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Boric Acid: A Highly Efficient Catalyst for Transamidation of Carboxamides with Amines

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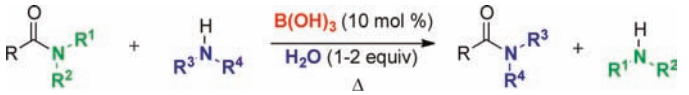
ABSTRACT



A novel method of transamidation of carboxamides with amines using catalytic amounts of readily available boric acid under solvent-free conditions has been developed. The scope of the methodology has been demonstrated with (i) primary, secondary, and tertiary amides and phthalimide and (ii) aliphatic, aromatic, cyclic, acyclic, primary, and secondary amines.

Amide linkage is one of the most important functional groups in chemistry and plays a central role in living systems.[1] It is usually created by reactions of amines with carboxylic acid derivatives (chlorides, anhydrides or esters or acids),[2,3] alcohols,[4] or aldehydes.[5]

Transamidation is an attractive tool in synthetic organic chemistry. However, the high inertness of the amide function hampered such transformations under thermal non-catalytic conditions.[6] Great efforts have been made to develop more convenient procedures that allow the reactions to take place at relatively lower temperatures by utilizing activating reagents or catalysts.[7] Despite their wide scope, these protocols involved either energetically favorable systems (ring-opening of four-membered rings,[7d,e] intramolecular assitance,[7f] or both factors) or the use of moisture-sensitive and/or expensive activation reagents (2−3 equiv; borate esters,[7a] dialkylformamide dialkyl acetals,[7b] $AlCl_3$,[7g] $AlMe_3$[7c]). The reaction can also

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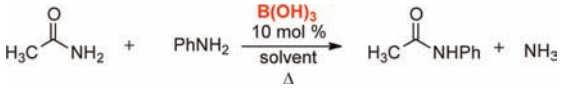
result in mixtures of amides as a consequence of the reversible nature of the catalytic process.[8] Very recently, new copper-[9] and cerium-catalyzed[7i] transamidations for carboxamides[7i,9] and ureas[9] were disclosed. For metal-free catalyzed methods of transamidation, only one example has been reported[10] in which $NH_2OH \cdot HCl$ was used in important quantities (up to 50 mol %). However, the scope of these three methods[7i,9,10] is limited to primary amides and in most cases to primary amines.

Table 1. Reaction Conditions Screening[a]



entry	catalyst/additive	solvent	temp (° C)	conversion (%)[b]
1		PhMe[c]	140	0
2	$B(OH)_3$	PhMe[c]	140	10
3	$B(OH)_3$	*p*-xylene	140	11
4	$B(OH)_3$	DMF	140	<5
5	$B(OH)_3$	DMSO	140	<5
6	$B(OH)_3$	*i*-PrOH[c]	140	<5
7	$B(OH)_3$	*n*-C_5H_9OH	140	<5
8	$B(OH)_3$	–	140	26
9	$B(OH)_3/H_2O$ (1 equiv)	–	140	45
10	–	–	140	<5
11	H_2O (1 equiv)	–	140	<5
12	**$B(OH)_3/H_2O$ (1 equiv)**	–	**150**	**80**

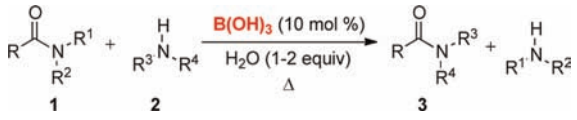
[a] Reaction conditions: aniline (10 mmol), acetamide (10 mmol), catalyst (1 mmol) in solvent (4 mL) for 20 h. [b] Determined by ^1H NMR spectroscopy of the methyl group. [c] Reaction carried out in a sealed tube.

Although boron-mediated transamidation has been reported in the literature,[7a,11b,11c] the boron reagents had to be used in stoichiometric or excess amounts[7a] or as reaction media in an intramolecular version.[11b,c]

Herein, we wish to report a general solvent-free boric acid-catalyzed transamidation of amines with amides and phthalimide, which provides an attractive alternative for the existing protocols. During the course of our research program aiming at developing new methods for our own total syntheses, we envisioned that readily available, low-cost, nontoxic, and environmentally friendly boric acid could constitute a highly effective catalyst for transamidation.[11]

First, transamidation of aniline and acetamide was chosen as a model system (Table 1). Without boric acid, the complete lack of reactivity was observed in toluene at 140 °C (Table 1, entry 1). Addition of boric acid (10 mol %) to the reaction mixture resulted in the desired transformation, but these conditions were not very active (Table 1, entry 2). Different solvents were screened in order to increase the conversion. Aromatic hydrocarbon solvents such as toluene and *p*-xylene (Table 1, entries 2, 3) were found to be better reaction media than polar aprotic (DMF, DMSO; Table 1, entries 4, 5) or protic solvents (Table 1, entries 6, 7). Pleasingly, higher conversions were found under solvent-free conditions.

