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Primary Alkylboronic Acids as Highly Active Catalysts for the Dehydrative Amide Condensation of α-Hydroxycarboxylic Acids

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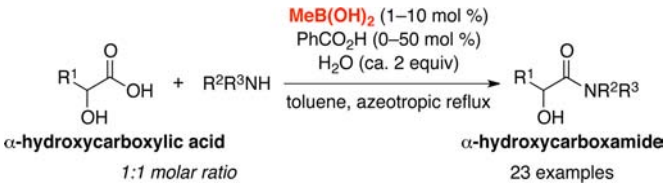
ABSTRACT



Primary alkylboronic acids such as methylboronic acid and butylboronic acid are highly active catalysts for the dehydrative amide condensation of α-hydroxycarboxylic acids. The catalytic activities of these primary alkylboronic acids are much higher than those of the previously reported arylboronic acids. The present method was easily applied to a large-scale synthesis, and 14 g of an amide was obtained in a single reaction.

Dehydrative amide condensation between carboxylic acids and amines is a fundamental organic transformation in not only enzymatic biosynthesis but also the chemical synthesis of a variety of organic compounds.[1] Recent advances in this field include the development of arylboronic acids [$ArB(OH)_2$] and boric acid [$B(OH)_3$] as catalysts for the dehydrative amide condensations.[2−9] In 1996, Yamamoto reported the first catalytic use of electron-deficient arylboronic acid **1** for direct amidation (Figure 1).[2] In 2006, Whiting reported that 2-[(diisopropylamino)methyl]-phenylboronic acid **2** is also an effective catalyst.[3] In 2008, Hall demonstrated that 2-iodophenylboronic acids **3** were catalytically active under mild conditions at rt ∼50 °C in the presence of 4Å molecular sieves.[4]

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(2) (a) Maki, T.; Ishihara, K.; Yamamoto, H. *Tetrahedron* **2007**, *63*, 8645. (b) Maki, T.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2006**, *8*, 1431. (c) Maki, T.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2005**, *7*, 5043. (d) Ishihara, K.; Ohara, S.; Yamamoto, H. *Org. Synth.* **2002**, *79*, 176. (e) Ishihara, K.; Ohara, S.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4196.

(3) (a) Arnold, K.; Davies, B.; Giles, R. L.; Grosjean, C.; Smith, G. E.; Whiting, A. *Adv. Synth. Catal.* **2006**, *348*, 813. (b) Arnold, K.; Batsanov, A. S.; Davies, B.; Whiting, A. *Green Chem.* **2008**, *10*, 124. (c) Georgiou, I.; Ilyashenko, G.; Whiting, A. *Acc. Chem. Res.* **2009**, *42*, 756.

(4) (a) Gernigon, N.; Al-Zoubi, R. M.; Hall, D. G. *J. Org. Chem.* **2012**, *77*, 8386. (b) Al-Zoubi, R. M.; Marion, O.; Hall, D. G. *Angew. Chem., Int. Ed.* **2008**, *47*, 2876. According to ref 4b, **3** is more active than **1** and **2** under conditions of rt to 50 °C in the presence of 4Å molecular sieves. See note 11.

(5) (a) Mylavarapu, R. K.; GCM, K.; Kolla, N.; Veeramalla, R.; Koilkonda, P.; Bhattacharya, A.; Bandichhor, R. *Org. Process Res. Dev.* **2007**, *11*, 1065. (b) Tang, P. *Org. Synth.* **2005**, *81*, 262.

(6) For the $B(OH)_3$-catalyzed ester condensation of α-hydroxycarboxylic acids, see: (a) Levonis, S. M.; Bornaghi, L. F.; Houston, T. A. *Aust. J. Chem.* **2007**, *60*, 821. (b) Maki, T.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2005**, *7*, 5047. (c) Houston, T. A.; Wilkinson, B. L.; Blanchfield, J. T. *Org. Lett.* **2004**, *6*, 679.

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(8) For the arylboronic acid catalyzed dehydrative condensation of di- and tetracarboxylic acids, see: (a) Sakakura, A.; Yamashita, R.; Ohkubo, T.; Akakura, M.; Ishihara, K. *Aust. J. Chem.* **2011**, *64*, 1458. (b) Sakakura, A.; Ohkubo, T.; Yamashita, R.; Akakura, M.; Ishihara, K. *Org. Lett.* **2011**, *13*, 892.

(9) Ishihara, K. In *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, 2005; pp 1−99.

