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In Situ Assembled Boronate Ester Assisted Chiral Carboxylic Acid Catalyzed Asymmetric Trans-Aziridinations

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Supporting Information

ABSTRACT: We developed herein a new chiral Brønsted acid catalyst which is composed of two independent organic molecules, a chiral diol, and 2-boronobenzoic acid. In situ formation of a boronate ester was utilized as a key process to generate an active catalyst. This boronate ester assisted chiral carboxylic acid catalyst was successfully applied to the trans-aziridination of *N*-Boc and *N*-benzyl imines with *N*-phenyldiazoacetamide. This is the first catalyst to achieve high enantioselectivities using *N*-benzyl imines.

Stronger chiral Brønsted acid catalysis has become a major research field in the past 10 years pioneered by Akiyama and Terada's invention of chiral phosphoric acid catalysis.[1−3] As is the case for all kinds of asymmetric catalysis, this research area has grown in synergy with the evolution of new catalysts having distinct acidities and chiral environments, such as *N*-triflyl phosphoramides by Yamamoto,[4] axially chiral dicarboxylic acids by us,[5] and imidodiphosphoric acids by List,[6] among others.[7,8]

These chiral Brønsted acids are in common single molecules, consisting of a conjugate base as a chiral scaffold and a proton as a catalytically active site. Since the proton cannot be electronically and sterically modified, the acidity, thus the reactivity, and the chirality of a catalyst are both dictated by the basicity and the structure of its conjugate base (Figure 1a). Our

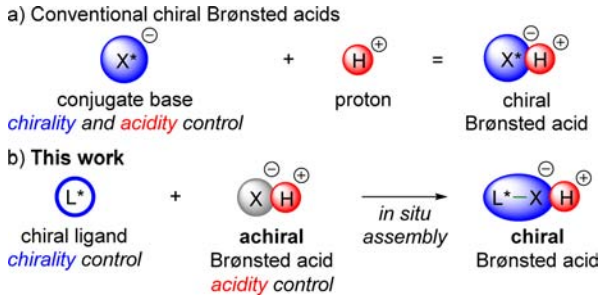

Figure 1. Classification of chiral Brønsted acids.

idea is to split a chiral Brønsted acid into two organic molecules, a chiral ligand which mainly controls the chiral environment and an achiral Brønsted acid which governs the acidity of the catalyst, and assemble these two in situ (Figure 1b).[9−11] In such a system, each component can be tuned independently to quickly generate a diverse array of chiral Brønsted acid catalysts having different catalytic properties, making it easier to identify an optimal catalyst as is often the case for chiral metal catalysts.

As an actual catalyst system to investigate, we set our focus on the combination of a readily available chiral diol and 2-boronobenzoic acid which are assembled in situ by the formation of a boronate ester (Figure 2).[12,13] This is expected

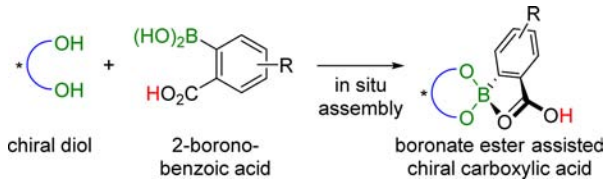

Figure 2. Concept of in situ assembled boronate ester assisted chiral carboxylic acid catalyst.

to form a boronate ester assisted chiral carboxylic acid catalyst wherein the carboxylic acid coordinates to the Lewis acidic boron atom. This coordination would help to rigidify the structure of the catalyst and enhance the acidity of the carboxylic acid.[5] Actually, the enhanced acidity of preformed achiral 2-Bpin benzoic acid was disclosed by Mattson during the course of our study.[14] Since a variety of chiral diols are readily available, such a catalyst system could easily offer diverse chiral environments. In addition, use of electronically modified 2-boronobenzoic acids, enabled by the attachment of functional groups on the aromatic ring, is expected to directly change the acidity of the catalyst.

