JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

pubs.acs.org/JACS

Boronic Acid-Catalyzed, Highly Enantioselective Aza-Michael Additions of Hydroxamic Acid to Quinone Imine Ketals

Takuya Hashimoto, Alberto Osuna Gálvez, and Keiji Maruoka*

Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan

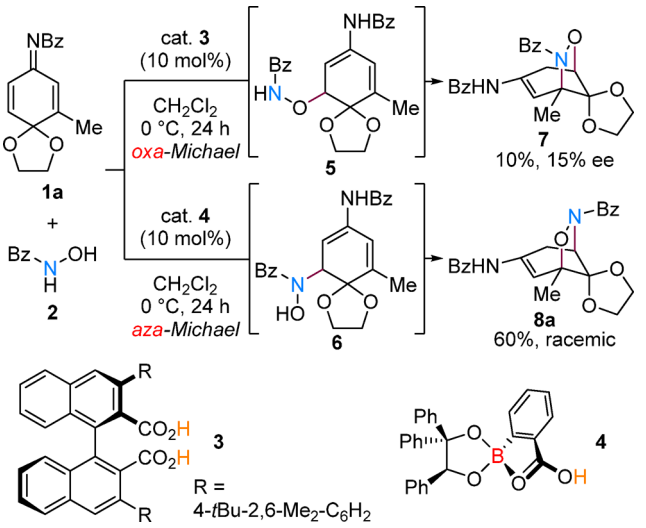
Supporting Information

ABSTRACT: Boronic acid is one of the most versatile organic molecules in chemistry. Its uses include organic reactions, molecular recognition, assembly, and even medicine. While boronic acid catalysis, which utilizes an inherent catalytic property, has become an important research objective, it still lags far behind other boronic acid chemistries. Here, we report our discovery of a new boronic acid catalysis that enables the aza-Michael addition of hydroxamic acid to quinone imine ketals. By using 3-borono-BINOL as a chiral boronic acid catalyst, this reaction could be implemented in a highly enantioselective manner, paving the way to densely functionalized cyclohexanes.

As represented by Suzuki–Miyaura coupling,[1] there are a myriad of organic transformations that rely on boronic acid as a key functionality.[2] The unique property of boronic acids—forming covalent bonds reversibly with alcohols—has also been extensively applied in molecular recognition, sensors, and self-assembly.[3,4] More recently, this property of boronic acids has even found use in medicine, such as in the commercialized drugs bortezomib and tavaborole.[5,6] Far less developed, compared with these applications, is the use of boronic acid itself as a catalyst in organic synthesis, although it has received increasing attention recently due to its distinct mode of action, facilitating transformations unachievable by other catalyses.[7−9] From the practical point of view, the ready availability, stability, and low toxicity of boronic acid also justify its use as a catalyst. One obstacle to expanding boronic acid catalysis is the limited knowledge about its mode of action, as the electrophilic activation of carboxylic acids, reported as early as 1996, still stands as the only reliable protocol.[10] Another challenge is the lack of a boronic acid catalyst that controls the stereoselectivity rigorously. In the field of asymmetric catalysis, boronic acid catalysis has not been recognized as a viable option, and only a few examples exist in the literature, with limited success reported.[11,12]

Here, we report our discovery of a new boronic acid-catalyzed reaction which turned into a highly enantioselective catalysis. It was revealed that the aza-Michael addition of hydroxamic acid to quinone imine ketals is uniquely promoted by a catalytic amount of boronic acid, and the reaction could be implemented smoothly with enantioselectivities >90% by use of 3-borono-BINOL. The asymmetric reaction proceeded even at 2 mol% catalyst loading, which is unusually low in boronic acid catalysis. We also shed new light on the mechanism of boronic acid catalysis by disclosing the operation of a catalyst dimer in the reaction.

