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Lipase-catalyzed asymmetric acylation of boron cluster-containing secondary alcohols

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ABSTRACT

The lipase-catalyzed asymmetric acetylation of secondary alcohols containing a carborane (boron cluster) moiety was investigated. Most lipases examined showed poor catalytic activity toward carborane-containing secondary alcohol **1a**, but lipase TL efficiently catalyzed the acetylation of **1a** with high enantioselectivity, to afford (*R*)-**3a**. This selectivity is similar to that of the general lipase-catalyzed acylation of secondary alcohols. Utilizing lipase TL, we succeeded in the resolution of carborane-containing alcohol **5**, synthesized as a progesterone receptor ligand candidate, and evaluated the activities of the two enantiomers.

1. Introduction

Carboranes (more specifically, dicarba-*closo*-dodecaboranes, $C_2B_{10}H_{12}$) are icosahedral boron clusters with a bulky spherical surface. There are three isomers, which involve the positional relationship of the two carbon atoms, namely *o*-, *m*-, and *p*-carboranes. Carboranes have remarkable thermal and chemical stability, and exceptionally high hydrophobicity,[1] and have been employed as hydrophobic core structures of bioactive molecules in the field of medicinal chemistry. We have developed several potent carborane-based ligands of nuclear receptors, such as retinoid receptors,[2] estrogen receptor,[3] androgen receptor,[4] progesterone receptor,[5] and vitamin D receptor.[6] Most carborane-containing bioactive molecules that have been developed so far are achiral or racemic. In the case of vitamin D derivatives, the optically active side chain was introduced onto the carborane cage, and the binding structure of each enantiomer was discussed.[6a] Therefore, the development of efficient synthetic methods to prepare optically active carborane derivatives is of interest in order to develop novel modulators of various physiological targets and to investigate the structure–activity relationships in detail.

One method to obtain optically active molecules is to use an enzyme-catalyzed enantioselective reaction. For example, lipases have been used for the kinetic resolution of optically active alcohols and carboxylic acids because they possess broad substrate specificity and high enantioselectivity.[7] It is well established that lipases act selectively on the (*R*)-enantiomer of secondary alcohols to afford acylated products by discriminating between 'large' and 'small' substituents at the stereogenic center.[8] However, there are structural limitations on the substrates of the lipases that can be effectively converted. For example, enzymatic asymmetric acylation of 1-(1-adamantyl)ethanol has been reported, but either the reactivity was very low[9] or an unusual enzyme had to be used.[10] Therefore, it is of interest to know whether or not bulky carboranes can be recognized by lipases and, if they can, how they are recognized. Herein we examined the catalytic potency of lipases toward carborane-containing secondary alcohols, with the aim of developing an efficient method for the preparation of enantiomerically pure carborane derivatives.

2. Results and discussion

2.1. Design and synthesis of model substrates

Secondary alcohols with an aromatic group as a 'large' substituent, such as 1-phenylethanol or 1-naphthylethanol, have been investigated in detail as model substrates for lipase-catalyzed asymmetric acylation. On the other hand, we have shown that phenylcarborane is a useful core structure of nuclear receptor ligands.[3–5] Here we have designed 1-(7-phenyl-1,7-dicarba-*closo*-dodecaboran-1-yl)ethanol **1a** as a model substrate for investigating the lipase-catalyzed asymmetric acylation of carboranes (Fig. 1). In order to clarify the structural requirements of carborane derivatives as lipase substrates, we also synthesized compounds **1b–1d**.

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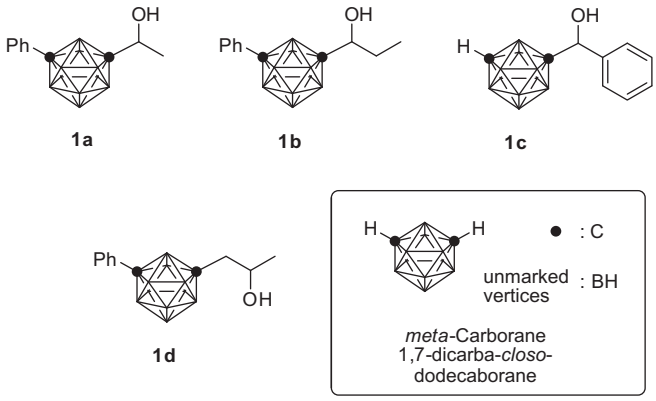
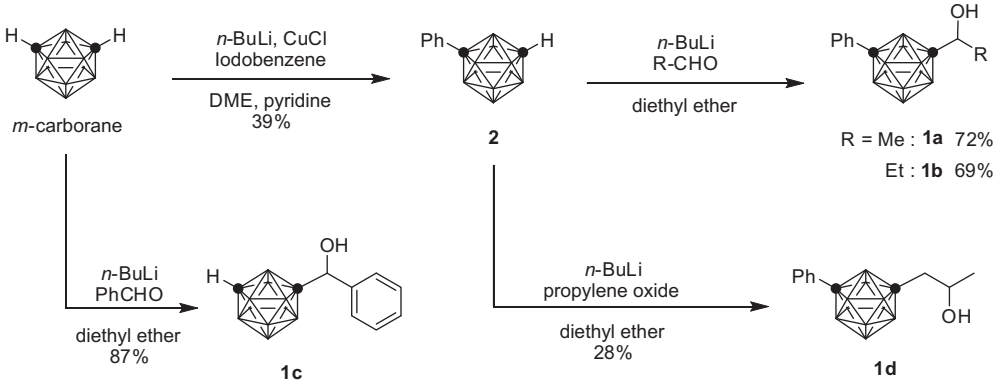


Figure 1. Structures of carborane-containing secondary alcohols **1a**–**1d**.

The synthetic procedures are shown in Scheme 1. An Ullmann-type coupling reaction between the C-copper(I) derivative of *m*-carborane and iodobenzene gave 1-phenyl-*m*-carborane **2**. Hydroxyalkyl groups were introduced on the carbon atom of **2** by using *n*-butyl lithium as a base and acetaldehyde, propanal, or propylene oxide as an electrophile to afford racemic **1a** (72%), **1b** (69%), and **1d** (28%), respectively. Treatment of *m*-carborane with 1.1 equiv of *n*-butyllithium, followed by benzaldehyde, afforded **1c** in 87% yield.

