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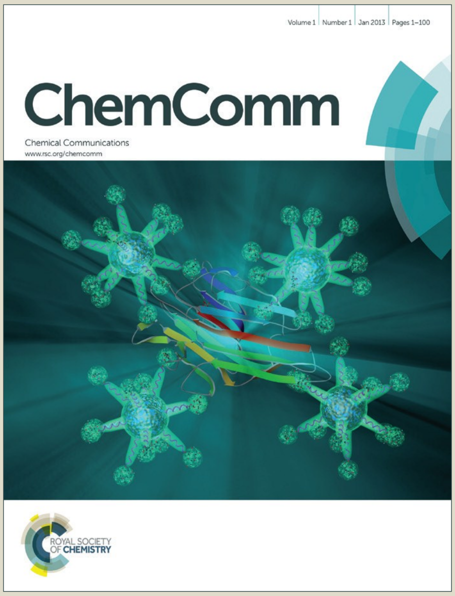

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Synthesis, Characterization, and Properties of a Benzofuran-based Cage-shaped Borate: Photo Activation of Lewis Acid Catalysts

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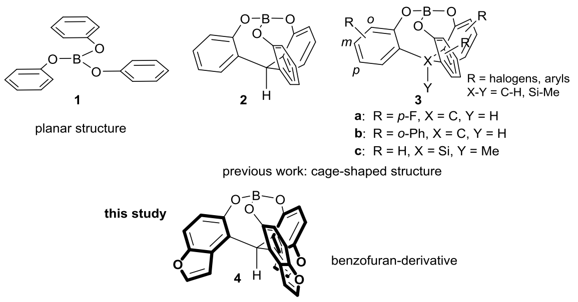
A cage-shaped borate with benzofuran moieties was synthesized. This borate showed a higher degree of catalytic activity for Mukaiyama-aldol type reactions than a simple benzene-based cage-shaped borate induced by self-aggregation. Moreover, the exposure of the complex to black-light irradiation enhanced the catalytic activity.

Precise control of Lewis acidity is very important for organic synthesis because activation of molecules mainly depends on the character of the Lewis acid.[1] The Lewis acidity is often controlled by the steric or electronic factors of the species. Recently, we developed cage-shaped borate esters that have a triphenolic ligand with a tripod-chelated structure such as **2,** which shows significantly different characteristics than those of the planar structure of a common borate **1**.[2] As shown in Scheme 1, a cage-shaped borate **3** can be tuned by the introduction of substituents, R, such as halogens[3] or aryl groups.[4] The structure of the cage shape in **3** allows precise control of the dihedral angles of C-O-B-O in the cage and LUMO levels by changing a tether atom, X, from carbon to silicon.[5] These factors lead to Lewis acids with the same type of template but a variety of characteristics. A complete replacement of the benzene rings with heteroaromatic rings or with a partial embedding of heteroatoms in the π-conjugated system has been an attractive way to control either the physical or chemical properties.[6] Thus, the ring-fusion of heteroaromatic moieties to the aromatic portions in the cage-shaped borates would cause electronic perturbations in the Lewis acid center without steric effect, which would allow precise control of the Lewis acidity. In the present study, heteroaromatic moieties in the form of benzofuran-frameworks were introduced into the cage structure, which conferred characteristics that differed from those of the previously synthesized borates **2** and **3**. A benzofuran moiety has an intrinsic dipole[7] due to the ring oxygen with a polarity that affects the Lewis acidity of the complex.



Scheme 1 Chemical structures of planer and cage-shaped triphenolic borates.