Scheme 1. Use of Different Chiral Catalysts



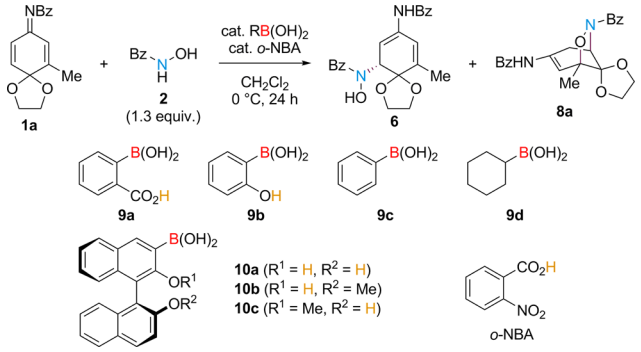
The initial clue for the development of new chiral boronic acid catalysis emerged serendipitously in the course of our study using quinone imine ketals as prochiral electrophiles in chiral Brønsted acid catalysis.[13,14] Stimulated by a recent report on the base-mediated addition of hydroxamic acid to quinone ketals,[15] we became interested in the development of oxa-Michael addition of hydroxamic acid **2** to quinone imine ketals **1** catalyzed by chiral Brønsted acid (Scheme 1). As a preliminary experiment, we set up two reactions using different chiral Brønsted acid catalysts, **3** and **4**, both developed in this group.[16,17] The use of axially chiral dicarboxylic acid **3** gave the expected bicyclic compound **7**, derived from the oxa-Michael addition (**1a** to **5**) and sequential intramolecular cyclization. On the other hand, the reaction catalyzed by the boronate ester-assisted chiral carboxylic acid **4** gave rise to the product **8a**, derived from the initial aza-Michael addition (**1a** to **6**), in a racemic form.[18] The fact that the product was obtained in a racemic form indicated that the chiral diol moiety of catalyst **4** is dissociated and does not interfere in this catalysis, and that 2-boronobenzoic acid is acting as a unique boronic acid catalyst.

To confirm this assumption, we screened some achiral boronic acids, as shown in Table 1. As anticipated, 2-

Received: November 4, 2015
Published: December 13, 2015

DOI: 10.1021/jacs.5b11518
J. Am. Chem. Soc. 2015, 137, 16016−16019

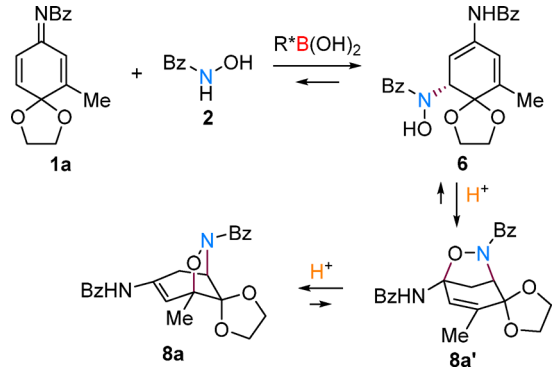
Table 1. Optimization of the Reaction Conditions[a]



entry	$RB(OH)_2$	$RB(OH)_2$, amount	*o*-NBA amount	yield of **6** (%)	ee of **6** (%)	yield of **8a** (%)	ee of **8a** (%)
1	**9a**	10 mol%		trace		67	
2	**9b**	10 mol%		10		37	
3	**9c**	10 mol%		trace		9	
4	**9d**	10 mol%		9		38	
5	**10a**	10 mol%		17	77	55	77
6	**10a**	10 mol%	10 mol%	trace		78	88
7	**10a**	10 mol%	25 mol%	trace		69	91
8	**10a**	10 mol%	50 mol%	trace		76	95
9[b]	**10a**	10 mol%	50 mol%	trace		84	97
10[b]	**10b**	10 mol%	50 mol%	trace		42	45
11[b]	**10c**	10 mol%	50 mol%	trace		19	36
12[b,c]	**10a**	2 mol%	10 mol%	trace		91	86
13[b,d]	**10a**	2 mol%	30 mol%	trace		92	94

[a]Performed with **1a** (0.1 mmol), **2** (0.13 mmol), and a catalytic amount of $RB(OH)_2$ in CH_2Cl_2 (1.0 mL) at 0 °C for 24 h. [b]Performed at −10 °C. [c]Performed for 120 h on 1.0 mmol scale. [d]Performed for 72 h on 1.0 mmol scale.

