Brønsted Base-Assisted Boronic Acid Catalysis for the Dehydrative Intramolecular Condensation of Dicarboxylic Acids
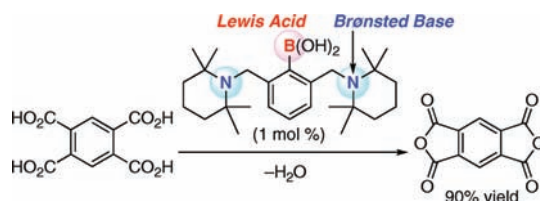
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ABSTRACT

Brønsted base-assisted boronic acid catalysis for the dehydrative self-condensation of carboxylic acids is described. Arylboronic acid bearing bulky (*N,N*-dialkylamino)methyl groups at the 2,6-positions can catalyze the intramolecular dehydrative condensation of di- and tetracarboxylic acids. This is the first successful method for the catalytic dehydrative self-condensation of carboxylic acids.

Carboxylic anhydrides are widely used as activated carboxylic acids for the synthesis of (poly)esters, (poly)amides, (poly)imides, and so on.[1] For example, thermoplastic aromatic polyimides are synthesized from aromatic carboxylic dianhydrides and diamines[2] via the intermediary poly-(amidocarboxylic acid).[2b] The aromatic carboxylic dianhydrides are industrially synthesized from the corresponding tetracarboxylic acids using excess acetic anhydride as a dehydration reagent. In this case, however, remaining acetic anhydride and resultant acetic acid should be completely removed before the subsequent reaction with a diamine because the diamine preferentially reacts with acetic anhydride or acetic acid to give the corresponding acetamide or ammonium acetate. In another method, the aromatic carboxylic dianhydrides are synthesized by thermal dehydration of tetracarboxylic acids, which requires extremely high reaction temperature (220–270 °C).[3] From the perspective of green chemistry, the catalytic dehydrative self-condensation of carboxylic acids should be an ideal method for the synthesis of carboxylic anhydrides since it generates water as the only byproduct.[4] In addition, the reaction mixture can be used for the subsequent reaction with a diamine without any purification procedures. However, no practical method of the catalytic dehydrative self-condensation of carboxylic acids under mild conditions has been reported to date.

It has been reported that electron-deficient arylboronic acids catalyze dehydrative amide and ester condensation

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reactions through the formation of monoacyl boronate intermediates.[5,6] However, these arylboronic acids are not effective for the catalytic dehydrative self-condensation of carboxylic acids because of the much lower nucleophilicity of carboxylic acids than amines and alcohols. In 2006, Whiting and co-workers reported arylboronic acid **1a** bearing an (*N,N*-diisopropylamino)methyl group at the 2-position as an efficient catalyst for amide condensation reaction.[7] In some cases, **1a** is more advantageous than electron-deficient arylboronic acids, although the role of the (*N,N*-diisopropylamino)methyl group is unclear for the amide condensation reaction.[8] On the basis of these previous results, we envisioned that an arylboronic acid of general type **1** bearing an (*N,N*-dialkylamino)methyl group[7,9−14] would promote the dehydrative self-condensation of carboxylic acids under mild conditions through activation of the other carboxyl group using the (*N,N*-dialkylamino)methyl group as a Brønsted base in a mono-acyl boronate intermediate **2** (Figure 1). We report here Brønsted base-assisted boronic acid catalysis for the intramolecular dehydrative condensation of di- and tetra-carboxylic acids.

According to our working hypothesis, we first investigated the catalytic activities of various arylboronic acids
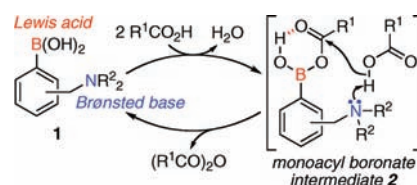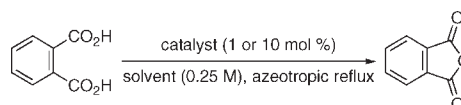

Figure 1. Working hypothesis: Brønsted base-assisted boronic acid catalysis.

