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New boron(III)-catalyzed amide and ester condensation reactions

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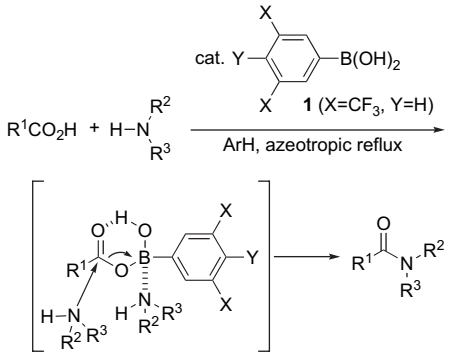
Abstract—In 1996, we reported that benzeneboronic acids bearing electron-withdrawing groups at the *meta*- or *para*-position are highly effective catalysts for the amide condensation reaction in less-polar solvents. In this paper, we report that *N*-alkyl-4-boronopyridinium halides are more effective catalysts than the previous ones in more polar solvents. *N*-Alkyl-4-boronopyridinium halides are effective not only for amide condensation between equimolar mixtures of carboxylic acids and amines but also for the esterification of α-hydroxycarboxylic acids in alcohol solvents. Furthermore, perchlorocatecholborane is more effective than areneboronic acids for the amide condensation of sterically demanding carboxylic acids. In addition, Lewis acid-assisted Brønsted acid (LBA), which is prepared from a 1:2 M mixture of boric acid and tetrachlorocatechol, is effective for the Ritter reaction from alcohols and nitriles to amides.

1. Introduction

It is becoming increasingly desirable to replace current chemical processes with more environmentally benign alternatives.[1] The condensation of carboxylic acids with alcohols or amines is one of the most fundamental and important reactions in organic synthesis.[2] To promote atom efficiency and to avoid the generation of environmental waste, the use of stoichiometric amounts of condensing reagents should be avoided. Therefore, the direct condensation of equimolar mixtures of carboxylic acids with alcohols or amines using small amounts of catalysts is the most ideal method.

In 1996, we found that the dehydrative condensation of equimolar mixtures of carboxylic acids and amines or ureas proceeds under azeotropic reflux conditions with the removal of water in less-polar solvents such as toluene or xylene in the presence of benzeneboronic acids bearing electron-withdrawing groups at the *meta*- or *para*-position, such as 3,4,5-trifluorobenzeneboronic acid, 3,5-bis(trifluoromethyl)-benzeneboronic acid (**1**), and 3,5-bis(perfluorodecyl)benzeneboronic acid (Scheme 1).[3]

However, the scope of suitable substrates has been limited because the catalytic activities of these neutral boronic acids are greatly reduced in polar solvents and for sterically demanding substrates. In this paper, we report that various boron(III) compounds such as boronic acids (**2** and **3a–d**), boric acid, and catecholborane derivatives (**4a–c**) are highly effective catalysts for the amidation,[4,6] esterification,[5] and/or the Ritter reaction[6] (Fig. 1).



Scheme 1. Boronic acid-catalyzed dehydrative amide condensation reaction.

2. Results and discussion

2.1. Amide condensation reaction catalyzed by *N*-alkyl-4-boronopyridinium salts

In 2000, we found that 4-borono-*N*-methylpyridinium iodide (**2**) was effective as a polar-solvent-tolerable catalyst for amide condensation.[7] Cationic boronic acid **2** was much

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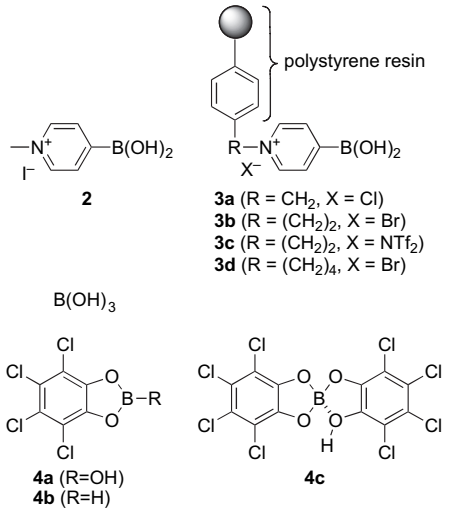
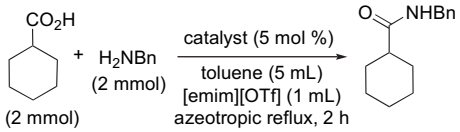


Figure 1. Boron(III) compounds as catalysts for dehydrative condensation reaction.

more active than neutral boronic acids in polar solvents, such as anisole, acetonitrile, and *N*-methylpyrrolidinone (NMP) because the boron atom in **2** shows greater Lewis acidity in polar solvents.[7] Thus, **2** was successfully used as a catalyst for the direct polycondensation of arenedicarboxylic acids with diaminoarenes in a mixed solvent of terphenyl and *N*-butylpyrrolidinone (NBP). In 2001, Wang et al. reported 3-borono-*N*-methylpyridinium iodide (**5**) and *N*-polystyrene resin-bound 3-boronopyridinium chloride (**6**) as amide condensation catalysts.[8] In this section, we report that *N*-alkyl-4-boronopyridinium salts are more thermally stable than *N*-alkyl-3-boronopyridinium salts.[4] A homogeneous catalyst **2** could be reused through the use of an ionic liquid–toluene biphasic system. Furthermore, we developed *N*-polystyrene resin-bound 4-boronopyridinium salts **3a–d** as heterogeneous amide condensation catalysts, which could be reused even in a single solvent such as toluene.

According to some reports,[9] the thermostability of pyridineboronic acids for hydrolytic protodeboration increases in the order: 2-pyridineboronic acid<<3-pyridineboronic acid (**7**)<4-pyridineboronic acid (**8**). First, the thermostability of *N*-methyl boronopyridinium iodides was investigated under heating at 120 °C in DMF. The half-life of **2** was 8 h under the above conditions. On the other hand, **5** was completely decomposed to boric acid and *N*-methylpyridinium iodide within 8 h via hydrolytic protodeboration. In contrast, **7** and **8** were stable even after heating at 120 °C for 1 day. 2-Borono-*N*-methyl boronopyridinium iodide could not be prepared from 2-pyridineboronic acid because of its high sensitivity to hydrolysis. Thus, we determined their thermostabilities, which increased in the order 2-pyridineboronic acid<<**5**<**2**<**7**≤**8**. Next, the catalytic activities of pyridineboronic acids and boronopyridinium iodides were examined for the model amide condensation reaction of cyclohexanecarboxylic acid with benzylamine in 5:1 (v/v) biphasic solvents of toluene and 1-ethyl-3-methylimidazolium trifluoromethanesulfonate [emim][OTf]. The reactions were carried out under azeotropic reflux conditions with the removal of water for 2 h. The results are shown in Table 1. As expected, **2** was the most active catalyst (entry 1). The catalytic activity of **5** was slightly lower than that of **2** (entry 2). 3- and 4-Pyridineboronic acids, **7** and **8**, were less active than the corresponding boronopyridinium iodides (entries 3 and 4). The catalytic activity of **8** was quite low, probably because of its low solubility under these reaction conditions.

Table 1. Catalytic activities of boronic acids



Entry	Catalyst	Conv. (%)	Entry	Catalyst	Conv. (%)
1	**2**	59	3	**7**	43
2	**5**	54	4[a]	**8**	8

[a] Compound **7** did not dissolve under these conditions.

In the course of the experiment in which **2** was heated in DMF at 120 °C, we observed that **2** completely changed to a yellow precipitate within 1 h, and then gradually underwent hydrolytic protodeboration. We isolated this yellow precipitate as an orange crystal from water. Surprisingly, the crystal was unambiguously confirmed to be a dodecamer of **2**, $[\mathbf{2}]_{12}$, by single-crystal X-ray diffraction (Fig. 2). To the best of our knowledge, this is the first example of a dodecamer of an arylboronic acid. Interestingly, $[\mathbf{2}]_{12}$ was dissolved and stable even in water because the 12 hydrophilic pyridinium ion moieties were oriented on the outside of $[\mathbf{2}]_{12}$.