We planned to prepare a benzofuran-based triphenolic ligand from a commercially available 5-methoxybenzofuran **5** (Scheme 2). As our previously reported synthetic route for the simple cage-shaped borate **2**,[2a] 5-methoxybenzofuran **5** was deprotonated by *n*BuLi and treated with ethyl chloroformate, giving an undesired regioisomeric carbinol **6** bound at the 2-position of the methoxybenzofuran. Then, as a regioselective bromination at the *ortho*-position of phenols has been reported,[8] 5-hydroxybenzofuran **7** was prepared via the deprotection of a methoxy group of **5** by BBr_3. The bromination of **7**[8] by NBS/*i*Pr_2NH successfully afforded 4-bromo-5-hydroxybenzofuran **8**. After the protection of OH into OMe, the addition of *n*BuLi for a halogen-lithium exchange followed by treatment with ethyl chloroformate gave the desired triarylmethanol **10** selectively bound at the 4-position of methoxy-4-benzofuran. A reduction of **10** under acidic conditions in THF/MeCN[9] and a deprotection of the methoxy groups by BBr_3 afforded the tris(5-hydrofuranyl)methane **12**. A mixing of **12** with BH_3·THF in THF readily generated the cage-shaped borate **4**·THF (Scheme 2).

The NMR spectroscopy of **4**·THF showed typical signals for a cage-shaped borate; the upfield/downfield shift of the $\delta(^1H)$/ $\delta(^{13}C)$ of C-H at the tether position was compared with those of the ligand 12: ($\delta(^1H)$ 6.69→6.32 ppm, $\delta(^{13}C)$ 38.9→43.2 ppm)[3]. The coordinating THF

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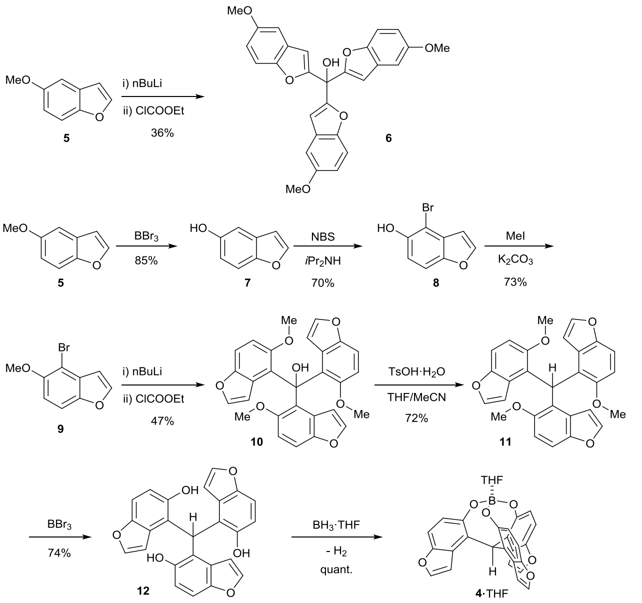
showed broad signals at the lower chemical shifts compared with that of free THF. The recrystallization of **4**·THF from hexane/CH_2Cl_2 gave a suitable crystal for X-ray analysis. The ORTEP drawings are shown in Fig. 1.[10] The bond length of the B-O(THF) was 1.575(3) Å, which was shorter than that (1.595(8) Å) of the simple cage-shaped borate **2**·THF. The sum of the bond angles of O-B-O (O: ligand) was 343.96° for **4**·THF, while the sum of the bond angles (344.81°) for **2**·THF was slightly larger. These structural features indicated that **4**·THF had a slightly higher Lewis acidity than **2**·THF.



Scheme 2 Synthesis of benzofuran-based triphenolic ligand **12** and cage-shaped borate **4**.

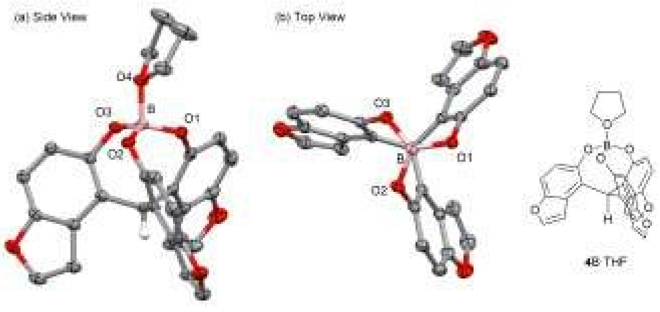
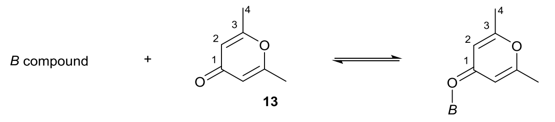