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These boronic acids catalyze the dehydrative amide condensation of a variety of carboxylic acids and amines. For example, in the reaction of 3-phenylpropionic acid with 3,5-dimethylpiperidine (1.0 equiv) conducted in toluene (bp 110 °C) under azeotropic reflux conditions for 4 h, arylboronic acids **1**, **2**, and **3a** (10 mol %) showed good catalytic activities, despite the fact that 3,5-dimethylpiperidine is a less reactive secondary amine (Table 1, entries 1−3). Especially, electron-deficient arylboronic acid **1** gave the best result (89% yield) under these azeotropic reflux conditions.[4b] However, these arylboronic acids were almost inert for the reaction of mandelic acid, an α-hydroxycarboxylic acid (6−8% yield). $B(OH)_3$[5] and $PhB(OH)_2$ also showed poor results for the same reaction (1% and 21% yields, entries 4 and 5), although $B(OH)_3$ catalyzes the dehydrative ester condensation of α-hydroxycarboxylic acids.[6]

On the basis of Marcelli's theoretical mechanistic study,[10] the amide condensation may proceed through nucleohpilic addition of amine to tetracoordinated monoacyl boronate **I**. Nevertheless, we cannot exclude the possibility that **I** is dehydrated to give an equilibrium mixture of monoacyl boronate intermediates **II** and **III** prior to the amide condensation under the azeotropic reflux conditions in toluene (Scheme 1A). An amine would coordinate to the boron atom or interact with the B-OH proton of monoacyl boronate. Although diacyl boronate **IV** is also a possible intermediate,[3] **IV** should be very unstable and rapidly decompose to **III** under the reaction conditions. These monoacyl boronates would provide electrophilic activation through boron conjugation. Since the intermediate **III** would be more favorable than **II**, electron-withdrawing substituents on the aryl group (R^1) should increase the catalytic activity by enhancing the Lewis acidity of the boronic acid catalyst.

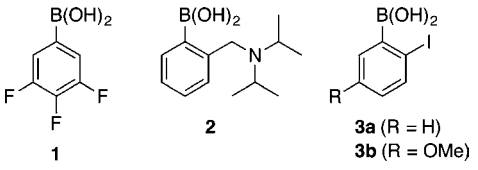
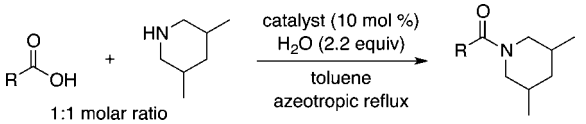


Figure 1. Arylboronic acids **1**−**3** as catalysts for the dehydrative amide condensation reaction.

In a similar way, in the amide condensation of α-hydroxycarboxylic acids, five-membered cyclic monoacyl boronate intermediates **VI** and **VII** would be generated as an equilibrium mixture through the dehydration of **V** (Scheme 1B).[10] X-ray single crystallographic analysis of a complex of $MeB(OH)_2$, phenylpyruvic acid, and 1,2,3,4-tetrahydroquinoline[11] and ^{11}B NMR experiments suggested

Table 1. Catalytic Activities of Boronic Acids for the Amide Condensation of Mandelic Acid[a]



		yield (%)	
entry	catalyst	R = PhCH(OH)	R = $Ph(CH_2)_2$
1	**1**	8	89
2	**2**	8	57
3	**3a**	6	38
4	$B(OH)_3$	1	45
5	$PhB(OH)_2$	21	59
6	$MeB(OH)_2$	73 (96)[b]	48
7	$BuB(OH)_2$	89 (99)[b]	31
8	$^iPrB(OH)_2$	2 (5)[b]	29
9	no catalyst	0	~0

[a] The reaction of mandelic acid (1.25 mmol) and 3,5-dimethylpiperidine (1.25 mmol) was conducted in toluene (5 mL) in the presence of a catalyst (10 mol %) and water (2.2 equiv) under azeotropic reflux conditions for 14 h (for mandelic acid) or 4 h (for 3-phenylpropionic acid). [b] The reaction was conducted in the presence of benzoic acid (10 mol %).

the formation of cyclic intermediates. Because the carboxylate anion is a weaker base than the amine, carboxylate-coordinated **VII** would be more reactive than amine-coordinated **VI**. However, it is conceivable that **VI** was more favorable than **VII** in the arylboronic acid catalyzed reaction, and the electron-withdrawing substituents on the aryl group further shifted the equilibrium toward **VI** to decrease the reactivity. Thus, for successful promotion of the dehydrative amide condensation of α-hydroxycarboxylic acids, a new boronic acid catalyst, which could preferentially form plausible active species **VII**, is required.

