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C_3-Symmetric Boron Lewis Acid with a Cage-Shape for Chiral Molecular Recognition and Asymmetric Catalysis

Akihito Konishi,[a,b] Koichi Nakaoka,[a] Hikaru Maruyama,[a] Hideto Nakajima,[a] Tomohiro Eguchi,[a] Akio Baba,[a] and Makoto Yasuda*[a]

Abstract: Chiral Lewis acids have played an important role in the precise construction of various types of chiral molecules. Here, we designed and synthesized a cage-shaped borate **2** as a chiral Lewis acid, which possesses a unique C_3-symmetric structure composed of three homochiral binaphthyl moieties. The highly symmetrical structure of **2** with homochirality was clearly elucidated by X-ray crystallographic analysis. The peculiar chiral environment of **2**·THF exhibited the chiral recognition of some simple amines and a sulfoxide. Moreover, the application of **2**·THF to hetero Diels-Alder reactions as a chiral Lewis acid catalyst successfully gave the enantioselective products, which proceeded through an entropy-controlled path according to the analysis of the relationship between optical yield and reaction temperature. In particular, the robust chiral reaction field of **2**·THF allowed the first example of an asymmetric hetero Diels-Alder reaction using a simple diene despite the requirement of high temperature.

Chiral Lewis acids contribute to organic synthesis in the construction of various types of stereocontrolled molecules, and numerous studies of them have been reported.[1,2] Most have C_2-symmetric structures probably due to the ease of preparation and a mechanism that allows chiral recognition.[3] Surprisingly, studies of Lewis acids with C_3-symmetric structures for chiral recognition are scarce. Therefore, few strategies for the design of C_3-symmetric Lewis acids are available for chiral recognition or asymmetric catalysis. Some C_3-symmetric Lewis acids[4–8] have been prepared, but in most cases they exist as a racemic mixture and are not separated as individual enantiomers because of the relatively low energy barrier between them.[9,10] Bull and Davidson, et al., prepared a pseudo-C_3-symmetric titanium Lewis acid with a propeller-like chirality,[11] which was applied to the asymmetric oxidation of sulfide, although the enantioselectivity was moderate even in the highest case.[12] The ligation of an optically active substrate to a racemic C_3-symmetric Lewis acid induces homochirality on the complex, and its effective steric environment leads to a high stereoselective reaction system.[13] A few examples giving high enantioselectivity have been reported using C_3-symmetric trisimidazoline as an organocatalyst for carbon-carbon bond formation or cyclization reactions.[14–16] In this context, the design of a novel type of C_3-symmetric Lewis acid for chiral recognition remains a challenging problem. Here, we have synthesized a new type of C_3-symmetric chiral Lewis acid that has a rigid structure and a cage-shaped ligand framework. These have shown effective recognition of simple amines and the possibility of application to some organic reactions.

We recently reported a cage-shaped borate **1** with an intramolecular triaryloxy ligand, as shown in Figure 1 (A). These exist as a racemic mixture of helical structures of *P*- and *M*-forms.[17–19] The enantiomers lie in a fast interconversion between the two forms, even at room temperature, and, thus, one or two of them seem impossible to isolate under usual conditions. We also succeeded in synthesizing *ortho*-aryl substituted or heteroaromatic ring-fused cage-shaped borates, which also exist as a racemic mixture.[17,20,21] As shown in Figure 1 (B), if the phenyl groups in the cage-shaped borate **1** are replaced by binaphthyl units like **2**, which have an axial chirality, the borate gives diastereomers rather than enantiomers. The equilibrium may lie at one side of the two diastereomers and thus a single isomer could be isolated for chiral recognition.