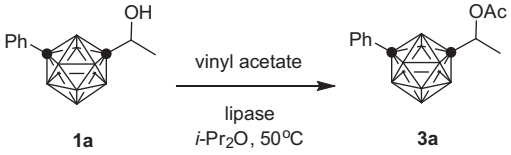
2.2. Lipase-catalyzed asymmetric acetylation of 1a

First, the lipase-catalyzed asymmetric acetylation of racemic **1a** using vinyl acetate as an acyl donor was investigated. In order to find a suitable enzyme, we screened 19 lipases and some other enzymes, including proteases and esterases (Table 1). Most of these enzymes exhibited no or very low catalytic activity for the acetylation of **1a**, although they did have potent catalytic activity toward general secondary alcohols such as 1-phenylethanol. On the other hand, all of the lipases that showed low catalytic activity toward **1a** also showed extremely high enantioselectivity, affording a single enantiomer of the acetylated product **3a**. The slow reaction rate and high enantioselectivity in these reactions might be attributed to the characteristic bulkiness of the carborane. Among the enzymes examined herein, lipase TL, isolated from *Pseudomonas stutzeri*,



Scheme 1. Synthesis of secondary alcohols **1a**–**1d**.

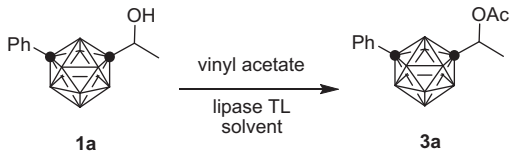
Table 1
Screening of suitable lipases for the asymmetric acetylation of **1a**



Lipase (origine, supplier)[a]	Time (h)	ee_S (%)[b]	ee_P (%)[c]	Conv. (%)
AK (*Pseudomonas fluorescens*, Amano)	8	17	> 99	14
AL (*Achromobacter sp.*, Meito)	8	3	> 99	3
AYS (*Candida rugosa*, Meito)	8	2	> 99	2
CALB (*Candida antarctica*, Sigma)	8	52	> 99	34
MY (*Candida rugosa*, Meito)	8	0.4	> 99	0.4
PL (*Alcaligenes sp.*, Meito)	8	23	> 99	19
PS (*Pseudomonas cepacia*, Amano)	8	10	> 99	9
QL (*Alcaligenes sp.*, Meito)	8	77	> 99	43
SL (*Pseudomonas cepacia*, Meito)	8	23	> 99	19
TL (*Pseudomonas stutzeri*, Meito)	8	> 99	> 99	50
Type VII (*Candida rugosa*, Sigma)	8	8	> 99	7

[a] The following enzymes showed no catalytic activity toward **1a**: lipase A (*Aspergillus* sp., Amano), lipase AS (*Aspergillus niger*, Amano), lipase F-AP15 (*Rhizopus oryzae*, Amano), lipase M (*Mucor javanicus*, Amano), lipase OF (*Candida rugosa*, Meito), lipase R (*Penicillium roqueforti*, Amano), lipase type II (porcine pancreas, Sigma), lipase UL (*Rhizopus* sp., Meito), talipase (*Rhizopus delemar*, Tanabe), chymotrypsin (bovine pancreas, Sigma), newlase F (*Rhizopus* sp., Amano), papain (*Carica papaya*, Sigma), and subtilisin (*Bacillus licheniformis*, Sigma).
[b] Enantiomeric excess of the substrate.
[c] Enantiomeric excess of the product.

Table 2
Optimization of reaction conditions for the lipase TL-catalyzed asymmetric acetylation of **1a**



Solvent	Temp. (°C)	Time (h)	ee_S (%)[a]	ee_P (%)[b]	Conv. (%)
acetone	30	1	12	> 99	11
DMF	30	1	0.7	> 99	0.7
MeCN	30	1	35	> 99	26
DME	30	1	2.7	> 99	2.6
i-Pr_2O	30	1	46	> 99	31
CH_2Cl_2	30	1	3.4	> 99	3.3
n-hexane	30	1	48	> 99	33
i-octane	30	1	30	> 99	23
i-Pr_2O	30	0.5	37	> 99	27
i-Pr_2O	40	0.5	44	> 99	31
i-Pr_2O	50	0.5	62	> 99	36
i-Pr_2O	50	2.3	>99	> 99	50

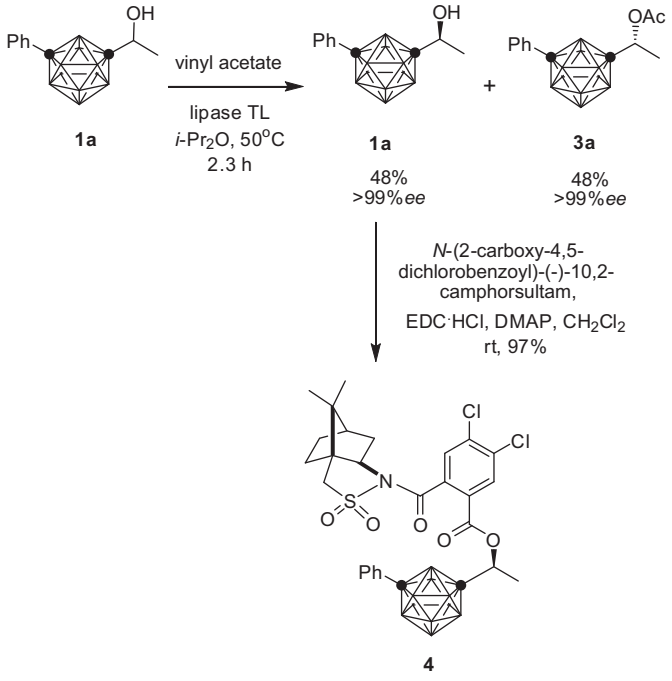
[a] Enantiomeric excess of the substrate.
[b] Enantiomeric excess of the product.

exhibited an exceptionally high reaction rate while maintaining high enantioselectivity: one enantiomer of secondary alcohol **1a** was converted almost completely in 8 h into enantiomerically pure **3a** with an enantiomeric excess of both substrate (ee_s) and product (ee_p) of more than 99%. It has already been reported that lipase TL acylates relatively bulky substrates, such as benzoin, with a high reaction rate and enantioselectivity.[11]

Next, we optimized the reaction conditions for the lipase TL-catalyzed acetylation of **1a** (Table 2). Lipase TL displayed high catalytic activity in nonpolar organic solvents such as diisopropyl ether and *n*-hexane. When diisopropyl ether was used as the solvent, increasing the reaction temperature to 50 °C improved the reaction rate while maintaining high enantioselectivity. Thus, we succeeded in the lipase TL-catalyzed kinetic resolution of **1a**, with almost 100% enantiomeric excess of both the product **3a** and unreacted **1a** and a maximum yield of 50% in 2.3 h in diisopropyl ether at 50 °C.

