N-Alkyl-4-boronopyridinium Halides versus Boric Acid as Catalysts for the Esterification of α-Hydroxycarboxylic Acids
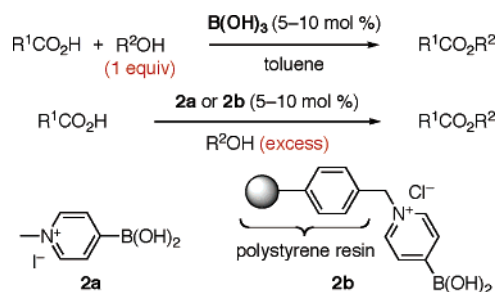
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ABSTRACT

Boric acid is a highly effective catalyst for the dehydrative esterification reaction between equimolar mixtures of α-hydroxycarboxylic acids and alcohols. In contrast, *N*-methyl-4-boronopyridinium iodide (2a) is a more effective catalyst than boric acid for the similar esterification in excess alcohol. A heterogeneous catalyst, such as *N*-polystyrene-bound 4-boronopyridinium chloride, is also an effective catalyst and can be recovered by filtration.

In 1996, we found that the dehydrative condensation of equimolar mixtures of carboxylic acids and amines proceeds under azeotropic reflux conditions with the removal of water in less-polar solvents, such as toluene and xylene, in the presence of benzeneboronic acids **1** bearing electron-withdrawing groups at the *m*- or *p*-positions, such as 3,4,5-trifluorobenzeneboronic acid (**1a**) and 3,5-bis(trifluoromethyl)-benzeneboronic acid (**1b**).[1] We also found that *N*-alkyl-4-boronopyridinium halides **2**, such as 4-borono-*N*-methylpyridinium iodide (**2a**) and *N*-polystyrene resin-bound 4-borono-

pyridinium chloride (**2b**), were effective as cationic catalysts for amide condensation in polar solvents, such as anisole, acetonitrile, *N*-methylpyrrolidinone (NMP), and ionic liquid.[2] Unfortunately, these boronic acids were much less effective for the esterification of simple carboxylic acids because an alkoxyborane species was preferentially produced rather than the desired acyloxyborane species.[1a] In 2004, however, Houston et al. reported that boric acid (B(OH)$_3$, 10−20 mol %) was effective as a catalyst for the chemoselective esterification of α-hydroxycarboxylic acids with excess alcohol as solvents even at ambient temperature (Scheme 1).[3,4] This
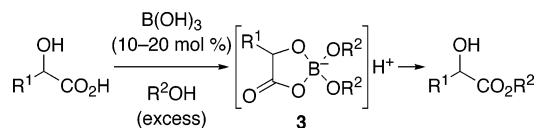
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(1) (a) Ishihara, K.; Ohara, S.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4196−4197. (b) Ishihara, K.; Ohara, S.; Yamamoto, H. *Macromolecules* **2000**, *33*, 3511−3513. (c) Ishihara, K.; Ohara, S.; Yamamoto, H. *Org. Synth.* **2002**, *79*, 176−185. (d) Maki, T.; Ishihara, K.; Yamamoto, H. *Synlett* **2004**, 1355−1358. (e) Ishihara, K.; Kondo, S.; Yamamoto, H. *Synlett* **2001**, 1371−1374.

(2) (a) Ohara, S.; Ishihara, K.; Yamamoto, H. *The 77th Spring Meeting of Chemical Society of Japan*, 2000. (b) Ishihara, K.; Yamamoto, H. *Jpn. Kokai Tokkyo Koho* JP 2001−270939 (2001−10−02), Application: JP 2000−87495 (2000−03−27). (c) Maki, T.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2005**, *7*, 5043.

(3) Houston, T. A.; Wilkinson, B. L.; Blanchfield, J. T. *Org. Lett.* **2004**, *6*, 679.

dodecamer under dehydrative conditions,[2c] this is prevented by excess alcohol.

To explore the generality and scope of the esterification catalyzed by **2a** in excess alcohol, various substrates were examined in the presence of 5 mol % of **2a**. Representative results are shown in Table 2. Not only α-hydroxycarboxylic

unexpected reactivity of α-hydroxycarboxylic acids with alcohols can be understood by considering that thermally stable 2,2-dialkoxy-4-oxo-1,3,2-dioxaborolan-2-uide (**3**) is preferentially produced as an anionic active intermediate even in the presence of excess alcohol.