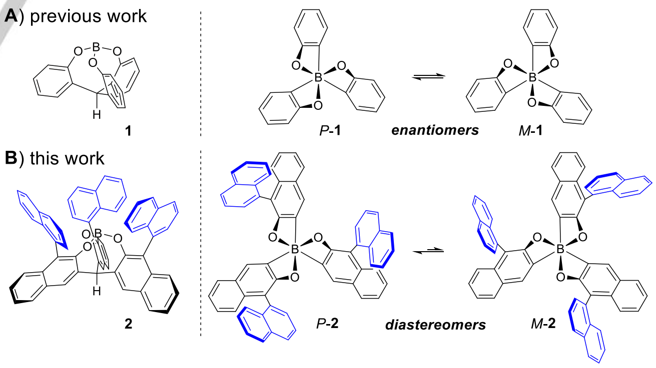

Figure 1. C_3-symmetric cage-shaped borate in conformational exchange. A) The cage-shaped borate **1** exists in an enantiomeric mixture. B) The cage-shaped borate **2** with a binaphthyl unit that has a homo axial chirality exists in a diastereomeric mixture.

The binaphthyl-containing chiral cage-shaped borate **2** was synthesized starting from readily available (*R*)-1,1'-bi-2-naphthol (BINOL), as shown in Scheme 1. Preparation of methoxy-binaphthyl **3**[22] from (*R*)-BINOL[23,24] and its lithiation at the *ortho*-position followed by condensation with ethyl chloroformate gave tris(2-methoxybinaphthyl)methanol **4**. Reduction of the carbinol **4**

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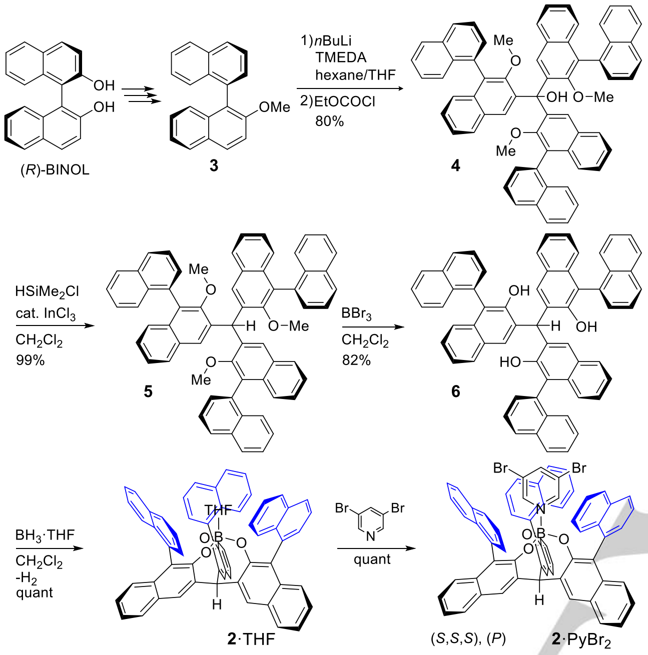
by a $Me_2SiHCl/InCl_3$ system[25] and deprotection of methoxy groups afforded the tris(2-hydroxybinaphthyl)methane **6** with axial chirality at three binaphthyl moieties. Mixing the compound **6** with BH_3·THF at 60 °C for 8 h generated the cage-shaped borate **2**·THF with a release of H_2, which was ligated by THF, in a quantitative yield.[26] A ligand exchange readily took place in the presence of 3,5-dibromopyridine without a dissociation of the cage-shaped ligand to give **2**·$PyBr_2$.



Scheme 1. Synthesis of homochiral cage-shaped borate **2** with C_3-symmetry.

The ^1H NMR spectra of the cage-shaped borates ligated with THF or 3,5-dibromopyridine (**2**·THF and **2**·$PyBr_2$) clearly showed the existence of a single isomer of two possible diastereomers in $CDCl_3$ solution at room temperature (see supporting information). After complexation, an up-field shift of the tethered C-H and a downfield shift of the 4-H of naphthyl ring were observed in the ^1H NMR spectra probably because of the rigid structure of the complex. The signal of the ligating pyridine appeared in the up-field shift region by anisotropic effect of the neighboring naphthyl groups.[20] Changing the temperature from -50 to 50 °C did not affect the spectra of the diastereomeric mixture. The helical structure was not changed, and the equilibrium overwhelmingly stayed on the one side.