(10 mol %) that promoted the intramolecular dehydrative condensation of phthalic acid (Table 1). The reaction was conducted in nonane (bp 151 °C) under azeotropic reflux conditions with the removal of water. Arylboronic acids bearing electron-withdrawing substituents, some of which

Table 1. Catalytic Dehydrative Condensation of Phthalic Acid[a]

entry	catalyst ArB(OH)₂	conv (%)[b] conditions (cat. loading/solvent/time)		
		10 mol %/ nonane (151 °C)[c]/ 1.5 h	10 mol %/ heptane (98 °C)[c]/ 12 h	1 mol %/ EtCN (97 °C)[c]/ 12 h
1	no catalyst	0	—	—
2	2-IC₆H₄B(OH)₂	21	—	—
3	3,4,5-F₃C₆H₂B(OH)₂	35	—	—
4	2,4,6-(iPr)₃C₆H₂B(OH)₂	12	—	—
5	**1a**	79	8	—
6	**1b**	94	4	—
7	**1c**	97	16	—
8	**1d**	99	40	—
9	**1e**	—	33	56
10	**1f**	—	52	71
11	**1g**	—	75	99
12	PhB(OH)₂	—	0 (0)[d]	—

[a] The reaction of phthalic acid (2.5 mmol) was conducted in the presence of an arylboronic acid (1 or 10 mol %) in solvent (10 mL). [b] Determined by ¹H NMR analysis. [c] Boiling point. [d] Data in parentheses refer to conversion yield in the presence of 1,2,2,6,6-pentamethylpiperidine (20 mol %).

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are highly active dehydrative amide condensation catalysts,[5−7] showed low catalytic activities (entries 1−3). Bulky 2,4,6-triisopropylphenylboronic acid also showed poor catalytic activity (entry 4). In contrast, as expected, arylboronic acid **1a**[7] bearing an (*N,N*-diisopropylamino)-methyl group at the 2-position showed high catalytic activities in nonane, even without electron-withdrawing substituents (entry 5). Interestingly, arylboronic acids **1b** and **1c** bearing an (*N,N*-diisopropylamino)methyl group at the 3- and 4-positions also showed high catalytic activities (entries 6 and 7). Theoretical calculations suggest that the (*N,N*-diisopropylamino)methyl group at the 2- and 3-positions can form hydrogen bonding with the carboxyl group of the monoacyl boronate intermediates generated from **1a** and **1b**.[15] In the case of **1c**, the 4-(*N,N*-diisopropylamino)methyl group may interact with the carboxyl group with the aid of the other molecules of **1c** or phthalic acid through hydrogen bondings. Detailed mechanistic studies are in progress.

Since the use of heptane (bp 98 °C) as a solvent significantly decreased the yield of phthalic anhydride due to the low reaction temperature, further investigation was conducted to promote the reaction under mild conditions. As a result, we found that the introduction of a methyl group at the 6-position surprisingly increased the catalytic activity despite the steric hindrance around the boronic acid moiety (catalyst **1d**, entry 8). Furthermore, the use of arylboronic acid **1f** bearing two (*N,N*-diisopropylamino)-methyl groups at the 2,6-positions successfully improved the reactivity (entry 10), while arylboronic acid **1e** bearing two (*N,N*-diisopropylamino)methyl groups at the 3,5-positions showed lower activity than **1f** (entries 9 versus 10). Arylboronic acid **1g** bearing sterically bulky 1-(2,2,6,6-tetramethylpiperidinyl)methyl groups at the 2,6-positions showed the highest catalytic activity (entry 11). Despite the high catalytic activities of **1f** and **1g** for the intramolecular condensation, they showed poor catalytic activities for the intermolecular dehydrative self-condensation of 4-phenylbutyric acid.[15]

Whiting and co-workers reported that for the dehydrative amide condensation, **1a**, which showed no N→B chelation in both solution and solid states, was more active than phenylboronic acid bearing a sterically less hindered (*N,N*-dimethylamino)methyl group at the 2-position, which showed N→B chelation.[7a,9b,11a,13,14] The steric hindrance of the *N,N*-diisopropylamino group might prevent the intramolecular interaction between the boronic acid group and the *N,N*-diisopropylamino group (N→B chelation) that causes the inactivation of the boronic acid group (Figure 2). The crystal structure of **1f** shows that the *N,N*-diisopropylamino groups interact with protons of the boronic acid group.[15] Saito and co-workers also reported the intramolecular hydrogen bonding between (*N,N*-dialkylamino)methyl groups and boron-coordinated water in aqua-aminoorganoboron compounds.[10a] Based on these analyses and the high catalytic activities of **1f** and **1g**, we can propose some plausible but significant roles of the bulky (*N,N*-dialkylamino)methyl groups in the present
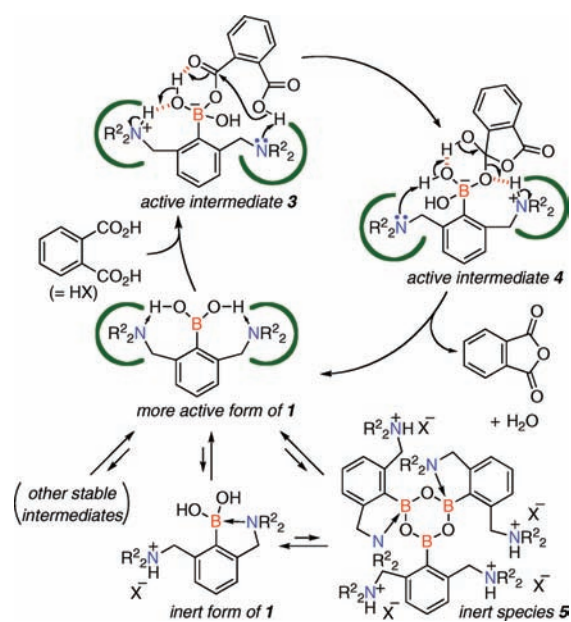
(15) See the Supporting Information for details.