Next, the catalytic activities of **2** and $[\mathbf{2}]_{12}$ (5 mol % for B-atom) were compared in the amide condensation of 4-phenylbutyric acid with benzylamine under azeotropic reflux conditions in toluene with the removal of water (entries 1 and 2, Table 2). The catalytic activity of $[\mathbf{2}]_{12}$ was much lower than that of **2**. Fortunately, the catalytic activities of **2** and $[\mathbf{2}]_{12}$ were dramatically improved in biphasic solvents of toluene and [emim][OTf] (entries 3 and 4). These results can be understood in terms of the good stability of **2** and the good solubility of **2** and $[\mathbf{2}]_{12}$ in the presence of [emim][OTf]. In contrast, **2** was partially soluble in toluene but $[\mathbf{2}]_{12}$ was insoluble. It is likely that **2** is regenerated from $[\mathbf{2}]_{12}$ by hydrolysis in the presence of [emim][OTf]. Furthermore, [emim][OTf] should play an important role in suppressing the condensation of **2** to $[\mathbf{2}]_{12}$. Thus, the amide condensation

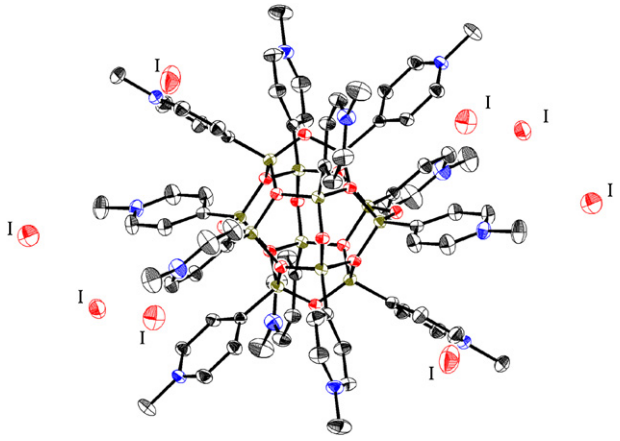
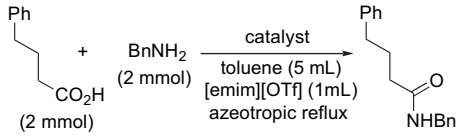


Figure 2. X-ray crystal structure of dodecamer $[\mathbf{2}]_{12}$, $[CH_3NC_5H_4BO_{14/12}]_{12}I_8 \cdot 10H_2O$. Water is omitted for clarity.

Table 2. Catalytic activities of **2** and $[\mathbf{2}]_{12}$ for amide condensation



Entry	Catalyst (mol %)	Time (h)	Yield (%)
1[a]	**2** (5)	1	41
2[a]	$[\mathbf{2}]_{12}$ (10)[b]	1	15
3	**2** (5)	1	74
4	$[\mathbf{2}]_{12}$ (5)[c]	1	75
5	**2** (5)	5	>99
6[d]	**2** (5)	5	>99
7[e]	**2** (5)	5	>99
8	**1** (5)	1	88
9[f]	**1** (5)	1	7

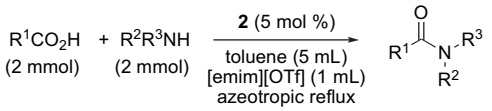
[a] Only toluene was used as a solvent.
[b] Compound $[\mathbf{2}]_{12}$ (10 mol % for B-atom) was used.
[c] Compound $[\mathbf{2}]_{12}$ (5 mol % for B-atom) was used.
[d] Compound **2** used in entry 5 was recovered and reused in entry 6.
[e] Compound **2** used in entry 6 was recovered and reused in entry 7.
[f] A solution of **1** in [emim][OTf] used in entry 8 was recovered and reused in entry 9.

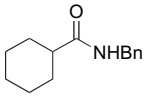
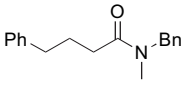
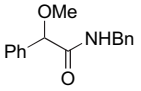
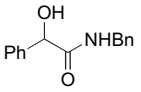
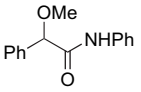
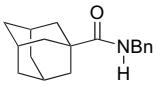
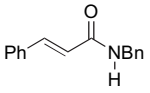
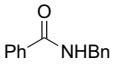
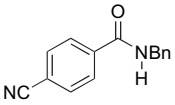
went to completion in the presence of 5 mol % of **2** in toluene/[emim][OTf] (5:1 (v/v)) within 5 h (entry 5). After amide condensation, the desired amide was obtained in quantitative yield by repeated extraction with Et_2O from an [emim][OTf] layer. Compound **2** remained in the [emim][OTf] layer. Thus, a solution of **2** in [emim][OTf] was repeatedly reused for the same amide condensation reaction without any loss of catalytic activity (entries 6 and 7). Neutral boronic acid **1** was also effective in the presence of [emim][OTf] because Lewis acidity of [emim][OTf] was much weaker than those of polar organic solvents such as THF and DMF (entry 8). However, **1** remained in a toluene layer without being extracted with [emim][OTf] (entry 9).

To explore the generality and scope of the amide condensation catalyzed by **2** in the presence of [emim][OTf], various substrates were examined. Representative results are shown in Table 3. Not only aliphatic but also aromatic substrates were condensed in the presence of 5 mol % of **2**.[10] The amide condensation of less-reactive substrates proceeded well under azeotropic reflux conditions in *o*-xylene in place of toluene. Functionalized substrates such as conjugated carboxylic acids, α-hydroxycarboxylic acids, α-alkoxycarboxylic acids, and cyanobenzoic acids were also applicable. Furthermore, a solution of **2** in [emim][OTf] was repeatedly reused without any loss of activity.

Next, to recover and reuse *N*-alkyl-4-boronopyridinium halides without any ionic liquids, we prepared *N*-polystyrene-bound 4-boronopyridinium chloride (**3a**) as well as *N*-polystyrene-bound 3-boronopyridinium chloride **6**, which had been developed by Wang and co-workers.[8] Catalysts **6** and **3a** (5 mol %) were recovered by filtration and reused five times for the amide condensation reaction of 4-phenylbutyric acid with benzylamine under azeotropic reflux conditions with the removal of water (Table 4). Unfortunately, the rate of the reaction catalyzed by **6** decreased every time **6** was reused. The existence of boric acid was confirmed by ^{11}B NMR analysis of the filtrate after amide condensation. These

Table 3. Direct amide condensation reaction catalyzed by **2**



Entry	Time (h)	Product	Yield (%)
1	6		92
2	18		95
3[a]	5 (First) 5 (Second) 5 (Third)		98 (First) 93 (Second) 95 (Third)
4[b]	18		91
5[b]	18		80
6[b]	10		91
7[b]	3		90
8[b]	6		98
9[a,b]	5 (First) 5 (Second) 5 (Third)		99 (First) 98 (Second) 99 (Third)

[a] A solution of **2** in [emim][OTf] was reused three times.
[b] *o*-Xylene was used as a solvent in place of toluene.

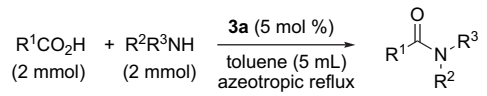
experimental results suggest that **6** was gradually decomposed to *N*-polystyrene-bound pyridinium chloride and boric acid by hydrolytic protodeboration. In contrast, no loss of catalytic activity was observed for our new *N*-polystyrene-bound boronic acid **3a** even after it was reused more than 5 times. The high catalytic activity of **3a**, which was observed even in the absence of [emim][OTf], can be understood by assuming that a polymer-support may prevent dodecamerization of the 4-boronopyridinium chloride moiety in **3a**.

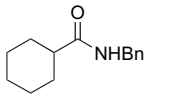
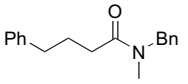
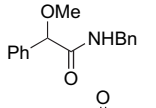
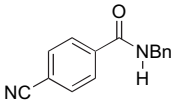
Table 4. Recovery and reuse of **6** and **3a**[a]

Run	Conv. (%)					
	Catalyst **6**			Catalyst **3a**		
	1 h	3 h	5 h	1 h	3 h	5 h
1	64	93	98	68	94	98
2	53	90	98	67	94	98
3	50	85	94	69	93	98
4	40	76	88	69	93	98
5	28	60	74	70	92	96

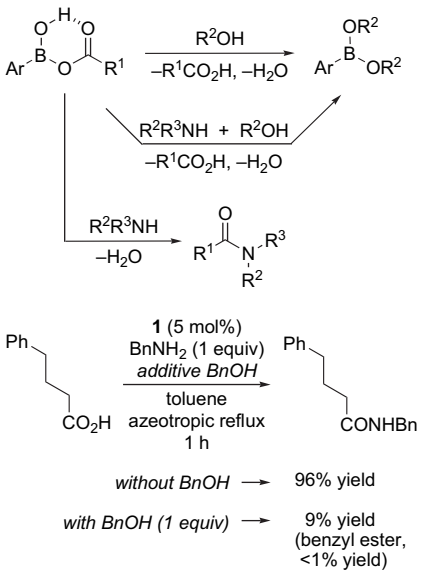
[a] See the equation in Table 2.