The dibromopyridine-ligated complex gave a suitable crystal in X-ray analysis, and its ORTEP drawings are shown in Figure 2.[27] A robust C_3-symmetric structure surrounded by three naphthyl groups was determined. All binaphthyl axes had (*S*)-forms that originated from the starting (*R*)-BINOL, and a propeller structure around boron had a (*P*)-type. The top view clearly shows the C_3-symmetric structure of this complex. The one species of a homochiral diastereomer existed in either solution or solid-states due to the large energy difference between the diastereomers.

To estimate the peculiarities of **2** based on its C_3-symmetric homochiral cage shapes as a chiral Lewis acid, the molecular recognition of chiral amines was first examined. High chiral recognition of functional amines[28] and ammonium ions were attained,[29,30] because these have extra interaction sites with the Lewis acid center, but a molecular recognition of simple neutral amines has been limited.[31] Although supramolecular nanocapsules assembled from cyclodextrin derivatives effectively resolve simple aromatic amines in specific cases,[32] the ability of chiral recognition has been moderate for simple amines and remains a challenging problem.

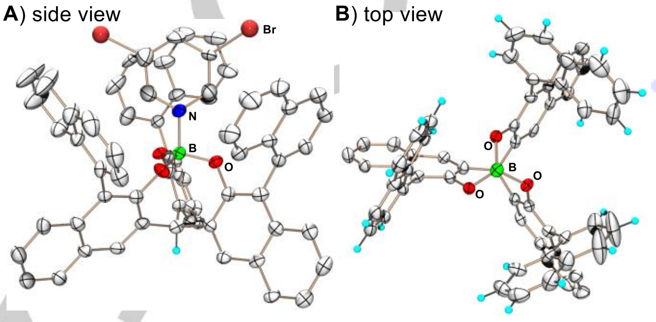

A) side view **B**) top view

Figure 2. X-ray crystal structures of **2**·$PyBr_2$. Thermal ellipsoids are at the 50% probability level. Some hydrogens are omitted for clarity. A) Side view. B) Top view (3,5-dibromopyridine is omitted for clarity).

We have examined racemic 1-phenylethylamine **7** for chiral recognition via use of the homochiral cage-shaped borate **2**·THF (Figure 3 and Table 1, see also Figure S1). The mixture of an excess amount of racemic 1-phenylethylamine **7** to the homochiral cage-shaped borate **2**·THF in CD_2Cl_2 was observed via ^1H NMR measurement (Figure 3 (A)). After mixing **7** with **2**·THF for 5 min at room temperature, the homochiral cage-shaped borate **2** definitely formed diastereomeric complexes with the amine as a 1:1 mixture of *R*- and *S*- amine adducts with **2.** The new two-doublet signals, which corresponded to the methyl protons of the diastereomeric complexes of the amine with **2**, discretely appeared at around -1 ppm in the ^1H NMR spectrum, presumably because the ring current from the rigid binaphthyl moieties effectively separated these signals from those of free amines. However, after the mixture was allowed to stand for 43 h at 80 °C, the ^1H NMR spectrum of the amine adducts dramatically changed and clearly showed the convergence of the signals into that of a diastereomeric complex; while the signal of the *S* amine adduct with **2** at -0.72 ppm almost disappeared, but the intensity of the signal of the *R* amine adduct with **2** at -0.99 ppm increased. The ratio between *R*- and *S*- amine adducts with **2** reached 18:1 (Entry 1 in Table 1), showing the highly selective enantio recognition of the simple amine.

When racemic 1-(2-naphthyl)ethylamine **8** was employed,[32] the chiral recognition of **8** with **2**·THF was more significant. After achieving equilibrium between the free amine and the amine adduct with **2**, the ratio reached a higher level of *R*:*S* (amine adducts with **2**·THF) at 23:1 (Figure 3 (B) and Entry 2 in Table 1). An effective recognition of the chirality of amines by chiral metal complexes is known only in the case of functionalized

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amines with chelation ability to the metal center.[28] In our case, higher recognition was successful when using a C_3-symmetrical cage-shaped chiral borate.

