Molecular Recognition

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Recognition of Aromatic Compounds by π Pocket within a Cage-Shaped Borate Catalyst**

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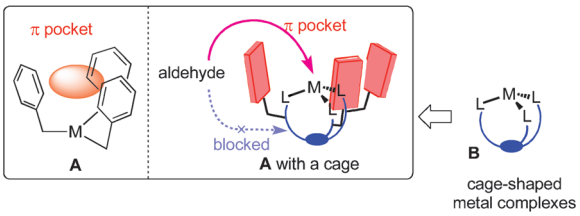
Molecular recognition contributes greatly to various fields in nature and artificial synthesis. Enzymes utilize an affinity for chemical bonding and steric demand to distinguish an appropriate target.[1] In addition, metal complexes have been often applied to the selective recognition of targeted molecules.[2] In almost all cases, useful protocols involve metal–heteroatom binding[3,4] and steric interactions between the ligands and the targeted molecules.[5] Namely, the recognition has been shown in terms of electronic or steric factors. However, metal complexes have never been applied to the discrimination between similarly sized aromatic and aliphatic aldehydes that have no functional anchors. To overcome this problem, we focused on clathrate compounds such as molecular clips,[6] molecular tweezers,[7] and cyclophanes,[8] which are known to recognize aromatic compounds within their π-space cavity through aromatic–aromatic interactions. The combination of a Lewis acid and clathrate compounds, giving compound **A**, could lead to a new strategy for a selective reaction of aromatic over aliphatic compounds (Scheme 1). The metal center of the Lewis acid in **A** is expected to capture certain aldehydes through the usual carbonyl–acid interaction, and a "π pocket" surrounded by aromatic moieties should distinguish aromatic over aliphatic aldehydes. However, to use compound **A** as a practical catalyst, the careful adjustment of both the strength of the Lewis acid and π affinity is required.



Scheme 1. Concept of a catalyst having a π pocket as a recognition site.

Recently, we designed a tripodal cage-shaped metal complex, **B**, which finely tunes Lewis acidity by changing the structure or substituents.[9] The cage-shaped complexes **B** have rigid structures; thus, we expected a high potential for the creation of a π pocket by introducing various aromatic substituents at appropriate positions as shown for the version of **A** with a cage (Scheme 1). Furthermore, the back-shielding framework of the cage effectively blocks the attack of the aldehydes from the opposite side of the π pocket. Herein, we report the synthesis of Lewis acid catalysts that selectively recognize aromatic aldehydes and are applied to an unprecedented substrate-selective reaction. The properties of the recognition site can be tuned by introducing various aryl groups to the cage-shaped complexes.

We chose a hetero-Diels–Alder addition as a model reaction for distinguishing an aromatic aldehyde from an aliphatic one. The competitive reaction between butanal (**1**) and benzaldehyde (**2a**), which have similar steric demands,[10] with Danishefsky's diene **3**[11] to produce cycloadducts **4** and **5a**, respectively, was studied (Table 1).[12] The previously reported cage-shaped borate catalyst **6**B·THF (10 mol%), having no π pocket,[9a,b,d,13] gave the products in a 73% yield with a **5a**/**4** ratio of 0.92:1 when dichloromethane was used as the solvent (entry 1). This result seemed reasonable as the two aldehydes, **1** and **2a**, had similar affinities to the boron center. Next, the phenyl-substituted cage-shaped borate **7**B·THF was used as a catalyst (10 mol%) in dichloromethane and afforded the products **5a** and **4** in a ratio of 2.37:1 (entry 5).[14] The increase in the amount of **5a** suggests that there is a π-pocket effect given by the three phenyl rings. Gratifyingly, this selectivity is the first example of the recognition of an aromatic aldehyde over an aliphatic one in a catalytic manner. An interesting difference between the catalysts **6**B·THF and **7**B·THF was observed with respect to the solvents employed. In the case of **6**B·THF, the use of coordinating solvents like diethylether, THF, and 1,4-dioxane decreased the yields of the addition product from 73% to around 20% (entries 2–4). In particular the yield of the adduct **5a** decreased from 35% to around 0%. In contrast, no change in the yield was observed when different solvents were used in the reactions with **7**B·THF (entries 5–8). These results suggest that the phenyl substituents in **7**B·THF blocked the external solvent from coordinating to the boron center and accelerated the reaction of benzaldehyde more effectively