Table 5. Amide condensation reaction catalyzed by **3a**



Entry	Time (h)	Product	Yield (%)
1	10		93
2	20		92
3[a]	5 (First) 5 (Second) 5 (Third)		95 (First) 95 (Second) 94 (Third)
4[a,b]	5 (First) 5 (Second) 5 (Third)		94 (First) 92 (Second) 94 (Third)

[a] Compound **3a** was reused three times.
[b] *o*-Xylene was used as a solvent in place of toluene.



Scheme 2. Amide condensation versus ester condensation.

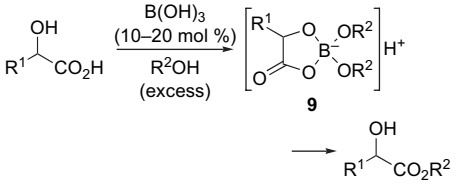
Next, the effects of several linkers between *N*-polystyrene resin and 4-boronopyridinium ion were examined. The catalytic activity and thermal stability of *N*-polystyrene-bound catalyst **3b** linked with ethylene and *N*-polystyrene-bound catalyst **3d** linked with butylene were the same as those of **3a** linked with methylene. The effect of a counter anion was also examined. Unexpectedly, no difference in catalytic activity was seen between counter anions such as Cl^- (**3a**), Br^- (**3b** and **3d**), and NTf_2^- (**3c**). After the amide condensation reaction, **3a** was repeatedly washed with 1 M HCl aqueous solution and ethyl acetate to be reused in the next reaction. When the treatment of **3a** with 1 M HCl aqueous solution was abbreviated, the catalytic activity was somewhat reduced. This unexpected decrease in the catalytic activity of **3a** can be understood by considering that chloride anions of **3a** would be partially exchanged to carboxylate anions through the amide condensation. Therefore, the acidic treatment of **3a** was significant to reactivate **3a**. Although we didn't ascertain whether other *N*-polystyrene-bound catalysts **3b–d** require the same acidic treatment for reactivation, the acidic treatment would assure reactivation of **3b–d**.

To ascertain the generality and scope of the amide condensation catalyzed by **3a**, several substrates were examined in the absence of ionic liquid (Table 5). Compound **3a** was sufficiently active, like **2**, regardless of the substrates examined.

2.2. Ester condensation reaction of α-hydroxycarboxylic acids catalyzed by boron(III) compounds

Generally, boron(III) compounds were much less effective for the esterification of simple carboxylic acids because an alkoxyborane species was preferentially produced rather than the desired acyloxyborane species (Scheme 2).[3a]

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 3).[11] This 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 (**9**) is preferentially produced as an anionic active intermediate even in the presence of excess alcohol. Based on Houston's report,[11] we explored the efficacy of boric acid, **1**, and **2** as catalysts for the esterification of α-hydroxycarboxylic acids. In this section, we report that **2** 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.

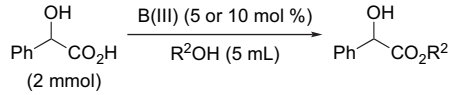


Scheme 3. Houston's boric acid-catalyzed esterification.

First, the catalytic activities of boric acid, neutral boronic acid **1**, and cationic boronic acid **2** were compared in the esterification of mandelic acid in several excess alcohols (Table 6). As expected, boric acid was not very effective. Compound **1** was also less active in polar solvents like alcohols. In each case, **2** gave the best results, probably because **2** was a tolerable cationic Lewis acid catalyst in polar alcohols. Although **2** is known to be condensed to a less-active dodecamer under dehydrative conditions,[5] this is prevented by excess alcohol.

To explore the generality and scope of the esterification catalyzed by **2** in excess alcohol, various substrates were examined in the presence of 5 mol % of **2**.[12] Representative results are shown in Table 7. Not only α-hydroxycarboxylic

Table 6. Catalytic activities of boric and boronic acids



Entry	R^2OH	Temp, time (h)	Conv. (%)		
			$B(OH)_3$	**1**	**2**
1[a]	MeOH	rt, 2	28	48	77
2[a]	EtOH	rt, 5	24	19	43
3[b]	*i*-BuOH	Reflux, 1	36	32	83
4[a]	*i*-PrOH	Reflux, 5	29	14	52
5[b]	$(CH_2OH)_2$	80 °C, 1.5	48[c]	29[c]	83[c]

[a] Catalyst (10 mol %) was used.
[b] Catalyst (5 mol %) was used.
[c] 2-Hydroxyethyl mandelate was produced.

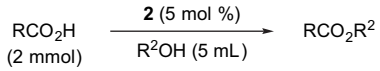
acids but also β-hydroxycarboxylic acids were condensed. In the esterification of 4-hydroxyisophthalic acid, the 3-hydroxycarbonyl group was selectively reacted (entry 12). The esterification condensation of less-reactive secondary alcohols and aromatic carboxylic acids proceeded well with the use of 10 mol % of **2** (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).

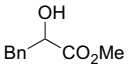
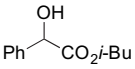
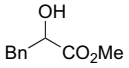
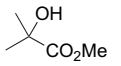
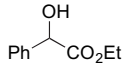
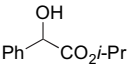
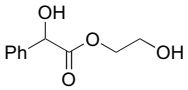
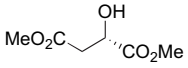
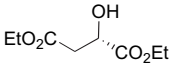
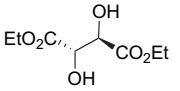
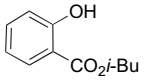
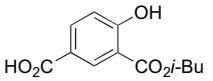
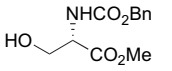
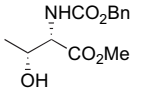
Next, to recover and reuse homogeneous catalyst **2**, *N*-polystyrene-bound 4-boronopyridinium chloride (**3a**) was examined as a heterogeneous catalyst. Compound **3a** was recovered by filtration and reused 10 times without any loss of activity for the esterification of mandelic acid in excess isobutanol under reflux conditions (Table 8).[13]

Next, the correlation between the catalytic activity of boron(III) compounds and the molar ratio of mandelic acid and butanol was examined for esterifications catalyzed by 2 mol % of boric acid, **1**, and **2**. 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 (Fig. 3). Surprisingly, boric acid was the most active catalyst with a molar ratio of mandelic acid/butanol of >1:2. On the other hand, **2** was the most active catalyst with a molar ratio of mandelic acid/butanol of <1:3. In contrast, **1** was less active than boric acid and **2** regardless of the molar ratio of mandelic acid/butanol. Two phenomena that were common to these three catalysts 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, **2** was still active in the presence of excess butanol because of its ability to tolerate polar compounds. Therefore, the addition of 4∼5 equiv of butanol was more suitable for the esterification catalyzed by **2**.

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

Table 7. Esterification of hydroxycarboxylic acids in alcohols catalyzed by **2**

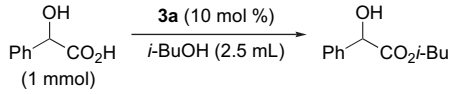


Entry	Temp, time (h)	Product	Yield (%)
1	rt, 10		93
2	Reflux, 6		99
3	rt, 10		96
4	Reflux, 15		92
5	Reflux, 4		95
6[a]	Reflux, 21		81
7	80 °C, 5		97
8[a]	Reflux, 15		95
9[a]	Reflux, 23		86
10[a]	Reflux, 18		92
11	Reflux, 17		85
12[b,c]	Reflux, 20		84
13	Reflux, 20		93
14	Reflux, 22		89

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

examined in the presence of 5 mol % of boric acid in toluene under azeotropic reflux conditions (Table 9).[12] Not only α-hydroxycarboxylic acids and primary alcohols but also β-hydroxycarboxylic acids and secondary alcohols were applicable. The esterification of less-reactive substrates such as conjugated carboxylic acids and secondary alcohols required 10 mol % of boric acid in toluene or xylene. Mercaptocarboxylic acid was less reactive than the corresponding hydroxycarboxylic acids (entries 1–3 vs entry 7).