2.3. Determination of the absolute configuration of the selectively reacted enantiomer of 1a

HPLC analysis using a chiral column revealed that the same enantiomer of **1a** was selectively acetylated by each usable lipase. In order to determine the stereochemistry of the catalytic reaction, the unreacted enantiomer of **1a** (ee_s >99%) after the lipase TL-catalyzed reaction was isolated by silica gel column chromatography, and was condensed with *N*-(2-carboxyl-4,5-dichlorobenzoyl)-(−)-10,2-camphorsultam[12] to afford ester **4**. X-ray crystallographical analysis showed that the ester **4** had *S*-configuration of the carbon atom attached to the carborane, which indicated that the unreacted enantiomer of **1a** had an (*S*)-configuration, and thus that the lipase selectively acetylates the (*R*)-enantiomer of **1a** (Scheme 2, Fig. 2). Thus, the lipase recognized the phenylcarborane moiety as a 'large' substituent in the same manner as substituents such as the phenyl and naphthyl groups of other general secondary alcohols,[8] and selectively acylates the (*R*)-enantiomer of carborane-containing secondary alcohols.



Scheme 2. Preparation of enantiomerically pure **1a** and conversion into ester **4**.

2.4. Permissiveness of substrate structure

We next investigated the lipase-catalyzed asymmetric acetylation of **1b**, which has an ethyl group at the stereogenic center, instead of the methyl group of **1a** (Table 3). The enantioselectivity was very high for the acetylation of **1b** by lipase TL, as observed in the reaction of **1a**. However, the reaction rate was very low for this reaction, which proceeded with only 12% conversion in 193 h at 50 °C in diisopropyl ether. Furthermore, acetylation of **1c** bearing a phenyl group did not proceed under the same conditions up to 95 h, although the carboranyl moiety is smaller than that of **1a** due to the lack of a phenyl group on the carborane ring in **1c**. Generally, the lipase-catalyzed acylation of secondary alcohols with a medium-sized substituent (such as 1-phenylpropanol) at the stereogenic center as the 'small' substituent proceeded with a high reaction rate and enantioselectivity, comparable with those of alcohols with a small-sized substituent, such as 1-phenylethanol.[13] In contrast to these reports, the permissiveness of the substituent ('small' substituent) at the stereogenic center of 1-substituted carboranylmethanols is low, probably due to the bulkiness of the spherical carborane moiety.

In the lipase-catalyzed acylation of substrate **1d** with a methylene group between the stereogenic center and carborane moiety, lipase QL exhibited more efficient catalytic activity than lipase TL (Table 3). Lipase TL converted only 33% of **1d** after 141 h under the same conditions as those used for **1a**, while lipase QL converted almost all of one enantiomer of **1d** into the acetylated product **3d** after 24 h. Although CALB is a useful lipase with a similar range of substrates to lipase TL, it exhibited a similar reaction rate, but lower enantioselectivity. This might be due to the longer distance between the carborane moiety and the stereogenic center in **1d**.

2.5. Resolution of a progesterone receptor antagonist candidate and biological activity of the enantiomers

The application of the lipase-catalyzed enantioselective acylation of carboranyl alcohols to the resolution of biologically active compounds was examined next. We had previously proposed that both *C*-(cyanophenyl)-*m*-carborane and *C*-(cyanophenyl)-*p*-carbo-

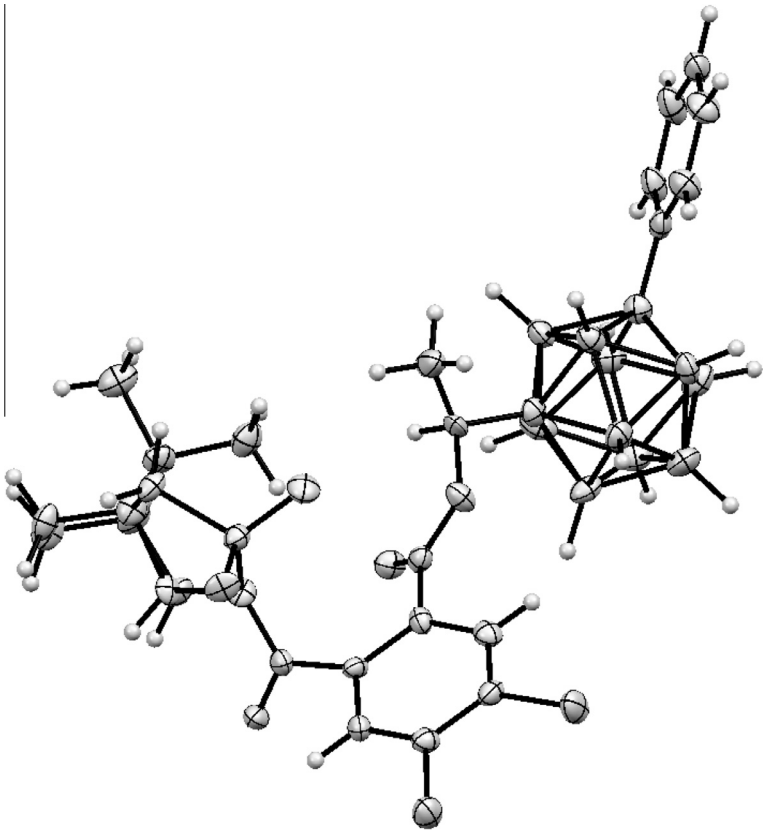
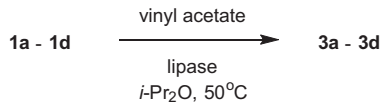


Figure 2. ORTEP view of **4** synthesized from unreacted **1a** in lipase TL-catalyzed reaction, displaying the thermal ellipsoids at 50% probability.