[*] H. Nakajima, Dr. M. Yasuda, R. Takeda, Prof. Dr. A. Baba
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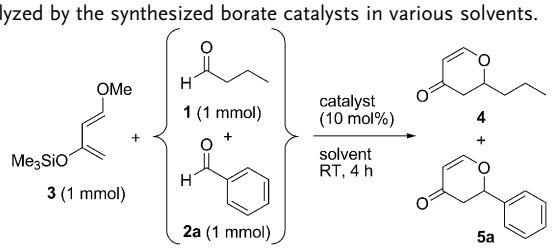
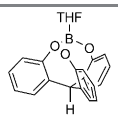
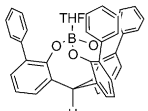
Table 1: Competitive reaction of Danishefsky's diene with **1** and **2a** catalyzed by the synthesized borate catalysts in various solvents.

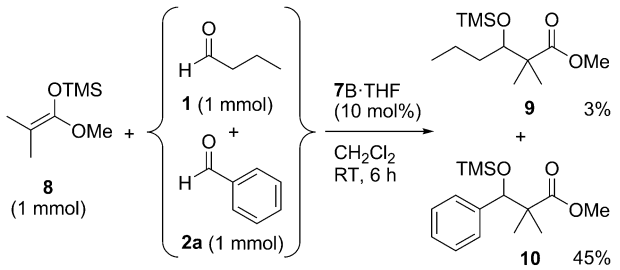


Entry	Catalyst	Solvent	Yield [%][a]	**5a**/**4**[b]
1	 **6**B·THF	CH_2Cl_2	73 (35 + 38)	0.92:1
2		Et_2O	24 (5 + 19)	0.26:1
3		THF	18 (n.d. + 18)	≈0:1
4		1,4-dioxane	19 (n.d. + 19)	≈0:1
5	 **7**B·THF	CH_2Cl_2	71 (50 + 21)	2.37:1
6		Et_2O	69 (50 + 19)	2.63:1
7		THF	66 (37 + 29)	1.30:1
8		1,4-dioxane	64 (45 + 19)	2.37:1

[a] Yield as determined by NMR spectroscopy. The values within the parentheses indicate the yields of **5a** and **4** individually. [b] Ratio determined by ^{1}H NMR analysis. n.d. = not determined.

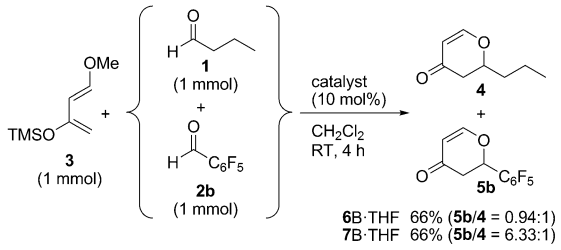
than that of butanal. The π pocket supported by the rigid structure of the cage selectively recognized the aromatic aldehyde.

The catalyst **7**B·THF was used in a Mukaiyama aldol reaction using 1-methoxy-1-(trimethylsilyloxy)-2-methyl-1-propene (**8**) with a mixture of aldehydes **1** and **2a** (Scheme 2). The phenyl-substituted borate catalyst **7**B·THF showed a significant π-pocket effect, thus leading predominantly to the formation of the adduct **10** from benzaldehyde with a very high selectivity (**10**/**9** = 15.3:1).[15]



Scheme 2. Competitive reaction of Mukaiyama aldol Reaction with butanal (**1**) and benzaldehyde (**2a**) catalyzed by **7**B·THF. TMS = trimethylsilyl.

