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Benzoxaborole catalyst for site-selective modification of polyols

Shuhei Kusano[‡]*, Shoto Miyamoto, Aki Matsuoka, Yuji Yamada, Ryuta Ishikawa and Osamu Hayashida*

Abstract: The site-selective modification of polyols bearing several hydroxyl groups without the use of protecting groups remains a significant challenge in synthetic chemistry. To address this problem, herein novel benzoxaborole derivatives were designed as efficient catalysts for the highly site-selective and protecting-group-free modification of polyols. To identify the effective substituent groups enhancing the catalytic activity and selectivity, a series of benzoxaborole catalysts **1a-k** were synthesized. In-depth analysis for the substituent effect revealed that **1i-k,** bearing multiple electron-withdrawing fluoro- and trifluoromethyl groups, exhibited the greatest catalytic activity and selectivity. Moreover, **1i**-catalyzed benzoylation, tosylation, benzylation, and glycosylation of various cis-1,2-diol derivatives proceeded with good yield and site-selective manner.

Introduction

Benzoxaborole, which is a cyclic monoester homologue of phenyl boronic acid, has had significant impacts in the areas of the pharmaceutical science and the molecular recognition chemistry (**Fig. 1**). The discovery of the antifungal activity in p-fluroro benzoxaborole (AN2690) opened a new field in pharmaceutical science.[1] Similarly, in the field of molecular recognition chemistry, the superior binding affinity of bnenzoxaborole for cis-1,2-diols enabled a saccharide recognition in neutral aqueous conditions.[2] This remarkable affinity for cis-1,2-diols displayed by benzoxaborole has enabled several applications that are otherwise impossible with phenylboronic acid.[3] These reports show that the key characteristic of benzoxaborole is its ability to form the tetra-coordinated boronate adduct (**Fig. 1**).

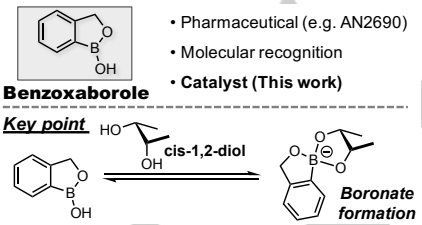

Figure 1. The applications of benzoxaborole.

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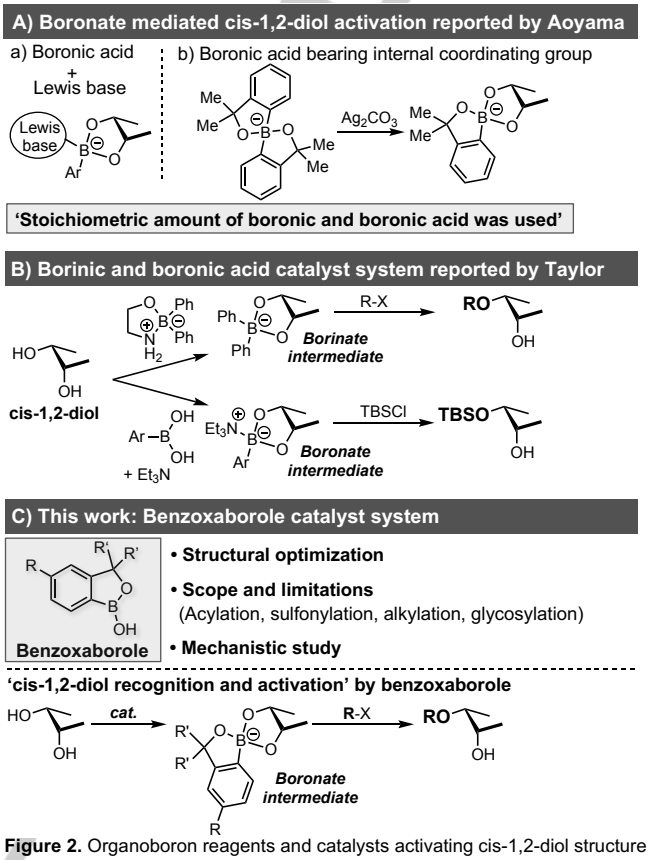


Figure 2. Organoboron reagents and catalysts activating cis-1,2-diol structure

We recently commenced the development of benzoxaborole-based functional molecules,[4] utilizing the selective recognition of cis-1,2-diol via the boronate formation. In this context, we here envisioned the catalytic application of benzoxaborole for the site selective modification of non- or partially protected polyols bearing cis-1,2-diol scaffold (**Fig. 2C**). We hope that the benzoxaborole catalyst reported herein allows the straightforward synthesis of polyol derivatives without the need for protecting groups.