Scheme 2. Plausible Reaction Pathway



boronobenzoic acid **9a** promoted the reaction efficiently, giving **8a** in good yield (entry 1). In addition, 2-boronophenol **9b**, phenylboronic acid **9c**, and even cyclohexylboronic acid **9d** accelerated the reaction to give **8a**, albeit in poorer yields (entries 2−4). In these latter cases, the uncyclized aza-Michael adduct **6** was also isolated in a substantial amount.

With these preliminary results in hand, we commenced the development of a chiral boronic acid catalyst. By screening a variety of chiral boronic acids, we found out that easily accessible 3-borono-BINOL **10a** is a promising chiral catalyst, with which the product was obtained with modest enantioselectivity (entry 5). The aza-Michael adduct **6** was also isolated with the same level of enantioselectivity. In consideration of the fact that 2-boronobenzoic acid **9a**, which has a boronic acid and a carboxylic acid in the molecule, promoted the reaction smoothly (entry 1), we decided to add an achiral Brønsted acid as a co-catalyst to improve the reactivity. For this purpose, *o*-

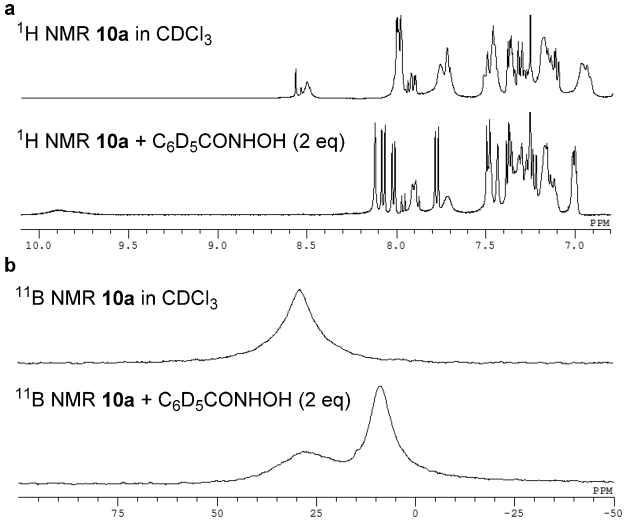


Figure 1. Investigation of the catalytic species.

nitrobenzoic acid (*o*-NBA) was identified as a proper co-catalyst with which exclusive formation of **8a** was achieved (entry 6). Moreover, an increase in the enantioselectivity was observed when using more of the co-catalyst (entries 7 and 8). In the end, optimized conditions for this enantioselective reaction were set to the use of 10 mol% catalyst **10a** and 50 mol % co-catalyst at −10 °C in CH_2Cl_2, by which the reaction afforded the product **8a** in 84% yield with 97% ee (entry 9). The importance of the OH group of 3-borono-BINOL was confirmed by carrying out the reaction using methyl-capped catalysts **10b** and **10c**, with which lower yields and selectivities were attained (entries 10 and 11). To demonstrate the