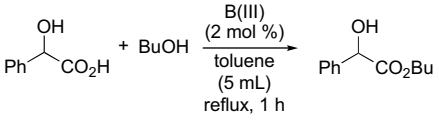
Table 8. Recovery and reuse of **3a** for esterification



Run	Conv. (%)	Run	Conv. (%)
1	96	6	99
2	99	7	98
3	98	8	95
4	99	9	97
5	96	10	95

The boric acid-catalyzed chemoselective esterification of α-hydroxy-α-methylpropanoic acid proceeded in the presence of 4-phenylbutyric acid or benzoic acid (Scheme 4). Houston previously reported a similar boric acid-catalyzed chemoselective esterification in excess alcoholic solvents.[11] However, our new procedure using boric acid does not require the use of excess substrates.

Why was the catalytic activity of boric acid remarkably increased in the presence of excess α-hydroxycarboxylic acids (Fig. 3)? 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 **10**,[14] which should be more active than monomeric 2,2-dialkoxy-4-oxo-1,3,2-dioxaborolan-2-uide **9** (Scheme 5). However, equilibrium has been observed between **9** and **10**.[14] The more active species **10** should exist as a major intermediate in an esterification reaction solution with a higher molar ratio of α-hydroxycarboxylic acid, while the less-active species **9** would be present as a major



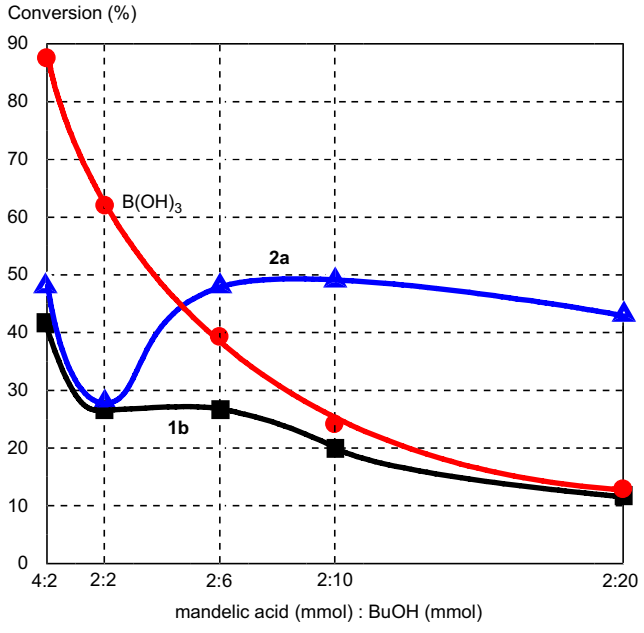
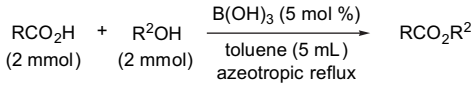
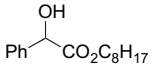
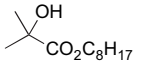
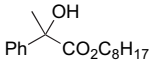
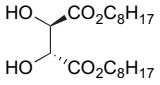
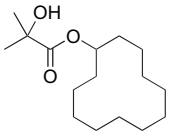
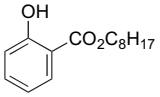
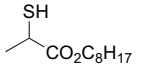


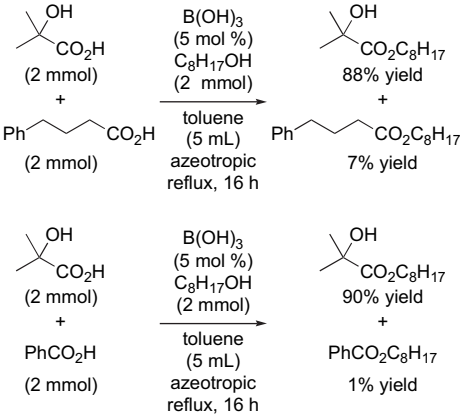
Figure 3. Correlation between the catalytic activity of boron(III) compounds and the molar ratio of mandelic acid and butanol.

Table 9. Esterification of equimolar mixtures of hydroxycarboxylic acids and alcohols catalyzed by boric acid



Entry	Time (h)	Product	Yield (%)
1	4		93
2	21		99
3	21		90
4[a]	21		87
5[a]	20		82
6[a,b]	21		86
7	24		44

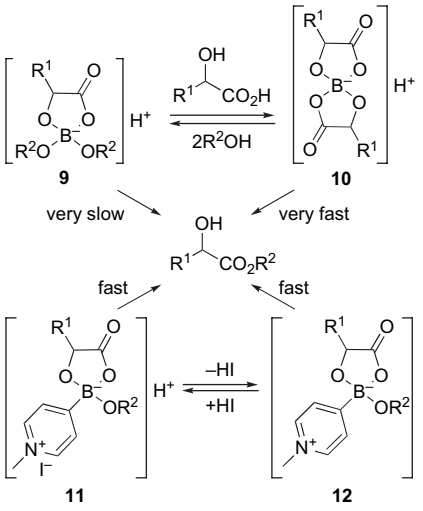
[a] Boric acid (10 mol %) was used.
[b] *o*-Xylene was used in place of toluene.



Scheme 4. Boric acid-catalyzed chemoselective esterification of α-hydroxy-α-methylpropanoic acid without excess substrates.

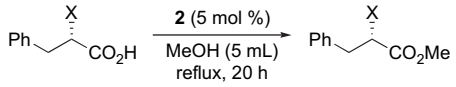
intermediate in excess alcohol. Based on the experimental results shown in Figure 3, the reactivity of intermediates with alcohols should increase in the order: **9**<2-alkoxy-2-(*N*-methylpyridinium-4-yl)-4-oxo-1,3,2-dioxaborolan-2-uides (**11** and **12**)[15]<**10**.

Methyl esterification of L-phenylalanine and its *N*-protected derivatives in methanol was examined in the presence of **2** (5 mol %) because **2** was the most active catalyst in alcohol solvents (Table 10). Interestingly, *N*-tosyl-L-phenylalanine (entry 1) was much more reactive than L-phenylalanine itself



Scheme 5. Proposed reaction mechanism.

Table 10. Methyl esterification of α-functionalized carboxylic acids



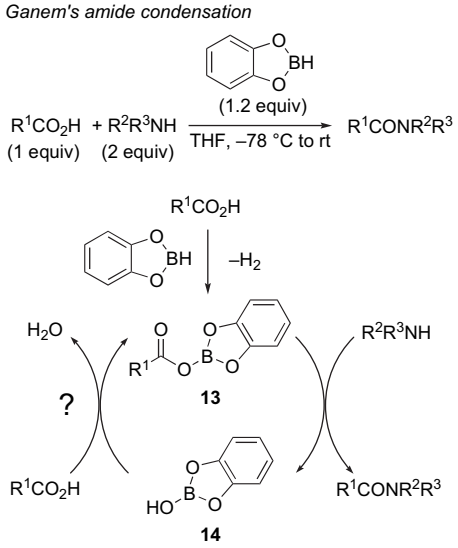
Entry	X	Yield (%)	Entry	X	Yield (%)
1	TsNH	76	5	TfNH	24
2	CbzNH	61	6	NH_2[a]	N.R.
3	BzNH	45	7	OMe[b]	71
4	AcNH	28	8	Me[c]	28

[a] L-Phenylalanine was not dissolved.
[b] α-Methoxyphenylacetic acid was used as a substrate.
[c] α-Phenylpropanoic acid was used as a substrate.

and *N*-carboxyl derivatives. α-Methoxyphenylacetic acid (entry 7) also showed a similar reactivity to that of *N*-tosyl-L-phenylalanine. In contrast, α-phenylpropionic acid was much less reactive (entry 8). These good results (entries 1 and 7) can be understood by the weak coordination of α-tosylamino and α-methoxy groups to the boron(III) atom.