Fig. 1. ORTEP drawing of **4**·THF at the 50% probability level (aryl hydrogens are omitted for clarity) (a) Side view and (b) top view (THF is omitted for clarity). Selected bond lengths (Å): B-O(1) 1.441(3), B-O(2) 1.435(3), B-O(3) 1.435(3), B-O(4) 1.575(3). Selected bond angles (deg): O(1)-B-O(2) 114.3(2), O(2)-B-O(3) 114.5(2), O(3)-B-O(1) 115.2(2), O(1)-B-O(4) 104.2(2), O(2)-B-O(4) 103.6(2), O(3)-B-O(4) 103.1(2).

Lewis acidity was also estimated via the NMR chemical shift $\delta(^{13}C)$ and infrared stretching frequency of the 2,6-dimethyl-γ-pyrone **13** ligated to borates **4,** as shown in Table 1.[3] The $\Delta\delta(^{13}C)$ shift of C3 and the stretching frequency of the carbonyl (C=O) groups in **13** clearly show the degree of Lewis acidity. The borate **4** showed a large $\Delta\delta$ (^{13}C) and $\Delta\nu$(C=O), which indicated a Lewis acidity that was slightly higher than that of **2**.

Table 1. Complexation of boron compounds with carbonyl compound **13**.



entry	*B* compound	$\Delta\delta(^{13}C)$ of C3/ ppm	$\Delta\nu$(C=O)/ cm^{-1}
1	**2**·THF	6.78	13.69
2	**4**·THF	6.82	13.90
3	BBr_3	-	25.07
4	$BF_3·OEt_2$	8.71	-
5	$B(OPh)_3$ **1**	0.77	2.89

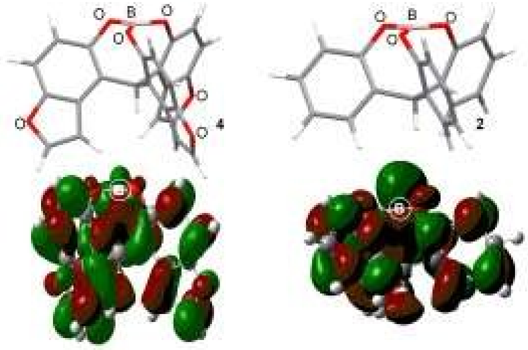


Fig.2. Optimum structures and its MO diagram of **4** and **2**.

The DFT calculation of **4** at the B3PW91/6-31+G (d,p) level showed it to be a ligand-free, three-coordinated structure, which would contribute to an active Lewis acid species during the reaction course (Fig. 2 and Table S1 in the Supplementary Information). The dihedral angles C-O-B-O, which reflect the shape of the cage, were almost the same as those of the species **2**.[2a] However, an effective conjugation between the B atom and the benzofuran skeleton in **4** was estimated, which would lead to a decrease in the energy level of the unoccupied orbital of a Lewis acid (in this case, next-LUMO level), while the orbital of **2** is located closer to its B atom. The energy level of the next-LUMO was -21.6 kcal/mol (-0.94 eV) for **4,** which was lower than those of the benzene-based borates **2** (-18.3 kcal/mol) and **3c** (-16.8 kcal/mol) (Table S1)[3]. Although a lower next-LUMO level of **4** was expected to contribute to a large reaction rate, the pyridine-complexation energy, Δ*E*, reflected a catalytic turnover of **4** (-18.8 kcal/mol) that was similar to that of **2** (-19.2 kcal/mol). Generally, when a next-LUMO energy level becomes lower, the stabilization energy shows larger (larger negative for Δ*E*), which means that Lewis acidity and catalytic turnover have a trade-off relationship. It should be noted that the borate **4** showed an unexpected relationship that resulted in a high affinity to the substrate and a high catalytic turnover. Significant differences between **4** and **2** were found in the magnitude of the dipole moment and in the charge distribution (Fig. S1). Both compounds had a dipole moment that was directed from the cage center to the tether position, but the magnitude of the dipole of **4** is 1.5 times larger than that of **2**, presumably due to the effective fixation of the dipole vector of each furan ring that resulted from the formation of its rigid cage-structure. The Mulliken charge distribution also reflected the difference in dipole; the Mulliken charge of the B

