# 3,4,5-Trifluorobenzeneboronic Acid as an Extremely Active Amidation Catalyst

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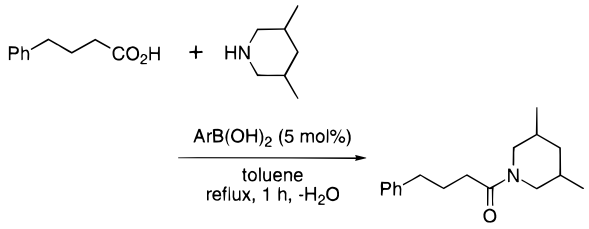
There are several different routes to carboxamides.[1] In most of these reactions, a carboxylic acid is converted to a more reactive intermediate, e.g., the acid chloride, which is then allowed to react with an amine. For practical reasons, it is preferable to form the reactive intermediate *in situ*. A carboxamide-forming reaction of the latter type has attracted our interest in the development of a reaction between carboxylic acids and primary or secondary amines promoted by a catalytic amount of metallic compounds. There have been some reports on this reaction in the literature,[2] but an efficient catalytic procedure has not yet been developed. We report here that arylboronic acids with electron-withdrawing groups, 3,4,5-trifluorobenzeneboronic acid (**1**) and 3,5-bis(trifluoromethyl)benzeneboronic acid (**2**), act as highly efficient catalysts in the amidation between carboxylic acids and amines.

Acyloxyboron intermediates generated from carboxylic acids and boron reagents such as $BR_3$ (R = $C_8H_{17}$, OMe),[3a] $ClB(OMe)_2$,[3a] $HB(OR)_2$ (R = *i*-Pr, *t*-Am),[3a] $BH_3{\cdot}R_3N$ (R = Me, Bu),[3b] $BF_3{\cdot}Et_2O$,[3c] and catecholborane[3d] react with amines to furnish amides in moderate to good yield, but only in uniformly stoichiometric reactions. In these boron-mediated amidations, boron reagents transform into inactive boron species after the reaction of (acyloxy)boron derivatives and amines. We reasoned that arylboronic acids with electron-withdrawing substituents at the aryl group could be used to circumvent these difficulties, since they are water-, acid-, and base-tolerant Lewis acids that can generate (acyloxy)boron species. They are also thermally stable and can be readily handled in air.[4] We theorized that their strong Lewis acidity might enhance the rate of the generation of (acyloxy)boron species and their reactivity with amines.

We first investigated the catalytic activities of various arylboronic acids (5 mol %), which promote the model reaction of 4-phenylbutyric acid (1 equiv) with 3,5-dimethylpiperidine (1 equiv) in toluene at reflux with removal of water (4-Å molecular sieves in a Soxhlet thimble) for 1 h (Table 1). The boronic acid **1**[5] with *m*- and *p*-fluorine substituents on the phenyl group was the most effective catalyst for the present reaction (Table 1, entry 1). 3-Nitrobenzeneboronic acid and 3,5-bis(trifluoromethyl)benzeneboronic acid (**2**),[6] which are commercially available, were also effective amidation catalysts (Table 1, entries 2 and 3). The *ortho*-substituted benzeneboronic acids 2,4,6-tris(trifluoromethyl)benzeneboronic acid and 2,3,4,5-tetrafluorobenzeneboronic acid were less effective than simple benzeneboronic acid, even if the substituent group was a sterically small electron-withdrawing group like fluorine (Table 1, entries 6 and 7 vs entry 5). Amidation rarely occurred in the absence of catalysts (Table 1, entry 8).

**Table 1. Amidation Reaction between 4-Phenylbutyric Acid and 3,5-Dimethylpiperidine Catalyzed by Various Arylboronic Acids**[a]




| entry | Ar | yield[b] (%) | entry | Ar | yield[b] (%) |
|---|---|---|---|---|---|
| 1 | 3,4,5-$F_3C_6H_2$ | 74 | 5 | $C_6H_5$ | 23 |
| 2 | 3-$NO_2C_6H_4$ | 60 | 6 | 2,4,6-$(CF_3)_3C_6H_2$ | 21 |
| 3 | 3,5-$(CF_3)_2C_6H_3$ | 56 | 7 | 2,3,4,5-$F_4C_6H$ | 11 |
| 4 | 4-$CF_3C_6H_4$ | 54 | 8 | c | <2 |

[a] In the presence of 5 mol % of arylboronic acid, a mixed solution of 1 equiv of 4-phenylbutyric acid (0.2 M) and 1 equiv of 3,5-dimethylpiperidine (0.2 M) in toluene was refluxed with removal of water (4-Å molecular sieves in a Soxhlet thimble). [b] Isolated yield. [c] No catalyst was added.

To explore the generality and scope of boronic acid **1**-catalyzed amidation, the reaction was examined with various structurally diverse carboxylic acids and primary or secondary amines (Table 2). In most cases, the reactions proceeded cleanly, and the desirable carboxylic amides were obtained in high yields. Although the isolated yield by column chromatography on silica gel is indicated in Table 2, adequate purification is obtained by aqueous workup. The catalyst was useful for reacting not only primary but also secondary amines with various carboxylic acids. Surprisingly, sterically-hindered 1-adamantanecarboxylic acid was easily amidated at reflux in mesitylene. Aromatic substrates such as anilines and benzoic acid also reacted well under similar conditions.