2.3. Amide condensation reaction of sterically demanding carboxylic acids catalyzed by 4,5,6,7-tetrachlorobenzo[*d*][1,3,2]dioxaborol-2-ol

In 1978, Ganem et al. reported that carboxylic acids condense with amines via 2-acyloxy-1,3,2-benzodioxaborolane (**13**) in the presence of stoichiometric amounts of catecholborane under mild conditions (THF, −78 °C to rt) (Scheme 6).[16] Two equivalents of amine are required because the reaction proceeds via nucleophilic attack of amine to [**13**·amine]. One equivalent of catecholborane is required because benzo[*d*][1,3,2]dioxaborol-2-ol (**14**), which is obtained together with amide, is inert as a condensing reagent under the same conditions. Nevertheless, based on a consideration of our results, we envisaged that **14** as well as arylboronic acids such as **1** might serve as dehydrative catalysts under azeotropic conditions with the removal of water in less-polar solvents (Scheme 6). In this section, we report that 4,5,6,7-tetrachlorobenzo[*d*][1,3,2]dioxaborol-2-ol (**4a**), which is prepared from tetrachlorocatechol and boric acid in situ, is sufficiently active as a catalyst for the dehydrative condensation of equimolar mixtures of carboxylic acids and amines. Notably, **4a**

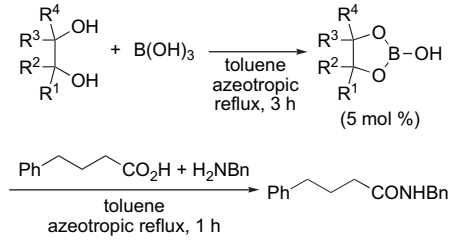


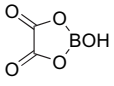
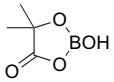
Scheme 6. Ganem's amide condensation of carboxylic acids with amines using catecholborane as a condensing reagent and a possible catalytic pathway.

was greatly superior to **1** for the amide condensation of sterically demanding carboxylic acids. In addition, we found that Lewis acid-assisted Brønsted acid (LBA)[17] **4c**, which was prepared from a 1:2 M mixture of boric acid and tetrachlorocatechol, was quite effective for the Ritter reaction to give amides from the corresponding nitriles and benzylic alcohols.

First, benzo[*d*][1,3,2]dioxaborol-2-ol **14**, which was prepared in situ from equimolar mixtures of boric acid and catechol in toluene under azeotropic reflux conditions, was examined as a catalyst (5 mol %) for the dehydrative condensation of 4-phenylbutyric acid and benzylamine (entry 1, Table 11). As expected, **14** could be used as a dehydration catalyst and was found to be more active than boric acid[18]

Table 11. Catalytic activities of 1,3,2-dioxaborolan-2-ol derivatives for the amide condensation of 4-phenylbutyric acids with benzylamine



Entry	Catalyst	Conv. (%)
1	**14**	61
2	**4a**	93
3		64
4		74
5[a]	$B(OH)_3$	31
6[a]	**1**	96

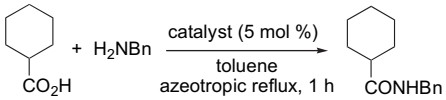
[a] Boric acid and **1** were used instead of 1,3,2-dioxaborolan-2-ol derivatives.

(entry 5), but its activity was still insufficient. Fortunately, 4,5,6,7-tetrachlorobenzo[*d*][1,3,2]dioxaborol-2-ol **4a** was much more active than **14** (entry 2). Surprisingly, the catalytic activity of **4a** was almost the same as that of **1** (entry 6). According to the *Chemicals* price catalog (*Chemicals*, 33rd ed.; Wako Pure Chemical Industries, Ltd.: Japan, 2004), **1** is 40 times more expensive than tetrachlorocatechol. Since boric acid is also available at a rather low price, **4a**, which can be prepared from them in situ, is very economical and practical. In contrast, boric acid/oxalic acid and boric acid/2-hydroxy-2-methylpropanoic acid were less active than **4a**, probably due to the instability of their 1,3,2-dioxaborolan-2-ol structures (entries 3 and 4).

Next, the catalytic activities of **4a**, **1**, and boric acid were examined for the dehydrative condensation of cyclohexanecarboxylic acid, which is a more sterically demanding carboxylic acid than 4-phenylbutyric acid, with benzylamine (Table 12). Interestingly, **4a** was greatly superior to **1** as a catalyst (entry 2 vs entry 3). Tetrafluoro- and tetrabromobenzo[*d*][1,3,2]dioxaborol-2-ols also exhibited good catalytic activities, as well as **4a**. Boric acid was almost inert (entry 4).[18] Furthermore, 4,5,6,7-tetrachlorobenzo[*d*][1,3,2]dioxaborole (**4b**), which was isolable,[19,20] gave slightly better results than **4a** (entry 1). However, **4c**, which was prepared in situ from a 1:2 M mixture of boric acid and tetrachlorocatechol, was almost inert probably due to the lack of any hydroxy groups on the boron atom of **4c** (entry 5).

To explore the generality and scope of the amide condensation catalyzed by **4b**, the catalytic activities of **4b** were compared with those of **1** in the amide condensation of various substrates in toluene or *o*-xylene in the presence of 5 mol % of the catalysts. Representative results are shown in Table 13. Although **4b** gave inferior results compared to **1** with sterically small aliphatic and aromatic carboxylic acids (entries 1–4), it still showed adequate catalytic activity for these substrates. In contrast, **4b** was superior to **1** for not only sterically bulky aliphatic and aromatic carboxylic acids but also functionalized carboxylic acids such as Boc-L-Ala-OH (entries 5–14). Without exception, amide condensation was completed within 24 h in the presence of 5 mol % of **4b**. The scope of suitable carboxylic acids was extended by using **4b** as a catalyst instead of **1**. In contrast, **1** and **4b** showed a similar trend in catalytic activity with regard to the steric bulkiness of amines (entries 2, 4, and 12). Less-hindered **4a** should have an advantage over **1** at the regeneration step from hydroxyboron compounds to acyloxyboron species.

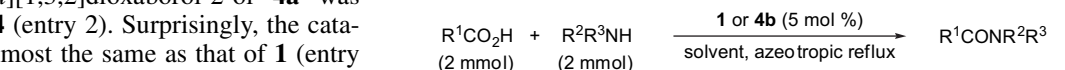
Table 12. Catalytic activities of boron(III) compounds for the dehydrative condensation of cyclohexanecarboxylic acid with benzylamine

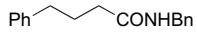
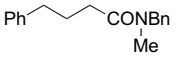
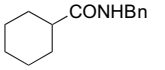
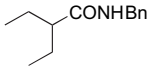
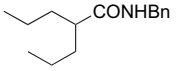
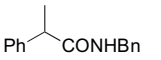
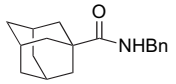
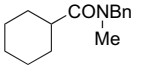
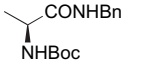
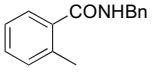


Entry	Catalyst[a]	Conv. (%)
1	**4b**	62
2	**4a**	52
3	**1**	32
4	$B(OH)_3$	2
5	**4c**	3

[a] Compounds **4a** and **4c** were prepared from boric acid and tetrachlorocatechol in situ before the addition of carboxylic acids and amines.

Table 13. Amide condensation of various carboxylic acids with amines catalyzed by **1** or **4b**



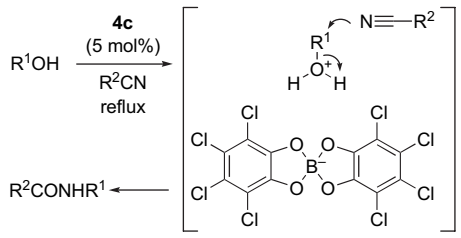
Entry	Product	Solvent	Time (h)	Yield (%)	
				1	**4b**
1		Toluene	0.25	60	41
2		Toluene	1	42	26
3	PhCONHBn	*o*-Xylene	0.5	59	51
4	PhCONMeBn	*o*-Xylene	1	37	16
5		Toluene	1	32	62
		Toluene	*5*	—	*94*
6		*Toluene*	*24*	8	*93*
7		Toluene	19	11	55
		o-Xylene	*24*	—	*99*
8	*t*-BuCONHBn	Toluene	20	5	55
		o-Xylene	*15*	—	*94*
9		Toluene	2	25	77
		Toluene	*5*	—	*95*
10		Toluene	24	15	22
		o-Xylene	*20*	20	*99*
11	$Ph_2CHCONHBn$	Toluene	2	30	32
		Toluene	*11*	—	*93*
12		*o*-Xylene	5	47	53
		o-Xylene	*19*	—	*93*
13		Toluene	5	35	42
		Toluene	*20*	—	*91*[a]
14		*o*-Xylene	1	32	62
		o-Xylene	*9*	—	*92*

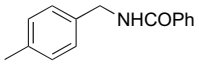
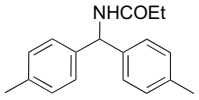
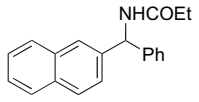
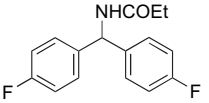
[a] Optical purity of the amide was reduced from >99 to 86% ee through amide condensation.