Next, we performed the competitive reaction (Scheme 3) using pentafluorobenzaldehyde (**2b**) instead of benzaldehyde (**2a**). A perfluorophenyl ring has a similar size to that of the benzene ring and is known to associate well with other arenes owing to the electrostatic attraction induced by their reversed quadrupoles.[16] The phenyl-substituted borate catalyst

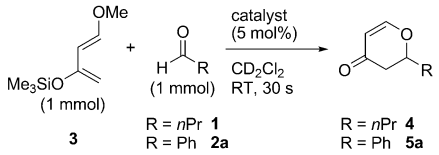


Scheme 3. Competitive reaction of Danishefsky's diene with butanal (**1**) and pentafluorobenzaldehyde (**2b**) catalyzed by the borates **6**B·THF or **7**B·THF.

7B·THF showed a significantly increased product ratio (**5b**/**4** = 6.33:1) as compared with that for the benzaldehyde system (**5a**/**4** = 2.37:1; Table 1, entry 5). In contrast, the unsubstituted borate catalyst **6**B·THF showed no selectivity (**5b**/**4** = 0.94:1). These results suggest that the recognition is ascribed to the difference in the aromatic–aromatic interaction between the substituted-phenyl rings of the catalysts and the aromatic ring of aldehydes.[17]

The reaction rates were estimated by the product yields after 30 seconds of reaction, as the hetero-Diels–Alder reaction proceeds quickly (Table 2).[18] By using **6**B·THF as

Table 2: Hetero-Diels–Alder reaction of Danishefsky's diene with either **1** or **2a** catalyzed by the synthesized borate catalysts.



Entry	Catalyst	R	Product	Yield [%][a]
1	**6**B·THF	*n*Pr	**4**	75
2	**6**B·THF	Ph	**5a**	56
3	**7**B·THF	*n*Pr	**4**	53
4	**7**B·THF	Ph	**5a**	64

[a] Yield as determined by NMR spectroscopy.

a catalyst, butanal gave the cycloadduct in higher yield than benzaldehyde (entries 1 and 2). In contrast, **7**B·THF gave a higher yield of the adduct from benzaldehyde (entries 3 and 4). The increase of the yield of **5a** in switching from catalyst **6**B·THF to **7**B·THF strongly indicates the enhancement of the catalytic activity of **7**B·THF. These results clearly show acceleration of the reaction by π–π interactions between **7**B·THF and benzaldehyde.

To create a more effective π pocket, we modified **7**B·THF by introducing either 1-naphthyl or 2-naphthyl groups instead of a phenyl group (Figure 1).[19] Compared with the phenyl groups, the naphthyl groups were expected to interact with the aromatic moiety more effectively because of their large π framework. Crystals of pyridine-ligated borates **7**B·Py,[9d] **11**B·Py,[9d] and **12**B·Py (Py = pyridine), suitable for X-ray analysis, were grown from a mixture of dichloromethane and *n*-hexane.[20] The results of the structural determination are shown in Figure 1. The top view of **11**B·Py shows that the

