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A Cyclodextrin-Modified Ketoester for Stereoselective Epoxidation of Alkenes

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A β-cyclodextrin-modified ketoester **2** was prepared by covalent attachment of a reactive ketone moiety to β-cyclodextrin. Treatment of **2** with Oxone as terminal oxidant would produce CD-substituted dioxirane, which can effect stereoselective alkene epoxidation. The **2**-mediated (*S*)-α-terpineol epoxidations proceeded to give terpineol oxides in high yields, and the stereoselectivities (i.e., *cis*-/*trans*-epoxide ratio) decreased from 2.5:1 to 1:1.2 with increasing steric bulkiness of the terpenes. This steric-dependent stereoselectivity can be understood based on different binding geometries of the **2**/terpene inclusion complexes according to the ^{1}H NMR titration and 2D ROESY experiments. Enantioselective epoxidation of styrenes has also been achieved with **2** as catalyst (20−50 mol %) in aqueous acetonitrile solution, and up to 40% ee was obtained in 4-chlorostyrene epoxidation at 0 °C. Similar enantioselectivities were also obtained for the **2**-mediated epoxidation of 1,2-dihydronaphthalene (37% ee), 4-chlorostyrene (36% ee), and *trans*-stilbene (31% ee).

Introduction

Design of artificial enzymes that exhibit superior substrate selectivities and catalytic efficiency to the natural counterparts remains a long-standing interest in supramolecular catalysis.[1] Cyclodextrins (CDs), which possess a hydrophobic cavity for substrate binding, have been recognized as versatile enzyme mimics (Figure 1). In the literature, there are extensive reports concerning supramolecular catalysis based on CD/substrate inclusion complex formation.[2] As functional mimics of cytochrome P450, cyclodextrins have been covalently attached to metalloporphyrins for catalytic organic oxidations.[3] Notably, Breslow and co-workers have demonstrated that metalloprophyrins carrying two or four covalently linked

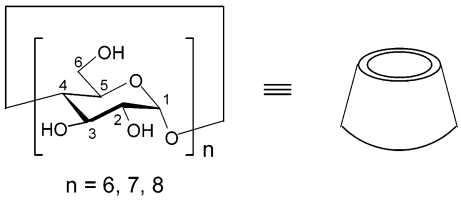

FIGURE 1. General structure of cyclodextrins.

β-CD binding groups could selectively bind and epoxidize *trans*-stilbenes.[3c] Through proper design of the catalyst/substrate complexes, these CD-metalloporphyrins can effect catalytic regioselective hydroxylation of unactivated C−H bonds of bound steroids in the presence of reactive functional groups including alcohols and alkenes.[3d−g]

Dioxiranes are powerful oxidizing agents that can be generated in situ from the reaction of Oxone ($KHSO_5$) with a catalytic amount of ketones for epoxidation, C−H bond oxidation, and heteroatom oxidation.[4] Significant advancements have been made in asymmetric epoxidation of unfunctionalized alkenes using chiral ketone catalysts.[5,6] We are attracted to a recent work by Davies and co-workers that cyclodextrin dioxiranes (generated in situ from keto-cyclodextrins and Oxone) were employed for catalytic oxidation of phenols, amines, and sulfoxides.[7] A major problem of this approach is that these keto-cyclodextrins were derived from non-regioselective bro-

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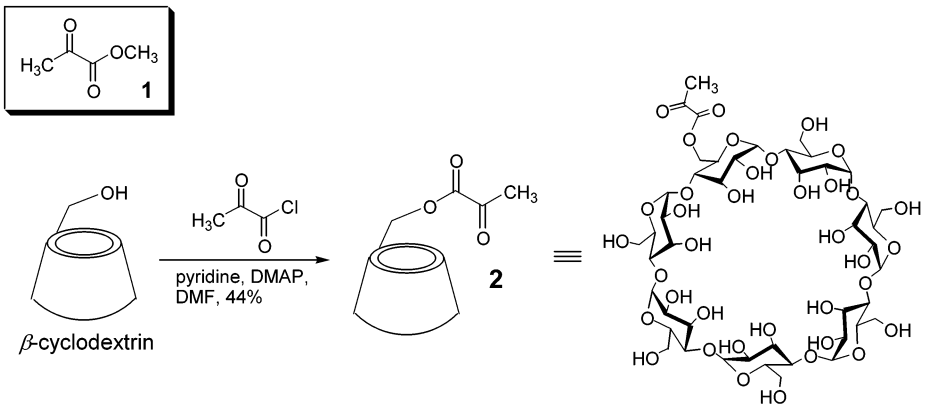