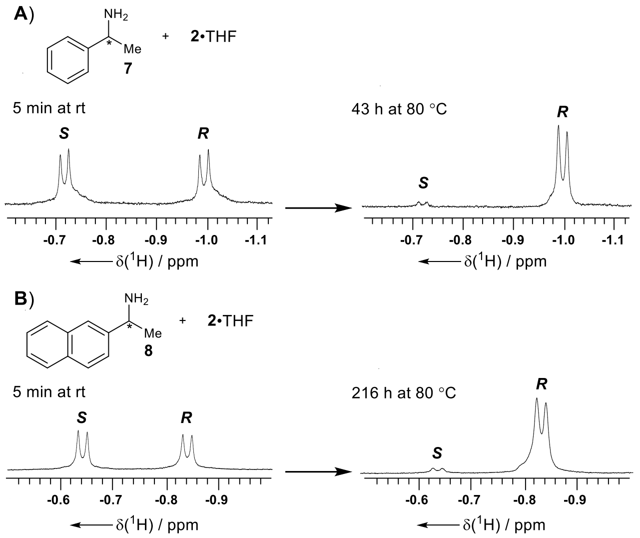
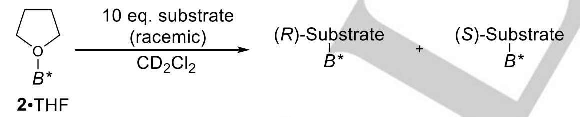
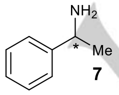
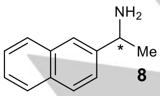
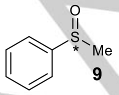


Figure 3. ^{1}H NMR spectra of the amine adducts with **2**·THF around the methyl proton signals in CD_2Cl_2. A) 1-phenylethylamine **7** and B) 1-(2-naphthyl)ethylamine with **2**·THF; (left) After mixing the amine with **2**·THF for 5 min at room temperature, and (right) after achieving equilibrium at 80 °C.

In the use of methyl phenyl sulfoxide **3**, even at the initial stage after mixing of the sulfoxide with **2**·THF, a ratio of 7:1 was observed and remained unchanged after further stirring for several hours (Entry 3 in Table 1, and Figure S2). As a low Lewis basicity of the sulfoxide compared to amines, a fast ligand exchange and fast equilibrium between the diastereomeric adducts was accomplished due to the robust and highly symmetric chiral environment of **2**·THF.

Table 1. Recognition of chiral substrates by complexation with **2**·THF.



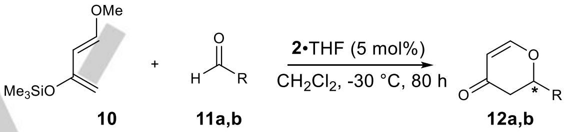
Entry	Substrate	*R* : *S*[a]
1	 **7**	18 : 1[b]
2	 **8**	23 : 1[c]
3	 **9**	7 : 1[d]

[a] The ratios and absolute configurations except entry 3 were determined by ^{1}H NMR measurement.
[b] Heating for 43 h at 80 °C. [c] Heating for 216 h at 80 °C.
[d] The absolute configuration was not determined.

Next, in order to investigate the catalytic ability of the chiral borate complex for an asymmetric synthesis as a chiral Lewis acid, the reaction of a cycloaddition of the Danishefsky diene **10** with aldehydes **11a** and **b** in hetero Diels-Alder reactions was chosen as a model transformation (Table 2 (A)). In the use of benzaldehyde **11a**, the cycloadduct **12a** was obtained in 77% yield with 31% enantiomeric excess (*ee*) (Entry 1). Higher enantioselectivity and yields were successfully obtained using cyclohexanecarboxaldehyde **11b**, which gave 84% *ee* in 78% yield (Entry 2). The replacement of a nucleophile from the Danishefsky diene to allyltributylstannane **13** simultaneously supported a good yield and high selectivity (Table 2 (B)); after optimization of the reaction conditions, the reaction with 5.0 mol% of **2**·THF at 60 °C afforded the corresponding carbonyl adduct **14** in 71% yield with 89% *ee* (entry 2).

Table 2. Asymmetric reactions using chiral cage-shaped borate **2**·THF.