DOI: 10.1021/jacs.5b11518
J. Am. Chem. Soc. 2015, 137, 16016−16019

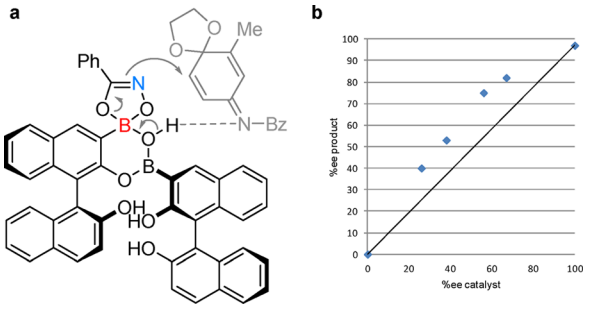
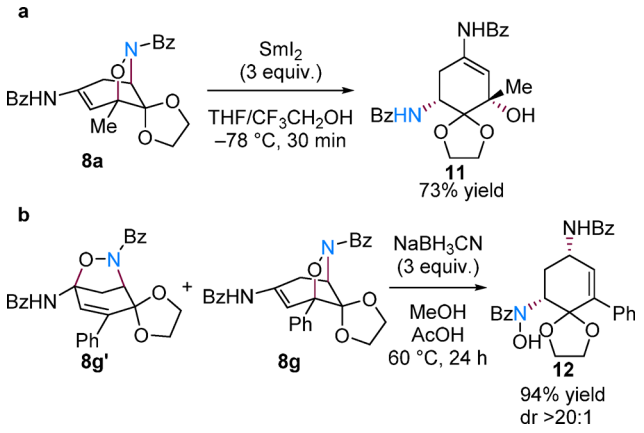


Figure 2. (a) Plausible transition state and (b) observation of the nonlinear effect.

scalability, the reaction was then conducted on 1 mmol scale using 2 mol% chiral boronic acid catalyst **10a**. It was found out that increasing the ratio of *o*-NBA is critical to attain good results. While the use of 10 mol% *o*-NBA and 2 mol% **10a** took 5 days for completion of the reaction with a substantial decrease of the ee (entry 12), the combination of 30 mol% *o*-NBA and 2 mol% **10a** gave rise to the product in 92% yield with 94% ee within 3 days (entry 13). In the additional experiments, we also confirmed that the reaction proceeds with N-Boc-quinone imine ketal, while quinone ketal is not reactive under these conditions.[19]

At this stage, we moved our attention to the elucidation of the reaction pathway and the role of the chiral boronic acid and *o*-NBA (Scheme 2). For this purpose, the uncyclized aza-Michael adduct **6** was isolated and treated with either the boronic acid or *o*-NBA. On the one hand, the treatment of **6** with chiral boronic acid **10a** gave a mixture of substrates **1a** and **2**, the remaining **6**, and the bicyclic product **8a**, indicating that the boronic acid catalyzes the reversible aza-Michael addition and also promotes cyclization slowly. On the other hand, the treatment of **6** with *o*-NBA resulted in the exclusive formation of **8a**, clarifying that the Brønsted acid accelerates the intramolecular cyclization. These observations account for the increase of the enantioselectivity in the reaction employing more *o*-NBA (see Table 1, entries 6–8, 12, and 13). Additional insight was obtained by the ^{1}H NMR monitoring of the *o*-NBA-catalyzed cyclization of **6**, which showed the accumulation of N,O-acetal **8a**′ before the formation of **8a**.

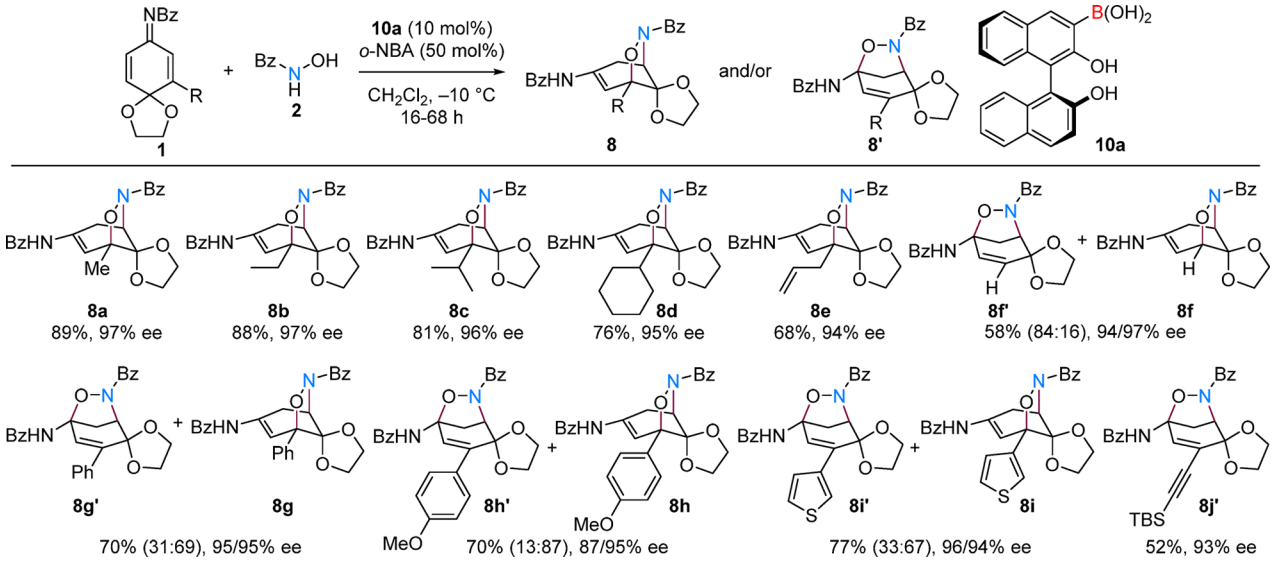
Scheme 3. Derivatization of the Products