The catalytic amidation of optically active aliphatic α-hydroxycarboxylic acids with benzylamine proceeded with no measurable loss (<2%) of enantiomeric purity under conditions of reflux in toluene. However, slight racemization was observed in the case of (*S*)-(+)-mandelic acid. In all cases, no esters were observed.

Most amino acids are barely soluble in nonaqueous solvents. Nevertheless, their lactams can be prepared by the present technique under heterogeneous conditions. For example, when 6-aminocaproic acid and 1 mol % of boron catalyst **1** were suspended in xylene at reflux, the solid slowly dissolved and caprolactam was formed in 93% yield (Table 3). 5-Aminovaleric acid similarly gave

(1) For a review of the synthesis of amides and related compounds, see: Benz, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: New York, 1991; Vol. 6, Chapter 2.3.

(2) For catalytic amidations between carboxylic acids and amines, see the following. $TiCl_4$: (a) Nordahl, Å.; Carlson, R. *Acta Chem. Scand., Ser. B.* **1988**, 28. $Ti(O\text{-}i\text{-}Pr)_4$: (b) Mader, M.; Helquist, P. *Tetrahedron Lett.* **1988**, *59*, 3049. $Ph_3SbO/P_4S_{10}$: (c) Nomura, R.; Nakano, T.; Yamada, Y.; Matsuda, H. *J. Org. Chem.* **1991**, *56*, 4076. $Sb(OEt)_3$: (d) Ishihara, K.; Kuroki, Y.; Hanaki, N.; Ohara, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 1569.

(3) (a) Pelter, A.; Levitt, T. E.; Nelson, P. *Tetrahedron* **1970**, *26*, 1539. (b) Trapani, G.; Reho, A.; Latrofa, A. *Synthesis* **1983**, 1013. (c) Tani, J.; Oine, T.; Inoue, I. *Synthesis* **1975**, 714. (d) Collum, D. B.; Chen, S.-C.; Ganem, B. *J. Org. Chem.* **1978**, *43*, 4393.

(4) We were unable to prepare aliphatic perfluoroalkylboronic acids.

(5) Boronic acid **1** was prepared by addition of trimethyl borate to Grignard reagent, which was generated *in situ* from 3,4,5-trifluorobromobenzene and magnesium (turnings) in THF.

(6) We previously used **2** as an efficient Lewis acid catalyst; see: (a) Ishihara, K.; Mouri, M.; Gao, Q.; Maruyama, T.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 11490. (b) Ishihara, K.; Maruyama, T.; Mouri, M.; Gao, Q.; Furuta, K.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3483. (c) Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 3049.

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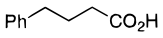
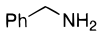
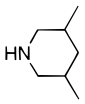
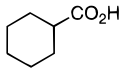
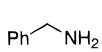
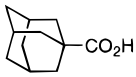
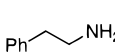
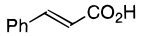
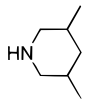
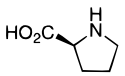
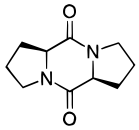
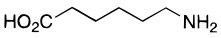
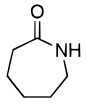
**Table 2. Amidation Reaction between Carboxylic Acids and Amines Catalyzed by 1[a]**

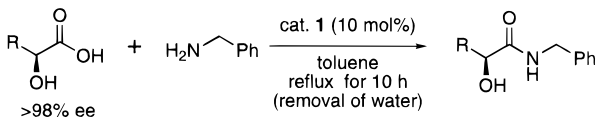
| carboxylic acid | amine | solvent | time (h) | yield[b] (%) |
|---|---|---|---|---|
|  |  | toluene | 18 | 96 |
| |  | toluene | 16 | >99 |
| | $Bu_2NH$ | xylene | 20 | 56 |
| | | mesitylene | 14.5 | 99 |
| | $PhNH_2$ | mesitylene[c] | 4 | 99 |
|  |  | xylene | 18 | 96 |
|  |  | mesitylene[c] | 2 | 92 |
|  |  | xylene | 29 | 99 |
| $PhCO_2H$ | | mesitylene | 20 | 95 |

[a] Unless otherwise noted, in the presence of 1 mol % of **1**, a mixed solution of 1 equiv of carboxylic acid (0.2 M) and 1 equiv of amine (0.2 M) in toluene, xylene, or mesitylene was refluxed with removal of water (4-Å molecular sieves in a Soxhlet thimble). [b] Isolated yield by column chromatography on silica gel. [c] A mixed solution of 1 equiv of carboxylic acid (2 M) and 1 equiv of amine (2 M) in mesitylene was used.