Table 3
Permissiveness of substrate structure for the lipase-catalyzed asymmetric acetylation of carborane-containing secondary alcohols



Substrate	Lipase	Time (h)	ee_S (%)[a]	ee_P (%)[b]	Conv. (%)
1a	TL	2.3	> 99	> 99	50
1b	TL	193	14	> 99	12
1c	TL	95	0	-	0
1d	TL	141	42	> 99	33
1d	QL	24	> 99	> 99	50
1d	CALB	141	30	97	34

[a] Enantiomeric excess of the substrate.
[b] Enantiomeric excess of the product.

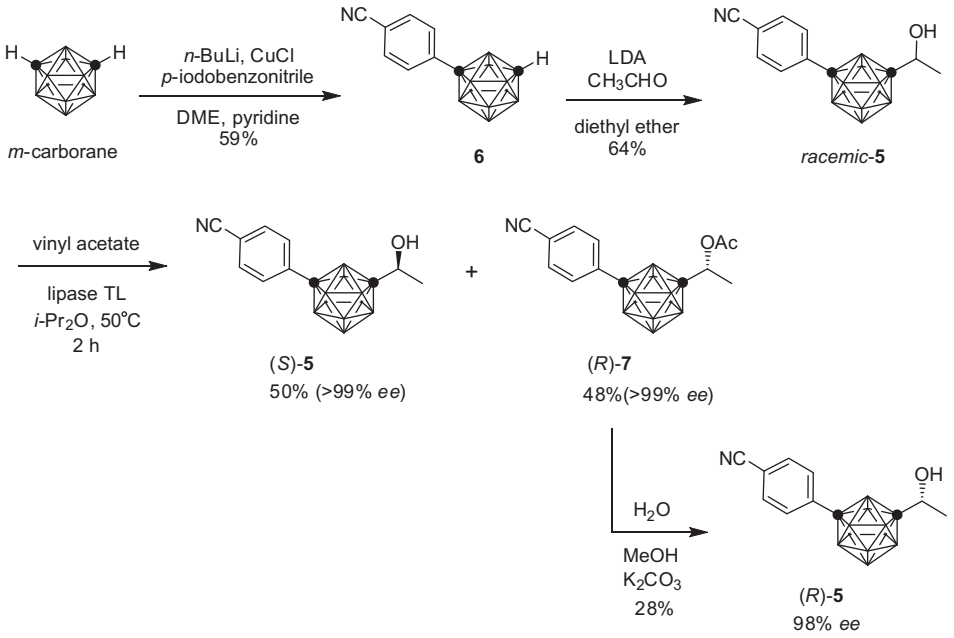
rane bearing a suitable substituent on the other carbon atom of the carborane would be a key structure for progesterone receptor (PR) ligands.[5] Considering the structure–activity relationships of these compounds, we designed 1-(7-(4-cyanophenyl)-1,7-dicarba-*closo*-dodecaboran-1-yl)ethanol **5** as a novel PR ligand candidate, and examined the lipase-catalyzed kinetic resolution of racemic **5**. The synthesis and lipase-catalyzed kinetic resolution procedure of **5** are shown in Scheme 3. Under the optimized reaction conditions for **1a** (lipase TL in diisopropyl ether for 2 h at 50 °C), the asymmetric acetylation of **5** was achieved in maximum yield with complete enantioresolution (ee_s, ee_p >99%). Although the absolute configurations of unreacted **5** and the acetylated product **7** were not determined independently, we assume that the selectively acetylated product was (*R*)-**7** because of the similarity of the backbone structure between **1a** and **5**. After the isolation of unreacted (*S*)-**5** and product (*R*)-**7** by silica gel column chromatography, (*R*)-**7** was hydrolyzed with K_2CO_3 aq to obtain (*R*)-**5**.

The PR ligand activity of the purified (*R*)- and (*S*)-enantiomers of **5** was examined by alkaline phosphatase assay using a T47D breast-carcinoma cell line (Fig. 3 and Table 4).[14] Both enantiomers of **5** and racemic **5** acted as PR partial agonists, whose maximum response was approximately 60% of that caused by progesterone. Compound (*S*)-**5** exhibited more potent agonistic activity than (*R*)-**5**. On the other hand, in the presence of 2 nM progesterone, compound **5** acted as a PR antagonist at a lower concentration range compared with its effective concentration as an agonist. Chirality had little influence on the antagonistic activity, compared to the case of the agonistic activity.

For transcriptional activation of PR, induced conformational change of the ligand-binding domain (LBD) is important, as is generally the case for the nuclear receptor family.[15] In other words, potent agonists induce a conformation of the PR LBD that can interact with several transcriptional coactivators, while antagonists induce slightly or considerably different conformations of the PR LBD.[16] Therefore, activation by an agonist requires a strict conformational change of LBD, while the antagonistic action that resulted from various LBD conformations differs from the active conformation, and this may be the reason as to why the chirality of the ligands has a greater effect on the agonistic activity than on the antagonistic activity. Thus, enantioseparation using enzymatic reactions, as illustrated herein, is likely to be useful in medicinal–chemical studies of carborane derivatives.

3. Conclusion

This is the first report on the enzymatic reaction of boron cluster-containing substrates.[17] The present results on the lipase-cata-



Scheme 3. Synthesis and lipase TL-catalyzed resolution of **5**.