As a result of extensive studies, we found that primary alkylboronic acids such as $MeB(OH)_2$ and $BuB(OH)_2$ successfully catalyzed the dehydrative amide condensation of mandelic acid (Table 1, entries 6 and 7), despite the fact that 3,5-dimethylpiperidine was a sterically hindered less reactive secondary amine.[12,13] The appropriate electron-donating nature of methyl and butyl groups might suppress the formation of less active **VI** to promote the dehydrative amide condensation. In contrast to these primary alkylboronic acids that were stable under heating conditions, a secondary alkylboronic acid such as i-$PrB(OH)_2$ showed

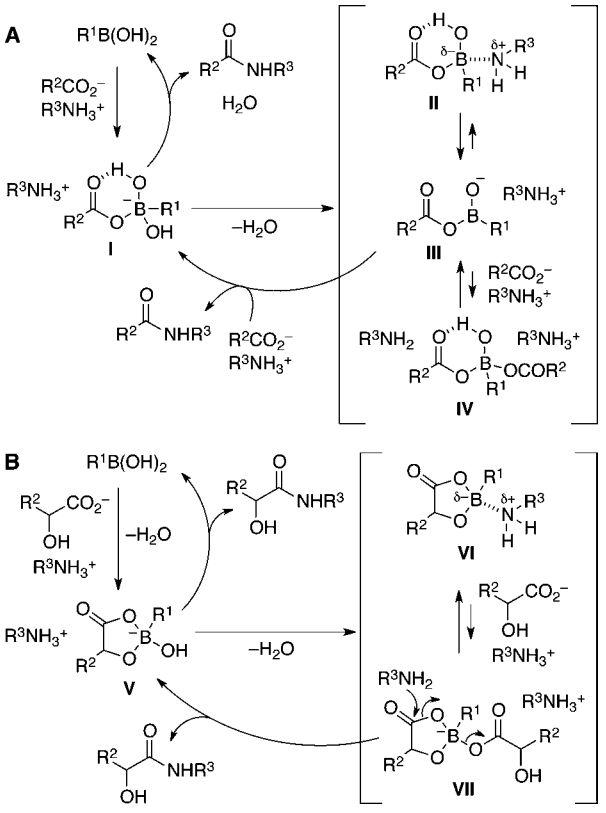
(10) Boronate **V** should be much less reactive than **I** due to the strong coordination of hydroxide anion. Marcelli, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 6840.

(11) CCDC-933866 contains supplementary crystallographic data for this paper. This information can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. See the Supporting Information for details.

(12) When the reaction of mandelic acid (1.1 equiv) with 3,5-dimethylpiperidine was conducted in CH_2Cl_2 at ambient temperature in the presence of 10 mol % of $MeB(OH)_2$ or **3a** and MS 4Å,[4] the corresponding amide was not obtained. See the Supporting Information for details.

(13) When the $MeB(OH)_2$-catalyzed reaction of mandelic acid methyl ether with 3,5-dimethylpiperidine was conducted for 14 h, the corresponding amide was obtained in 37% yield, while the use of **1** as a catalyst gave the amide in 84% yield. These results suggested that the α-methoxy functionality did not show the positive effect for the present amide condensation. See the Supporting Information for details.

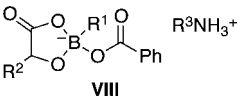
Scheme 1. Plausible Active Intermediates for the Boronic Acid Catalyzed Amide Condensation[a]



[a] (A) Reaction of carboxylic acids without an α-hydroxy group. (B) Reaction of α-hydroxycarboxylic acids.

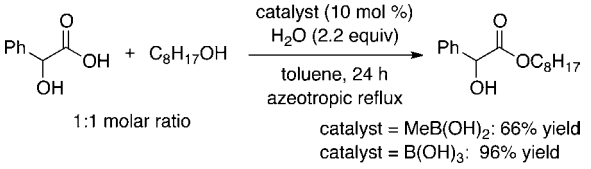
poor catalytic activity (entry 8), probably due to the decomposition to $B(OH)_3$.