**Table 3. Lactamization Reaction of Aminocarboxylic Acids Catalyzed by 1[a]**

| aminocarboxylic acid | solvent | time (h) | product | yield[b] (%) |
|---|---|---|---|---|
|  | anisole | 11 |  | 94[c] |
|  | xylene | 18 |  | 90 |
|  | xylene | 22 |  | 93 |

[a] Unless otherwise noted, in the presence of 1 mol % of **1**, a solution of 1 equiv of amino carboxylic acid (0.2 M) was refluxed with removal of water (4-Å molecular sieves in a Soxhlet thimble). [b] Isolated yield. [c] 5 mol % of **1** was used.




R=Ph: 95% yield, 94% ee
R=*i*-Bu: 87% yield, >98% ee
R=*i*-Pr: 96% yield, >98% ee

$\delta$-valerolactam in 90% yield. Interestingly, (*S*)-(−)-proline selectively gave the cyclic dimer with no measurable loss (<2%) of enantiomeric purity (94% yield).

As an extension of the boronic acid catalyst system, we examined the esterification of 4-phenylbutyric acid in alcohols. Esterification was relatively slow, as had been presumed from the preceding selective amidation of α-hydroxycarboxylic acid, since nucleophilicity of alcohols was lower than that of amines. Nevertheless, esterification proceeded smoothly if heavy alcohols such as 1-butanol (bp 117.7 °C) were used.

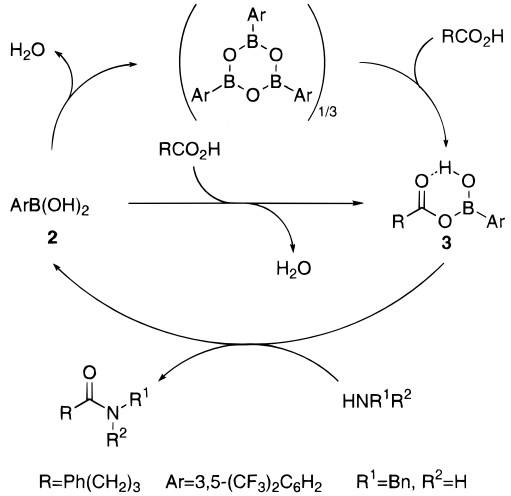
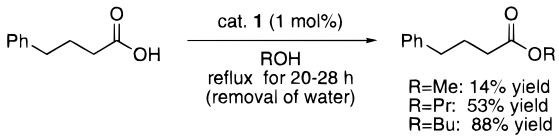



**Figure 1.** Proposed catalytic cycle.




The mechanism we propose to explain boron-catalyzed amidation is depicted in Figure 1. In general, arylboronic acid contains varying amounts of cyclic trimeric anhydrides (boroxines).[6c,7] To explore this mechanism, we carried out some experiments using **2**. The 2:1 mixture of 4-phenylbutyric acid and **2** in toluene-$d_8$ was heated at reflux with removal of water for 2 h. The mono(acyloxy)boronic acid **3** was produced and characterized by $^1$H NMR and IR analyses.[8] The corresponding bis(acyloxy)boron derivative was not observed at all. To a solution of **3** in toluene was added 1 equiv of benzylamine at room temperature without removal of the water that had been generated. Interestingly, the amidation proceeded even at room temperature, but the reaction stopped before 50% conversion because **3** was decomposed by hydrolysis with water. These experimental results suggest that the rate-determining step is the generation of **3**.

In summary, we have demonstrated that 3,4,5-trifluorobenzeneboronic acid is a practical and useful catalyst for amidation between carboxylic acids and amines because of its remarkable catalytic potential.[9]

**Supporting Information Available:** Experimental procedures and compound characterization data (6 pages).

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(7) **1** (monomer:trimer = 14:86): $^1$H NMR ($CDCl_3$) $\delta$ 4.74−4.82 (br, 0.28H (for monomer)), 7.35 (t, $J$ = 7.0 Hz, 0.28H (for monomer)), 7.77 (t, $J$ = 7.9 Hz, 1.72H (for trimer)). **2** (monomer:trimer = 12:88); $^1$H NMR (toluene-$d_8$) $\delta$ 4.02−4.08 (br, 0.24H, OH (for monomer)), 7.82 (s, 0.12H, *p*-H (for monomer)), 8.01 (s, 0.24H, *o*-H (for monomer)), 8.03 (s, 0.88H, *p*-H (for trimer)), 8.48 (s, 1.76H, *o*-H (for trimer)).

(8) 4-Phenylbutyric acid: IR ($CHCl_3$) 1709 cm$^{-1}$ ($CO_2H$); $^1$H NMR (toluene-$d_8$) $\delta$ 2.00 (t, $J$ = 7.4 Hz, 2H, $CH_2CO_2H$). **3**: IR ($CHCl_3$) 1586 cm$^{-1}$ ($CO_2B$); $^1$H NMR (toluene-$d_8$) $\delta$ 1.80 (t, $J$ = 7.4 Hz, 2H, $CH_2CO_2B$), 7.96 (s, 1H, *p*-H), 8.51 (s, 2H, *o*-H).

(9) This study was supported in part by the Yamada Science Foundation.