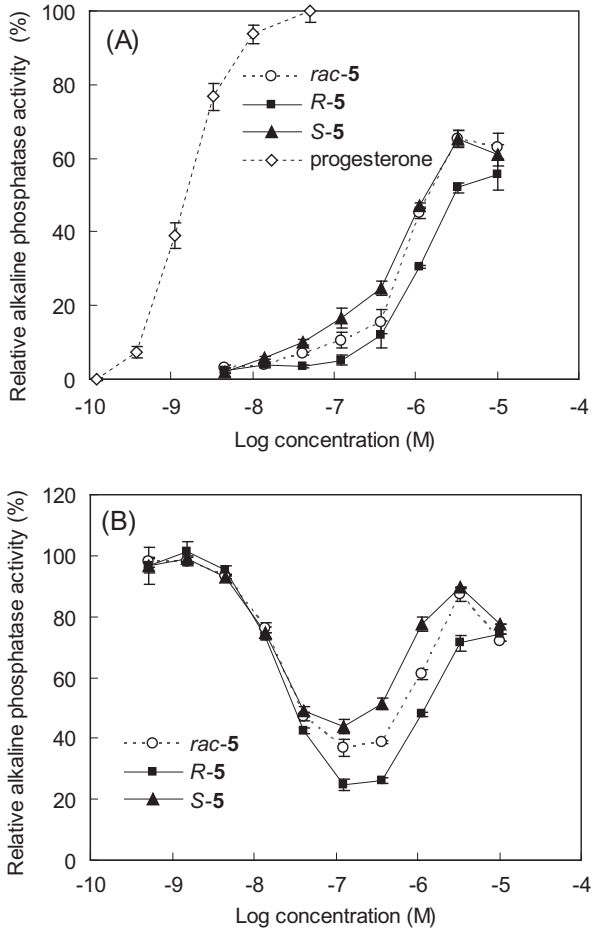


Figure 3. Dose–response curves of both enantiomers of **5** (A) alone and (B) in the presence of 2 nM progesterone on alkaline phosphatase activities in T47D cells.

lyzed asymmetric acetylation of secondary alcohols with carborane at the stereogenic center indicate that some lipases recognize carborane as a 'large substituent' and selectively acetylate the (*R*)-enantiomer in the same manner as general secondary alcohols. However, the carborane's bulkiness resulted in a low reaction rate or poor permissiveness regarding the 'small' substituent at the stereogenic center. These results offer useful information about the scope and limitations of lipase-catalyzed reactions of carborane derivatives and may also be relevant to other non-natural substrates with bulky substituents. In particular, this methodology would be effective toward secondary alcohols containing the other isomers of carborane; *o*- and *p*-carboranes. Since carborane is a useful hydrophobic core structure of ligands for nuclear receptors and other receptor proteins, the methodology and results reported herein should also be useful in structure–activity relationship studies of carborane derivatives.

Table 4
Agonistic and antagonistic activity of both enantiomers of **5** toward progesterone receptor evaluated by alkaline phosphatase assay using T47D cells

Compound	*ee* (%)	EC_{50} (μM)[a]	IC_{50} (μM)[b]
racemic-**5**	0	0.79	0.037
(*R*)-**5**	98	1.05	0.032
(*S*)-**5**	>99	0.57	0.039
progesterone	-	0.0015	-

[a] Half-maximum effective concentration of compound as an agonist. The response of compound **5** was 60% of that induced by progesterone.
[b] Half-maximum inhibitory concentration of compound **5** toward activity of coexisting 2 nM progesterone.

4. Experimental

4.1. General

All reagents were purchased from Sigma-Aldrich, Tokyo Kasei, Wako Chemicals, and Kanto Chemicals and were used without further purification. NMR spectra were recorded on Bruker AVANCE 400 or AVANCE 500 spectrometers. Chemical shifts for NMR are reported as parts of per million (ppm) relative to chloroform (7.26 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR).

Mass spectra were collected on a Bruker Daltonics microTOF-2focus spectrometer in the positive and negative ion modes. HPLC data were recorded with a Hitachi D-2000 Elite type HPLC system manager. Chiral column IC (4.6 mm Φ × 250 mm) and IE (4.6 mm Φ × 250 mm) were purchased from Daicel Chemical Industries. All lipase reactions were performed in a Bio Shaker BR-23 FH·MR from TAITEC.

4.2. Synthesis of 1-phenyl-1,7-dicarba-*closo*-dodecaborane 2

At first, 1.6 M *n*-butyllithium in *n*-hexane (87.8 mmol) was added to a solution of *m*-carborane (11.5 g, 79.8 mmol) in DME (80 mL) at 0 °C under Ar, and the mixture was stirred at 0 °C for 30 min. Copper(I) chloride (10.3 g, 104 mmol) was added to the solution at room temperature. After 1 h, pyridine (3.2 mL) and *p*-iodobenzene (87.8 mmol) were added, and the mixture was stirred at 80 °C for 4 h. After cooling, the reaction mixture was diluted with ether and insoluble materials were filtered off through Celite. The filtrate was washed with 5% aqueous sodium thiosulfate, 2 M HCl, and brine, dried over sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (eluent: *n*-hexane/CH_2Cl_2, 40/1) to give **2** (39%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.41 (m, 2H), 7.32–7.23 (m, 3H), 3.6–1.6 (br m, 10H), 3.06 (br s, 1H).

4.3. Synthesis of 1-(7-phenyl-1,7-dicarba-*closo*-dodecaboran-1-yl)ethanol 1a

At first, 1.6 M *n*-butyllithium in *n*-hexane (7.2 mmol) was added to a solution of **2** (1.4 g, 6.5 mmol) in diethyl ether (30 mL) at 0 °C under Ar, and the mixture was stirred at 0 °C for 30 min. Acetaldehyde (27 mmol) was added to the solution at 0 °C. The reaction mixture was stirred for 90 min at room temperature, then poured into saturated ammonium chloride, and extracted with ether. The organic layer was washed with water and brine, dried over sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate, 8/1) to give **1a** (72% yield) as a white solid. Recrystallization from *n*-hexane gave plate crystals. Mp 30–31 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.42 (m, 2H), 7.30–7.23 (m, 3H), 4.09 (quin, J = 6.4 Hz, 1H), 3.7–1.6 (br m, 10H), 1.90 (d, J = 6.4 Hz, 1H), 1.32 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.3, 128.8, 128.5, 127.9, 82.5, 77.7, 69.4, 23.8; HRMS Calcd for $C_{10}H_{19}B_{10}O$ [M−H]: 265.2374. Found 265.2373. HPLC: CHIRALPAK IC (25 cm), flow rate 1 mL/min, *n*-hexane/ethanol = 100/0.3, detection 254 nm, (*R*)-**1a** 16.4 min, (*S*)-**1a** 15.3 min. Lipase TL-catalyzed asymmetric acetylation of *rac*-**1a** followed by silica gel column chromatography gave (*S*)-**1a** (>99% ee) as a white solid. Recrystallization from *n*-hexane gave plate crystals. $[\alpha]_D^{25}$ = −12.3 (*c* 0.54, CH_2Cl_2); mp 34–35 °C.

