ORGANIC
LETTERS

2005
Vol. 7, No. 22
5043−5046

N-Alkyl-4-boronopyridinium Salts as Thermally Stable and Reusable Amide Condensation Catalysts

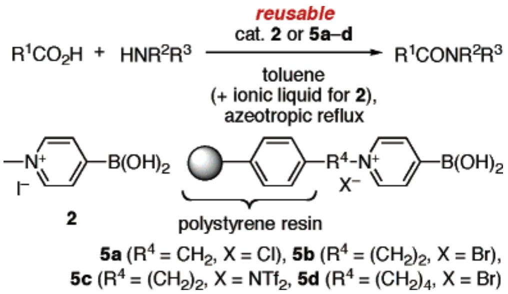
Toshikatsu Maki,[†] Kazuaki Ishihara,*,[†] and Hisashi Yamamoto*,[‡]

*Graduate School of Engineering, Nagoya University, Furo-cho, Chikusa,
Nagoya 464-8603, Japan, and Department of Chemistry, The University of Chicago,
5735 South Ellis Avenue, Chicago, Illinois 60637*

ishihara@cc.nagoya-u.ac.jp; yamamoto@uchicago.edu

Received August 25, 2005

ABSTRACT



***N*-Alkyl-4-boronopyridinium salts are highly effective and reusable catalysts for the dehydrative amide condensation reaction between equimolar mixtures of carboxylic acids and amines. *N*-Alkylboronopyridinium salts are thermally stabilized in the order *N*-alkyl-2-boronopyridinium salt ≪ *N*-alkyl-3-boronopyridinium salt < *N*-alkyl-4-boronopyridinium salt. Homogeneous catalysts, such as 4-borono-*N*-methylpyridinium iodide, are more effective in the presence of ionic liquid and can be recovered by extraction with ionic liquid. In contrast, heterogeneous catalysts, such as polystyrene-bound 4-boronopyridinium salts, are effective even in the absence of ionic liquid and can be recovered by filtration.**

We have previously reported 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 and xylene in the presence of benzeneboronic acids bearing electron-withdrawing groups at the *m*- or *p*-positions, such as 3,4,5-trifluorobenzeneboronic acid and 3,5-bis(trifluoromethyl)benzeneboronic acid (**1**).[1] Furthermore, we have succeeded in the design of a fluorous amide condensation catalyst, 3,5-bis(perfluorodecyl)benzeneboronic acid, which can be recovered without any fluorous solvents and reused repeatedly.[2] The catalytic activities of these neutral boronic acids are greatly diminished in polar solvents. This solvent limitation has restricted the scope of substrates suitable for this dehydrative condensation.

In 2000, we found that 4-borono-*N*-methylpyridinium iodide (**2**) was effective as a polar-solvent-tolerable catalyst for amide condensation. Cationic boronic acid **2** was much 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.[3a] Thus, **2** was successfully applied as a catalyst for the direct polycondensation of arenedicarboxylic acids with diaminoarenes in a mixed solvent of terphenyl

---

[†] Nagoya University.

[‡] The University of Chicago.

(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. *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, Germany, 2005; pp 377−409.

(2) Ishihara, K.; Kondo, S.; Yamamoto, H. *Synlett* **2001**, 1371−1374.

(3) (a) Ohara, S.; Ishihara, K.; Yamamoto, H. *The 78th Spring Meeting of Chemistry Society of Japan*, 2000, 3-B5-10. (b) Ishihara, K.; Yamamoto, H. *Jpn. Kokai Tokkyo Koho* JP 2001−270939 (2001−10−02), Application: JP 2000−87495 (2000−03−27).

10.1021/ol052060l CCC: $30.25

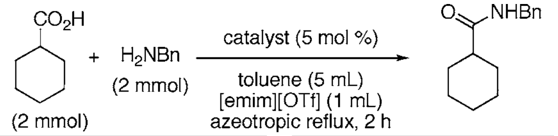
and *N*-butylpyrrolidinone (NBP).[3] In the next year, Wang et al. reported 3-borono-*N*-methylpyridinium iodide (**3**) and *N*-polystyrene resin-bound 3-boronopyridinium chloride (**4**) as amide condensation catalysts.[4]

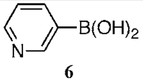
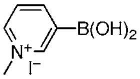
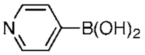
We report here that *N*-alkyl-4-boronopyridinium salts are more thermally stable than *N*-alkyl-3-boronopyridinium salts. We found that a homogeneous catalyst **2** could be reused through the use of ionic liquid-toluene biphasic solvents. Furthermore, we developed *N*-polystyrene resin-bound 4-boronopyridinium salts **5a**−**d** as heterogeneous and reusable amide condensation catalysts without the need for ionic liquids.