We report herein the development of an in situ assembled boronate ester assisted chiral carboxylic acid whose catalytic performance was proven in the catalytic asymmetric trans-aziridination of *N*-Boc imines and *N*-phenyldiazoacetamide.[15,16] Furthermore, by taking advantage of the facile electronic tuning of the catalyst, we applied this catalyst to the yet-unrealized trans-aziridination of *N*-benzyl imines wherein the use of a stronger acid catalyst became crucial for the successful implementation. It is also worth emphasizing that we succeeded in establishing a rare catalyst independent of a binaphthyl unit, of which most stronger chiral Brønsted acids are composed.[17]

As a model reaction to evaluate this concept, we chose trans-aziridination of *N*-Boc imines and *N*-phenyldiazoacetamide developed in this laboratory (Table 1).[15] The actual reactions were conducted as follows. In a flask containing molecular sieves were added 10 mol % of 2-boronobenzoic acid **1a** and 12

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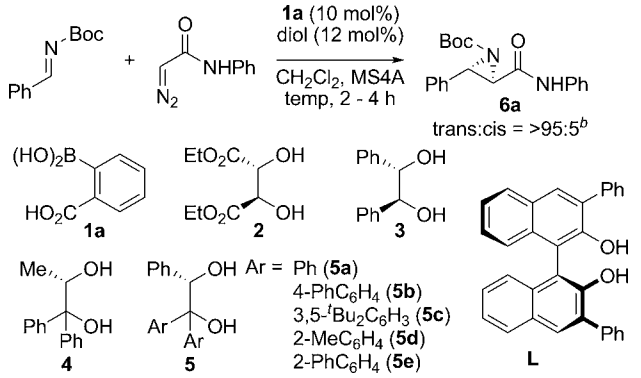
Table 1. Optimization of the Catalyst[a]



entry	diol	°C	% yield[c]	% ee[d]
1	**2**	0	44	0
2	**3**	0	50	44
3	**4**	0	56	−61
4	**5a**	0	52	−60
5	**5b**	0	51	−70
6	**5c**	0	50	−70
7	**5d**	0	40	47
8	**5e**	0	63	89
9	**5e**	−20	64	92
10	**L**	0	45	14

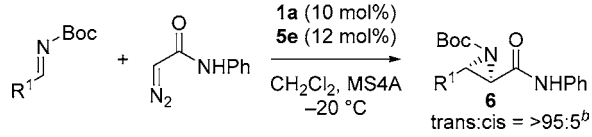
[a]Performed with *N*-Boc imine (0.10 mmol), *N*-phenyldiazoacetamide (0.12 mmol), chiral diol (0.012 mmol), **1a** (0.010 mmol), and MS4A (100 mg) in CH_2Cl_2 (1.0 mL). [b]Determined by ^1H NMR analysis of the crude material. [c]Isolated yield. [d]Determined by chiral HPLC analysis.

mol % of a chiral diol in CH_2Cl_2, and the mixture was stirred for 30 min at rt to form the complex. Molecular sieves were added to scavenge water generated in this event. After the addition of the imine, the solution was cooled to the reaction temperature, and *N*-phenyldiazoacetamide was then added to start the reaction.

At first, we examined two commercial *C*2-symmetric chiral diols, (*R*,*R*)-diethyl tartrate **2** and (*S*,*S*)-hydrobenzoin **3**, to determine the viability of our concept. Whereas the use of **2** gave the *trans*-aziridine **6a** in a racemic form (entry 1), use of **3** was found to give the product with apparent asymmetric induction (entry 2). It should be noted that 2-boronobenzoic acid **1a** itself was able to promote the reaction despite its low solubility in CH_2Cl_2, while chiral diols were not sufficiently acidic to facilitate the reaction. In a further attempt we carried out reactions using (*S*)-1,1-diphenyl-1,2-propanediol **4** and (*S*)-1,1,2-triphenylethanediol **5a** (entries 3 and 4). Contrary to our initial assumption that these *C*1-symmetric diols would not exceed *C*2-symmetric diols in terms of the enantioselectivity, both diols **4** and **5a** furnished **6a** with promising enantioselectivities. Encouraged by this result, we then examined several (*S*)-1,1-diaryl-2-phenylethanediols **5b**−**5e**, which were prepared in one step from commercial (*S*)-mandelic acid methyl ester. Whereas the 4- and 3,5-substitution of the aryl group had no significant influence (entries 5 and 6), use of 2-tolyl substituted diol **5d** resulted in the inversion of the sense of the enantioselectivity (entry 7). Finally, 2-biphenyl substituted diol **5e** was found to be optimal with which **6a** was obtained in 63% yield with 89% ee (entry 8). By lowering the reaction temperature to −20 °C, the enantioselectivity could be further improved to 92% ee (entry 9). It is noteworthy that use of 3,3′-disubstituted BINOLs such as **L** failed to give high enantioselectivity (entry 10), presumably due to the poor ability of less basic BINOLs to form a boronate ester complex, resulting in the competitive reaction catalyzed by free **1a**.