To gain insight into the interaction of boronic acid and hydroxamic acid, we carried out NMR experiments of the complex (Figure 1). Addition of deuterated benzohydroxamic acid **2**-d_5 to 3-borono-BINOL **10a** in $CDCl_3$ led to a drastic shift of the ^{1}H NMR and ^{11}B NMR signals, as shown in Figure 1 (see Supporting Information (SI) for details). ^{1}H NMR of the complex showed 22 discernible proton signals, indicating the involvement of two molecules of **10a** in an asymmetric manner. The ^{11}B NMR of the complex showed two peaks at 27.7 and 8.9 ppm, also indicative of a dimeric species having one boron and one borate. In addition, ESI-MS measurement provided a peak at m/z 744.2 $(M-H)^-$, which corresponds to two molecules of **10a** and one hydroxamic acid **2** complexed by the dehydration of three H_2O.

Taking these facts into account, we postulated the catalyst resting state which consists of a dioxazaborole[20,21] and a boronate half-ester (Figure 2a). From this species, acid–base catalysis may operate to facilitate the aza-Michael addition, wherein the quinone imine ketal is activated by hydrogen-bonding with the free boronic acid and attacked by the nucleophilically activated hydroxamic acid (indicated in gray).

Chart 1. Substrate Scope



DOI: 10.1021/jacs.5b11518
J. Am. Chem. Soc. 2015, 137, 16016–16019

The alcohol moieties of the BINOLs might form hydrogen bonds with each other and rigidify the dimeric catalyst structure. Further support for the formation of a dimeric species was provided experimentally by the observation of a positive nonlinear effect (Figure 2b).[22]

With the optimized reaction conditions in hand, we examined the substrate scope of this chiral boronic acid catalysis (Chart 1). A variety of 3-alkyl- and 3-allyl-substituted quinone imine ketals were applied without difficulty to give **8b**−**8e** in good yields, with enantioselectivities >94%. The use of 3-unsubstituted quinone imine ketal gave a mixture of N,O-acetals **8f′** and **8f**, presumably due to the equilibration between these two structural isomers (see Scheme 2). Aromatic substituents were tolerated to give a mixture of structural isomers **8g′**−**8i′** and **8g**−**8i**, the ratios of the isomers depending on the aryl group. Both isomers were obtained with high enantioselectivities. The reaction of 3-TBS-ethynyl quinone imine ketal gave the corresponding N,O-acetal **8j′** exclusively with 93% ee.

Considering the importance of chiral functionalized cyclohexylamines as building blocks for aminoglycoside antibiotics and antiviral drugs, we implemented the synthetic derivatization of the products (Scheme 3). As one example, we attempted the SmI_2-mediated N−O bond cleavage of **8a** to directly give aminocyclohexanol **11** (Scheme 3a). By carrying out the reaction at low temperature in the presence of trifluoroethanol as a proton source, the desired product was obtained in good yield. As another example, reductive amination was examined using a mixture of structural isomers **8g′** and **8g** (Scheme 3b). The reduction was accomplished by use of $NaBH_3CN$ under acidic conditions to converge the mixture into *cis*-diamine **12** in good yield with high diastereoselectivity.