4.4. Synthesis of 1-(7-phenyl-1,7-dicarba-*closo*-dodecaboran-1-yl)-1-propanol 1b

At first, 1.6 M *n*-butyllithium in *n*-hexane (1.5 mL, 2.5 mmol) was added to a solution of **2** (501 mg, 2.3 mmol) in diethyl ether (9 mL) at 0 °C under Ar, and the mixture was stirred at 0 °C for 30 min. Propionaldehyde (0.3 mL, 4.3 mmol) was added to the solution at 0 °C. The reaction mixture was stirred for 1 h at room temperature, then poured into saturated ammonium chloride, and extracted with ether. The organic layer was washed with water and brine, dried over sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate, 5/1) to give **1b** (69% yield) as a white solid. Recrystallization from *n*-hexane gave plate crystals. Mp 66–67 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.41 (m, 2H), 7.29–7.25 (m, 3H), 3.73 (m, 1H), 3.6–1.6 (br m, 10H), 1.84 (d, J = 6.4 Hz, 1H), 1.75–1.67 (m, 1H), 1.43–1.34 (m, 1H), 1.00 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.4, 128.8, 128.5, 127.9, 82.4, 77.6, 74.4, 30.6, 11.3; HRMS Calcd for $C_{11}H_{21}B_{10}O$ [M−H]: 279.2531. Found 279.2532. HPLC: CHIRALPAK IC (25 cm), flow rate 1 mL/min, *n*-hexane/ethanol = 100/0.3, detection 254 nm, (*R*)-**1b** 16.3 min, (*S*)-**1b** 12.1 min.

4.5. Synthesis of 1-(1,7-dicarba-*closo*-dodecaboran-1-yl)benzyl alcohol 1c

At first, 1.6 M *n*-butyllithium in *n*-hexane (2.3 mL, 3.8 mmol) was added to a solution of *m*-carborane (504 mg, 3.5 mmol) in diethyl ether (13 mL) at 0 °C under Ar, and the mixture was stirred at 0 °C for 30 min. Benzaldehyde (0.4 mL, 3.8 mmol) was added to the solution at 0 °C. The reaction mixture was stirred for 1 h at room temperature, then poured into saturated ammonium chloride, and extracted with ether. The organic layer was washed with water and brine, dried over sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate, 10/1) to give **1c** (87% yield) as a white solid. Recrystallization from *n*-hexane gave plate crystals. Mp 65–66 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.33 (m, 3H), 7.30–7.25 (m, 2H), 6.03 (s, 1H), 3.4–1.4 (br m, 10H), 2.86 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.7, 129.3, 128.6, 127.4, 78.1, 74.5, 54.8; HRMS Calcd for $C_9H_{17}B_{10}O$ [M−H]: 251.2217. Found 251.2216. HPLC: CHIRALPAK IC (25 cm), flow rate 1 mL/min, *n*-hexane/ethanol = 100/0.3, detection 254 nm, 12.6 min and 13.3 min (absolute configurations were not identified).

4.6. Synthesis of 1-(7-phenyl-1,7-dicarba-*closo*-dodecaboran-1-yl)-2-propanol 1d

At first, 1.6 M *n*-butyllithium in *n*-hexane (1.4 mL, 2.2 mmol) was added to a solution of **2** (452 mg, 2.1 mmol) in diethyl ether (8 mL) at 0 °C under Ar, and the mixture was stirred at 0 °C for 30 min. Propylene oxide (0.2 mL, 2.5 mmol) was added to the solution at 0 °C. The reaction mixture was stirred for 1 h at room temperature, then poured into ammonium chloride, and extracted with ether. The organic layer was washed with water and brine, dried over sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate, 8/1) to give **1d** (28% yield) as a white solid. Recrystallization from *n*-hexane gave plate crystals. Mp 69–71 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.41 (m, 2H), 7.31–7.25 (m, 3H), 3.90 (m, 1H), 3.6–1.7 (br m, 10H), 2.16 (dd, J = 15.0 and 8.5 Hz, 1H), 2.12 (dd, J = 15.0 and 3.0 Hz, 1H), 1.59 (d J = 4.5 Hz, 1H), 1.17 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.3, 128.8, 128.5, 127.9, 78.5, 73.7, 67.2, 46.2, 24.1; HRMS Calcd for $C_{11}H_{21}B_{10}O$ [M−H]: 279.2531. Found 279.2531. HPLC: CHIRALPAK IC (25 cm), flow rate 1 mL/min, *n*-hexane/ethanol = 100/0.3, detection 254 nm, (*R*)-**1d** 34.1 min, (*S*)-**1d** 12.1 min. Lipase QL-catalyzed asymmetric acetylation of *racemic*-**1d** followed by silica gel column chromatography gave (*S*)-**1d** (estimated configuration, >99% ee) as a colorless liquid. $[\alpha]_D^{25}$ = +23.5 (*c* 0.3, CH_2Cl_2).

4.7. Synthesis of 4

N-(2-Carboxy-4,5-dichlorobenzoyl)-(−)-10,2-camphorsultam (112 mg, 0.26 mmol) was added to a solution of **1a** (recovered from the enzymatic reaction mixture, Scheme 2, 44 mg, 0.17 mmol) in dichloromethane (5 mL) at room temperature. Next, EDC·HCl (42 mg, 0.2 mmol) and DMAP (4.2 mg, 0.03 mmol) were added. The reaction mixture was stirred for 17 h at room temperature and then poured into water. The organic layer was washed with 2 M hydrochloric acid, saturated sodium bicarbonate, and brine, dried over sodium sulfate, and concentrated. The crude product

was purified by recrystallization from DMF to give **4** (97% yield) as needles. $[\alpha]_D^{25} = -82.1$ (*c* 0.2, CH_2Cl_2); mp 164–166 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.54 (s, 1H), 7.43–7.40 (m, 2H), 7.31–7.21 (m, 3H), 5.40 (q, *J* = 6.5 Hz, 1H), 4.05 (br s, 1H), 3.6–1.5 (br m, 10H), 3.42 (d, *J* = 13.5 Hz, 1H), 3.38 (d, *J* = 13.5 Hz, 1H), 2.47 (br d, *J* = 13.0 Hz, 1H), 2.18 (m, 1H), 1.98–1.88 (m, 3H), 1.46–1.38 (m, 2H), 1.38 (d, *J* = 6.5 Hz, 3H), 1.16 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 161.8, 137.6 135.3, 135.3, 134.9, 131.6, 131.2, 129.0, 128.6, 128.0, 127.9, 77.9, 77.8, 71.0, 65.9, 53.3, 48.6, 47.9, 44.9, 37.6, 33.3, 26.6, 21.0, 20.7, 20.2; HRMS Calcd for $C_{28}H_{37}B_{10}Cl_2NO_5SNa$ [M+Na]: 702.2636. Found 702.2636.