With the optimized reaction conditions in hand, we then examined the substrate scope of this catalytic asymmetric trans-aziridination (Table 2). Use of aromatic imines bearing 3- or 4-

Table 2. *N*-Boc Imine Scope[a]



entry	R^1	% yield[c]	% ee[d]
1	Ph	64 (**6a**)	92
2	4-tolyl	44 (**6b**)	89
3	3-tolyl	42 (**6c**)	90
4	$4\text{-}FC_6H_4$	56 (**6d**)	92
5	$3\text{-}ClC_6H_4$	54 (**6e**)	93
6	$4\text{-}MeO_2CC_6H_4$	42 (**6f**)	90
7	$3\text{-}MeOC_6H_4$	68 (**6g**)	90
8	$4\text{-}PivOC_6H_4$	77 (**6h**)	91
9	2-Np	54 (**6i**)	89

[a]Performed with *N*-Boc imine (0.10 mmol), *N*-phenyldiazoacetamide (0.12 mmol), **5e** (0.012 mmol), **1a** (0.010 mmol), and MS4A (100 mg) in CH_2Cl_2 (1.0 mL). [b]Determined by ^1H NMR analysis of the crude material. [c]Isolated yield. [d]Determined by chiral HPLC analysis.

substituents was tolerated to give the corresponding *trans*-aziridines **6b**−**6h** with modest yields and high enantioselectivities (entries 2−8). Whereas a 3-methoxybenzaldehyde derived imine could be utilized to give the aziridine **6g** in good yield with high enantioselectivity (entry 7), the use of a 4-methoxybenzaldehyde derived imine gave a complex mixture (data not shown). To circumvent this issue, a 4-pivaloxy substituted imine was used as a less electron-rich alternative (entry 8). A 2-naphthaldehyde derived imine could be utilized as well (entry 9). 2-Substituted aromatic imines and aliphatic imines were not applicable, showing limitations of this methodology.

With the success of catalytic asymmetric trans-selective aziridination of *N*-Boc imines using the in situ assembled boronate ester assisted chiral carboxylic acid, we turned our attention to the use of *N*-benzyl imines. Compared with *N*-Boc imines, *N*-benzyl imines are less electrophilic and less reactive in nature while their facile synthesis and cleavage of the benzyl group offer synthetic advantages. Although Wulff's study using a chiral boroxinate Brønsted acid catalyst revealed that *N*-diarylmethyl imines can be used in catalytic asymmetric trans-aziridination with *N*-phenyldiazoacetamide,[16] simple *N*-benzyl imines have not yet been used.

An initial attempt using the above-mentioned reaction conditions gave *N*-benzyl *trans*-aziridine **7a** in 51% yield with 94% ee (Scheme 1). While the enantioselectivity was already high enough, we encountered difficulty in achieving a higher conversion and yield in this reaction.[18] In such a case, it is desirable that the acidity of the catalyst be tuned to improve the catalytic activity without affecting its chiral environment. This could be easily realized in our catalyst system by replacing 2-boronobenzoic acid with an electronically modified one. Actually, by using the combination of the same diol **5e** and

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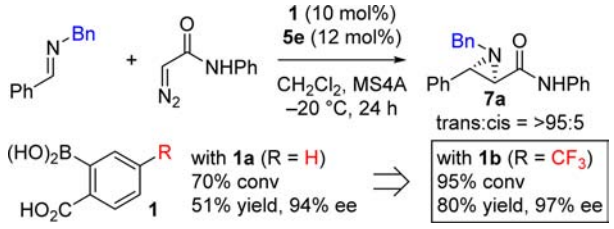
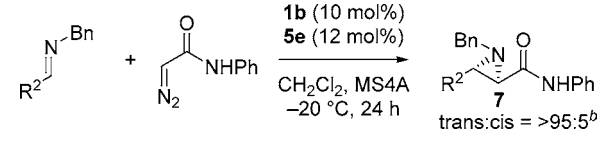
Scheme 1. Optimization of the Catalyst for the Trans-Aziridination Using *N*-Benzyl Imine



2-boronobenzoic acid **1b** bearing an electron-withdrawing 4-trifluoromethyl group, the conversion reached 95% and a considerable increase of the yield was observed while retaining the high enantioselectivity.