On the basis of Houston's report,[3] we explored the efficacy of boric acid, **1**, and **2** as catalysts for the esterification of α-hydroxycarboxylic acids. We report here that **2a** is a more effective catalyst than boric acid for the esterification of α-hydroxycarboxylic acids in excess alcohol solvents (Houston's conditions). On the other hand, boric acid is a more effective esterification catalyst for equimolar mixtures of α-hydroxycarboxylic acids and alcohols.

First, the catalytic activities of boric acid, neutral boronic acid **1b**, and cationic boronic acid **2a** were compared in the esterification of mandelic acid in several excess alcohols (Table 1). Expectedly, boric acid was not very effective. **1b**
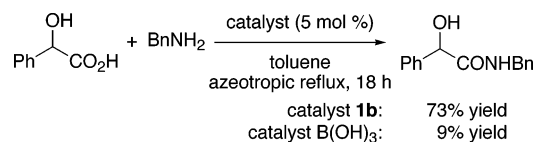
Table 1. Catalytic Activities of Boric and Boronic Acids

entry	R^2OH	conditions	$B(OH)_3$	**1b**	**2a**
				conversion (%)	
1[a]	MeOH	rt, 2 h	28	48	77
2[a]	EtOH	rt, 5 h	24	19	43
3[b]	i-BuOH	reflux, 1 h	36	32	83
4[a]	i-PrOH	reflux, 5 h	29	14	52
5[b]	$HO(CH_2)_2OH$	80 °C, 1.5 h	48[c]	29[c]	83[c]

[a] 10 mol % of catalyst was used. [b] 5 mol % of catalyst was used. [c] 2-Hydroxyethyl mandelate was produced.

was also less active in polar solvents, such as alcohols. In every case, **2a** gave the best results, probably because **2a** was a tolerable cationic Lewis acid catalyst in polar alcohols. Although **2a** is known to be condensed to a less-active

(4) Tang, P. *Org. Synth.* **2005**, *81*, 262−272. Tang reported that boric acid, which was less active than **1**, was still effective for the amide condensation reaction. According to our experiments concerning the amide condensation of an equimolar mixture of mandelic acid and benzylamine, **1b** was much more effective than boric acid:

Table 2. Esterification of Hydroxycarboxylic Acids in Alcohols Catalyzed by **2a**

entry	temp, time	product	yield (%)	entry	temp, time	product	yield (%)
1	rt, 10 h		93	8	reflux, 15 h		95
2	reflux, 6 h		99	9	reflux, 23 h		86
3	rt, 10 h		96	10	reflux, 18 h		92
4	reflux, 15 h		92	11[a]	reflux, 17 h		85
5	reflux, 4 h		95	12[a,b]	reflux, 20 h		84
6[a]	reflux, 21 h		81	13	reflux, 20 h		93
7	80 °C, 5 h		97	14	reflux, 22 h		89

[a] 10 mol % of **2a** was used. [b] Diisobutyl 4-hydroxyisophthalate and 2-hydroxy-5-(isobutoxycarbonyl)benzoic acid were produced in respective yields of 5 and 2%.

acids but also β-hydroxycarboxylic acids were condensed. In the esterification of 4-hydroxyisophthalic acid, the 3-hydroxycarbonyl group was selectively reacted (entry 12). The esterification condensation of less-reactive secondary alcohols and conjugated carboxylic acids proceeded well with the use of 10 mol % of **2a** (entries 6, 11, and 12). β-Hydroxycarboxylic acids bearing a benzyloxycarbonylamino group at the α-position also reacted (entries 13 and 14). Although ethylene glycol is known to react with boronic acid, leading to the corresponding cyclic boronic ester, esterification with mandelic acid was unexpectedly preferred (entry 7).

Next, to recover and reuse homogeneous catalyst **2a**, we prepared *N*-polystyrene-bound 4-boronopyridinium chloride (**2b**) from Merrifield resin and pyridin-4-ylboronic acid.[2c] **2b** was recovered by filtration and reused at 10 times without any loss of activity for the esterification reaction of mandelic acid in excess isobutanol under reflux conditions (Table 3).