In synthetic organic chemistry, the site-selective modification of a polyol such as a carbohydrate bearing multiple-hydroxyl groups with similar reactivity, usually requires lengthy and inefficient synthetic processes due to the need for multiple protection-deprotection sequences.[5] To overcome this problematic issue in the polyol modification, the catalyst-controlled reactions using dialkyltin dichloride,[6] chiral copper (II) catalyst,[7] iron (III) catalyst,[8] and chiral organocatalysts[9-13] have been developed in the last decade to achieve the direct and selective modification of polyols without protecting groups. Alternatively, the pioneering work by Aoyama et al. demonstrated that the boronate adduct generated from a stoichiometric amount of boronic acid and Lewis base, or borinic

acid precursor, enhances the nucleophilicity of the equatorial oxygen atom on the cis-1,2-diol (**Fig. 2A**).[14] Based on these reports, Taylor et al. exploited the diphenylborinic acid catalyst for acylation,[15a] tosylation,[15b] alkylation,[15c] and glycosylation[16] of non- or partially-protected pyranosides. In the same studies, a boronic acid and Lewis base co-catalyst system was used for site-selective silylation (**Fig. 2B**).[17] Very recently, benzoazaborole was also reported as a cis-1,2-diol activating catalyst.[18]

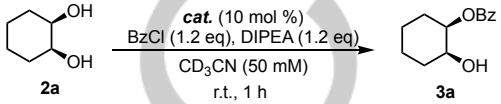
Inspired by the previous studies by Aoyama and Taylor, we set about out our own catalytic system based on benzoxaborole. The tetra-coordinated boronate generated from benzoxaborole and cis-1,2-diol should be activated and hence allowing the site-selective modification of polyols. Furthermore, the highly Lewis acidity of benzoxaborole among organoboron reagents promises to promote the formation of the active boronate intermediate.[2] We in this study designed the electronically and sterically modified benzoxaboroles **1a-k** to elicit the relationship between structure and catalytic activity. Herein, we report the successful development of the benzoxaborole catalyst **1** and its scope and limitations.

Results and Discussion

Benzoxaborole catalyst **1** was synthesized from the corresponding tertiary alcohol precursor utilizing known procedures (**Scheme S1**).[19] Benzoxaborole **1** exhibited remarkable stability both as a solid and in a solution. When left on the bench, no decomposition was admitted over several months (**Fig. S1**). All of the benzoxaoboroles **1** are well crystallized with the exception of **1j** and **1k** substituted with trifluoromethyl group. As such, X-ray crystallographic analysis was undertaken on compounds **1b** and **1d**.[20] In the solid state, compound **1b** and **1d** exists in the dimeric form, linked through two intermolecular hydrogen bonds (**Fig. S2** and **S3**).[19, 21] No significant difference in the structural parameters, including bond lengths and angles, was observed between **1b** and **1d**.