Since both mandelic acid and 3,5-dimethylpiperidine were less reactive in the dehydrative amide condensation, yields of the corresponding α-hydroxyamide were not sufficiently high (73% and 89%), even when Me- or Bu-$B(OH)_2$ was used as a catalyst. However, they were increased to 96% and 99% when the reaction was conducted in the presence of benzoic acid (10 mol %). It is conceivable that benzoic acid promoted ligand exchange between the product and the substrate on the catalyst. As another possibility, more reactive intermediate **VIII** might be generated in place of **VII**. In the dehydrative amide condensation shown in Table 1, the boronic acid catalyst was treated with a small amount of water (2.2 equiv) prior to heating under azeotropic reflux to obtain the amide in a highly reproducible yield. The use of water could facilitate the hydrolysis of triboroxines, which are catalytically less active trimers of boronic acids,[9] to give catalytically active monomeric boronic acids.[7] The present method could be easily applied to a gram-scale synthesis of α-hydroxycarboxamide. *When the reaction of mandelic acid (50 mmol, 7.6 g) and 3,5-dimethylpiperidine (50 mmol, 6.8 mL) was conducted in the presence of MeB(OH)$_2$ (1 mol %), benzoic acid (50 mol %) and water (2 mL), 14.0 g of the corresponding α-hydroxycarboxamide was obtained (99% yield).*[14]



In contrast to the amide condensation in which $MeB(OH)_2$ showed excellent catalytic acitivity while $B(OH)_3$ was almost inert, the use of $MeB(OH)_2$ for the dehydrative ester condensation of mandelic acid gave moderate results, while $B(OH)_3$ showed high catalytic activity[6] (Scheme 2). These results indicated that the catalysis of boronic and boric acids for the amide condensation was quite different from that for the ester condensation.

Scheme 2. Dehydrative Ester Condensation of Mandelic Acid



With the highly active catalysts in hand, the amide condensation reactions of various α-hydroxycarboxylic acids were examined to explore the generality and scope of the present method (Figure 2). The reaction was conducted in the presence of $MeB(OH)_2$ (1 mol %). Both 3-phenyllactic acid and 2-hydroxyoctanoic acid were highly reactive, and the reaction with both primary and secondary amines gave the corresponding amides in high yields without a measurable loss of optical purity (entries 1−11). In the reaction with less reactive amines such as cyclododecylamine, 3,5-dimethylpiperidine, and dibutylamine, the use of 10 mol % of the catalyst and the addition of benzoic acid (10 mol %) successfully improved the yields (entries 5−7).

Mandelic acid was less reactive than 3-phenyllactic acid and 2-hydroxyoctanoic acid. Although the amide condensation with sterically hindered dibutylamine gave moderate results (entry 15), the reaction of mandelic acid generally gave the corresponding amides in good to high yields (entries 12−15). In contrast to 3-phenyllactic acid, mandelic acid was susceptible to racemization under the reaction conditions. However, the use of 1,2-dichloroethane (bp 83 °C) as the reaction solvent instead of toluene (bp 110 °C) significantly suppressed racemization in the reaction with 2-phenylethylamine (entry 12).

Since $MeB(OH)_2$ showed high catalytic activity for the dehydrative amide condensation but was not efficient for the ester condensation, it was envisioned that the selective amide condensation with an aminoalcohol could be achieved. Indeed, when the reaction of mandelic acid with 6-aminohexan-1-ol was conducted under the optimized reaction conditions, the corresponding amide was selectively

(14) For another methodology of the synthesis of α-hydroxyamides, see: Leighty, M. W.; Shen, B.; Johnston, J. N. *J. Am. Chem. Soc.* **2012**, *134*, 15233.