According to some reports,[5] the thermostability of pyridineboronic acids for hydrolytic protodeboration increases in the order 2-pyridineboronic acid ≪ 3-pyridineboronic acid (**6**) < 4-pyridineboronic acid (**7**). First, the thermostability of *N*-methyl boronopyridinium iodides was investigated under heating conditions at 120 °C in DMF. The half-life of **2** was 8 h under the above conditions. On the other hand, **3** was completely decomposed to boric acid and *N*-methylpyridinium iodide within 8 h via hydrolytic protodeboration. In contrast, **6** and **7** were stable even after heating at 120 °C for 1 day. 2-Borono-*N*-methylboronopyridinium 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 ≪ **3** < **2** < **6** ≤ **7**.

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 **3** was slightly lower than that of **2** (entry 2). 3- and 4-Pyridineboronic acids, **6** and **7**, were less active than the corresponding boronopyridinium iodides (entries 3 and 4). The catalytic activity of **7** was quite low, probably because of its low solubility under these reaction conditions.

Table 1. Catalytic Activity of Boronic Acids



entry	catalyst	conv. (%)	entry	catalyst	conv. (%)
1	**2**	59	3	 **6**	43
2	 **3**	54	4[a]	 **7**	8

[a] **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 deboration. We isolated this yellow precipitate as an orange crystal from water. Surprisingly, the crystal was unambiguously confirmed to be a dodecamer of **2**, [**2**]$_{12}$, by single-crystal X-ray diffraction (Figure 2). To the best of our knowledge, this is the first example of a dodecamer of an arylboronic acid. Interestingly, [**2**]$_{12}$ was dissolved and stable even in water because the 12 hydrophilic pyridinium ion moieties were oriented on the outside of [**2**]$_{12}$.

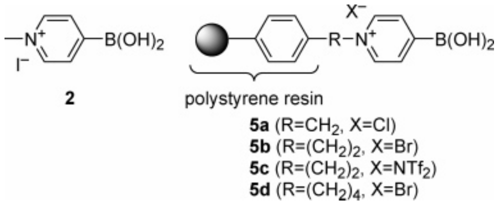


Figure 1. Thermally stable and reusable boronopyridinium salt catalysts **2** and **5a**−**d**.

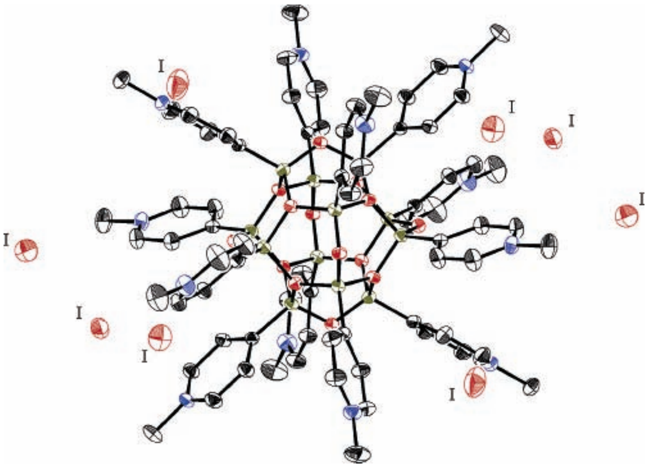


Figure 2. X-ray crystal structure of dodecamer [**2**]$_{12}$, $[CH_3NC_5H_4BO_{14/12}]_{12}I_8\cdot 10H_2O$. Water is omitted for clarity.