Table 2. Boric Acid-Catalyzed Transamidation[a]



entry	amide	amine	temp (°C)	*t* (h)	yield (%)
1	CH_3CONH_2, **1a**	$BnNH_2$, **2a**	120	16	**3a**, 81
2	**1a**	$PhNH_2$, **2b**	150	20	**3b**, 76
3	**1a**	BnNHMe, **2c**	150	16	**3c**, 71
4	$BnCONH_2$, **1b**	$BnNH_2$, **2a**	120	16	**3d**, 82
5	**1b**	$PhNH_2$, **2b**	150	16	**3e**, 76
6	**1b**	morpholine **2d**	150	24	**3f**, 85
7	**1b**	BnNHMe[c], **2e**	150	24	**3g**, 90
8	**1b**	*p*-$MeOC_6H_4NH_2$, **2f**	150	16	**3h**, 50
9	**1b**	*p*-$ClC_6H_4NH_2$, **2g**	150	16	**3i**, 78
10	$PhCONH_2$, **1c**	$BnNH_2$, **2a**	150	24	**3j**, 40[b]
11	**1c**	$BnCH_2NH_2$, **2h**	150	24	**3k**, 40[b]
12	*i*-$PrCONH_2$, **1d**	$BnNH_2$, **2a**	150	16	**3l**, 77
13	$HCONH_2$, **1e**	**2a**	100	16	**4a**, 88
14	HCONHMe, **1f**	**2a**	100	16	**4a**, 79
15	$CH_3CONHMe$, **1g**	**2a**	150	24	**3a**, 51
16	$CH_3CONHPh$, **3a**	**2a**	150	20	**3a**, 63
17	$HCONMe_2$, **1h**	**2a**	140	20	**4a**, 67
18	**1h**	**2a**	150	20	**4a**, 83
19	CH_3CONMe_2, **1i**	**2a**	160	32	**3a**, 56
20	**1i**	$BnCH_2NH_2$, **2h**	160	32	**3m**, 42

[a] Reaction conditions: amide (10 mmol), amine (10 mmol), $B(OH)_3$ (1 mmol), H_2O (10−20 mmol), unless stated otherwise. [b] Conversions determined by ^1H NMR spectroscopy. [c] $B(OH)_3$ (20 mol %) was used.

Gratifyingly, we found that the presence of water (1−2 equiv; Table 1, entry 8) had a positive effect on the conversion. To confirm this observation, we conducted two control experiments in which both starting materials were mixed together without boric acid (Table 1, entry 10) or only with water (1 equiv) (Table 1, entry 11). These two experiments resulted in trace amounts of acetanilide, which

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(10) Allen, C. L.; Atkinson, B. N.; Williams, J. M. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 1383.

(11) $B(OH)_3$ was found to be an effective catalyst for direct amidation: (a) Tang, P. *Org. Synth.* **2005**, *81*, 262. Sodium borate was found to accelerate cyclization of glutamine into pyroglutamic acid: (b) Gilbert, J. B.; Price, V. E.; Greenstein, J. P. *J. Biol. Chem.* **1949**, *180*, 209. γ-Aminobutyramide to 2-pyrrolidone: (c) Martin, R. B.; Parcell, A.; Hedrick, R. I. *J. Am. Chem. Soc.* **1964**, *86*, 2406.

demonstrated that boric acid played a crucial catalytic role in this reaction. Finally, the conversion was improved significantly when temperature was raised to 150 °C (Table 1, entry 12) without any degradation. With the optimized catalytic conditions in hand, we then investigated the generality of this boric acid-catalyzed transamidation. The results are summarized in Table 2. In general, aliphatic amines were more reactive than aromatic amines and required shorter reaction time and/or lower reaction temperature (Table 2, entries 1 vs 2; 4 vs 5, 8, 9).

