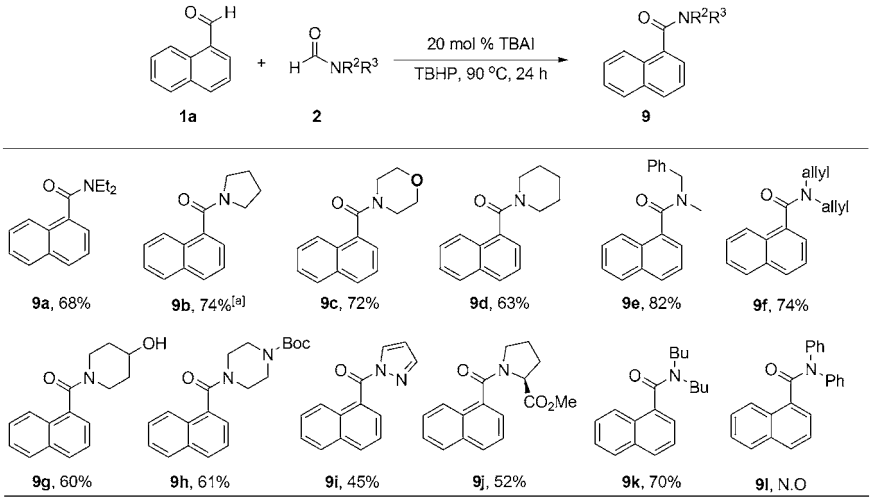
reactions that involved *ortho*-substituted aldehydes (**3s** and **3t**). A wide variety of functional groups, including benzylic C–H (**3b**), CN (**3c** and **3t**), CF_3 (**3h**), alkyne (**3j**), *O*-(4-toluenesulfonyl) (OTs, **3n**), ether (**3r**), ester (**3l**, **3m**, and **3o**), *O*-*tert*-butyloxycarbonyl (Boc, **3q**), and amide (**3p**), were tolerated under the optimized conditions. The presence of halide substituents on the aromatic groups did not interfere with the formation of the amide bond, and these reactions afforded the corresponding products, which could be further manipulated by traditional cross-coupling reactions (**3f** and **3g**). Even functional groups that are sensitive to oxidation, such as sulfides and double bonds, were not affected during the reaction (**3i**, **3k**, and **3l**). The reaction could be scaled up to 100 mmol (1-naphthaldehyde (**1a**), 15.6 g), and the desired amide **3a** was produced in 76% yield. When aliphatic aldehydes were subjected to the reaction, only small amount of the corresponding amides were obtained.[27]

To show the synthetic utility of the method, a variety of heteroaryl aldehydes, including furan, thiophene, thiazole, and pyridine, were subjected to the optimized conditions. As shown in Scheme 5, the desired amides **8a**–**8f** were obtained in satisfactory yields. The catalytic synthesis of α,β-unsaturated amides remains a challenge in the literature.[4–14] In this study, both enal and ynal groups were suitable reaction partners in the transformation, and led to the corresponding amides **8g**, **8h**, and **8i** in good yields.

Scheme 6 presents the scope of the *N*,*N*-disubstituted formamides which can be used in this reaction. Although large amounts (15 equiv relative to aldehydes) of *N*,*N*-disubstituted formamides were required in the reaction, a range of *N*,*N*-disubstituted formamides, which includes cyclic and acyclic formamides, were suitable for the formation of the corresponding amides **9a**–**9k** in moderate to high yields. Other than alkyl substituted formamides, the synthetically more important benzyl- and allyl-substituted formamides gave good yields (**9e** and **9f**). Unprotected hydroxy groups and the removable Boc group were tolerated in the amide formation reaction (**9g** and **9h**). Pyrazole was also a compatible substrate for this transformation and gave the desired amide **9i** in moderate yield. Notably, the method also proved applicable to amino acid derivatives (**9j**). *N*,*N*-Diphenylformamide did not form the desired product (**9l**). The strong conjugation between the amide group and phenyl ring most likely



Scheme 5. Scope of the reaction with other aromatic aldehydes.



Scheme 6. Scope of the reaction with *N*,*N*-disubstituted formamides. 2.0 mL of ethyl acetate was used for **9f**. N.O = not obtained

results in poor decarbonylation of the *N*,*N*-diphenylformamide under the optimized conditions.

In summary, an amide synthesis that is based upon the coupling of acyl and aminyl radicals has been demonstrated. Both aldehydes and *N*,*N*-disubstituted formamides were commercially available or easily synthesized. This mechanistically distinct amide synthesis is free of metal catalysts, tolerant of many substrates, operationally simple, and continues to perform on scale-up, which renders it a powerful complement to traditional approaches for the synthesis of amides. Further studies on the mechanistic details and expansion of the scope of the reaction are currently underway in our laboratory.

Experimental Section

General procedures for amides **3a**–**3t**, **8a**–**8l**, and **9a**–**9k**: The aldehyde (0.5 mmol), *N*,*N*-disubstituted formamide (7.5 mmol), Bu_4NI (0.1 mmol, 20 mol%), TBHP (2.9 mmol, 0.4 mL of a 70% aqueous solution), and 1,1,2-trichloroethane (2.0 mL) were added to a test tube in air. The reaction mixture was heated in an oil bath at 90 °C for 24 h and was quenched with a saturated solution of Na_2SO_3 (for removal of excess TBHP) and extracted with ethyl acetate. The organic solvent was removed under vacuum and purification by chromatography on a silica gel column afforded the desired product.

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