FIGURE 2. Synthesis of β-cyclodextrin ketoester **2**.

mine oxidation of the secondary hydroxyl groups of the CDs leading to poorly defined ketone products. Furthermore, unactivated secondary ketone groups are well-known for their poor reactivities toward dioxirane formation resulting in low oxidation efficiency of the keto-cyclodextrins. Yet, it remains uncertain as to whether the keto-cyclodextrin-mediated oxidations proceed via inclusion-complex formation.

In this work, we intend to explore the potential of CD-modified ketones as supramolecular catalysts for stereoselective alkene epoxidation. Compared to unactivated secondary ketones, ketoesters are far more reactive for the dioxirane-mediated oxidations. Here, we prepared a structurally well-defined cyclodextrin ketoester **2** by functionalization of the primary hydroxyl rim of the cyclodextrin with pyruvyl chloride. Our experimental findings suggested that **2** would bind alkenes into its chiral hydrophobic pocket, followed by oxidation with the covalently tethered dioxirane. With this supramolecular approach, enantioselective epoxidation of styrenes has been achieved with up to 40% ee, and sub-stoichiometric amount of the CD-ketoester (20−50 mol %) could be used without compromise of the enantioselectivity.

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Results and Discussion

Synthesis of β-Cyclodextrin Ketoester 2. Previous studies already showed that methyl pyruvate (**1**) is effective for alkane oxidation with Oxone as terminal oxidant (Figure 2).[8] In this work, we have tethered **1** to a primary hydroxyl group of β-cyclodextrin by the coupling reaction of pyruvyl chloride with β-cyclodextrin, and **2** was obtained in 44% isolated yield.

2-Mediated Epoxidation of Terpenes 3a−d. To evaluate the activity of **2**, we set out to examine the oxidation of (*S*)-α-terpineol and derivatives, which are known to form inclusion complexes with β-cyclodextrin. In general, the epoxidation reaction was performed by adding **2** (100 mol %) to the terpenes in an aqueous Na_2·EDTA solution (4×10^{-4} M), followed by addition of CH_3CN and a mixture of Oxone and $NaHCO_3$ at room temperature. As illustrated in Table 1, (*S*)-α-terpineol (**3a**) was epoxidized to afford a mixture of *cis*- and *trans*-**4a** (cis/trans = 2.5:1) in 85% yield based on 97% conversion in 40 min (entry 1). Epoxidation of (*S*)-**3b** with the tertiary hydroxyl group being protected as a methoxy ether furnished similar results (compare entries 1 vs 6). However, (*S*)-**3c** bearing a more bulky OAc group was oxidized to afford **4c** in significantly lower stereoselectivity (cis/trans = 1.6:1) (entry 9). Notably, epoxidation of (*S*)-**3d** bearing a sterically demanding OOCPh group proceeded nonstereoselectively to give an equimolar mixture of *cis*- and *trans*-**4d** (entry 12). The above results indicate that the stereoselectivity of the **2**-mediated terpineol epoxidations is sensitive to the steric size of the terpineol protecting groups.

Epoxidation of (*S*)-**3a** using β-cyclodextrin and **1** was found to give equimolar mixtures of *cis*-/*trans*-epoxides (Table 1, entry 2). This result is in fact identical to the case when **1** alone was used as catalyst (i.e., no β-cyclodextrin used) and no diastereoselectivity was observed (entry 4). We found that there was a significant background reaction between Oxone and terpenes such as **3a**, and an equimolar mixture of *cis*-/*trans*-epoxide was obtained in 86% yield at 49% conversion (entry 5). And yet, addition of β-cyclodextrin to the reaction mixture of "Oxone + **3a**" did not induce important diastereoselectivity (cis/trans = 1:1.2) (entry 3). These control experi-