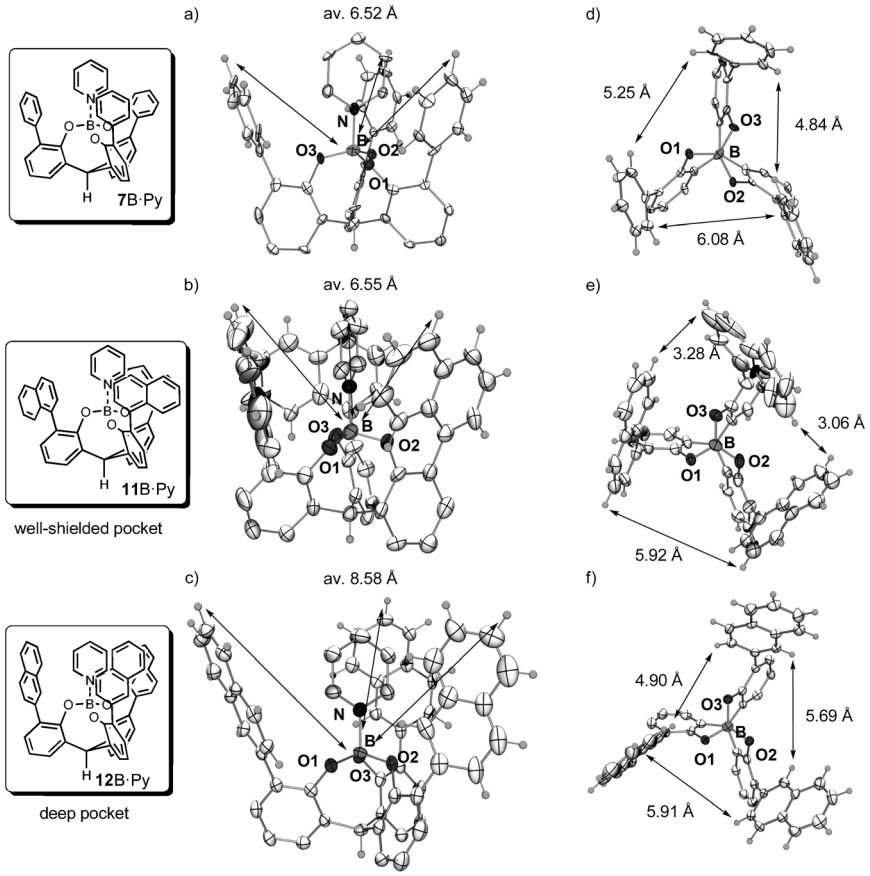


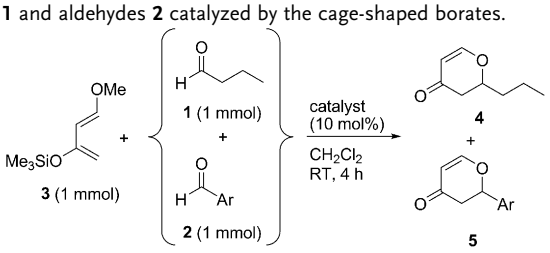
Figure 1. ORTEP Drawing of **7**B·Py, **11**B·Py, and **12**B·Py (thermal ellipsoids are at 50% probability level. Some hydrogen atoms are omitted for clarity). a) Side view of **7**B·Py. b) Side view of **11**B·Py. c) Side view of **12**B·Py. d) Top view of **7**B·Py (pyridine is omitted for clarity). e) Top view of **11**B·Py (pyridine is omitted for clarity). f) Top view of **12**B·Py (pyridine is omitted for clarity).

boron center is well shielded by the three 1-naphthyl rings as compared with the phenyl rings in **7**B·Py. The distances between the rings in **11**B·Py are shorter (3.06 Å, 3.28 Å and 5.92 Å) than those in **7**B·Py (4.84 Å, 5.25 Å and 6.08 Å). A side view of **12**B·Py revealed that a deep pocket is generated around boron by the three 2-naphthyl rings. The average distance from the top of substituted aromatic rings to boron in **12**B·Py is longer (8.58 Å) than that in **7**B·Py (6.52 Å). The fine-tuned environments around boron were successfully created by introducing various aromatic rings into the cage framework.

We examined the ability of the aryl-substituted borates (**7**B·THF, **11**B·THF, and **12**B·THF) to recognize aromatic aldehydes in a competitive reaction of butanal (**1**) with various aromatic aldehydes **2a–c** (Table 3). In the case of benzaldehyde (**2a**), the naphthyl-substituted borates **11**B·THF and **12**B·THF more selectively catalyzed the reaction of the aromatic aldehyde (**5a**/**4** = 2.71:1, and 3.62:1, respectively) than **7**B·THF (**5a**/**4** = 2.37:1; entries 2–4). When pentafluorobenzaldehyde (**2b**) was used as an aromatic aldehyde, the ratios of **5b**/**4** in the cases of aryl-substituted borates (entries 6–8) were significantly increased relative to those of **5a**/**4** (entries 2–4). A very high selectivity was observed by using **11**B·THF (**5b**/**4** = 15.9:1; entry 7). In the case of the electron-deficient aldehyde **2c**, the selectivities for **5c**/**4** were also high (entries 10–12). Interestingly, the **5c**/**4** product ratio was increased (27.5:1) by using **12**B·THF. These results suggest that the naphthyl rings in **11**–**12**B·THF are more effective for the recognition of aromatic compounds than the phenyl rings in **7**B·THF. The substituents at the *ortho* positions on the cage significantly influenced the shape of the π pocket, and the reaction field can be controlled to give a different selectivity. Each substrate has its own appropriate Lewis acid catalyst with a suitable π pocket for high selectivity. This method precisely controls the selectivity through a change in the substituents.