Next, the correlation between the catalytic activity of B(III) and the molar ratio of α-mandelic acid and butanol was

Table 3. Recovery and Reuse of **2b** for Esterification
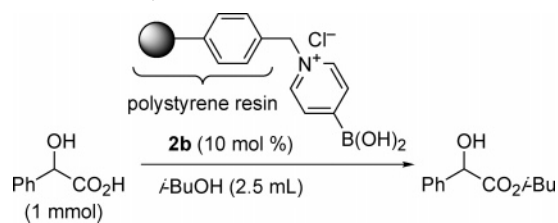
run	conversion (%)	run	conversion (%)
1	96	6	99
2	99	7	98
3	98	8	95
4	99	9	97
5	96	10	95

examined for esterifications catalyzed by 2 mol % of boric acid, **1b**, and **2a**. The conversion to butyl mandelate after heating under reflux conditions in toluene for 1 h was plotted in terms of the molar ratio of mandelic acid to butanol (Figure 1). Surprisingly, boric acid was the most active catalyst with
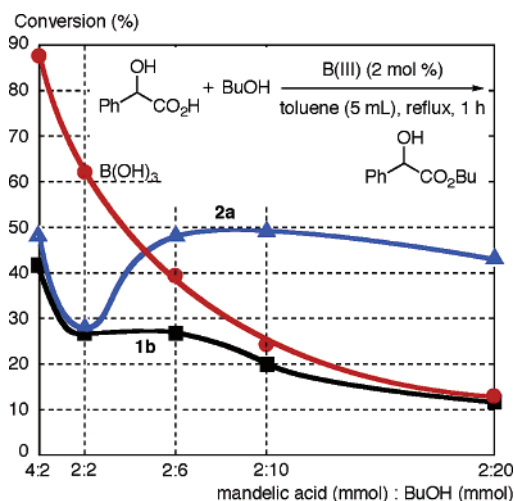
Figure 1. Correlation between the catalytic activity of B(III) and the molar ratio of mandelic acid and butanol.

a molar ratio of mandelic acid/butanol of >1:2. On the other hand, **2a** was the most active catalyst with a molar ratio of mandelic acid/butanol of <1:3. In contrast, **1b** was less active than boric acid and **2a** regardless of the molar ratio of mandelic acid/butanol. Two phenomena that were common to these three catalyses were noted: (1) excess mandelic acid accelerated the esterification, and (2) excess butanol suppressed the esterification probably because excess butanol diluted the concentration of mandelic acid, and the Lewis basicity of excess butanol weakened the Lewis acidity of catalysts. However, **2a** was still active in the presence of excess butanol because of its ability to tolerate polar compounds. Therefore, excess butanol (4−5 equiv) accelerated the esterification catalyzed by **2a**.

To ascertain the generality and scope of the esterification of equimolar mixtures of α-hydroxycarboxylic acids and alcohols catalyzed by boric acid, several substrates were examined in the presence of 5 mol % of boric acid in toluene under azeotropic reflux conditions (Table 4). Not only

Table 4. Esterification of Equimolar Mixtures of Hydroxycarboxylic Acids and Alcohols Catalyzed by B(OH)$_3$

entry	time (h)	product	yield (%)	entry	time (h)	product	yield (%)
1	4		93	4^a	21		87
2	21		99	5^a	20		82
3	21		90	$6^{a,b}$	21		86

^{a} B(OH)$_3$ (10 mol %) was used. ^{b} Xylene was used in place of toluene.

α-hydroxycarboxylic acids and primary alcohols but also β-hydroxycarboxylic acids and secondary alcohols were applicable. It was ascertained that α-hydroxyesters produced were optically pure (>99% ee) (entries 1 and 4). The esterification of less-reactive substrates, such as conjugated carboxylic acids and secondary alcohols, required 10 mol % of boric acid in toluene or xylene.

The boric acid-catalyzed chemoselective esterification of α-hydroxy-α-methylpropanoic acid proceeded in the presence of 4-phenylbutyric acid or benzoic acid (Scheme 2). Houston previously reported that a similar boric acid catalyzed chemoselective esterification in excess alcohol solvents.[3] However, our new procedure using boric acid does not require the use of excess substrates.