Figure 2. Plausible reaction mechanism.

catalysis (Figure 2). The condensation of phthalic acid would occur via monoacyl boronate **3** as an active intermediate. Then, the *N,N*-dialkylamino nitrogen and the *N,N*-dialkylammonium proton of **3** would synergistically promote the intramolecular cyclization to **4**: the former would act as Brønsted base to activate the carboxyl group, and the latter would act as Brønsted acid to activate the carbonyl group through two consecutive hydrogen-bonding interactions supported by the B-hydroxyl group (C=O···H−O···H−N+). The subsequent elimination of phthalic anhydride from the intermediate **4** would also be synergistically promoted by the *N,N*-dialkylamino nitrogen and the *N,N*-dialkylammonium proton of **4**. The intramolecular hydrogen-bonding interaction between the B-hydroxyl group and the *ortho*-Brønsted base substituent of arylboronic acids has also been suggested by the theoretical study for the dehydrative amide condensation catalyzed by 2-iodophenylboronic acid.[8] In addition, the introduction of two bulky substituents at the 2,6-positions might prevent formation of less active species such as triarylboroxines **5**.[11b,13b]

Propionitrile (EtCN, bp 97 °C) was suitable as a solvent, probably due to the high polarity and good solubility. In EtCN, only 1 mol % of **1f** and **1g** could catalyze the reaction to give phthalic anhydride in respective yields of 71 and 99%. The combination of phenylboronic acid (10 mol %) and 1,2,2,6,6-pentamethylpiperidine (20 mol %) showed no catalytic activity (entry 12). This control experiment indicates that an intramolecular Lewis basic function on **1g** was essential to the successful promotion of the condensation.[7a]

With highly active dehydration catalyst **1g** in hand, we next examined the catalytic dehydrative condensation of aromatic tetracarboxylic acids **6** to dianhydrides **7** (Table 2). The reactions of **6a−e** were successfully catalyzed by **1g**

Table 2. 1g-Catalyzed Dehydrative Condensation of Aromatic Tetracarboxylic Acids 6[a]

entry	tetracarboxylic acid	6 [X]	7, yield (%)[b]
1	(aromatic tetracarboxylic acid with HO₂C, CO₂H groups)	6a	7a, 90 (7)
2[c]		6a	7a, 8
3	(diaryl X-linked tetracarboxylic acid)	6b [S(=O)₂]	7b, 92 (0)
4		6c [C=O]	7c, 98 (7)
5		6d [[O]]	7d, 90 (3)
6		6e [C(CF₃)₂]	7e, 85[d]

[a] Unless otherwise noted, the reaction of **6** (2.5 mmol) was conducted in the presence of **1g** (1 mol %) in *n*-PrCN (10 mL) for 12 h. [b] Isolated yield. Data in parentheses refer to conversion yield in the absence of **1g**. [c] TsOH (10 mol %) was used as a catalyst. [d] Conversion yield was >99%.

(1 mol %) in butyronitrile (*n*-PrCN, bp 115 °C) under azeotropic reflux conditions to give the corresponding dianhydrides **7a–e** in excellent isolated yields. Carboxylic dianhydrides **7** were easily isolated by filtration of the reaction mixture. The use of *n*-PrCN was effective mainly because of the rather good solubility of **6** and **7** under the reaction conditions. In contrast, dianhydrides **7** were obtained in poor yields in the absence of **1g**. TsOH was almost inert for the reaction of **6a** (entry 2).