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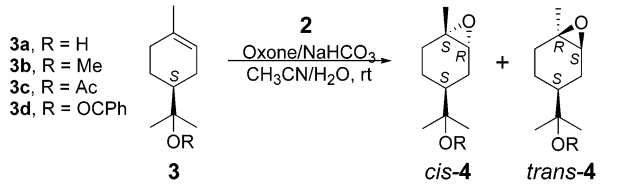
TABLE 1. Stereoselective Epoxidation of (*S*)-Terpenes 3[a]



entry	substrate	R	% convn.[b]	% yield[c]	epoxide: cis/trans[d]
1	**3a**	H	97	85	2.5:1
2[e]	**3a**		100	81	1.1:1
3[f]	**3a**		53	62	1:1.2
4[g]	**3a**		100	77	1.2:1
5[h]	**3a**		49	86	1.2:1
6	**3b**	Me	91	79	2.6:1
7[e]	**3b**		96	76	1:1.2
8[f]	**3b**		58	40	1:1.2
9	**3c**	Ac	74	78	1.6:1
10[e]	**3c**		98	84	1.1:1
11[f]	**3c**		36	46	1:1.4
12	**3d**	OCPh	65	90	1:1.2
13[e]	**3d**		91	86	1:1.4
14[f]	**3d**		9	-	1:1.3

[a] Unless otherwise indicated, all epoxidation reactions were carried out at room temperature with 0.1 mmol of **2**, 0.1 mmol of alkene, 0.1 mmol of Oxone, and 0.31 mmol of $NaHCO_3$ in 2 mL of aqueous Na_2·EDTA solution (4×10^{-4} M) and 3 mL of CH_3CN for 40 min. [b] Conversion was calculated from the amount of unreacted alkene recovered by flash column chromatography. [c] Isolated yield with percentage based on alkene consumption. [d] Determined by ^{1}H NMR. [e] 0.1 mmol of β-cyclodextrin, 0.1 mmol of **1**. [f] 0.1 mmol of β-cyclodextrin. [g] 0.1 mmol of **1**. [h] Without **2**.

ments confirm the unique reactivity of the CD-modified ketoester **2** for stereoselective terpineol epoxidation.

As illustrated in Table 1, stereoselectivity of the **2**-mediated epoxidation decreased with the increase of steric bulkiness of the terpenes **3a**−**d**. This observation could be attributed to the differences in binding geometries between **2** and the terpenes. To support our hypothesis, we decided to study the inclusion complex formation between **2** and terpenes by ^{1}H NMR titration and 2D ROESY NMR experiments.

^{1}H NMR Titration for Binding of 3a to 2. Binding of **3a** into the cyclodextrin cavity of **2** was confirmed by ^{1}H NMR titration experiments.[9] Incremental addition of neat **3a** into a D_2O solution of **2** induced significant changes of the chemical shifts of H3 and H5 (located inside the CD cavity), whereas only little changes of chemical shifts of H2 and H4 (located outside the CD cavity) were observed (Figure 3). This observation is consistent with inclusion complex formation between **2** and **3a**. Moreover, an NMR titration curve for the inclusion complex formation was obtained by plotting $\Delta\delta$H3 of **2** against the mole ratio of **2** and **3a** (Figure 4). By extrapolation of the curve, the stoichiometry for the inclusion complex formation was determined to be 1:1. By nonlinear regression method, the binding constant was evaluated to be 113 M^{-1} at 298 K. Noted that both