With the quickly optimized catalyst in hand, we investigated the substrate scope using a variety of *N*-Bn imines. Compared with the trans-aziridination using *N*-Boc imines, the yields and enantioselectivities were found to be generally higher (Table 3,

Table 3. N-Bn Imine Scope[a]



entry	R^2	% yield[c]	% ee[d]
1	Ph	80 (**7a**)	97
2	4-tolyl	80 (**7b**)	95
3	3-tolyl	67 (**7c**)	96
4	2-tolyl	74 (**7d**)	95
5	$4\text{-BrC}_6\text{H}_4$	70 (**7e**)	98
6	$3\text{-ClC}_6\text{H}_4$	77 (**7f**)	97
7	$2\text{-ClC}_6\text{H}_4$	61 (**7g**)	98
8	$3\text{-MeOC}_6\text{H}_4$	87 (**7h**)	98
9	$2\text{-MeOC}_6\text{H}_4$	53 (**7i**)	91
10	$4\text{-PivOC}_6\text{H}_4$	53 (**7j**)	97
11	2-Np	78 (**7k**)	94
12	$(\text{CH}_3)_2\text{CH}$	55 (**7l**)	84
13	Cy	48 (**7m**)	74

[a]Performed with *N*-Bn imine (0.10 mmol), *N*-phenyldiazoacetamide (0.12 mmol), **5e** (0.012 mmol), **1b** (0.010 mmol), and MS4A (100 mg) in CH_2Cl_2 (1.0 mL). [b]Determined by ^{1}H NMR analysis of the crude material. [c]Isolated yield. [d]Determined by chiral HPLC analysis.

entries 2–11). The reaction was not sensitive to the position of the functionality, as a variety of 2-substituted benzaldehyde-derived imines could all participate in the reaction (entries 4, 7, and 9). This reaction was also applied to branched aliphatic imines in modest yields with a slight decrease of the enantioselectivity (entries 12 and 13).[19] Linear aliphatic aldehydes were not suitable substrates, and the corresponding aziridines were obtained in low yields (data not shown).

We then set out to elucidate the catalyst structure by ^{1}H NMR experiments in $CDCl_3$.[20] Shown in Figure 3a and 3b are the charts of diol **5e** and the catalyst solution prepared in situ from a 1.2:1 mixture of **5e** and **1a** in the presence of molecular sieves. The OH signals of **5e** which appeared around 3 ppm (filled circles) diminished in the catalyst solution, and the doublet at 5.6 ppm (filled triangle) which corresponds to the α-hydrogen of the alcohol moiety appeared as a singlet at 5.9 ppm (open triangle). While 2-boronobenzoic acid itself is poorly

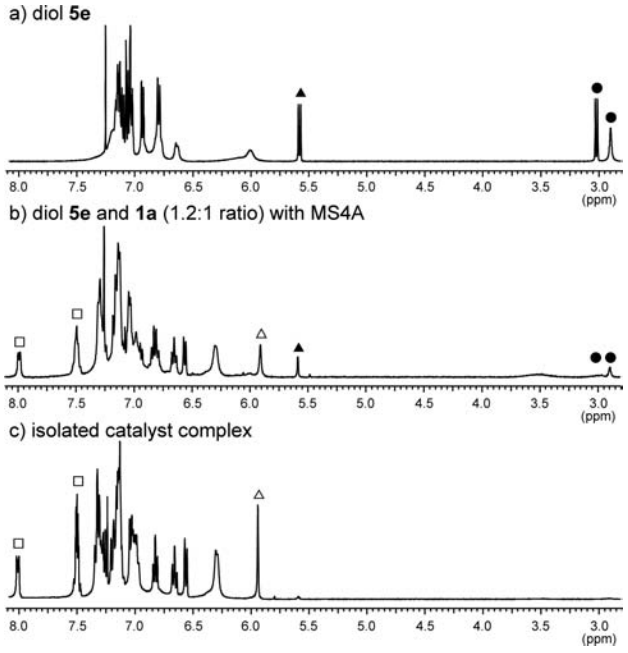


Figure 3. NMR study of the catalyst.

soluble in $CDCl_3$ and hard to detect by ^{1}H NMR, the catalyst solution apparently showed the signals corresponding to its aromatic regions (open squares). These observations clearly supported the formation of a boronate ester between the diol and boronic acid moieties. In further study, we found that the catalyst complex was actually isolable as a bench stable solid (see Supporting Information for details), whose ^{1}H NMR shown in Figure 3c matched that of the in situ formed catalyst.[21] ESI-MS measurement of this isolated complex provided an intense peak at m/z 571.21 $(M-H)^-$, which corresponded to the expected boronate ester.