2.4. Ritter reaction of nitriles with benzylic alcohols catalyzed by 4c

In the course of our present study, we were interested in the utility of **4c** as an acid catalyst for the amidation of alcohols with nitriles, which is known as the Ritter reaction.[21] This method works well only under strongly acidic conditions (e.g., cat. concd H_2SO_4,[21,22a] cat. $BF_3{\cdot}Et_2O$,[22b] formic acid as a solvent,[22c] and so on) in strongly ionizing solvents, which limits its applicability to compounds containing functional groups that are stable toward acid. Although tetrachlorocatechol and boric acid were much milder acidic compounds than traditionally strong acid catalysts, it was expected that their ate complex **4c** might synergistically serve as a Lewis acid-assisted Brønsted acid (LBA).[17] The Ritter reaction of several benzylic alcohols with nitriles was examined in nitriles in the presence of 5–10 mol % of **4c** under reflux conditions (Table 14). In all cases, the corresponding amides were isolated in high yield.

Table 14. Ritter reaction catalyzed by **4c**



Entry	Time (h)	Product	Yield (%)
1[a]	11	$Ph_2CHNHCOMe$	93
2	4	$Ph_2CHNHCOEt$	92
3[b]	3	$Ph_2CHNHCOPh$	94
4[a,b]	5	BnNHCOPh	80
5[a,b]	3		78
6[a]	3		84
7	3		93
8	3		96

[a] Compound **4c** (10 mol %) was used.
[b] The reaction was carried out at 120 °C.

3. Conclusion

In summary, *N*-alkyl-4-boronopyridinium salts are thermally stable and reusable catalysts for not only the amidation but also the esterification of α-hydroxycarboxylic acids in excess alcohols. Boric acid is also an effective catalyst for not only the amidation[18] but also the esterification of equimolar mixtures of α-hydroxycarboxylic acids and alcohols. Furthermore, catecholborane derivatives such as **4a** and **4b** are economically and practically useful catalysts for the amidation of sterically demanding carboxylic acids and **4c** is useful as a LBA catalyst for the Ritter reaction.

4. Experimental

4.1. General

Infrared (IR) spectra were recorded on a JASCO FT/IR 460 plus spectrometer. ^{1}H NMR spectra were measured on a Varian Gemini-2000 spectrometer (300 MHz) at ambient temperature. Data were recorded as follows: chemical shift in parts per million from internal tetramethylsilane on the δ scale, multiplicity (s=singlet; d=doublet; t=triplet; m=multiplet), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on Varian Gemini-2000 (75 MHz) spectrometer. Chemical shifts were recorded in parts per million from the solvent resonance employed as the internal standard (deuterochloroform at 77.00 ppm). Melting points were determined using a Yanaco MP-J3. All experiments were carried out under an atmosphere of dry nitrogen. For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254} 0.25 mm or silica gel NH_2 F_{254S} 0.25 mm) were used. The products were purified by column chromatography on silica gel (E. Merck Art. 9385 or Fuji Silysia Chemical Ltd. Cromatorex® NH-DM1020). Microanalyses were performed at the Graduate School of Agriculture, Nagoya University. High-resolution mass spectral analysis (HRMS) was performed at Chemical Instrument Center, Nagoya University. In experiments that required dry solvent, ether, *N*,*N*-dimethylformamide (DMF), and tetrahydorofuran (THF) were purchased from Aldrich or Wako as the 'anhydrous' and stored over 4 Å molecular sieves. Benzene, hexane, toluene, and dichloromethane were freshly distilled from calcium hydride. Other simple chemicals were analytical-grade and obtained commercially. 1-Ethyl-3-methylimidazolium trifluoromethanesulfonate [emim][OTf] was purchased from Aldrich. The follwing obtained amides are known compounds: *N*-benzyl-4-phenylbutanamide[3a] (Tables 2, 4, 10, and 12), *N*-benzylcyclohexanecarboxamide[3a] (Tables 1, 3, 5, 11, and 12), *N*-benzyl-*N*-methyl-4-phenylbutanamide[4] (Tables 3, 5, and 12), *N*-benzyl-2-methoxy-2-phenylacetamide[23] (Tables 3 and 5), *N*-benzyl-2-hydroxyl-2-phenylacetamide[3a] (Table 3), 2-methoxy-*N*-phenyl-2-phenylacetamide[24] (Table 3), *N*-benzyl-1-adamantanecarboxamide[4] (Tables 3 and 13), (*E*)-*N*-benzylcinnamide[25] (Table 3), *N*-benzylbenzamide[26] (Tables 3, 13, and 14), *N*-benzyl-*p*-cyanobenzamide[27] (Tables 3 and 5), (*S*)-methyl 2-(4-methylphenylsulfonamido)-3-phenylpropanoate (Table 10),[28] (*S*)-methyl 2-(benzyloxycarbonylamino)-3-phenylpropanoate (Table 10),[29] (*S*)-methyl 2-benzamido-3-phenylpropanoate (Table 10),[30] (*S*)-methyl 2-acetamido-3-phenylpropanoate (Table 10),[31] methyl 2-methoxy-2-phenylacetate (Table 10),[32] methyl 2-phenylpropanoate (Table 10),[33] *N*-benzyl-*N*-methylbenzamide[6] (Table 13), *N*-benzyl-2-ethylbutanamide[6] (Table 13), *N*-benzyl-2-propylpentanamide[6] (Table 13), *N*-benzylpivalamide[34] (Table 13), *N*-benzyl-2-phenylpropanamide[35] (Table 13), *N*-benzyl-2,2-diphenylacetamide[36] (Table 13), *N*-benzyl-*N*-methylcyclohexanecarboxamide[6] (Table 13), (*S*)-*tert*-butyl 1-(benzylamino)-1-oxopropan-2-ylcarbamate[37] (Table 13), *N*-benzyl-2-methylbenzamide[26] (Table 13), *N*-benzhydrylacetamide[38] (Table 14), *N*-benzhydrylpropionamide[22c] (Table 14), *N*-benzhydrylbenzamide[22c] (Table 14), *N*-(4-methylbenzyl)benzamide[39] (Table 14), *N*-[di(*p*-tolyl)methyl]propionamide[6] (Table 14), *N*-[naphthalen-2-yl(phenyl)methyl]propionamide[6] (Table 14), *N*-[di(*p*-fluorophenyl)methyl]propionamide[6] (Table 14). The following obtained esters are known compounds: methyl 2-hydroxy-2-phenylacetate[26] (Tables 6 and 7), isobutyl 2-hydroxy-2-phenylacetate[5] (Tables 6–8), methyl 2-hydroxy-3-phenylpropanoate[40] (Table 7), methyl 2-hydroxy-2-methylpropanoate[26] (Table 7), ethyl 2-hydroxy-2-phenylacetate[26] (Tables 6 and 7), isopropyl 2-hydroxy-2-phenylacetate[11] (Tables 6 and 7), 2-hydroxyethyl 2-hydroxy-2-phenylacetate[5] (Tables 6 and 7), (*S*)-dimethyl 2-hydroxysuccinate[26] (Table 7), (*S*)-diethyl 2-hydroxysuccinate[41] (Table 7), (2*R*,3*R*)-diethyl 2,3-dihydroxysuccinate[26] (Table 7), isobutyl 2-hydroxybenzoate[26] (Table 7), 4-hydroxy-3-(isobutoxycarbonyl)benzoic acid[5] (Table 7), (*S*)-methyl 2-(benzyloxycarbonylamino)-3-hydroxypropanoate[26] (Table 7), (2*S*,3*R*)-methyl 2-(benzyloxycarbonylamino)-3-hydroxybutanoate[26] (Table 7), butyl 2-hydroxy-2-phenylacetate[5]

(Fig. 3), octyl 2-hydroxy-2-phenylacetate[5] (Table 9), octyl 2-hydroxy-2-methylpropanoate[5] (Table 9 and Scheme 2), octyl 2-hydroxy-2-phenylpropanoate[5] (Table 9), (+)-(2*R*,3*R*)-dioctyl 2,3-dihydroxysuccinate[42] (Table 9), cyclododecyl 2-hydroxy-2-methylpropanoate[5] (Table 9), octyl 2-hydroxybenzoate[5] (Table 9), octyl 4-phenylbutyrate[43] (Scheme 2), and octyl benzoate[44] (Scheme 2).