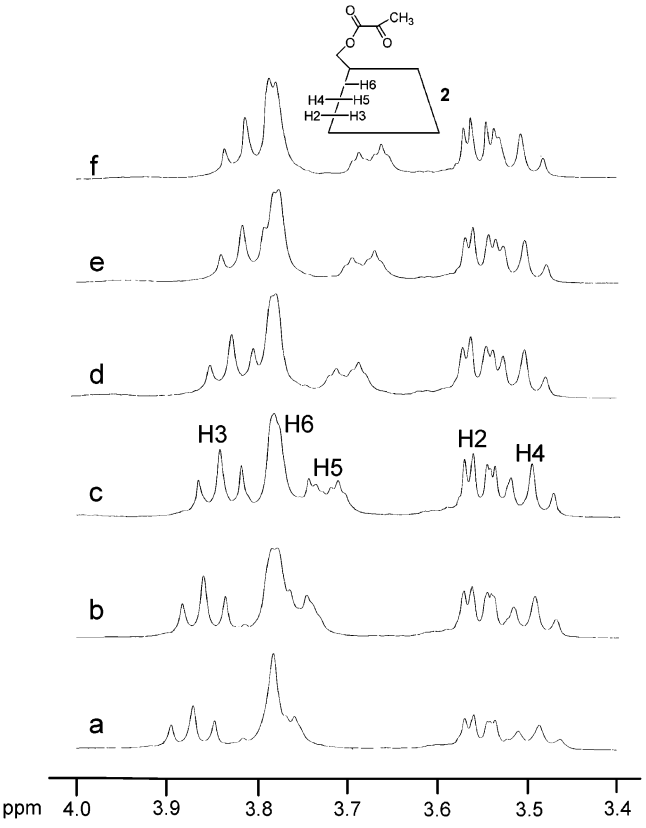


FIGURE 3. Partial 400 MHz ^{1}H NMR spectra (only protons of **2** are shown) for solutions of **2**/**3a** complex. [**3a**]/[**2**] ratios: (a) 0, (b) 0.20, (c) 0.44, (d) 0.71, (e) 0.93, and (f) 1.08.

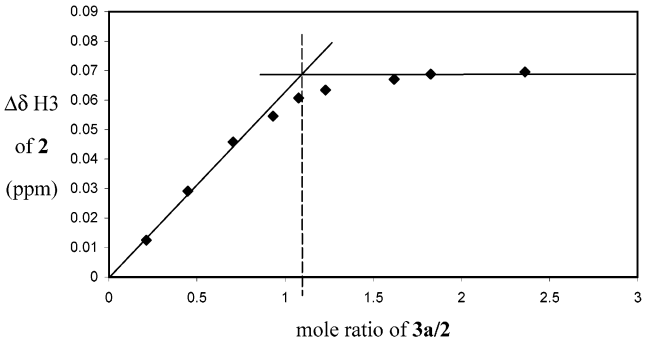


FIGURE 4. ^{1}H NMR titration curve for **2** and **3a**.

2 and **3a** are chiral molecules, and different binding modes (see later section) of **3a** would in principle give diastereomeric inclusion complexes. However, no apparent peak resolution corresponding to the diastereomeric inclusion complex formation was observed throughout the NMR titration experiment. The lack of peak resolution may indicate a rapid interconversion between diastereomeric binding modes at 298 K.

Studies on Binding Geometries between 2 and 3a−c by 2D ROESY Experiments. Knowing that **2** would bind to **3a** to form inclusion complex, we proceeded to probe the binding geometries between **2** and **3a**−**c** by 2D ROESY experiments.[9] As depicted in Figure 5, the Me9 and Me10 groups of **3a** show strong NOE correlation peaks with H3, H5, and H6 of **2**, suggesting *complete* inclusion of the $-C(CH_3)_2OH$ group into the CD cavity. Considering the 1:1 stoichiometry, two binding geom-

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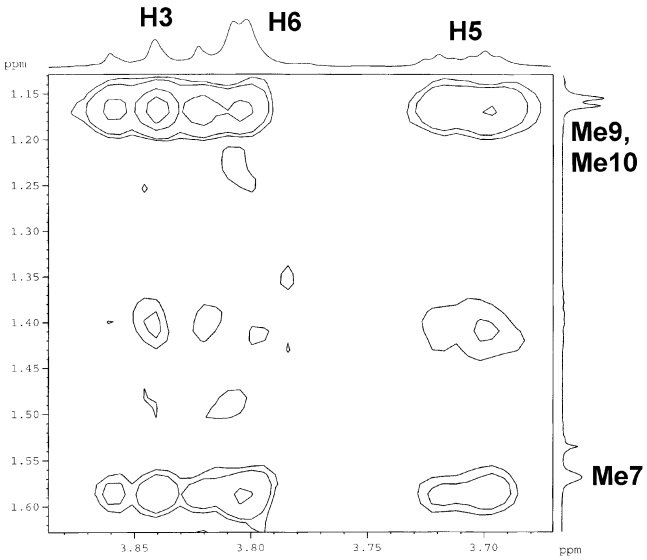

FIGURE 5. Partial contour plot of the 500 MHz ROESY spectrum for binding of **3a** (6.0 mM) to **2** (5.9 mM) in D_2O.