Steric hindrance appeared to play an important role in the outcome of the reaction as exemplified by the excellent conversion of benzylamine or 2-phenethylamine to their respective amides, but in the case of secondary amines such as morpholine, piperidine, *N*-methylbenzylamine, dibenzylamine, and *N*-methylaniline, higher reaction temperatures were required in order to provide useful conversions.

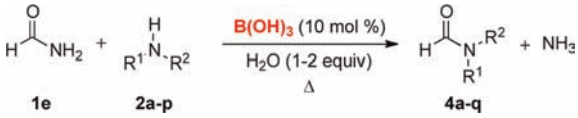
Moreover, high reactivities were observed with unhindered amides (formamide, acetamide, phenylacetamide). The lower reactivity of benzamide compared to that of isobutyramide (Table 2, entries 10, 11 vs 12) is in agreement with the stabilization of metal centers by arylamidate ligands, thus reducing the catalyst efficiency.[12]

It is noteworthy to emphasize that in contrast to most catalyzed transamidation methods,[7−10] which are limited to primary amides, the present method is applicable to substrate primary, secondary, and even tertiary amides. As evaluated on a structurally diverse set of amides and amines, the scope and utility of the protocol proved to be quite general.

We were particularly intrigued by the high reactivity of the unsubstituted formamide toward benzylamine under boric acid-catalyzed conditions. Typically, the *N*-formylation[13] of an amine is carried out using hazardous, toxic, and unstable reagents (mixed formic−acetic anhydride, cyanomethyl formate, pentafluorophenyl formate, formyl fluoride). This led us to carry out a more comprehensive study of scope and limitation of formylation using the present methodology (Table 3).

We decided to further optimize the reaction between unsubstituted formamide and benzylamine. Even at 50 °C, good yield of *N*-benzylformamide was obtained. Using a slight excess of formamide (3 equiv) allowed lower reaction temperature (Table 3, entry 2), even without heating (Table 3, entry 3) with excellent yields.[14] To our delight, the reaction is quite general, which could be applied to aliphatic, aromatic, heteroaromatic, cyclic, acyclic, primary, and secondary amines. Reactions of hindered primary amines, secondary amines, and aromatic amines required higher temperatures but afforded a clean conversion without formation of side products. As exemplified clearly in the extreme cases of *N*-methyl-, *p*-methoxycarbonyl-, *p*-, and *m*-nitro-anilines and 2-aminopyridine, which are very poor nucleophiles, useful yields of the desired *N*-substituted amides have been obtained. Because *N*-formyl can serve as protecting group or as precursor for isocyanide chemistry, this new method of *N*-formylation under very mild conditions appears to be very useful. Compared to recently disclosed work of a simple protocol for *N*-formylation of amino acid esters and primary amines using *N*,*N*-dimethylformamide as formyl source in large excess quantity (solvent) and imidazole (2 equiv) at 50 °C, our present method is obviously of larger scope, more convenient, and environmentally friendly.[13e]

Table 3. $B(OH)_3$-Catalyzed Amine Formylation Using $HCONH_2$[a]



1e 2a-p 4a-q

entry	amine	temp (°C)	*t* (h)	**4**, yield (%)
1	$BnNH_2$, **2a**	50	16	**4a**, 77
2[c]	**2a**	40	24	**4a**, 98
3[c]	**2a**	25	48	**4a**, 97
4	$BnCH_2NH_2$, **2h**	100	16	**4b**, 93
5	**2h**	50	16	**4b**, 78[b]
6	1-phenethylamine, **2i**	40	24	**4c**, 52
7	**2i**	60	24	**4c**, 87
8	cyclohexylamine, **2j**	100	16	**4d**, 70
9	*t*-$BuNH_2$, **2k**	120	16	**4e**, 57
10	*p*-$MeOC_6H_4NH_2$, **2f**	150	16	**4f**, 44
11	*p*-$ClC_6H_4NH_2$, **2g**	150	17	**4g**, 92
12	*p*-$HOC_6H_4NH_2$, **2i**	150	16	**4h**, 57[b]
13	*p*-$MeO_2CC_6H_4NH_2$, **2j**	150	17	**4i**, 55
14	*p*-$O_2NC_6H_4NH_2$, **2k**	150	17	**4k**, 35
15	*m*-$O_2NC_6H_4NH_2$, **2l**	150	17	**4l**, 75
16	piperidine, **2m**	100	24	**4m**, 90
17	morpholine, **2d**	100	24	**4n**, 87
18	Bn_2NH, **2n**	100	24	**4o**, 40[b]
19	**2n**	150	24	**4o**, 88
20	PhNHMe, **2o**	150	16	**4p**, 70
21	2-aminopyridine, **2p**	150	17	**4q**, 26