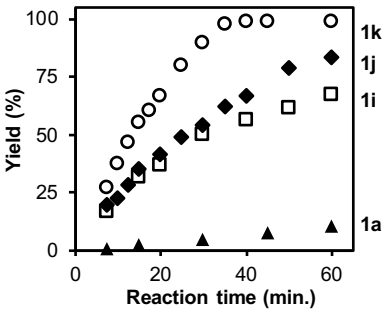
The catalytic activities of **1a**−**k** were evaluated by employing the benzoylation of cis-1,2-cyclohexanediol **2a** as a model reaction. The yield of the benzoylated product produced by each catalyst after one hour is summarized in **Table 1**. Comparing catalysts **1a-c** substituted at para-position to the boron atom, the electron-withdrawing fluoro group in **1c** exerted greater catalytic activity while the diminished activity of **1b** bearing electron-donating methoxy group relative to unsubstituted **1a**. A profound effect was seen in 3-position of the benzoxaborole. The installation of phenyl group (**1e**) was more effective rather than the alkyl substitution (**1a** and **1d**). Next, by exploring the electronic effect on the phenyl group (**1e**-**g**), we identified that para-fluorophenyl group on **1g** was significantly increased the catalytic activity. The benzo-annulated benzoxaborole **1h** (napthoxaborole) showed slightly higher activity in comparison to benzoxaborole **1a**. Considering those positive substituent effects, we designed **1i-k** functionalized with multiple fluoro or trifluoromethyl groups. As expected, these catalysts displayed significantly improved catalytic activity (**Fig. S4** and **S5**). Especially, catalyst **1k** was the most potent, competing the transformation of **2a** to **3a** in a quantitative manner in only 30 minutes. The tosylation of **2a** catalyzed by **1k** also proceeded quantitatively within 150 minutes (**Fig. S6**).

Table 1. Catalytic activity of **1a-k** in the benzoylation of cis-1.2-cyclohexanediol

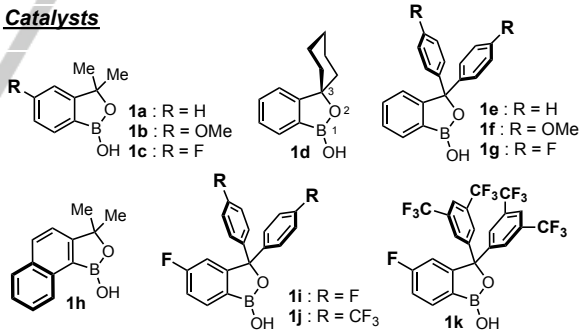


Catalyst	Yield (%)[a]
1a	11
1b	4
1c	22
1d	14
1e	24
1f	17
1g	40
1h	16
1i	68
1j	84
1k	> 98

Time course yield of the benzoylated product 3a using the three most active catalysts 1i-k along with 1a



Catalysts

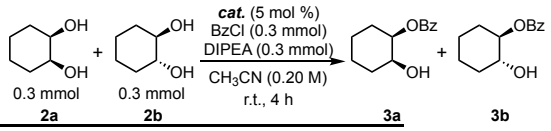


[a] This yield was determined by ^{1}H NMR using mesitylene as an internal standard. The product **3a** is a racemic mixture.

The cis-1,2-diol selectivity of the benzoxaborole catalysts **1a-k** was evaluated by competitive benzoylation in the presence of the equimolar amounts of cis- and trans-1,2-cyclohexanediol (**2a** and **2b**) (**Table 2**). Commensurate with the tendency of the catalytic activity, the active catalysts **1i-k** exhibited the higher cis-1,2-diol selectivity with higher conversion yield. By using most active catalyst **1k,** a ratio of >20:1 of benzoylated product cis-**3a** to trans-**3b** could be achieved. The cis-1,2-diol selectivity

achieved using catalyst **1k** is superior to that of diphenylborinic acid (**Table S2**).

Table 2. 1-catalyzed Competitive benzoylation of **2a** and **2b**



0.3 mmol **2a** + 0.3 mmol **2b** → **3a** + **3b**

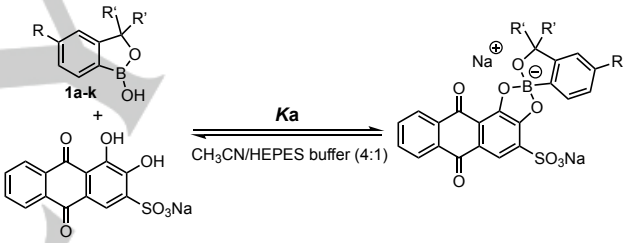
Catalyst	Conversion (%)[a)]	**3a** : **3b**[a)]
1a	28	4.8 : 1
1b	26	2.5 : 1
1c	33	6.1 : 1
1d	23	4.5 : 1
1e	33	5.5 : 1
1f	21	5.6 : 1
1g	36	11 : 1
1h	29	2.1 : 1
1i	50	12 : 1
1j	55	12 : 1
1k	65	> 20 : 1

[a] This product ratio and conversion yield were determined by ^{1}H NMR.