4.2. Preparation of 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)pyridine

A flame-dried, 100-mL round-bottom flask fitted with a Teflon-coated magnetic stirring bar was charged with 4-pyridineboronic acid (**8**) (1.23 g, 10 mmol) and neopentyl glycol (1.04 g, 10 mmol) in 1,4-dioxane (50 mL). This white suspension was brought to reflux with the removal of water with molecular sieves 4 Å for 12 h to be a homogeneous solution. The resulting mixture was cooled to ambient temperature and bulk solvent was removed in vacuo to afford 4-pyridineboronic acid neopentyl glycol ester (1.92 g, 10 mmol) as white solid in quantitative yield. IR (KBr) 3436, 2943, 2821, 1620, 1423, 1215, 1117, 1035, 768, 736, 674, 626 cm^{-1}; ^1H NMR (CD_3CN, 300 MHz) δ 0.98 (s, 6H), 3.76 (s, 4H), 7.57 (d, J=5.7 Hz, 2H), 8.55(d, J=5.7 Hz, 2H); ^{13}C NMR (CD_3CN, 75 MHz) δ 21.6 (2C), 67.5, 72.3 (2C), 128.6 (2C), 149.9 (2C), and one carbon was not observed. HRMSFAB (*m/z*): $[M+H]^+$ calcd for $C_{10}H_{15}NO_2$, 192.1198; Found, 192.1197.

4.3. Preparation of 4-borono-*N*-methylpyridinium iodide (2)[45]

4-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)pyridine (1.92 g, 10 mmol) was suspended in acetonitrile (50 mL) and added methyl iodide (3.11 mL, 50 mmol). The mixture was brought to heat at reflux for 6 h followed by removal of acetonitrile in vacuo to afford 4-borono-*N*-methylpyridinium iodide neopentyl glycol ester as yellow solid in quantitative yield. The resulting yellow solid was added to a mixture of acetone (30 mL) and water (30 mL). After this light yellow solution was stirred at room temperature for 1 day, acetone was removed in vacuo, and the aqueous solution was washed with Et_2O until neopentyl glycol was extracted completely. The aqueous solution was concentrated and resulting yellow solid was precipitated from methanol/Et_2O to give **2** (2.26 g, 9.0 mmol, 90% yield from **7**). IR (KBr) 3347, 3026, 1637, 1461, 1404, 1344, 1272, 1012, 853, 678, 627 cm^{-1}; ^1H NMR (DMSO-d_6 with 1 drop of D_2O, 300 MHz) δ 4.32 (s, 3H), 8.24 (d, J=6 Hz, 2H), 8.88 (d, J=6 Hz, 2H); ^{13}C NMR (DMSO-d_6 with 1 drop of D_2O, 75 MHz) δ 48.3, 132.0 (2C), 144.3 (2C), and one carbon was not observed. Anal. Calcd for $C_6H_9O_2BNI$: C, 27.21; H, 3.43. Found: C, 27.02, H, 3.47.

4.4. Preparation of dodecamer $[2]_{12}$

A dry, 5-mL round-bottom flask equipped with a Teflon-coated magnetic stirring bar was charged with **2** (3 mmol) and DMF (3 mL). The mixture was heated at 120 °C for 1 h to form yellow precipitate. After the resultant mixture was cooled to ambient temperature, the precipitate was collected by filtration and washed with DMF several times to obtain white solid. The white solid was recrystallized from water to get $[2]_{12}$ as an orange crystal. IR (KBr) 3465, 3030, 1636, 1558, 1456, 1208, 1123, 932, 843, 799, 748, 683 cm^{-1}; ^1H NMR (DMSO-d_6 with 1 drop of D_2O, 300 MHz) δ 4.16 (s, 3H), 7.51 (d, J=6.3 Hz, 2H), 8.43 (d, J=6.3 Hz, 2H); ^{13}C NMR (DMSO-d_6 with 5 drops of D_2O, 300 MHz) δ 47.9, 131.4 (2C), 143.3 (2C), and one carbon was not observed. Anal. Calcd for $C_{72}H_{84}B_{12}I_8N_{12}O_{14}\cdot 10H_2O$: C, 32.43; H, 3.93; N, 6.30; I, 38.07. Found: C, 32.15; H, 3.71; N, 6.20; I, 38.44.

4.5. X-ray crystallographic analysis of $[2]_{12}$

Crystal data: $C_{72}H_{104}B_{12}N_{12}O_{24}I_8$, M=2666.59, crystal dimensions 0.40×0.40×0.30 mm^3, monoclinic, space group $P21/n$, a=17.136(4), b=14.073(3), c=21.289(5) Å, V=5115.6(19) $Å^3$, Z=2, D_c=1.731 g/cm^3, μ=2.495/mm, T=223 K. X-ray crystallographic analysis was performed with a Bruker SMART APEX diffractometer (graphite monochromator, Mo Kα radiation, λ=0.71073 Å). The structure was solved by direct methods and expanded using Fourier techniques. Reflections 13,391 were independent and unique, and 10,822 with $I>2\sigma(I)$ ($2\theta_{max}$=29.16°) were used for the solution of the structure. R=0.0438 and Rw=0.1235.

Crystallographic data have been deposited with Cambridge Crystallographic Data Centre: Deposition number CCDC-27344 for compound $[2]_{12}$. Copies of the data can be obtained free of charge via http//www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

4.6. Preparation of *N*-polystyrene-bound 4-borono-pyridinium salts 3

A mixture of 4-(haloalkyl)polystrene resin crosslinked with divinyl benzene (2.4 mmol) and 4-pyridineboronic acid neopentyl glycol ester (990 mg, 4.8 mmol) in acetonitrile (20 mL) was heated at reflux for 2 days. After the resultant mixture was cooled to ambient temperature, the resin was collected by filtration and washed with THF, DMF, and Et_2O. The resin was added to a mixture of THF (15 mL) and water (5 mL). This mixture was stirred at room temperature for 1 day. The resultant resin was collected by filtration and washed with THF, water, DMF, EtOAc, hexane, and Et_2O, and dried at 50 °C under reduced pressure for 12 h to give **3**.

Compound ***3a***:[45] Merrifield resin (ca. 1.0 mmol-Cl/g, 400–500 mm, crosslinked with 1% divinylbenzene) purchased from Fluka was used as a polymer-support; 0.74 mmol-B/g (estimated based on nitrogen content as determined by elemental analysis). IR (KBr) 3409, 3025, 2923, 1635, 1602, 1493, 1452, 757, 698, 538 cm^{-1}. Anal. Found: C, 84.21; H, 7.51; N, 1.04.

Compound ***3b***: 4-(2-Bromoethyl)polystyrene resin (ca. 0.8–1.2 mmol-Br/g, 500–560 mm, crosslinked with 1% divinylbenzene) purchased from Fluka was used as a polymer-support; 0.81 mmol-B/g (estimated based on nitrogen content as determined by elemental analysis). Anal. Found: C, 82.00; H, 7.56; N, 1.14; Br, 6.52.

Compound ***3c***: 4-(2-Bromoethyl)polystyrene resin (ca. 0.8–1.2 mmol-Br/g, 500–560 mm, crosslinked with 1%

divinylbenzene) purchased from Fluka was used as a polymer-support; 0.48 mmol-B/g (estimated from weight difference). Anal. Found: C, 77.01; H, 6.78; N, 1.47.