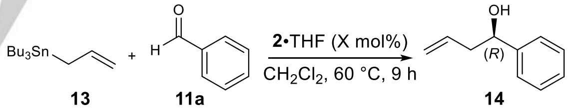
A) hetero Diels-Alder reaction



Entry	R	Aldehyde	Prod.	Yield / %	*ee* / %[a]	Abs. config. [b]
1	Ph	**11a**	**12a**	77	31	*S*
2	*c*-C_6H_{11}	**11b**	**12b**	78	84	*S*

[a] The *ee* values were determined by chiral HPLC analysis.
[b] The absolute configurations were determined by comparision to literature values. See the Supporting information.

B) allylation by allyltributylstannane **13**

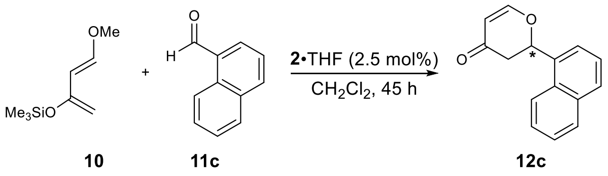


Entry	X /mol%	Yield / %	*ee* / %[a]	Abs. config. [b]
1	2.5	55	90	*R*
2	5.0	71	89	*R*

[a] The *ee* values were determined by chiral HPLC analysis.
[b] The absolute configurations were determined by comparision to literature values. See the Supporting information.

We found an interesting relationship between the reaction temperature and enantioselectivity, which was notably observed in the case of the reaction of the Danishefsky diene **10** with 1-naphthaldehyde **11c** (Table 3). Elevating the temperature led to a higher level of enantioselectivity, and a lower temperature afforded lower selectivity and the opposite stereoisomer.[33] These results suggest that the entropic effect in the transition state is more important than enthalpy in this system. The aldehyde-borate complex could be attacked by the Danishefsky diene from either face of the carbonyl group. The difference in the activation enthalpy, $\Delta\Delta H^\ddagger$, between them should have been small, but the difference in the activation entropy $\Delta\Delta S^\ddagger$ was relatively large owing to the steric demands of aryl substituents on the substrate and the catalyst. As shown in Figure S3, we estimated the $\Delta\Delta H^\ddagger$ and $\Delta\Delta S^\ddagger$ values from the plot of ln [(100 + %*ee*)/(100 - %*ee*)] as a function of the reciprocal of temperature ($1/T$) to afford 6.72 kJ/mol and 27.2 J/(mol·K), respectively. These values suggest that the entropy term ($T\Delta S$) should be a dominant factor in determining the reaction profile above room temperature. This property enables reactions to accelerate at higher temperatures with increases in enantioselectivity that are uncommon in organic synthesis.

Table 3. Relationship between temperature and enantioselectivity in the reaction of the Danishefsky's diene **10** with 1-naphthaldehyde **11c** catalyzed by **2**·THF.

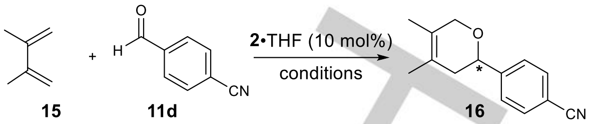


Entry	Temp. / °C	Yield / %	Recovery / %	*ee* / %[a]
1[b]	-60	14	73	-7
2	-30	42	53	-1
3	-25	63	31	-3
4	-20	70	20	-3
5	-15	93	4	0
6	0	98	0	0
7	20	71	0	15
8	60	52	21	40
9[c]	80	21	2	62

[a] The *ee* values were determined by chiral HPLC analysis. The absolute configurations were not determined.
[b] The reaction time was 105 h. [c] The solvent was chlorobenzene, and reaction time was 5 h.