In conclusion, we synthesized cage-shaped boron complexes bearing a recognition site for aromatic aldehydes. Application of a competitive reaction revealed that the aryl-substituted borates were able to selectively activate aromatic aldehydes by using an aromatic–aromatic interaction. This is the first example of a Lewis acid effectively distinguishing between aromatic and aliphatic aldehydes in a catalytic manner.

Table 3: Competitive hetero-Diels–Alder reaction of Danishefsky's diene with **1** and aldehydes **2** catalyzed by the cage-shaped borates.



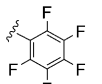
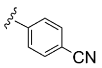
Entry	Catalyst	Ar	Yield [%][a] (**4**+**5**)	**5**/**4**[b]
				5a/**4**
1	**6**B·THF	 **2a**	73	0.92:1
2	**7**B·THF		71	2.37:1
3	**11**B·THF		63	2.71:1
4	**12**B·THF		60	3.62:1
				5b/**4**
5	**6**B·THF	 **2b**	66	0.94:1
6	**7**B·THF		66	6.33:1
7	**11**B·THF		74	15.9:1
8	**12**B·THF		63	6.00:1

Table 3: (Continued)

Entry	Catalyst	Ar	Yield [%][a] (4+5)	5/4[b]
				5c/4
9	6B·THF	 2c	72	2.00:1
10	7B·THF		79	8.88:1
11	11B·THF		27	12.5:1
12	12B·THF		57	27.5:1

[a] Yield as determined by NMR spectroscopy. [b] Ratio determined by ^{1}H NMR.

Experimental Section

Full experimental details and the structural data for cage-shaped boron complexes are given in the Supporting Information.[20]

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[12] The hetero-Diels–Alder reaction of Danishefsky's diene with aldehydes (butanal or benzaldehyde) did not proceed under uncatalyzed conditions at room temperature.

[13] The external THF ligand was always at the boron center after our preparation of the cage-shaped borates because the borate has a Lewis acidity that is higher than that of the planar structural borate.[9a,b,d]

[14] We used other aliphatic aldehydes such as cyclohexanecarbaldehyde (**1b**) and isobutyraldehyde (**1c**) instead of butanal (**1**) in the competitive hetero-Diels–Alder reaction with dichloromethane as a solvent under the same reaction conditions as used in Table 1. The cage-shaped borate **7**B·THF gave the products **5a**/**4b** with a ratio of 5.8:1 (74% yield) and **5a**/**4c** with a ratio of 7.3:1 (77% yield). These ratios were higher than that for **5a**/**4** (2.37:1). These results show that the bulkiness of the substrate controlled the selectivity as well as the aromatic–aromatic interaction. To focus on the only aromatic–aromatic interaction, the less bulky butanal (**1**) was chosen as an aliphatic aldehyde for the estimation of catalyst properties.

[15] The unsubstituted borate **6**B·THF did not give the products and we are not able to precisely compare the catalytic activity between **6**B·THF and **7**B·THF. Therefore, the selectivity was discussed by performing the hetero-Diels–Alder reaction.

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[18] See the Supporting Information for further details.

[19] The materials and methods are available in the Supporting Information.

[20] Crystals of **7**B·THF and **11**B·THF suitable for X-ray diffraction were successfully obtained. Unfortunately, in the case of **12**B·THF, a crystal suitable for X-ray diffraction was not obtained. However, the structural features of **7**B·THF and **11**B·THF were similar to those of **7**B·Py and **11**B·Py. Therefore, we discuss the structure of the cage-shaped borates **7**B, **11**B, and **12**B by using pyridine-ligated complexes. The results of the structural determination of **7**B·THF and **11**B·THF are provided in the supporting information. CCDC 837105 (**12**B·Py), 837103 (**7**B·THF), and 837104 (**11**B·THF) contain the 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.