Scheme 1. Catalytic Synthesis of Diimide 8 and One-Pot Synthesis of Bis(amidocarboxylic acid)s 9
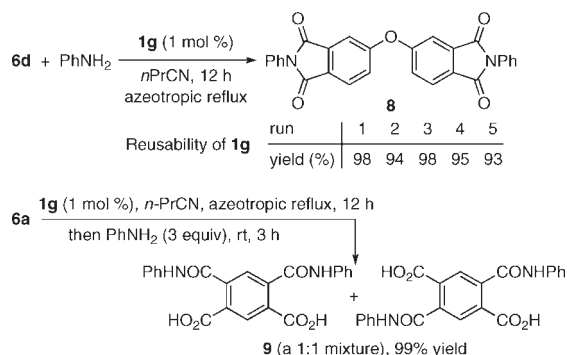
On the basis of the present catalytic condensation, the direct synthesis of a diimide from a tetracarboxylic acid and a primary amine was investigated as a model reaction for the synthesis of polyimides[2] (Scheme 1). When the **1g**-catalyzed condensation of **6d** was conducted in the presence of aniline (2.5 equiv), diimide **8** was obtained in 98% yield by simple filtration of the reaction mixture. Catalyst **1g** could be easily recovered by concentration of the filtrate, and could be reused repeatedly without any loss of activity. Furthermore, one-pot synthesis of bis-(amidocarboxylic acid)s **9** could be achieved by the direct addition of aniline (3 equiv) to the reaction mixture of **7a** at ambient temperature (Scheme 1).[2b] After being stirred for 3 h, a 1:1 isomeric mixture of **9** was obtained in 99% yield by filtration of the reaction mixture.

We next investigated the **1g**-catalyzed dehydrative condensation of aliphatic dicarboxylic acids **10** (Table 3).[16]

Table 3. 1g-Catalyzed Dehydrative Condensation of Aliphatic Dicarboxylic Acids 10[a]

entry	dicarboxylic acid	10	11, conv (%)[b]
1	(cyclohexane *cis*-1,2-di-CO₂H)	10a	11a, 99 (48)[c]
2	(cyclohexane *trans*-1,2-di-CO₂H)	10b	11a, 89 (0)[c]
3	(R³ substituted succinic)	10c, [R³ = H]	11c, 96
4		10d, [R³ = NHBoc]	11d, 94 (0)[d]
5[e]	(R⁴, R⁵ substituted glutaric)	10e, [R⁴, R⁵ = H, H]	11e, 73
6		10f, [R⁴, R⁵ = (CH₂)₄]	11f, 99
7[f]		10g, [R⁴ = Me, R⁵ = H]	11g, 90
8[f]		10h, [R⁴ = Ph, R⁵ = H]	11h, 100

[a] Unless otherwise noted, the reaction of **10** (2.5 mmol) was conducted in the presence of **1g** (1 mol %) in EtCN (10 mL) for 12–24 h. [b] Determined by ¹H NMR analysis. [c] Data in parentheses refer to conversion yield in the absence of **1g**. [d] Data in parentheses refer to yield in the presence of TsOH (10 mol %) instead of **1g**. [e] The reaction was conducted in *n*-BuCN for 24 h. [f] The reaction was conducted in *n*-PrCN.

The reaction of cyclic *cis*-1,2-dicarboxylic acid **10a** gave the *cis*-anhydride **11a** in 99% yield (entry 1). Interestingly, cyclic *trans*-1,2-dicarboxylic acid **10b** selectively gave the corresponding *cis*-anhydride **11a** via epimerization (entry 2). Not only cyclic 1,2-dicarboxylic acids but also linear 1,2-dicarboxylic acids, such as succinic acid (**10c**) and *N*-Boc-aspartic acid (**10d**), could be converted to the corresponding anhydrides **11c** and **11d**[17] in good yields (entries 3 and 4). Although glutaric acid (**10e**), a 1,3-dicarboxylic acid, was less reactive than 1,2-dicarboxylic acids, the use of valeronitrile (*n*-BuCN, bp 140 °C) as a solvent significantly improved the yield of **11e** (entry 5). 3-Substituted 1,3-dicarboxylic acids **10f–h** significantly improved the reactivity to give the corresponding anhydrides **11f–h** in high yields (entries 6–8).

In conclusion, we have developed bifunctional Brønsted base-assisted boronic acid catalyst **1g**, an arylboronic acid bearing two bulky (*N,N*-dialkylamino)methyl groups at the 2,6-positions, for the green synthesis of carboxylic anhydrides. This is the first successful method of the catalytic intramolecular dehydrative condensation of di- and tetracarboxylic acids.

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

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(17) The enantiomeric excess of the obtained **11d** was 41%.