We suspected that this catalyst **2**·THF could work even at high temperature, although it was not desirable for a general asymmetric synthetic procedure. An asymmetric hetero Diels-Alder reaction using a simple diene was a very challenging problem[34] for organic synthesis because it has low reactivity and requires high temperature, as well as either a large amount of catalytic loading, or an extended reaction time to complete the reaction. Therefore, the cage-shaped chiral borate **2**·THF was applied to the reaction system of the simple diene **15** with *p*-cyanobenzaldehyde **11d** and gratifyingly afforded the product **16** enantioselectively. At room temperature, the yield was quite low (17%) as expected, but 60% *ee* was obtained (Entry 3 in Table 4). Higher temperature reasonably improved the yields and surprisingly only a minimal loss of enantioselectivity with a greater than 50% *ee* (Entry 1). After optimization of the reaction conditions, neat conditions at 60 °C gave the product in 78% yield with 58% *ee* (Entry 2). It should be noted that this represents the first example of an asymmetric hetero Diels-Alder reaction using a simple diene. The robust chiral reaction field of our Lewis acid catalyst, which is a result of sterically congested aromatic systems, could successfully lead to the compatibility of high reactivity and acceptable enantioselectivity even at high temperature.

Table 4. Asymmetric reactions using chiral cage-shaped borate **2**·THF.



Entry	Conditions Sol.	 Temp. / °C	 Time / h	Yield / %	*ee* / %[a]
1	toluene	120	16	91	51
2	-	60	14	70	58
3	-	rt	23	17	60
4	-	-40	23	trace	61

[a] The *ee* values were determined by chiral HPLC analysis. The absolute configurations were not determined.

In summary, a new type of Lewis acid with C_3-symmetry showed unique properties by recognizing simple amines and an asymmetric catalyst. A sterically hindered reaction field was important for the recognition of chirality and an interesting temperature dependency of enantioselectivity. This borate could be an important template for C_3-symmetric Lewis acid chemistry as a novel type of chiral Lewis acids.

Acknowledgements

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Keywords: Chiral Lewis acid • Cage-shaped borate • Hetero Diels-Alder reaction • Chiral molecular recognition • binaphthyl

[1] H. Yamamoto, Ed. , *Lewis Acid Reagents: A Practical Approach*, **1999**.

[2] H. Yamamoto, K. Ishihara, Eds. , *Acid Catalysis in Modern Organic Synthesis.*, **2008**.

[3] J. K. Whitesell, *Chem. Rev.* **1989**, *89*, 1581–1590.

[4] J. Zhou, Y. Tang, *Chem. Soc. Rev.* **2005**, *34*, 664–676.

[5] C. Dro, S. Bellemin-Laponnaz, R. Welter, L. H. Gade, *Angew. Chemie - Int. Ed.* **2004**, *43*, 4479–4482.

[6] L. H. Gade, S. Bellemin-Laponnaz, *Chem. - A Eur. J.* **2008**, *14*, 4142–4152.

[7] M. Sircoglou, S. Bontemps, G. Bouhadir, N. Saffon, K. Miqueu, W. Gu, M. Mercy, C.-H. Chen, B. M. Foxman, L. Maron, et al., *J. Am. Chem. Soc.* **2008**, *130*, 16729–16738.

[8] A. Amgoune, D. Bourissou, *Chem. Commun.* **2011**, *47*, 859–871.

[9] M. Kol, M. Shamis, I. Goldberg, Z. Goldschmidt, S. Alfi, E. Hayut-Salant, *Inorg. Chem. Commun.* **2001**, *4*, 177–179.

10.1002/chem.201605712

[10] S. D. Bull, M. G. Davidson, A. L. Johnson, M. F. Mahon, D. E. J. E. Robinson, *Chem. - An Asian J.* **2010**, *5*, 612–620.

[11] P. Axe, S. D. Bull, M. G. Davidson, C. J. Gilfillan, M. D. Jones, D. E. J. E. Robinson, L. E. Turner, W. L. Mitchell, *Org. Lett.* **2007**, *9*, 223–226.

[12] P. Axe, S. D. Bull, M. G. Davidson, M. D. Jones, D. E. J. E. Robinson, W. L. Mitchell, J. E. Warren, *Dalt. Trans.* **2009**, 10169.

[13] H. Ito, T. Nagahara, K. Ishihara, S. Saito, H. Yamamoto, *Angew. Chemie Int. Ed.* **2004**, *43*, 994–997.

[14] K. Murai, S. Fukushima, S. Hayashi, Y. Takahara, H. Fujioka, *Org. Lett.* **2010**, *12*, 964–966.

[15] K. Murai, T. Matsushita, A. Nakamura, S. Fukushima, M. Shimura, H. Fujioka, *Angew. Chemie Int. Ed.* **2010**, *49*, 9174–9177.