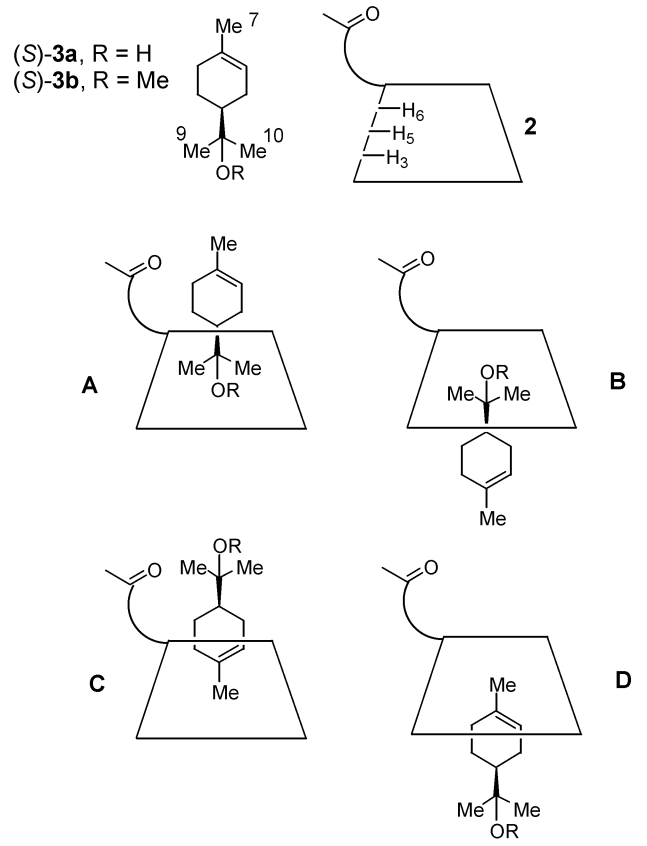

FIGURE 6. Proposed binding geometries for the inclusion of (*S*)-**3a** and **3b** into **2**.

etries **A** and **B** are discernible (Figure 6). In addition, the presence of NOE correlation peaks between Me7 of **3a** and H3, H5, and H6 of **2** revealed the inclusion of the terpenic double bond into the CD cavity (Figure 5), and two other binding geometries **C** and **D** are also expected (Figure 6). For binding of **3b** to **2**, a similar ROESY spectrum was obtained (see the Supporting Information); therefore, binding geometries **A**−**D** should also apply (Figure 6).

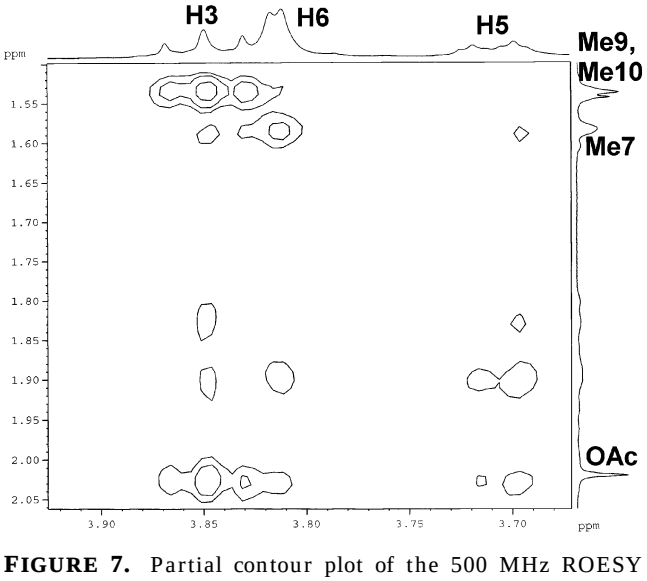

FIGURE 7. Partial contour plot of the 500 MHz ROESY spectrum for binding of **3c** (5.1 mM) to **2** (4.9 mM) in D_2O.

