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4,5,6,7-Tetrachlorobenzo[*d*][1,3,2]dioxaborol-2-ol as an Effective Catalyst for the Amide Condensation of Sterically Demanding Carboxylic Acids

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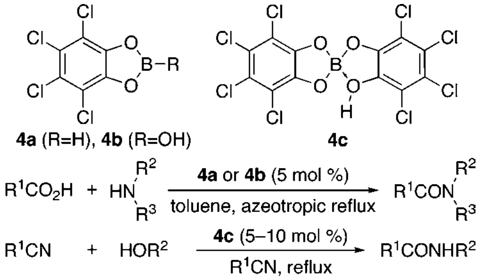
ABSTRACT



4,5,6,7-Tetrachlorobenzo[*d*][1,3,2]dioxaborole (4a) and 4,5,6,7-tetrachlorobenzo[*d*][1,3,2]dioxaborol-2-ol (4b) are effective catalysts for the dehydrative amide condensation between an equimolar mixture of carboxylic acids and amines. In particular, these catalysts are greatly superior to 3,5-bis(trifluoromethyl)phenylboronic acid (1) for the amide condensation of sterically demanding carboxylic acids. In contrast, 4c, which is prepared from a 1:2 molar mixture of $B(OH)_3$ and tetrachlorocatechol, is effective as a Lewis acid-assisted Brønsted acid (LBA) catalyst for Ritter reaction.

We have previously found that the dehydrative condensation of an equimolar mixture of carboxylic acids and primary or secondary 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 arylboronic acids bearing electron-withdrawing groups at the meta or para positions, such as 3,4,5-trifluorophenylboronic acid,[1] 3,5-bis(trifluoromethyl)phenylboronic acid (**1**),[1] 3,5-bis(perfluorodecyl)phenylboronic acid,[2] and *N*-alkyl-4-boronopyridinium halides.[3]

Before our discovery in 1978, Ganem et al. reported that carboxylic acids condense with amines via 2-acyloxy-1,3,2-benzodioxaborolane (**2**) in the presence of stoichiometric amounts of catecholborane under mild conditions (THF, −78 °C to rt) (Figure 1).[4] Two equivalents of amine are required because the reaction proceeds via nucleophilic attack of amine to [**2**·amine]. One equivalent of catecholborane is required because benzo[*d*][1,3,2]dioxaborol-2-ol (**3**), which is afforded together with amide, is inert as a condensing reagent under the same conditions. Nevertheless, taking our

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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.

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

[3] (a) Ishihara, K.; Ohara, S.; Yamamoto, H. *78th Spring Mtg Chem. Soc. Jpn.* **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). (c) Maki, T.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2005**, *7*, 5043−5046. (d) Maki, T.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2005**, *7*, 5047−5050. (e) Latta, R.; Springsteen, G.; Wang, B. *Synthesis* **2001**, 1611−1613.

[4] Collum, D. B.; Chen, S.; Ganem, B. *J. Org. Chem.* **1978**, *43*, 4393−4394.

10.1021/ol060216r CCC: $33.50

Ganem's amide condensation

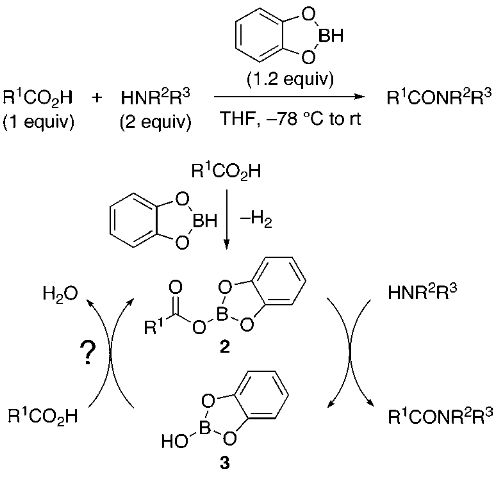


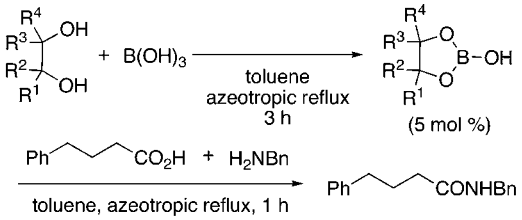
Figure 1. Ganem's amide condensation of carboxylic acids with amines using catecholborane as a condensing reagent and a possible catalytic pathway.