[16] K. Murai, S. Fukushima, A. Nakamura, M. Shimura, H. Fujioka, *Tetrahedron* **2011**, *67*, 4862–4868.

[17] M. Yasuda, H. Nakajima, R. Takeda, S. Yoshioka, S. Yamasaki, K. Chiba, A. Baba, *Chem. - A Eur. J.* **2011**, *17*, 3856–3867.

[18] M. Yasuda, S. Yoshioka, S. Yamasaki, T. Somyo, K. Chiba, A. Baba, *Org. Lett.* **2006**, *8*, 761–764.

[19] M. Yasuda, S. Yoshioka, H. Nakajima, K. Chiba, A. Baba, *Org. Lett.* **2008**, *10*, 929–932.

[20] H. Nakajima, M. Yasuda, R. Takeda, A. Baba, *Angew. Chemie Int. Ed.* **2012**, *51*, 3867–3870.

[21] A. Konishi, R. Yasunaga, K. Chiba, M. Yasuda, *Chem. Commun.* **2016**, *52*, 3348–3351.

[22] A. Bermejo, A. Ros, R. Fernández, J. M. Lassaletta, *J. Am. Chem. Soc.* **2008**, *130*, 15798–15799.

[23] Y. Uozumi, N. Suzuki, A. Ogiwara, T. Hayashi, *Tetrahedron* **1994**, *50*, 4293–4302.

[24] H. Sasaki, R. Irie, T. Katsuki, *Synlett* **1993**, *1993*, 300–302.

[25] M. Yasuda, Y. Onishi, M. Ueba, T. Miyai, A. Baba, *J. Org. Chem.* **2001**, *66*, 7741–7744.

[26] The chirality based on propeller-shape had not been determined at this stage before analysis by X-ray crystallography although the structure is illustrated in Figure 2.

[27] CCDC 1517554 (**2·PyBr2**) contains supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[28] H.-J. Kim, W. Kim, A. J. Lough, B. M. Kim, J. Chin, *J. Am. Chem. Soc.* **2005**, *127*, 16776–16777.

[29] S.-G. Kim, K. Kim, J. Jung, S. K. Shin, K. H. Ahn, *J. Am. Chem. Soc.* **2002**, *124*, 591–596.

[30] M. Schnopp, G. Haberhauer, *European J. Org. Chem.* **2009**, *2009*, 4458–4467.

[31] M. Inamo, I. Yoneda, *Inorg. Chem. Commun.* **1999**, *2*, 331–333.

[32] T. Kida, T. Iwamoto, H. Asahara, T. Hinoue, M. Akashi, *J. Am. Chem. Soc.* **2013**, *135*, 3371–3374.

[33] Y. Inoue, T. Yokoyama, N. Yamasaki, A. Tai, *Nature* **1989**, *341*, 225–226.

[34] P. Shaykhutdinova, M. Oestreich, *Organometallics* **2016**, *35*, 2768–2771.

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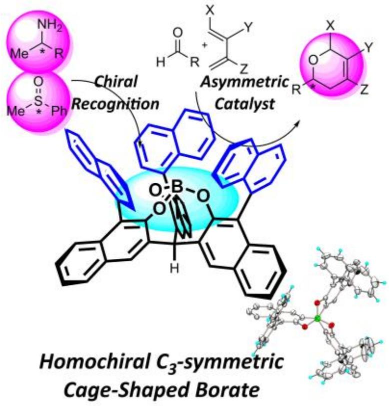
Layout 1:

COMMUNICATION

Chiral Cage-shaped Borate: C_3-symmetric cage-shaped borate with homochiral binaphthyl cores was synthesized and characterized as a single diastereomer. This borate exhibited chiral recognition and behaved as a chiral Lewis acid catalyst with an unusual relationship between stereoselectivity and temperature. The robust and high-symmetric chiral environment given by the binaphthyl cores characterized the peculiar stereoselective reactivity.



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C_3-Symmetric Boron Lewis Acid with a Cage-Shape for Chiral Molecular Recognition and Asymmetric Catalysis

Layout 2:

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