Scheme 2. Boric Acid-Catalyzed Chemoselective Esterification of α-Hydroxy-α-methylpropanoic Acid without Excess Substrates
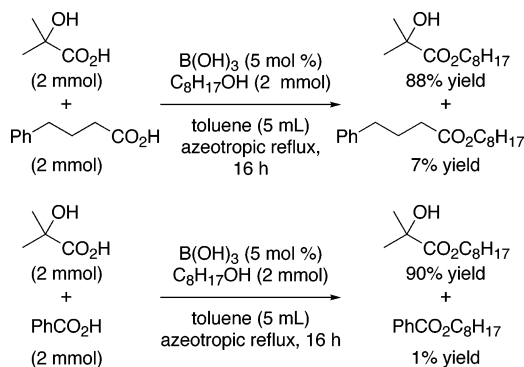
Another application of B(III)-catalyzed dehydrative condensation is shown in Scheme 3. Three successive dehydra-

Scheme 3. Three Successive Dehydrative Condensations of Three Components without the Use of Excess Substrates
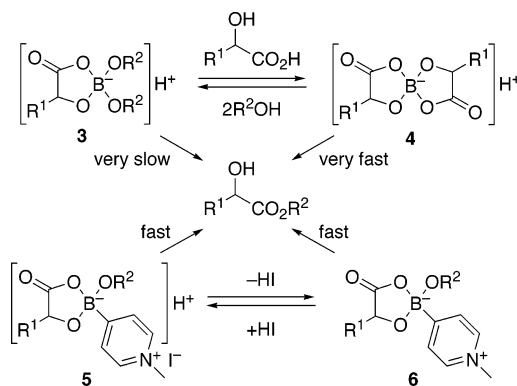

Scheme 4. Proposed Reaction Mechanism
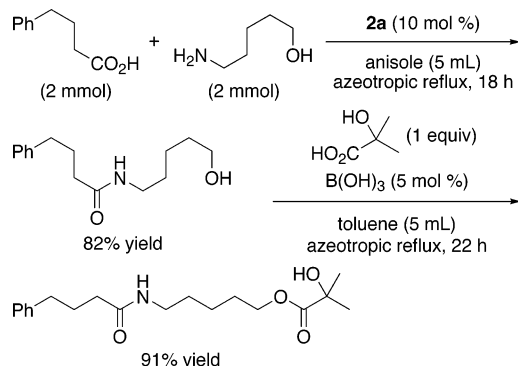
tive condensations of 4-phenylbutyric acid, 5-aminopentan-1-ol, and 2-hydroxy-2-methylpropanoic acid proceeded in high yield through the chemoselective amidation catalyzed by **2a** and subsequent esterification catalyzed by boric acid. No excess substrates were used.

Why was the catalytic activity of boric acid remarkably increased in the presence of excess α-hydroxycarboxylic acids (Figure 1)? Boric acid is known to react with 2 equiv of α-hydroxycarboxylic acids to give dimeric spiro 4-oxo-1,3,2-dioxaborolan-2-uide **4**,[5] which should be more active than monomeric 2,2-dialkoxy-4-oxo-1,3,2-dioxaborolan-2-uide **3** (Scheme 4). However, equilibrium has been observed between **3** and **4**.[5] The more active species **4** should exist as a major intermediate in a esterification reaction solution with a higher molar ratio of α-hydroxycarboxylic acid, while the less active species **3** would be present as a major intermediate in excess alcohol. Judging from the experimental results shown in Figure 1, the reactivity of intermediates with

alcohols should increase in the order **3** < 2-alkoxy-2-(*N*-methylpyridinium-4-yl)-4-oxo-1,3,2-dioxaborolan-2-uides (**5** and **6**)[6] < **4**.

In conclusion, *N*-alkyl-4-boronopyridinium halides are highly effective catalysts for not only the amide condensation reaction[2] but also the esterification reaction of α-hydroxycarboxylic acids in excess alcohol.[7] Boric acid is also effective as a catalyst for not only the amide condensation[4] but also the esterification of equimolar mixtures of α-hydroxycarboxylic acids and alcohols.[7] The former is practical for condensation with volatile alcohols which are useful as solvents, while the latter is practical for condensation with expensive alcohols.

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

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(6) It is not clear that which is a more active intermediate, **5** or **6**.
(7) Tertiary alcohols were not condensed with α-hydroxycarboxylic acids.