As the optimal chiral diol **5e** has *C*1 symmetry, its complexation with 2-boronobenzoic acid potentially gives a diastereomeric pair (*S*,*S*)-**8** and (*S*,*R*)-**8** arising from the additional chirality at the spiro boronate moiety (Figure 4a).

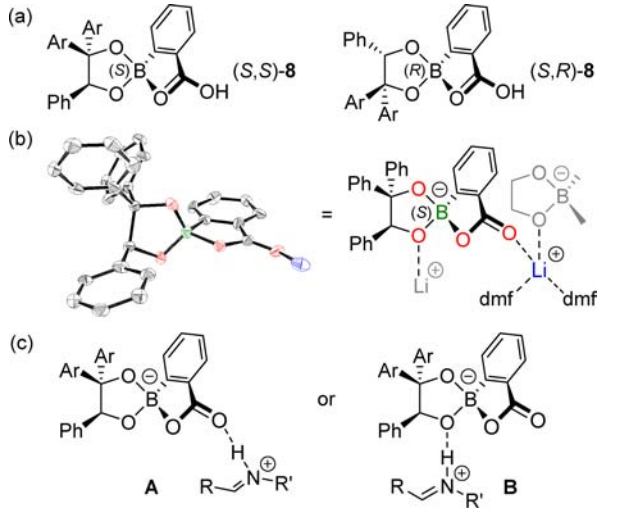


Figure 4. (a) Two diastereomers of the complex **8**. (b) Ortep diagram of the lithium salt of the 1:1 complex of **1a** and **5a** shown at the 50% probability level. Hydrogen atoms and DMF are omitted for clarity. (c) Two possible catalyst–substrate complexes.

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From the fact that essentially a single isomer was detected in the ^{1}H NMR experiment even at low temperature,[22] either one of these two complexes would be operating in the reaction. To gain insight into this, we worked extensively to obtain a crystal of the catalyst suitable for X-ray analysis. After many attempts, we finally found that the lithium salt of the complex derived from **5a** and **1a** could be crystallized in the presence of a small amount of DMF (Figure 4b). From this experiment, the chirality at the boron center of the **5a**·**1a** complex was determined to be (*S*). Accordingly, (*S*,*S*)-**8** was tentatively assigned as the true catalyst, although we could not exclude the possibility that the chirality at the boron may be inverted completely depending on the nature of a chiral diol. A closer look at the crystal structure indicated that it could be described as a lithium borate salt (Figure 4b, right) in which the double bond character of the carboxylate moiety resides on the exo C−O bond (1.22(1) Å) rather than the endo C−O bond (1.33(0) Å).[23,24] Uniquely, this lithium borate salt forms a 1-D coordination polymer in the crystalline state wherein the lithium cation coordinated not only to the oxygen atom of the carboxylic acid but also to the oxygen of the diol in addition to two molecules of DMF (see SI for details). From this observation, we assumed that the active catalyst complexed with an imine can be depicted as a spiro borate having the protonated imine either at the carbonyl oxygen (**A**) or at the oxygen derived chiral diol (**B**) as shown in Figure 4c.[25] Although it is not conclusive, complex **B** seems to be more likely, as it bears the substrate closer to the chiral environment of the diol.[26,27]

In summary, we succeeded in developing a new chiral Brønsted acid catalyst composed of two independent organic molecules, a chiral diol as a ligand and 2-boronobenzoic acid as an achiral Brønsted acid. This binary system offers an opportunity to tune the chiral environment and acidity of the catalyst independently, while avoiding a tedious synthesis of a variety of different catalysts. This concept was validated in catalytic asymmetric trans-aziridinations of *N*-Boc and *N*-benzyl imines with *N*-phenyldiazoacetamide. We have also succeeded in shedding light on the nature of the catalyst using ^{1}H NMR and X-ray crystallography.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(20) For the ^{11}B NMR of the catalyst, see SI.

(21) We subjected this preformed catalyst to the trans-aziridination of benzaldehyde-derived *N*-Boc imine and *N*-phenyldiazoacetamide, giving the *trans*-aziridine **6a** in 66% yield with 92% ee. The result was no different from that obtained by the in situ formed catalyst (see Table 2, entry 1).

(22) For the VT NMR of the catalyst, see SI.

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