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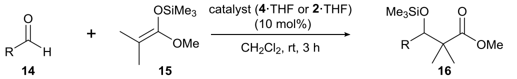
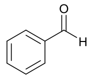
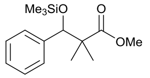
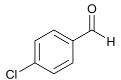
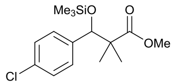
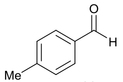
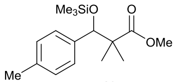
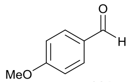
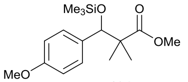
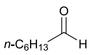
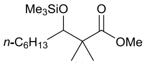
atom for **4** (+1.265 a.u.) was more positive than that of **2** (+1.161 a.u.) (Fig. S2).

Precise tuning of the electronic features of **4** clearly characterized its catalytic activities. To estimate the Lewis acid catalytic ability, the Mukaiyama-type reaction[11] of a variety of aldehydes **14a-e** with silylketene acetal **15** was examined in the presence of borate catalysts **4**·THF and **2**·THF.[12] The borate **4**·THF gave a much higher yield of the product **16a-d** compared with that given by **2**·THF for aromatic aldehydes **14a-d** in a short time, although prolonging the reaction time led to high yields even in the catalytic reaction with **2**·THF (Table 2). Moreover, the borate **4**·THF showed high tolerance to a variety of functional groups. While **4** would have limited applicability to aliphatic aldehydes (entry 5), it should be noted that **4** catalyzed a wide range of aromatic aldehydes to give the desired products in moderate yields in a short time. As expected from the theoretical analyses, the borate **4** showed high affinity to the substrate and high catalytic turnover, which was accomplished via an effective π-conjugation between the Lewis acid center and an aromatic core with a large dipole moment in the cage structure.

Table 2. Mukaiyama aldol reaction catalyzed by borate **4**·THF.



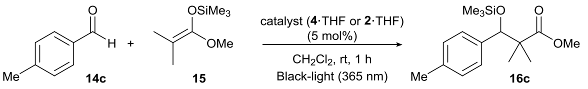
entry	substrate	product	yield / % 4·THF	yield / % 2·THF [a]
1	 **14a**	 **16a**	57	3
2	 **14b**	 **16b**	40	8
3	 **14c**	 **16c**	61	29
4	 **14d**	 **16d**	51	42
5 [b]	 **14e**	 **16e**	12	19

a Except for entry 5, the reaction time was 6 h. *b* The reaction time was 0.5 h.

To further explore the catalytic turnover, the ligand-exchange rate was investigated. The mixture of the complex **4**·DMAP in a pyridine-*d*5 solution was observed via ^{1}H-NMR (Table S4). The kinetic equation based on the first order of the borate in our previous report[3] unreasonably showed a large negative activation entropy, $\Delta S^{\ddagger}$(-33. 4 cal/K·mol),[13] and, thus, the first-order hypothesis was found to be incorrect because a step for releasing the DMAP from the ligated complex led to an increase in entropy. Based on these results, ligand dissociation does not proceed *via* a simple dissociation of the ligand but includes the assistance of another boron complex to release the DMAP. Based on the bimolecular contribution of the borate-to-ligand dissociation, kinetic analysis gave the activation parameters $\Delta G^{\ddagger}$25.4 kcal/mol, $\Delta H^{\ddagger}$ 20.3 kcal/mol, and $\Delta S^{\ddagger}$ -17.2 cal/K·mol. This unusual mechanism came from the intermolecular interaction of **4** (See also the Supplementary Information).