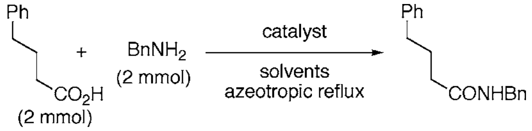
Next, the catalytic activities of **2** and [**2**]$_{12}$ (5 mol % for B-atom) were compared in the amide condensation of 4-phenylbutyric acid with benzylamine under azeotropic reflux conditions in toluene with the removal of water (entries 1 and 2, Table 2). The catalytic activity of [**2**]$_{12}$ was much lower than that of **2**. Fortunately, the catalytic activities of **2** and [**2**]$_{12}$ were dramatically improved in biphasic solvents

---

[4] Latta, R.; Springsteen, G.; Wang, B. *Synthesis* **2001**, 1611−1613.

[5] (a) Ishiyama, T.; Ishida, K.; Miyaura, N. *Tetrahedron* **2001**, *57*, 9813−9816. (b) Bouillon, A.; Lancelot, J.-C.; de Oliveria Santos, J. S.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedon* **2003**, *59*, 10043−10049. (c) Gros, P.; Doudouth, A.; Fort, Y. *Tetrahedron Lett.* **2004**, *45*, 6239−6241.

Table 2. Catalytic Activities of **2** and [**2**]$_{12}$ for Amide Condensation

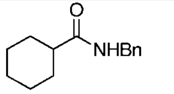
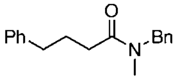
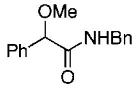
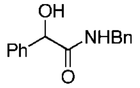
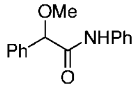
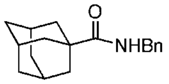
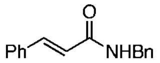
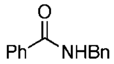
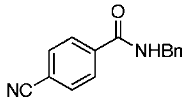


entry	catalyst (mol %)	solvents (mL)	time (h)	yield (%)
1	**2** (5)	toluene (5)	1	41
2	[**2**]$_{12}$ (10)[a]	toluene (5)	1	15
3	**2** (5)	toluene (5)−[emim][OTf] (1)	1	74
4	[**2**]$_{12}$ (5)[b]	toluene (5)−[emim][OTf] (1)	1	75
5	**2** (5)	toluene (5)−[emim][OTf] (1)	5	>99
6[c]	**2** (5)	toluene (5)−[emim][OTf] (1)	5	>99
7[d]	**2** (5)	toluene (5)−[emim][OTf] (1)	5	>99
8	**1** (5)	toluene (5)−[emim][OTf] (1)	1	88
9[e]	**1** (5)	toluene (5)−[emim][OTf] (1)	1	7

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

Table 3. Direct Amide Condensation Reaction Catalyzed by **2**

$$\underset{(2\ \text{mmol})}{R^1CO_2H} + \underset{(2\ \text{mmol})}{R^2R^3NH} \xrightarrow[\substack{\text{solvent (5 mL)} \\ \text{[emim][OTf] (1 mL)} \\ \text{azeotropic reflux}}]{\mathbf{2}\ \text{(5 mol \%)}} R^1CONR^2R^3$$

entry	solvent	time (h)	product	yield (%)
1	toluene	6		92
2	toluene	18		95
3[a]	toluene	5 (1st) 5 (2nd) 5 (3rd)		98 (1st) 93 (2nd) 95 (3rd)
4	*o*-xylene	18		91
5	*o*-xylene	18		80
6	*o*-xylene	10		91
7	*o*-xylene	3		90
8	*o*-xylene	6		98
9[a]	*o*-xylene	5 (1st) 5 (2nd) 5 (3rd)		99 (1st) 98 (2nd) 99 (3rd)

[a] A solution of **2** in [emim][OTf] was reused three times.

of toluene and [emim][OTf] (entries 3 and 4). These results can be understood in terms of the stability of **2** in the presence of [emim][OTf]. It is likely that **2** is regenerated from [**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 [**2**]$_{12}$. Thus, the amide condensation 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. **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 of the weak Lewis basicity of [emim][OTf] (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**.[7] 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 (**5a**) as well as *N*-polystyrene-bound 3-boronopyridinium chloride **4**, which had been developed by Wang and co-workers.[4] Catalysts **4** and **5a** (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 **4** decreased every time **4** was reused. The existence of $B(OH)_3$ was confirmed by ^{11}B NMR analysis of the filtrate after amide condensation. These

Table 4. Recovery and Reuse of Polystyrene-Bound 3- and 4-Boronopyridinium Chlorides **4** and **5a**

	Conversion (%) from Carboxylic Acid to Amide					
	Catalyst **4**			Catalyst **5a**		
run	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.