To elucidate the substituent effect to the catalytic activity, we carried out both experimental and theoretical analyses for the boronate adduct, which is anticipated to be the active intermediate. For this purpose, we at first confirmed whether the boronate is involved as an active intermediate by monitoring the ^{11}B NMR of **1c** during the benzoylation of **2a** (**Fig. S7**). In the absence of cis-1,2-diol **2a**, only single signal (δ = 36.4 ppm) corresponding to trigonal benzoxaborole **1c** was observed. Up on the addition of **2a**, a new signal (δ = 30.4 ppm) corresponding to tetra-coordinating boronate adduct was appeared in upfield region. This new signal was disappeared upon the addition of benzoyl chloride and converged to the signal of **1c**. These NMR shifts indicated that the boronate is in fact the active intermediate and participates in the catalytic system as expected. [2a-b, 22].

Next, we aimed to disclose how the substituent groups on the benzoxaborole influence the catalytic activity. The substituent groups could be concerned with modulating the formation of the boronate adduct or the nucleophilic reaction of the boronate adducts (**Fig. S8**). To confirm the former consideration, the binding affinity of **1a**−**k** towards cis-1,2-diols was evaluated by utilizing Alizarine Red S (ARS) as a chromophoric 1,2-diol.[2a-b, 23] The UV-Vis titration was performed in pH 7.4 HEPES buffer (CH_3CN-H_2O, 4:1), and the association constants (*K*a) of **1a**-**k** were calculated from the titration curve and summarized in **Table 3** (see also **Fig. S9**). As with similar tendency of previously reported phenylboronic acid derivative, the electron withdrawing groups were found to increase the *K*a values. The DFT-calculated binding affinity for **2a** at the B3LYP/6-311++G(d,p) level in vacuum showed good agreement with the experimental results using ARS (**Table S3**). Consequently, we found that the binding preference of **1a**−**k** towards cis-1,2-diol is consistent with the catalytic activity. Following this, the substituent effect in the nucleophilic step was investigated utilizing the DFT-calculated Mulliken charges as the indicator of the nucleophilicity of the oxygen atom (**Table S4**). Unfortunately, there were no mutual correlation between the Mulliken charges and the catalytic activity. The Mulliken charge may be unavailable index for nucleophilicity of the boronate adduct, unlikely the borinate adduct in Taylor's report.[14] Overall, electron-withdrawing groups on benzoxaborole catalyst **1** seem to promote the formation of anionic boronate intermediate through the inductive effects, and hence increases the catalytic activity (and *vice versa*), although its effect on the nucleophilic step was unclear. Underlying mechanistic study addressing the substituent effect is of our great interest to exploit a further active and selective catalyst.

Table 3. ARS assay evaluating cis-diol affinity of **1a-k**



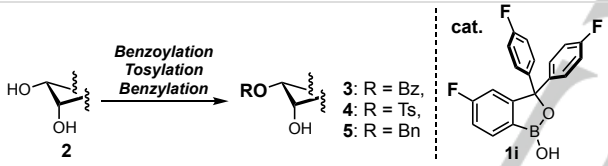
Alizarin Red S (ARS)

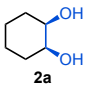
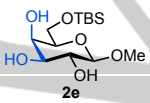
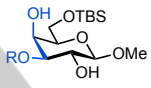
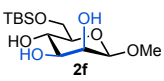
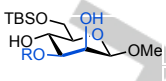
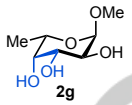
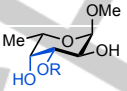
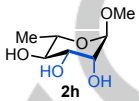
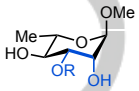
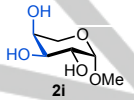
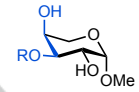
Catalyst	*K*a (M^{-1})[a)]
1a	$(1.7 \pm 0.3)\times10^{2}$
1b	71 ± 17
1c	$(3.1 \pm 0.1)\times10^{2}$
1d	$(1.6 \pm 0.1)\times10^{2}$
1e	$(3.9 \pm 0.7)\times10^{2}$
1f	$(2.4 \pm 0.2)\times10^{2}$
1g	$(7.0 \pm 0.2)\times10^{2}$
1h	$(2.1 \pm 0.2)\times10^{2}$
1i	$(1.6 \pm 0.2)\times10^{3}$
1j	$(2.3 \pm 0.3)\times10^{3}$
1k	$(4.8 \pm 0.6)\times10^{3}$

[a] These association constants are the average of the three separates experiments. The detail of the measurement condition is described in supporting information.