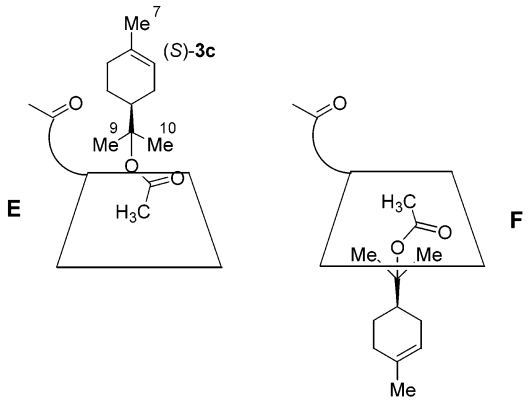

FIGURE 8. Proposed binding geometries for the inclusion of (*S*)-**3c** into **2**.

However, different binding geometries for **3c** were observed, in which case the $-C(CH_3)_2OAc$ group is only *partially* included based on the NOE correlation peaks between the OAc group of **3c** and the H3, H5, and H6 of **2** (Figure 7). Unlike **3a** and **3b**, the lack of NOE correlation peaks between Me9 and Me10 of **3c** and H5 and H6 of **2** suggests that the two methyl groups are not included. Thus, binding geometries **E** and **F** are proposed (Figure 8). The binding geometries of the inclusion of the terpenic double bonds are not shown. Attempts to perform 2D ROESY experiment for the inclusion complex formation between **2** and **3d** were unsuccessful owing to the very low solubility of **3d** in D_2O.

Steric Effects on the Stereoselective Terpene Epoxidations. As noted earlier, the **2**-mediated epoxidation of **3a** and **3b** resulted in similar stereoselectivity. Based on our NMR studies, the $-C(CH_3)_2OH$ group of **3a** and the $-C(CH_3)_2OMe$ group of **3b** should be *completely* included into the CD cavity. We reasoned that their double bonds should be in close proximity to the covalently linked dioxirane (Figure 9). Due to geometric constraints of the tethered dioxirane, epoxidation would be preferentially directed to one particular face of the double bond, leading to comparable facial selectivity

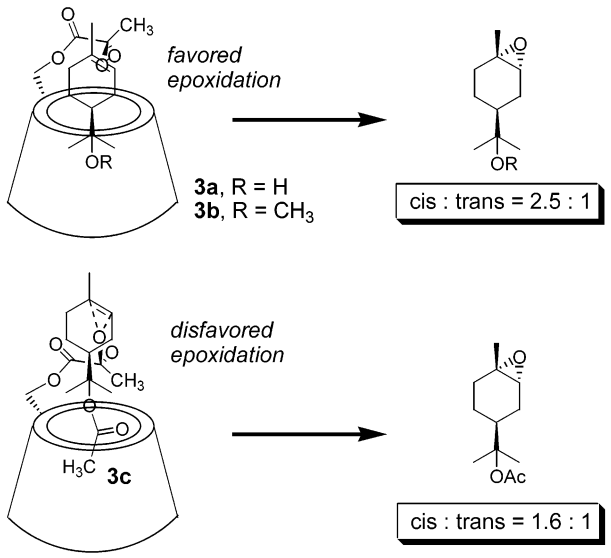

FIGURE 9. Schematic diagram for stereoselective epoxidation of **3a**−**c**.

TABLE 2. Double-Asymmetric Epoxidation of Limonenes[a]

entry	substrate	% convn.[b]	% yield[b]	1,2-epoxide	diastereomeric ratio[c]
1	(*S*)-**3e**	67	45[d]		2.5 : 1
2[e]		89[f]	39[d, g]		1.1 : 1
3[h]		< 5	–		1 : 1
4	(*R*)-**3e**	69	58[d]		4.1 : 1
5[e]		89[f]	40[d, g]		1 : 1
6[h]		< 5	–		1.1 : 1