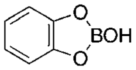
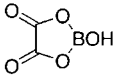
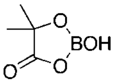
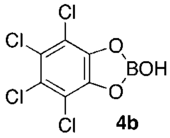
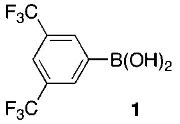
results into consideration, we envisaged that **3** as well as arylboronic acids such as **1** might serve as dehydrative catalysts under azeotropic reflux conditions with the removal of water in less polar solvents (Figure 1).

We report here that 4,5,6,7-tetrachlorobenzo[*d*][1,3,2]-dioxaborol-2-ol (**4b**), which is prepared from tetrachlorocatechol and $B(OH)_3$ in situ, is sufficiently active as a catalyst for the dehydrative condensation of an equimolar mixture of carboxylic acids and amines. Notably, **4b** was greatly superior to arylboronic acids for the amide condensation of sterically demanding carboxylic acids. In addition, we found that Lewis acid-assisted Brønsted acid (LBA)[5] **4c**, which was prepared from a 1:2 molar mixture of $B(OH)_3$ and 4,5,6,7-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 **3**, which was prepared in situ from an equimolar mixture of $B(OH)_3$ 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 1). Expectedly, **3** was usable as a dehydration catalyst and more active than $B(OH)_3$[6] (entry 5), but its activity was insufficient. Fortunately, 4,5,6,7-tetrachlorobenzo[*d*][1,3,2]dioxaborol-2-ol **4b** was much more active than **3** (entry 2). Surprisingly, the catalytic activity of **4b** was almost the same as that of **1** (entry 6). According to *Chemicals* price catalog (*Chemicals*, 33rd ed.; Wako Pure Chemical Industries, Ltd.: Japan, 2004), **1** is 40 times more expensive than tetrachlorocatechol. Since $B(OH)_3$ is also available at a rather low price, **4b**, which can be prepared from them in situ, is very economical and practical. In contrast, $B(OH)_3$−oxalic acid and $B(OH)_3$−2-hydroxy-2-methylpropanoic acid were less active than **4b**, probably due to the instability of their 1,3,2-dioxaborolan-2-ol structures (entries 3 and 4).

Table 1. Catalytic Activities of 1,3,2-Dioxaborolan-2-ol Derivatives for the Amide Condensation of 4-Phenylbutyric Acids with Benzylamine

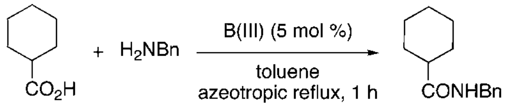


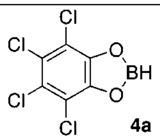
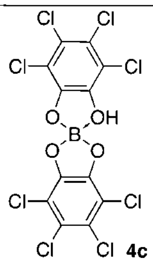
entry	B(III) catalyst	conv (%)	entry	B(III) catalyst	conv (%)
1	 **3**	61	3		64
			4		74
2	 **4b**	93	5[a]	$B(OH)_3$	31
			6[a]	 **1**	96

[a] $B(OH)_3$ and **1** were used instead of 1,3,2-dioxaborolan-2-ol derivatives.

Next, the catalytic activities of **4b**, **1**, and $B(OH)_3$ were examined for the dehydrative condensation of cyclohexanecarboxylic acid, which is a more sterically demanding carboxylic acid than 4-phenylbutyric acid, with benzylamine (Table 2). Interestingly, **4b** was geatly superior to **1** as a

Table 2. Catalytic Activities of B(III) Compounds for the Dehydrative Condensation of Cyclohexanecarboxylic Acid with Benzylamine



entry	B(III) catalyst[a]	conv (%)	entry	B(III) catalyst[a]	conv (%)
1	 **4a**	62	5	 **4c**	3
2	**4b**	52			
3	**1**	32			
4	$B(OH)_3$	2			

[a] **4b** and **4c** were prepared from $B(OH)_3$ and tetrachlorocatechol in situ before the addition of carboxylic acids and amines.