With the highly active catalyst **1i** in hand,[24] we investigated the catalyst-controlled benzoylation, tosylation, and benzylation of cis-1,2-diol derivatives (**Table 4**). For these reactions, we used the catalyst **1i** instead of more active **1j** and **1k** since it is well-crystallized and easily operable. Firstly, the simple structured of linear- and cyclic-diols (**2a-c**) were employed as substrates (Entry 1-3). Catalyst **1i** tolerated for both linear and cyclic diols and provided the mono-modified product **3**. In the case of the linear diols **2c** and **2d**, the secondary hydroxyl group was slightly modified even in the presence of primary alcohol (Entry 2 and 3). This preference was contrastive that the borinic acid catalyst exclusively provided primary alcohol modified product.[15] We subsequently explored the site-selective modification of carbohydrates including non- or partially protected methyl glycoside derivatives **6a-e** having cis-1,2-diol moiety. As shown in Table 4 (Entry 4-8), the 3-OH group was selectively modified with good yield in most cases. The tosylation of **6d-f** gave moderate yield (Entry 6-8). One limitation of our catalyst system was observed in the reaction of D-ribofuranoside derivative. Whilst is proceeded with good yield, the 2-OH and 3-OH groups were indistinguishable (**Table S5**).

Table 4. Site-selective modification of polyol derivatives catalyzed by **1i**

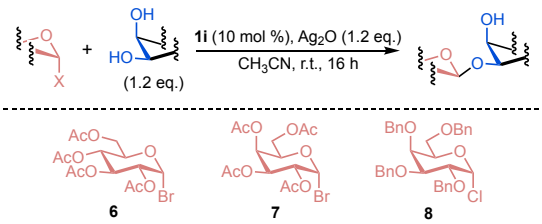


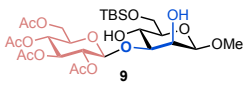
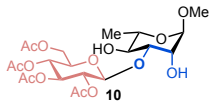
Entry	Substrate	Product	Yield (%)[a]
1	 **2a**		**3a**: R = Bz (83) **4a**: R = Ts (91) **5a**: R = Bn (>98)
2	 **2c**	 **c**  **c'**	R = Bz (>98) **3c** : **3c'** = 15 : 1[b] R = Ts (93) **4c** : **4c'** = 14 :1[b] R = Bn (>98) **5c** : **5c'** = 5.5 : 1[b]
3	 **2d**	 **d**  **d'**	R = Bz (68) **3d** : **3d'** = 9.1 : 1[b] **4d**: R = Ts (88) **5d**: R = Bn (83)
4	 **2e**		**3e**: R = Bz (82) **4e**: R = Ts (77) **5e**: R = Bn (91)
5	 **2f**		**3f**: R = Bz (91) **4f**: R = Ts (73) **5f**: R = Bn (92)
6	 **2g**		**3g**: R = Bz (83) **4g**: R = Ts (63) **5g**: R = Bn (88)
7	 **2h**		**3h**: R = Bz (86) **4h**: R = Ts (60) **5h**: R = Bn (81)
8	 **2i**		**3i**: R = Bz (80) **4i**: R = Ts (58) **5i**: R = Bn (92)[c]

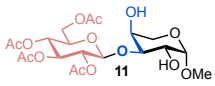
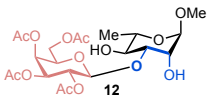
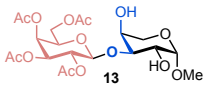
[a] Isolated yield. [b] This product ratio was determined by ^{1}H NMR. [c] containing 19% regioisomer. Benzoylation: **1i** (10 mol %), BzCl (1.2 eq.), DIPEA (1.2 eq.), CH_3CN, r.t., 4 hours. Tosylation: **1i** (10 mol %), TsCl (1.5 or 3.0 eq.), DIEPA (1.5 or 3.0 eq.), CH_3CN, r.t., 24 hours. Alkylation: **1i** (10 mol %), BnBr (1.5 eq.), KI (1.0 eq.), K_2CO_3 (1.1 eq.), CH_3CN, 60 °C, 24 hours. The products **3a-5a** are a racemic mixture.