4.8. Synthesis of 1-(4-cyanophenyl)-1,7-dicarba-*closo*-dodecaborane 6

At first, 1.6 M *n*-butyllithium, in *n*-hexane (7.4 mL, 11.9 mmol) was added to a solution of *m*-carborane (1.5 g, 10.8 mmol) in DME (12 mL) at 0 °C under Ar, and the mixture was stirred at 0 °C for 30 min. Copper(I) chloride (10.3 mg, 104 mmol) was added to the solution at room temperature. After 1 h, pyridine (3.8 mL) and *p*-iodobenzonitrile (2.8 g, 11.9 mmol) were added, and the mixture was stirred at 80 °C for 2.5 h. After cooling, the reaction mixture was diluted with ether, and insoluble materials were filtered off through Celite. The filtrate was washed with 5% sodium thiosulfate, 2 M hydrochloric acid, and brine, dried over sodium sulfate, and then concentrated. The residue was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate, 20/1) to give **6** (59% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.53 (m, 4H), 3.5–1.7 (br m, 10H), 3.12 (br s, 1H).

4.9. Synthesis of 1-(7-(4-cyanophenyl)-1,7-dicarba-*closo*-dodecaboran-1-yl)ethanol 5

At first, 1.1 M lithium diisopropylamide in *n*-hexane-tetrahydrofuran (8.7 mL, 9.7 mmol) was added to a solution of **6** (2.0 g, 8.1 mmol) in THF (30 mL) at −78 °C under Ar, and the mixture was stirred at −78 °C for 10 min. Acetaldehyde (9.0 mL) was then added to the solution at −78 °C. The reaction mixture was stirred for 30 min at −78 °C, then poured into saturated ammonium chloride, and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate, 8/1) to give **5** (64% yield) as a white solid. Mp 82–83 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58–7.53 (m, 4H), 4.09 (quin, *J* = 6.0 Hz, 1H), 3.7–1.8 (br m, 10H), 1.92 (d, *J* = 6.0 Hz, 1H), 1.32 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 140.0, 132.3, 128.8, 118.1, 112.9, 82.9, 75.8, 69.3, 23.8; Anal. Calcd for: $C_{11}B_{10}H_{19}NO$: C, 45.65; H, 6.62; N, 4.84. Found: C, 45.35; H, 6.53; N, 4.83; HRMS Calcd for $C_{11}H_{18}B_{10}NO$ [M−H]: 290.2327. Found 290.2327. HPLC: CHIRALPAK IE (25 cm), flow rate 1 mL/min, *n*-hexane/ethanol = 90/10, detection 254 nm, (*R*)-**5** 10.0 min, (*S*)-**5** 8.1 min.

4.10. General procedure for the synthesis of acetylated products of the lipase-catalyzed reaction for their use as authentic samples in HPLC

Triethylamine (162 mg, 1.6 mmol) and acetic anhydride (98 mg, 1.0 mmol) were added to a solution of alcohol (0.3 mmol) in dichloromethane (2.4 mL). The reaction mixture was stirred for 72 h at room temperature and then poured into 2 M hydrochloric acid. The organic layer was washed with water and brine, dried over sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography to give the acetylated product.

4.10.1. 1-(7-Phenyl-1,7-dicarba-*closo*-dodecaboran-1-yl)ethyl acetate 3a

Yield: 83%; colorless liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.40 (m, 2H), 7.32–7.24 (m, 3H), 5.27 (q, *J* = 6.5 Hz, 1H), 3.7–1.5 (br m, 10H), 2.08 (s, 3H), 1.30 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 135.2, 128.9, 128.5, 127.9, 78.5, 77.6, 69.3, 21.3, 21.1; HRMS Calcd for $C_{12}H_{22}B_{10}O_2Na$ [M+Na]: 331.2445. Found 331.2439. HPLC: CHIRALPAK IC (25 cm), flow rate 1 mL/min, *n*-hexane/ethanol = 100/0.3, detection 254 nm, (*R*)-**3a** 5.4 min, (*S*)-**3a** 4.8 min. Lipase TL-catalyzed asymmetric acetylation of *rac*-**1a** followed by silica gel column chromatography gave (*R*)-**3a** (>99% ee) as a colorless liquid. $[\alpha]_D^{25} = +68.0$ (*c* 0.42, CH_2Cl_2).

4.10.2. 1-(7-Phenyl-1,7-dicarba-*closo*-dodecaboran-1-yl)-propan-1-yl acetate 3b

Yield: 70%; colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.39 (m, 2H), 7.29–7.25 (m, 3H), 5.17 (dd, *J* = 10.8 and 2.8 Hz, 1H), 3.7–1.5 (br m, 10H), 2.11 (s, 3H), 1.78–1.68 (m, 1H), 1.61–1.49 (m, 1H), 0.87 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 135.2, 128.9, 78.5, 77.6, 73.1, 28.8, 20.8, 10.7; HRMS Calcd for $C_{13}H_{24}B_{10}O_2Na$ [M+Na]: 345.2602. Found 345.2602. HPLC: CHIRALPAK IC (25 cm), flow rate 1 mL/min, *n*-hexane/ethanol = 100/0.3, detection 254 nm, *R*-**3b** 5.4 min, *S*-**3b** 4.9 min. Lipase TL-catalyzed asymmetric acetylation of *rac*-**1b** followed by silica gel column chromatography gave *R*-**3b** (estimated configuration, >99% ee) as a colorless liquid. $[\alpha]_D^{25} = +52.9$ (*c* 0.22, CH_2Cl_2).

4.10.3. 1-(1,7-Dicarba-*closo*-dodecaboran-1-yl)benzyl acetate 3c

Yield: 97%; recrystallization from *n*-hexane gave plate crystals. Mp 64–65 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.33 (m, 2H), 7.28–7.23 (m, 3H), 6.03 (s, 1H), 3.5–1.5 (br m, 10H), 2.86 (br s, 1H), 2.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.3, 128.8, 128.5, 127.9, 69.4, 23.8; HRMS Calcd for $C_{11}H_{20}B_{10}O_2Na$ [M+Na]: 345.2602. Found 345.2602. HPLC: CHIRALPAK IC (25 cm), flow rate 1 mL/min, *n*-hexane/ethanol = 100/0.3, detection 254 nm, 5.5 min and 6.1 min (absolute configurations were not identified).