In conclusion, we have disclosed that the aza-Michael addition of hydroxamic acid to quinone imine ketal is uniquely facilitated by a boronic acid, and the reaction can be implemented in a highly enantioselective manner by use of the co-catalyst system composed of 3-borono-BINOL and *o*-nitrobenzoic acid. The mechanistic study revealed the dimeric nature of the boronic acid catalyst, which activates the hydroxamic acid as nucleophile by the formation of a dioxazaborole. This study thereby provided a new mechanistic foundation of boronic acid catalysis, proved its potential as a new class of asymmetric catalyst, and will stimulate further research in the field of chiral boronic acid catalysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b11518.

Experimental details and characterization data for new compounds (PDF)

X-ray crystallographic data for **13** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*maruoka@kuchem.kyoto-u.ac.jp

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was partially supported by a Grant-in-Aid for Scientific Research from the MEXT (Japan). A.O.G. thanks the Japanese Government (MEXT) Scholarship Program for the fellowship.

■ REFERENCES

(1) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.

(2) *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials*, Vols. 1 and 2; Hall, D. G., Ed.; Wiley-VCH: Weinheim, 2011.

(3) Kubo, Y.; Nishiyabu, R.; James, T. D. *Chem. Commun.* **2015**, *51*, 2005−2020.

(4) Sun, X.; James, T. D. *Chem. Rev.* **2015**, *115*, 8001−8037.

(5) Ban, H. S.; Nakamura. *Chem. Rec.* **2015**, *15*, 616−35.

(6) Adamczyk-Woźniak, A.; Borys, K. M.; Sporzyński, A. *Chem. Rev.* **2015**, *115*, 5224−5247.

(7) Zheng, H.; Hall, D. G. *Aldrichimica Acta* **2014**, *47*, 41−51.

(8) Dimitrijević, E.; Taylor, M. S. *ACS Catal.* **2013**, *3*, 945−962.

(9) Taylor, M. S. *Acc. Chem. Res.* **2015**, *48*, 295−305.

(10) Ishihara, K.; Ohara, S.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4196−4197.

(11) Lee, D.; Newman, S. G.; Taylor, M. S. *Org. Lett.* **2009**, *11*, 5486−5489.

(12) Arnold, K.; Davies, B.; Hérault, D.; Whiting, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 2673−2676.

(13) Hashimoto, T.; Nakatsu, H.; Takiguchi, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2013**, *135*, 16010−16013.

(14) Hashimoto, T.; Nakatsu, H.; Maruoka, K. *Angew. Chem., Int. Ed.* **2015**, *54*, 4617−4621.

(15) Yin, Z.; Zhang, J.; Wu, J.; Liu, C.; Sioson, K.; Devany, M.; Hu, C.; Zheng, S. *Org. Lett.* **2013**, *15*, 3534−3537.

(16) Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 10054−10055.

(17) Hashimoto, T.; Gálvez, A. O.; Maruoka, K. *J. Am. Chem. Soc.* **2013**, *135*, 17667−17670.

(18) Enders, D.; Wang, C.; Liebich, J. X. *Chem. - Eur. J.* **2009**, *15*, 11058−11076.

(19) The reaction of *N*-Boc-3-methylquinone imine ketal afforded the product in 48% yield with 64% ee (see SI for details).

(20) Ito, M.; Tokitoh, N.; Okazaki, R. *Tetrahedron Lett.* **1997**, *38*, 4451−4454.

(21) Vo, C.-V. T.; Mitchell, T. A.; Bode, J. W. *J. Am. Chem. Soc.* **2011**, *133*, 14082−14089.

(22) Kagan, H. B. *Synlett* **2001**, *2001*, 888−899.

DOI: 10.1021/jacs.5b11518
J. Am. Chem. Soc. 2015, 137, 16016−16019