After the successful site-selective modifications of pyranoside derivatives, we turned our attention to **1i**-catalyzed Koenigs-Knorr glycosylation using **2** as an acceptor and per-acetylated bromosugar (**6** and **7**) as donors (**Table 5**). In all cases, the β-glycosylated product at 3-OH position of the acceptor was predominantly obtained in moderate to good yields. Per-benzylated chlorosugar **8** was also tolerated in the **1i**-catalyzed glycosylation with mannoside **2f**, and β-linked disaccharide **14** was obtained in 65% yield (entry 6).

Table 5. Site-selective glycosylation catalyzed by **1i**



Entry	Donor	Acceptor	Product	Yield (%)[a]
1	**6**	**2f**	 **9**	82
2	**6**	**2h**	 **10**	81

3	**6**	**2i**	 **11**	75
4	**7**	**2h**	 **12**	75
5	**7**	**2i**	 **13**	61
6	**8**	**2f**	 **14**	65

[a] Isolated yield.

The typical reaction conditions for the electrophilic modification of a polyol require the exclusion of water to avoid its competitive reaction with the electrophilic reagents. In contrast, the organic transformation in water gains great attention because of the environmental concerns.[25] Accordingly, a polyol modification that tolerates aqueous media is a desirable synthetic strategy. Recently, the well-designed acylation[26] and glycosylation[27] of carbohydrates in aqueous media have been reported. We thus postulated that carbohydrate modification in water could be enabled by benzoxaborole, due to its outstanding cis-1,2-diol affinity and activation. To this end, we assessed the **1i**-catalyzed benzylation of **2h** in CH_3CN/H_2O co-solvent to verify the tolerance of the benzoxaborole catalyst to aqueous solvent systems (**Table S6**). Pleasingly, benzylated **5h** was produced in moderate yield in 5:1 ratio of CH_3CN/H_2O. The reaction was even possible in a solvent with over 50% water content, albeit with diminished yields. This is because the decomposition of benzylbromide by water occurs faster than desired benzylation reaction. However, this demonstrates the intrinsic potential of benzoxaborole catalysis in the aqueous media. The use of relatively stable and water-soluble electrophiles could enable the further application of benzoxaborole catalyst for the aqueous transformation.

Conclusions

As a novel application of benzoxaborole, we have demonstrated its use in the site-selective modification of polyols. A diverse family of benzoxaborole derivatives was synthesized, and the electron-withdrawing groups were identified as the optimal functional groups for enhanced catalytic activity and selectivity. The benzoxaborole catalyst was successfully used in the site-selective acylation, sulfonylation, alkylation, and glycosylation of non- or partially protected carbohydrates. On the basis of the cis-1,2-diol activation, benzoxaborole has the potential to catalyze many other reactions of polyols in which the nucleophilic attack of the hydroxyl group is a key reaction step. In this context, various reactions catalyzed by benzoxaborole are currently being explored in our laboratry to accomplish the structural diversity of polyols.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: Benzoxaborole • polyol • cis-1,2-diol • site-selective modification • glycosylation

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- Scope and limitations
- Mechanistic study

'cis-1,2-diol recognition and activation'

Novel benzoxaborole derivatives were designed as efficient catalysts for the highly site-selective and protecting-group-free modification of polyols such a carbohydrate. Additionally, the benzoxaborole catalyst could be tolerated to the diverse modifications of polyols including acylation, sulfonylation, alkylation, and glycosylation.

Key Topic: Organoboron catalyst

Shuhei Kusano, Shoto Miyamoto, Aki Matsuoka, Yuji Yamada, Ryuta Ishikawa and Osamu Hayashida**

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Benzoxaborole catalyst for site-selective modification of polyols