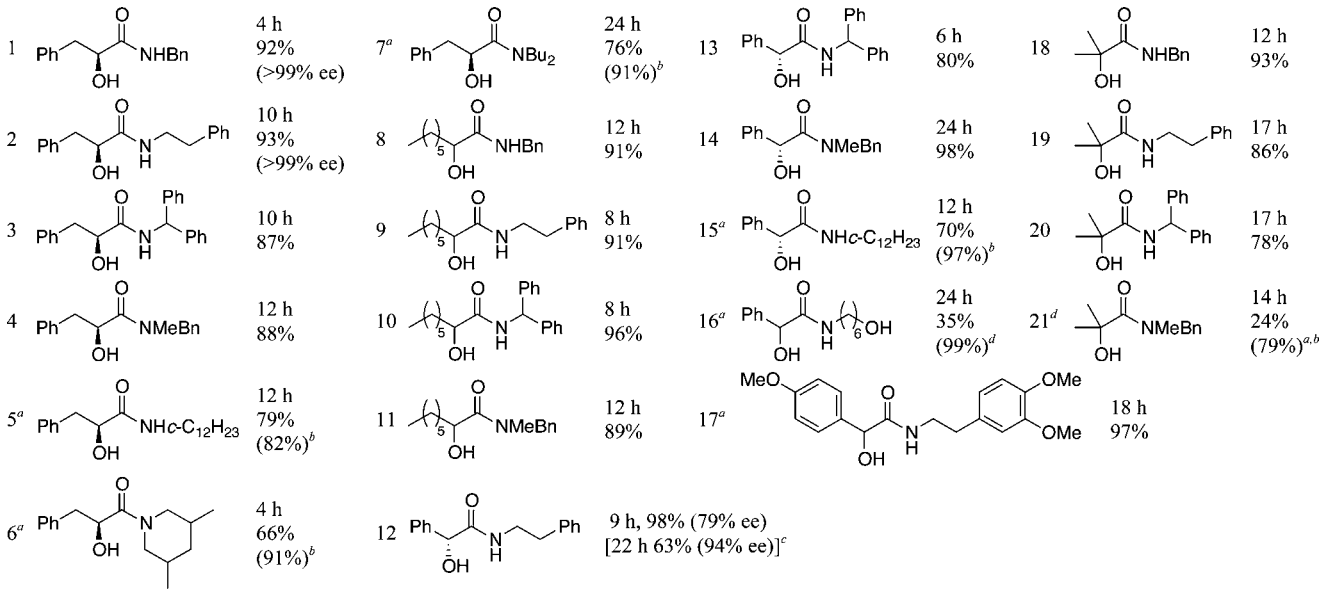


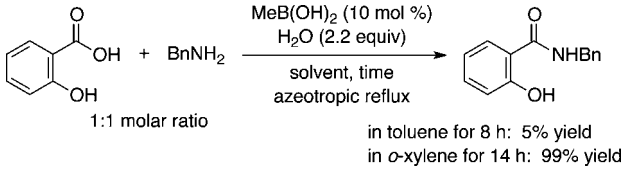
Figure 2. Products of methylboronic acid catalyzed dehydrative amide condensation of α-hydroxycarboxylic acids. The reaction of an α-hydroxycarboxylic acid (1.25 mmol) and an amine (1.25 mmol) was conducted in toluene (5 mL) in the presence of $MeB(OH)_2$ (1 mol %) and water (2.2 equiv) under azeotropic reflux conditions. Notes: [a]10 mol % of $MeB(OH)_2$ was used. [b]The reaction was conducted in the presence of benzoic acid (10 mol %). [c]The reaction was conducted in 1,2-dichloroethane. [d]The reaction was conducted in *o*-xylene.

obtained in quantitative yield (entry 16).[15] Amide condensation between 4-methoxymandelic acid and 2-(3,4-dimethoxyphenyl)ethylamine gave the corresponding amide in excellent yield (entry 17). $LiAlH_4$ reduction of this amide gave an *O*-methyl derivative of denopamine, a β1 adrenergic receptor agonist, in 78% yield.[16,17] The reactivity of 2-hydroxy-2-methylpropanoic acid was further reduced due to steric hindrance (entries 18−21). The use of benzoic acid (10 mol %) as an additive successfully promoted the reaction of 2-hydroxy-2-methylpropanoic acid with less reactive *N*-methylbenzylamine to give the desired amide in 79% yield (entry 21).

$MeB(OH)_2$ was highly efficient for the dehydrative amidation of salicylic acid, a β-hydroxycarboxylic acid (Scheme 3). Since the reactivity of salicylic acid was very low, the corresponding amide was not obtained when the reaction was conducted in toluene. However, the use of *o*-xylene (bp 144 °C) improved the reactivity and gave the amide in almost quantitative yield.

In conclusion, we have demonstrated that commercially available primary alkylboronic acids such as $MeB(OH)_2$ and $BuB(OH)_2$ successfully catalyzed the dehydrative amide condensation of α-hydroxycarboxylic acids. The catalytic activities of these primary alkylboronic acids were much higher than those of previously reported arylboronic acids. For the reaction of less reactive substrates, the use of benzoic acid (10−50 mol %) successfully improved the reactivity. The β1-receptor agonist denopamine derivative could be easily synthesized by the present method.

Scheme 3. Amide Condensation of Salicylic Acid



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Supporting Information Available. Experimental procedure and full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(15) Since the catalytic activity of $MeB(OH)_2$ was rather low for the transformation of ester to amide, the reaction with 6-aminohexan-1-ol was proposed to proceed via the direct amide condensation.

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