Compound ***3d***: 4-(4-Bromobutyl)polystyrene resin (2.8 mmol-Br/g, 200–400 mesh, crosslinked with 2% divinylbenzene) purchased from Novabiochem was used as a polymer-support; 1.47 mmol-B/g (estimated based on nitrogen content as determined by elemental analysis). Anal. Found: C, 65.06; H, 6.93; N, 2.06.

4.7. General procedure for the direct amide condensation of equimolar mixtures of carboxylic acids and amines catalyzed by 2 (Tables 1–3)

A dry, 20-mL round-bottom flask equipped with a Teflon-coated magnetic stirring bar and a Dean–Stark apparatus surmounted by a reflux condenser was charged with carboxylic acid (2 mmol), amine (2 mmol), and **2** (25 mg, 0.1 mmol) in [emim][OTf] (1 mL) and toluene (5 mL). The mixture was brought to reflux with the removal of water. After several hours, the resulting mixture was cooled to ambient temperature and a colorless toluene layer was separated from a yellow ionic liquid layer by simple extraction with Et_2O, and concentrated in vacuo. The desired amide was isolated from crude products by column chromatography on silica gel. On the other hand, **2** that remained in [emim][OTf] was reused in the next reaction without further purification.

4.8. General procedure for the direct amide condensation of equimolar mixtures of carboxylic acids and amines catalyzed by 3a (Tables 4 and 5).

A dry, 5-mL round-bottom flask equipped with a Teflon-coated stirring bar and a Dean–Stark apparatus surmounted by a reflux condenser was charged with carboxylic acid (1 mmol), amine (1 mmol), and **3a** (135 mg, 0.74 mmol-B/g, 0.1 mmol) in toluene (5 mL). The mixture was brought to reflux with the removal of water. After several hours, the resulting mixture was cooled to ambient temperature and filtered. Compound **3a** was washed with 1 M HCl aqueous solution and ethyl acetate repeatedly, and was reused in the next reaction without further purification. On the other hand, the desired amide was isolated from the combined filtrates by column chromatography on silica gel.

4.9. General procedure for the esterification of hydroxycarboxylic acids in alcohols catalyzed by 2 (Table 7)

To a stirring solution of hydroxycarboxylic acids (2 mmol) in alcohol (5 mL) was added **2** (26.5 mg, 0.1 mmol) in one portion and the mixture was dissolved soon. The solution was stirred at room temperature or was heated to reflux. After the reaction was complete, excess alcohol was removed in vacuo, and the residue was purified by column chromatography on silica gel to give the desired ester.

4.10. General procedure for the esterification of hydroxycarboxylic acids in alcohols catalyzed by 3a (Table 8)

To a stirring solution of hydroxycarboxylic acids (1 mmol) in alcohol (2.5 mL) was added **3a** (135 mg, 0.1 mmol, 0.74 mmol-B/g), and the mixture was brought to reflux. After the reaction was completed, the resulting mixture was cooled to ambient temperature and filtered. Compound **3a** was washed with 1 M HCl aqueous solution and ethyl acetate repeatedly, and was used directly in the next reaction without further purification. On the other hand, the desired ester was isolated from the combined filtrates by column chromatography on silica gel.

4.11. General procedure for the esterification of equimolar mixtures of carboxylic acids and alcohols catalyzed by $B(OH)_3$ (Table 9)

A dry, 10-mL round-bottom flask equipped with a Teflon-coated stirring bar and a Dean–Stark apparatus surmounted by a reflux condenser was charged with hydroxycarboxylic acids (2 mmol), alcohols (2 mmol), and $B(OH)_3$ (6.2 mg, 0.1 mmol) in toluene (5 mL). The mixture was brought to reflux with the removal of water. After the reaction was complete, the resulting mixture was cooled to ambient temperature and washed with sodium hydrogen carbonate, and the product was extracted with ethyl acetate. The organic layers were dried over magnesium sulfate. The solvents were evaporated, and the residue was purified by column chromatography on silica gel to give the desired ester.

Octyl 2-mercaptopropanoate (entry 7): IR (film) 2927, 2856, 1737, 1455, 1327, 1173, 1073 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J=6.6 Hz, 3H), 1.20–1.42 (m, 10H), 1.53 (d, J=7.2 Hz, 3H), 1.61–1.68 (m, 2H), 2.15 (d, J=8.1 Hz, 1H), 3.50 (dq, J=7.2, 8.1 Hz, 1H), 4.06–4.19 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.9, 21.0, 22.5, 25.7, 28.3, 29.0 (2C), 31.6, 35.6, 65.4, 173.5. Anal. Calcd for $C_{11}H_{22}O_2S$: C, 60.51; H, 10.16. Found: C, 60.48; H, 10.20.

4.12. In situ preparation of 4,5,6,7-tetrachlorobenzo-[*d*][1,3,2]dioxaborol-2-ol (4a) (Tables 11 and 12)

A dry, 20-mL round-bottom flask equipped with a Teflon-coated magnetic stirring bar and a Dean–Stark apparatus surmounted by a reflux condenser was charged with $B(OH)_3$ (6.1 mg, 0.10 mmol) and tetrachlorocatechol (25 mg, 0.10 mmol) in toluene (10 mL). The mixture was brought to heat at azeotropic reflux with the removal of water for 3 h to prepare a solution of **4a**. After 3 h, $B(OH)_3$ [^{11}B NMR (DMSO-d_6, 96 MHz) δ 20] was dissolved completely, and the resulting solution was used as catalyst directly in the amide condensation without further purification. ^{11}B NMR (DMSO-d_6, 96 MHz) δ 8.7; ^{13}C NMR (DMSO-d_6, 75 MHz) δ 119.7 (2C), 121.4 (2C), 143.8 (2C).

4.13. Preparation of 4,5,6,7-tetrachlorobenzo[*d*][1,3,2]-dioxaborole (4b) (Tables 12 and 13)

Tetrachlorocatechol (2.5 g, 10 mmol) in Et_2O (10 mL) was added slowly to a stirred solution of $BH_3\cdot SMe_2$ (1.2 mL, 12 mmol, 10 M) in ether (10 mL) at ambient temperature. Gas evolution began immediately. After a few minutes, all volatile components were removed in vacuo to yield almost pure light yellow solid, which after sublimation at 100 °C/1 Torr gave 2.2 g of pure **4b** (83% yield) as clusters of very fine needles. Mp 95–100 °C; ^{11}B NMR ($CDCl_3$,

96 MHz) δ 29.1; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 117.0 (2C), 127.8 (2C), 143.7 (2C).

4.14. Typical procedure for the amide condensation reaction of an equimolar mixture of carboxylic acids and amines catalyzed by 4b (Table 13)

A dry, 20-mL round-bottom flask equipped with a Teflon-coated magnetic stirring bar and a Dean–Stark apparatus surmounted by a reflux condenser was charged with carboxylic acids (2.0 mmol), amines (2.0 mmol), and **4b** (26 mg, 0.10 mmol, 5.0 mol %) in toluene or *o*-xylene (10 mL). The mixture was brought to heat at azeotropic reflux with the removal of water. After the reaction was completed, the resulting mixture was cooled to ambient temperature and washed with both aqueous solutions of ammonium chloride and sodium hydrogen carbonate, and the product was extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate. The solvent was evaporated, and the residue was purified by column chromatography on silica gel to give the desired amides.

4.15. Typical procedure for Ritter reaction catalyzed by 4c (Table 14)

A dry, 10-mL round-bottom flask equipped with a Teflon-coated magnetic stirring bar and a reflux condenser was charged with $B(OH)_3$ (6.2 mg, 0.10 mmol), tetrachlorocatechol (50 mg, 0.20 mmol), and benzylic alcohols (2.0 mmol) in nitriles (5 mL). The mixture was brought to reflux. After the reaction was completed, the resulting mixture was cooled to ambient temperature and washed with an aqueous solution of sodium hydrogen carbonate, and the product was extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate. The solvent was evaporated, and the residue was purified by column chromatography on silica gel to give the desired amides.

LBA **4c**: ^{11}B NMR (DMSO-d_6, 96 MHz) δ 14.7; ^{13}C NMR (DMSO-d_6, 75 MHz) δ 111.7 (4C), 120.3 (4C), 147.6 (4C).

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