4.10.4. 1-(7-Phenyl-1,7-dicarba-*closo*-dodecaboran-1-yl)-propan-2-yl acetate 3d

Yield: 80%; recrystallization from *n*-hexane gave plate crystals. Mp 49–50 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.39 (m, 2H), 7.31–7.23 (m, 3H), 4.85 (m, 1H), 3.6–1.7 (br m, 10H), 2.38 (dd, *J* = 15.5 and 10.0 Hz, 1H), 2.13 (dd, *J* = 15.5 and 2.5 Hz, 1H), 2.05 (s, 1H), 1.19 (d, *J* = 6.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 135.3, 128.8, 128.5, 127.9, 78.4, 73.0, 70.1, 42.8, 21.5, 20.6; HRMS Calcd for $C_{13}H_{24}B_{10}O_2Na$ [M+Na]: 345.2602. Found 345.2606. HPLC: CHIRALPAK IC (25 cm), flow rate 1 mL/min, *n*-hexane/ethanol = 100/0.3, detection 254 nm, (*R*)-**3d** 6.5 min, (*S*)-**3d** 6.9 min. Lipase QL-catalyzed asymmetric acetylation of *rac*-**1d** followed by silica gel column chromatography gave (*R*)-**3d** (estimated configuration, >99% ee) as a white solid. Recrystallization from *n*-hexane gave plate crystals. Mp 64–65 °C; specific rotation was not detected at (*c* 0.4, CH_2Cl_2).

4.10.5. 1-(7-(4-Cyanophenyl)-1,7-dicarba-*closo*-dodecaboran-1-yl)ethyl acetate 7

Yield: 92%; colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 10.8 Hz, 2H), 7.52 (d, *J* = 10.8 Hz, 2H), 5.27 (q, *J* = 6.4 Hz, 1H), 3.5–1.6 (br m, 10H), 2.09 (s, 3H), 1.30 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 140.0, 132.3, 128.8, 118.1, 112.9, 82.9, 75.8, 70.2, 23.8, 22.3; HRMS Calcd for $C_{13}H_{21}B_{10}NO_2Na$ [M+Na]: 345.2398. Found 356.2397. HPLC: CHIRALPAK IC (25 cm), flow rate 1 mL/min, *n*-hexane/ethanol = 90/10, detection 254 nm, *R*-**7** 7.5 min, *S*-**7** 7.2 min.

4.11. General procedure for the lipase-catalyzed asymmetric acetylation of alcohols

Lipase (15 mg) was added to a vial containing 1 mL of a solution of the racemic alcohol (0.02 mmol) and vinyl acetate (0.2 mmol), and the reaction mixture was shaken at 120 rounds/min at constant temperature. At frequent intervals, aliquots were withdrawn and filtered with a syringe filter, followed by HPLC analysis.

4.12. Preparation of the (*R*)- and (*S*)-enantiomers of 5 by lipase TL-catalyzed asymmetric acetylation

Lipase TL (1 g) was added to a solution of vinyl acetate (21 mmol) and racemic **5** (600 mg, 2.1 mmol) in diisopropyl ether (20 mL) and the mixture was stirred at 50 °C for 2 h. After removal of the lipase by filtration, the filtrate was concentrated. The residue was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate, 10/1) to give (*S*)-**5** (50% yield, >99% ee) as a colorless solid and (*R*)-**7** (49% yield, >99% ee) as a colorless liquid. Next, (*R*)-**7** was dissolved in 0.43 M potassium carbonate in methanol/water (4:1) and the mixture was stirred for 40 min at room temperature. The reaction mixture was extracted with ethyl acetate, dried over sodium sulfate, and then concentrated. The residue was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate, 4/1) to give (*R*)-**5** (28% yield, 98% ee) as a colorless solid. Recrystallization of (*R*)- and (*S*)-**5** from *n*-hexane gave plate crystals. (*R*)-**5**: $[\alpha]_D^{25} = +10.2$ (*c* 0.5, CH_2Cl_2); mp 98–99 °C; Anal. Calcd for: $C_{11}B_{10}H_{19}NO$: C, 45.65; H, 6.62; N, 4.84. Found: C, 45.60; H, 6.75; N, 4.83; *S*-**5**: $[\alpha]_D^{25} = -10.8$ (*c* 1.0, CH_2Cl_2); mp 99–100 °C; Anal. Calcd for: $C_{11}B_{10}H_{19}NO$: C, 45.65; H, 6.62; N, 4.84. Found: C, 45.80; H, 6.51; N, 4.56.

4.13. X-ray crystallography

Crystallographic data of compound **4** were collected on a Bruker ApexII CCD detector with graphite-monochromated Mo Kα and Quantum210. Crystal system: monoclinic; space group: $P2_1$; unit cell dimensions: $a = 20.92$ (7) Å, $b = 7.460$ (13) Å, $c = 23.51$ (4) Å, $B = 112.9$ (3)°, final *R* indices $[I > 2\sigma(I)]$ $R_1 = 0.0707$, $wR_2 = 0.1576$. The crystallographic data for **4** have been deposited at the Cambridge Crystallographic Data Centre as CCDC 1031421.

4.14. Alkaline phosphatase assay using T47D cells

T47D breast-carcinoma cells were cultured in an RPMI 1640 medium with 10% (v/v) fetal bovine serum. Cells were plated in 96-well plates at 10^4 cells/well and incubated overnight (37 °C, 5% CO_2 in air). The next day, cells were treated with fresh medium containing test compound, and further incubated for 24 h. The medium was aspirated and the cells were fixed with 100 μL of 1.8% formalin (in PBS). The fixed cells were washed with PBS and 75 μL of assay buffer (1 mg/mL *p*-nitrophenol phosphate in diethanolamine water solution, pH 9.0, 2 mM $MgCl_2$) was added. The mixture was incubated at room temperature with shielding from light for 2 h, and then the reaction was terminated by the addition of 100 μL of NaOH. The absorbance at 405 nm was measured.

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