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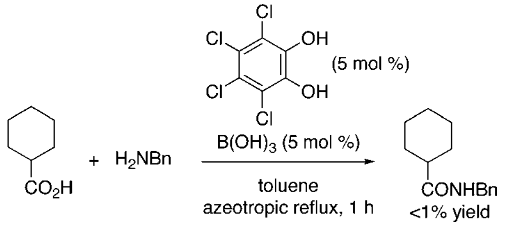
(5) (a) Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 1561−1562. (b) Ishihara, K.; Miyata, M.; Hattori, K.; Tada, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 10520−10524. (c) Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 3049−3050. (d) Ishihara, K.; Kondo, S.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1997**, *62*, 3026−3027. (e) Ishihara, K.; Kurihara, H.; Matsumoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 6920−6930.

(6) Tang, P. *Org. Synth.* **2005**, *81*, 262−272.

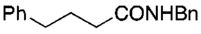
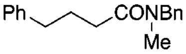
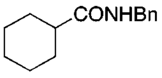
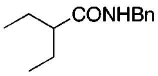
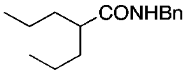
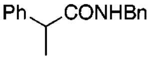
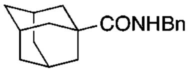
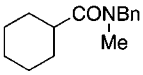
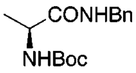
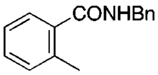
Scheme 1. Control Experiment for Entry 2 in Table 2



catalyst (entry 2 vs entry 3). 4,5,6,7-Tetrafluoro- and 4,5,6,7-tetrabromobenzo[*d*][1,3,2]dioxaborol-2-ols also exhibited good catalytic activities, as well as **4b**. $B(OH)_3$ was almost inert (entry 4).[6] Furthermore, 4,5,6,7-tetrachlorobenzo[*d*][1,3,2]dioxaborole (**4a**), which was isolable,[7,8] gave slightly better results than **4b** (entry 1). However, **4c**, which was prepared in situ from a 1:2 molar mixture of $B(OH)_3$ and tetrachlorocatechol, was almost inert probably due to the lack of any hydroxy groups on the boron atom of **4c** (entry 5).

Table 3. Amide Condensation of Various Carboxylic Acids with Amines Catalyzed by **1** or **4a**

$$\mathrm{RCO_2H} + \mathrm{R^2R^3NH} \xrightarrow[\text{toluene or } o\text{-xylene, azeotropic reflux}]{\mathbf{1}\text{ or }\mathbf{4a}\text{ (5 mol \%)}} \mathrm{R^1CONR^2R^3}$$

entry	product (**5–18**)	solvent, time (h)	yield (%)	
			1	4a
1	 **5**	toluene, 0.25	60	41
2	 **6**	toluene, 1	42	26
3	PhCONHBn **7**	*o*-xylene, 0.5	59	51
4	PhCONMeBn **8**	*o*-xylene, 1	37	16
5	 **9**	toluene, 1	32	62
		toluene, 5	–	**94**
6	 **10**	**toluene, 24**	8	**93**
7	 **11**	toluene, 19	11	55
		***o*-xylene, 24**	–	**99**
8	*t*-BuCONHBn **12**	toluene, 20	5	55
		***o*-xylene, 15**	–	**94**
9	 **13**	toluene, 2	25	77
		toluene, 5	–	**95**
10	 **14**	toluene, 24	15	22
		***o*-xylene, 20**	20	**99**
11	Ph$_2$CHCONHBn **15**	toluene, 2	30	32
		toluene, 11	–	**93**
12	 **16**	*o*-xylene, 5	47	53
		***o*-xylene, 19**		**93**
13	 **17**	toluene, 5	35	42
		toluene, 20	–	**91**[a]
14	 **18**	*o*-xylene, 1	32	62
		***o*-xylene, 9**	–	**92**

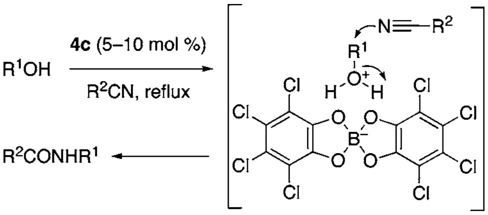
[a] Optical purity of the amide was reduced from >99% ee to 86% ee through amide condensation.