A bimolecular process requires the presence of an intermolecular interaction in the course of a ligand-exchange pathway. We performed UV measurements of **4**·THF under variable concentrations, since the electronic interactions between the chromophores cause spectral changes, which in most cases results in a hypochromic shift.[14] The absorption spectra of **4**·THF were recorded in CH_2Cl_2 in a concentration range from ca. 2.0×10^{-5} to 2.0×10^{-4} M. Under these conditions, the longest absorption bands of **4**·THF at 330–280 nm, which were mainly assigned to the HOMO → LUMO transition (π→ π*) via time-dependent DFT calculation (Fig. S3), exhibited remarkable spectral changes that resulted in hypochromic effects with slight red shifts at 330–300 nm and hyperchromic effects with slight blue shifts at 300–280 nm (Fig. S4(A)). On the other hand, the spectra of **2**·THF in CH_2Cl_2 exhibited no remarkable concentration dependence (Fig. S4(B)).[15] These results suggest that the benzofuran-based **4**·THF would benefit from self-intermolecular stabilization, presumably due to its dipole-dipole interaction.[16, 17]

Table 3. Mukaiyama aldol reaction catalyzed by borate **4**·THF under photo irradiation.



entry	catalyst	yield / % [a]
1	**4**·THF	56 (34)
2	**2**·THF	37 (35)

a The yields in parentheses were performed under dark conditions.

Finally, we describe the effect of photo irradiation on the control of Lewis acidity. A Mukaiyama-type aldol reaction of **14c** with **15** upon exposure to black-light (centred at 365 nm) irradiation at room temperature under the slightly modified conditions was performed. Although no significant change in reactivity was observed in the presence of borate **2**·THF, borate **4**·THF afforded **16c** in a 1.7-fold higher yield under the black-light irradiated conditions (Table 3). While the mechanistic details of the effect of the photo-irradiation have not been clarified, the excitation energy of **4** was lower than that of **2** as a result of the expanded π-conjugation, as well as the molecular geometry changes and charge reorientations in the first excited state, and this may have played a main role in controlling the Lewis acidity.

Conclusions

We synthesized a cage-shaped borate **4** composed of a benzofuran framework, characterized its molecular geometry via X-ray crystallography, and estimated its electronic features via DFT calculations. The synthesized complex exhibited a high Lewis acidity with a high catalytic turnover, which was confirmed via Mukaiyama-aldol type reaction, ligand-exchange rate determination, and the concentration dependence of the electronic absorptions. For the benzofuran-based caged borate **4**, an effective lowering of the next-LUMO level and an intermolecular stabilization of the ligand-free complex were achieved via photo activation, which allowed us to successfully balance two conflicting aims for Lewis acid catalysts:

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acidity and catalytic turnover. Although there is still room for improvement in the versatilities of the reactions catalyzed by **4**, the precise tuning of Lewis acid catalytic activity in association with the introduction of heteraromatic moieties to the cage-shaped borate core holds the potential to construct photo- or electro-responsive Lewis acid catalysts. Theoretical studies as well as further experimental investigations of the obtained Lewis acid catalyst are ongoing by our group.

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Notes and references

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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13 $\Delta G^{\ddagger}$ 24.6 kcal/mol, $\Delta H^{\ddagger}$ 14.9 kcal/mol, $\Delta S^{\ddagger}$ -33.4 cal/Kmol.

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15 ^{1}H NMR measurements under variable concentration were also performed, and, no remarkable peak shift was observed even under high concentration; see Fig. S5 while UV spectra showed the shift.

16 The basicity of the oxygen atoms in benzofuran, as well as the dipolar interaction between benzofuran cores, could contribute to the intermolecular stabilization. see : (a) J. R. Andreatta, G. B. Cieslinski, M. Batool, X. Z. Sun, M. W. George, E. N. Brothers, D. J. Darensbourg and A. A. Bengali, *Inorg. Chem.*, 2009, **48**, 7787; (b) We also estimated the stabilization energy of the aggergates assisted by the oxygen atoms to be -1.2 kcal/mol, details are shown in SI.

17 Since the dissociation of THF from the boron center should promote an intermolecular interaction, we attempted to observe the existence of the ligand-free complex under suitable conditions; see the Supplementary information.

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