[a] Reaction conditions: $HCONH_2$ (10 mmol), amine (10 mmol), $B(OH)_3$ (1 mmol), H_2O (10−20 mmol). [b] Conversions determined by ^1H NMR spectroscopy. [c] $HCONH_2$ (30 mmol) was used.

Finally, our study was completed by the investigation of the boric acid-catalyzed conditions for the reaction between a primary amine with the phthalimide PhthNH (Table 4). This two-step ring-opening followed by ring-closing sequence or transimidation would provide an alternative approach to introduce a phthalimide protection of primary amine.[15] Without catalyst, the reaction

(12) Yang, W.; Fu, H.; Song, Q. J.; Zhang, M.; Ding, Y. Q. *Organometallics* **2011**, *30*, 77.

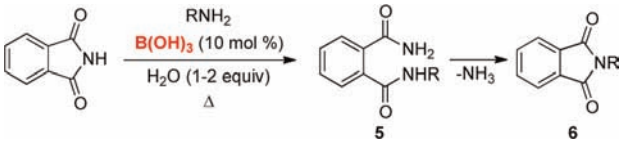
(13) (a) Huffman, C. W. *J. Org. Chem.* **1958**, *23*, 727. (b) Clemo, G. R.; Swan, G. A. *J. Chem. Soc.* **1945**, 603. (c) Waley, S. G. *Chem. Ind.* **1953**, 107. (d) Sheehan, J. C.; Yang, D. D. H. *J. Am. Chem. Soc.* **1958**, *80*, 1154–1158. (e) Suchy, M.; Elmehriki, A. A. H.; Hudson, R. H. E. *Org. Lett.* **2011**, *13*, 3952 and references cited therein.

(14) At rt, the uncatalyzed reaction gave < 5% conversion.[10]

(15) The phthalimides are usually synthesized by condensing phthalic anhydride with primary amines, *N*-alkylation of phthalimides with alcohols under Mitsunobu conditions and of potassium phthalimide with alkyl halides. For some recent examples, see: (a) Reddy, P. Y.; Kondo, S.; Toru, T.; Ueno, Y. *J. Org. Chem.* **1997**, *62*, 2652. (b) Le, Z. G.; Chen, Z. C.; Hu, Y.; Zheng, Q. G. *Synthesis* **2004**, 208. (c) Escudero, M. I.; Kremenchuzky, L. D.; Perillo, I. A.; Cerecetto, H.; Blanco, M. M. *Synthesis* **2011**, 571. (d) Sen, S. E.; Roach, S. L. *Synthesis* **1995**, 756.

between PhthNH and benzylamine gave a mixture of both starting materials, mixed diamide **5**, and the desired *N*-substituted phthalimide **6**. A full conversion into PhthNBn was observed in the presence of $B(OH)_3$ (10 mol %). This means $B(OH)_3$ catalyzed not only the ring-opening step but also the cyclization. The reaction could be carried out at lower temperature (Table 4, entry 3). For more hindered aliphatic amines (Table 4, entries 5, 6) or aromatic amine (Table 4, entry 7), heating at higher temperature was required.

Table 4. $B(OH)_3$-Catalyzed Reaction of PhthNH with Amines[a]



entry	amine	temp (°C)	*t* (h)	product, yield (%)
1[c]	$BnNH_2$, **2a**	100	4	**5a**, 30[b]; **6a**, 60[b]
2	**2a**	100	4	**6a**, 96
3	**2a**	80	4	**6a**, 88
4	$BnCH_2NH_2$, **2h**	80	24	**6b**, 70
5	1-phenethylamine, **2i**	100	24	**6c**, 73
6	*t*-$BuNH_2$, **2k**	130	24	**6d**, 19
7	*p*-$MeOC_6H_4NH_2$, **2f**	130	24	**6e**, 66