When tetrachlorocatechol, $B(OH)_3$, cyclohexanecarboxylic acid, and benzylamine were added to toluene at once, the amide condensation almost did not occur probably due to the lack of generation of **4b** (Scheme 1). As shown in Table 2, the in situ preparation of **4b** was required before the addition of carboxylic acids and amines.

To explore the generality and scope of the amide condensation reaction catalyzed by **4a**, catalytic activities of **4a** were compared with that of **1** in the amide condensation reaction of various substrates in toluene or *o*-xylene in the presence of 5 mol % of them. Representative results are shown in Table 3. Although **4a** gave slightly inferior results compared to **1** for sterically small aliphatic and aromatic carboxylic acids (entries 1−4), it still showed adequate catalytic activity for these substrates. In contrast, **4a** was greatly 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, the amide condensation reactions were completed within 24 h in the presence of 5 mol % of **4a**. The scope of suitable carboxylic acids was extended by using **4a** as a catalyst instead of **1**. In contrast, **1** and **4a** showed a similar trend in catalytic activity with regard to the steric bulkiness of amines (entries 2, 4, and 12). Less hindered **4b** should have an advantage over **1** at the regeneration step from hydroxyboron compounds to acyloxyboron species.

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.[9] This method works well only under strongly acidic conditions (e.g., cat. concd H_2SO_4,[9,10a] cat. $BF_3{\cdot}Et_2O$,[10b] formic acid as

Table 4. Ritter Reaction Catalyzed by **4c**



entry	**4c** (mol %)	time (h)	product (**7**, **19**−**25**)	yield (%)
1	10	11	Ph$_2$CHNHCOMe **19**	93
2	5	4	Ph$_2$CHNHCOEt **20**	92
3[a]	5	3	Ph$_2$CHNHCOPh **21**	94
4[a]	10	5	BnNHCOPh**7**	80
5[a]	10	3	*p*-MeC$_6$H$_4$CH$_2$NHCOPh **22**	78
6	10	3	(*p*-MeC$_6$H$_4$)$_2$CHNHCOEt **23**	84
7	5	3	(2-Naphthyl)PhCHNHCOEt **24**	93
8	5	3	(*p*-FC$_6$H$_4$)$_2$CHNHCOEt **25**	96

[a] The reaction was carried out at 120 °C.

a solvent,[9c] and so on) in strongly ionizing solvents, which limits its applicability to compounds containing functional groups that are stable to acid. Although tetrachlorocatechol and $B(OH)_3$ were much milder acidic compounds than traditional strong acid catalysts, it was expected that their ate complex **4c** might synergistically serve as a Lewis acid assisted Brønsted acid (LBA).[5] 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 4). In all cases, the corresponding amides were isolated in high yield.

In conclusion, compounds **4** are economically and practically useful catalysts for the direct amide condensation of sterically demanding carboxylic acids. Catalyst **4b** could be isolated and stored as **4a**. Furthermore, **4c** is useful as an LBA catalyst for the Ritter reaction.

Acknowledgment. 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 and full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) 4,5,6,7-Tetrafluoro- and 4,5,6,7-tetrabromobenzo[*d*][1,3,2]dioxaborol-2-ols could not be isolated by distillation techniques.

(8) Lang, A.; Nöth, H.; Thomann-Albach, M. *Chem. Ber./Recueil* **1997**, *130*, 363−369. In this paper, **4a** was prepared from 3,4,5,6-tetrachlorocyclohexa-3,5-diene-1,2-dione and $BH_3 \cdot THF$. We prepared **4a** from tetrachlorocatechol and $BH_3 \cdot SMe_2$ in Et_2O because THF was decomposed due to the strong Lewis acidity of **4a** under the distillation conditions.

(9) (a) Benson, F. R.; Ritter, J. J. *J. Am. Chem. Soc.* **1949**, *71*, 4128−4129. (b) Krimen, L. I.; Cota, D. J. *Org. React.* **1969**, *17*, 213−325.

(10) (a) Reddy, K. L. *Tetrahedron Lett.* **2003**, *44*, 1453−1455. (b) Firouzabadi, H.; Sardarian, A. R.; Badparva, H. *Synth. Commun.* **1994**, *24*, 601−607. (c) Gullickson, G. C.; Lewis, D. E. *Synthesis* **2003**, 681−684.