---

(6) The existence of [**2**]$_{12}$ in D_2O was ascertained by ^1H NMR spectral analysis.

experimental results suggest that **4** was gradually decomposed to *N*-polystyrene-bound pyridinium chloride and $B(OH)_3$ by hydrolytic protodeboration. In contrast, no loss of catalytic activity was observed for our new *N*-polystyrene-bound boronic acid **5a** even after it was reused more than five times. The high catalytic activity of **5a**, 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 **5a**.

Next, the effects of several linkers between *N*-polystyrene resin and 4-boronopyridinium ion were examined (Table 5).

Table 5. Recovery and Reuse of *N*-Polystyrene-Bound 4-Boronopyridinium Salts **5b**−**d**[a]

	Conversion (%) from Carboxylic Acid to Amide				
	5b	**5d**	**5c**		
run	5 h	5 h	1 h	3 h	5 h
1	92	98	68	98	>99
2	96	96	68	95	>99
3	95	98	71	96	>99
4			72	96	>99
5			64	95	>99
6			78	97	>99
7			71	94	>99
8			65	95	>99
9			68	95	>99
10			56	88	95

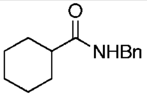
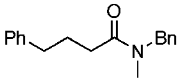
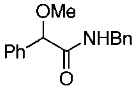
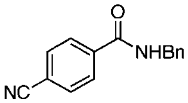
[a] See the equation in Table 2.

The catalytic activity and thermal stability of *N*-polystyrene-bound catalyst **5b** linked with ethylene and *N*-polystyrene-bound catalyst **5d** linked with butylene were the same as those of **5a** linked with methylene (Tables 4 and 5). The effect of a counteranion was also examined. Unexpectedly, no difference in catalytic activity was seen between counteranions, such as Cl^-, Br^-, and NTf_2^-. *N*-Polystyrene-bound 4-boronopyridinium triflylimide (**5c**) was reused 10 times without any significant loss of activity.

To ascertain the generality and scope of the amide condensation catalyzed by **5a**, several substrates were examined in the absence of ionic liquid (Table 6). **5a** was sufficiently active, like **2**, regardless of the substrates examined.

Table 6. Amide Condensation Reaction Catalyzed by **5a**

$$\underset{(2\ \text{mmol})}{R^1CO_2H} + \underset{(2\ \text{mmol})}{R^2R^3NH} \xrightarrow[\substack{\text{solvent (5 mL)}\\ \text{azeotropic reflux}}]{\mathbf{5a}\ \text{(5 mol \%)}} R^1CONR^2R^3$$

entry	solvent	time (h)	product	yield (%)
1	Toluene	10		93
2	Toluene	20		92
3[a]	Toluene	5 (1st) 5 (2nd) 5 (3rd)		95 (1st) 95 (2nd) 94 (3rd)
4[a]	*o*-xylene	5 (1st) 5 (2nd) 5 (3rd)		94 (1st) 92 (2nd) 94 (3rd)

[a] **5a** was reused three times.

In conclusion, *N*-alkyl-4-boronopyridinium salts are thermally stable and reusable catalysts for direct amide condensation.

Acknowledgment. We thank Dr. M. Hatano (Nagoya University) for performing X-ray single-crystal analysis. Financial support for this project was provided by SORST, JST, the 21st Century COE Program of MEXT, and the Iwatani Naoji Foundation. T.M. also acknowledges a JSPS Fellowship for Japanese Junior Scientists.

Supporting Information Available: Experimental procedures, full characterization of new compounds, and crystallographic data for $[\mathbf{2}]_{12}$. This material is available free of charge via the Internet at http://pubs.acs.org.

OL052060L

---

(7) According to the report by Wang and co-workers,[4] the amide condensation of less-reactive benzoic acid (1 equiv) with benzylamine (1.2 equiv) gave the product in 92% isolated yield in the presence of 1 mol % of 3-pyridineboronic acid or **3** in toluene. However, we could not duplicate Wang's results and obtained the amide in less than 10% yield under the same conditions.