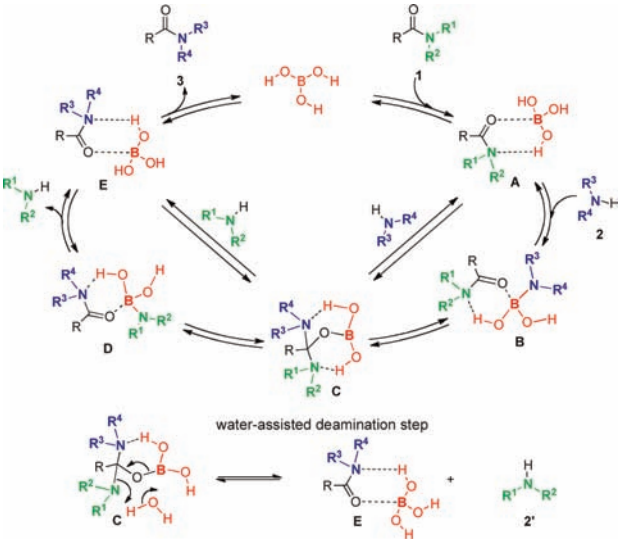
[a] Reaction conditions: phthalimide (10 mmol), amine (10 mmol), $B(OH)_3$ (1 mmol), H_2O (10−20 mmol) in toluene (2 mL) and 1,4-dioxane (2 mL). [b] Conversions determined by ^1H NMR spectroscopy. [c] Reaction performed without $B(OH)_3$.

The experiment indicated that boric acid is capable of catalyzing the transamidation, even for tertiary amide. We propose a mechanism that proceeds through intermediate **A** (Scheme 1), wherein $B(OH)_3$ played a double role: (i) Lewis acid at the boron atom by complexing with the oxygen atom of amide **1**; (ii) hydrogen-bond donor by forming H-bonds with the nitrogen atom of amide **1**. This activation would favor the direct amine exchange **A** ⇆ **B** via nucleophilic attack of amine **2** and removal of amine **2′**.

On the basis of the computational study of Marcelli[16] for the direct amidation catalyzed by boronic acids,[3] we tentatively propose the catalytic mode of $B(OH)_3$ for the transamidation reaction. The catalytic cycle could begin with the reaction of amide **1** with boric acid catalyst leading to adduct **A**, which could take place via concerted proton transfer and B−O bond formation. The next step of addition of amine **2** to the adduct **A** could occur directly at the C═O bond and results in **C**. Another possibility leading to **C** could be envisioned is the attack of amine **2** on the boron atom followed by intramolecular **B** → **C** rearrangement of the amino group. Elimination of amine **2′** from tetrahedral intermediate **C** can occur in the same manner. According to the data calculated by Marcelli for the direct amidation catalyzed by boronic acids, the formation of the boron-bound amide from the corresponding

(16) Marcelli, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 6840.

Scheme 1. Proposed Activation Mode of Boric Acid



aminal **C** is likely the rate determining step of the reaction. This deamination step **C** → **E** could be assisted by water as postulated in the Scheme 1. The catalytic cycle ends with the dissociation of amide **3** from boric acid.

The role of water[17] in enhancing the rate of transamidation can also be explained by its capacity to increase the solubility of boric acid and avoid the formation of boric acid aggregates,[18] which are less catalytically active than the boric acid.

In conclusion, we have developed a novel method of transamidation of carboxamides with amines using catalytic amounts of readily available boric acid under solvent-free conditions, which provides a wide range of amides. The scope of the methodology has been demonstrated with (i) primary, secondary, tertiary amides and phthalimide and (ii) aliphatic, aromatic, cyclic, acyclic, primary, and secondary amines. Considering the economic attractiveness, the operational simplicity, and excellent functional group tolerance of the boric acid homogeneous catalysis, we strongly believe that the procedure is of important synthetic value for access to a variety of significant products for organic chemistry, including amides, lactames, peptides, ureas, aza-heterocycles, etc., especially for large-scale preparations.

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Supporting Information Available. Experimental procedures, product characterization, and copies of the ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) Even in the presence of water at high temperature, no trace of amide hydrolyzed products was observed.

(18) Cotton, F. A.; Willkinson, G. *Advanced Inorganic Chemistry*, 5th ed.; John Wiley & Sons: New York, 1988; pp 169−170.

The authors declare no competing financial interest.