[a] Unless otherwise indicated, all epoxidation reactions were carried out at room temperature with 0.5 mmol of alkene, 0.5 mmol of **2**, 0.5 mmol of Oxone, and 1.55 mmol of $NaHCO_3$ in 10 mL of aqueous Na_2·EDTA solution (4×10^{-4} M) and 15 mL of CH_3CN, 20 min. [b] Conversion and yield of 1,2-epoxide were found by GC using the internal standard method. [c] Determined by ^1H NMR.[d] The yields of bis-epoxides and 8,9-epoxides were determined to be around 20% and 5%, respectively, by flash column chromatography. [e] Epoxidation reactions were carried out at room temperature with 1.0 mmol of alkene, 1.0 mmol of β-cyclodextrin, 1.0 mmol of **1**, 1.0 mmol of Oxone, and 3.1 mmol of $NaHCO_3$ in 20 mL of aqueous, Na_2·EDTA solution (4×10^{-4} M) and 30 mL of CH_3CN, 20 min. [f] Conversion was calculated from the amount of unreacted alkene recovered by flash column chromatography. [g] Isolated yield with percentage based on alkene consumption.[h] In place of **2**, 0.5 mmol of β-cyclodextrin was used.

(cis/trans = ~2.5:1) (Table 1, entries 1 and 6). On the other hand, the reduced facial selectivity (cis/trans = 1.6:1) in the epoxidation of **3c** could have arisen from the *partial* inclusion of its bulky $-C(CH_3)_2OAc$ group (binding geometry **E**) so that the double bond of **3c** was more distant from the linked dioxirane (Figure 9). It is also expected that nonstereoselective epoxidation would proceed by inclusion complex **F**, in which the double bond is not included within the CD cavity. Thus, epoxidation of the nonincluded double bond by Oxone would give equimolar mixtures of *cis*- and *trans*-epoxides. Indeed, control experiments already showed that the use of β-CD plus **1** and Oxone failed to effect any facial selectivity in the epoxidation reactions.

TABLE 3. Asymmetric Epoxidation of Styrenes Mediated by 2[a]

entry	substrate	% yield[b]	% ee[c]	epoxide config.[d]
1		99	31	(*R*,*R*)
2[e]		88	30	(*R*,*R*)
3[f]		88	29	(*R*,*R*)
4[g]		86	36	(*R*,*R*)
5		77	26	(*R*,*R*)
6		81[h]	35	(*R*,*R*)
7		80	37	(1*R*,2*S*)
8		75	36	(*R*)
9[i]		75	40	(*R*)
10		70	17	(*R*)

[a] Unless otherwise indicated, all epoxidation reactions were carried out at room temperature with 0.15 mmol of alkene, 0.15 mmol of **2**, 0.45 mmol of Oxone, and 1.40 mmol of $NaHCO_3$ in 3 mL of aqueous Na_2·EDTA solution (4×10^{-4} M) and 4.5 mL of CH_3CN, 1 h. [b] Isolated yield based on complete alkene consumption. [c] Determined by ^1H NMR using chiral shift reagent $Eu(hfc)_3$ (Aldrich no. 16,474-7). [d] The configuration of the major enantiomer was assigned by comparing the chiral NMR spectral patterns with those of authentic chiral epoxides. [e] 0.075 mmol of **2**, 1.5 h. [f] 0.03 mmol of **2**, 2.5 h, 73% conversion. [g] At 0 °C, 5.5 h, 74% conversion. [h] Based on 72% conversion. [i] At 0 °C, 2.5 h.

The **2**-mediated terpene epoxidation is likely to proceed via inclusion-complex formation. Additional support of this deliberation was obtained from double-asymmetric experiments. In this work, limonenes (*S*)-**3e** and (*R*)-**3e** were selected as substrates,[10] and their **2**-mediated epoxidations gave (1*S*,2*R*)-1,2-epoxides as the major products (Table 2, entries 1 and 4). This result showed that the **2**-mediated epoxidation of (*S*)- and (*R*)-**3e** proceeded with the same facial preference regardless of the absolute configurations of the limonenes. In agreement with our proposed binding geometries, the higher diastereoselectivity for (*R*)-**3e** (4.1:1) and (*S*)-**3e** (2.5:1) can be rationalized by matched (*R*)-**3e** and mismatched (*S*)-**3e** diastereomeric inclusion complexes.

Asymmetric Epoxidation of Styrenes Mediated by 2. Our previous results showed that the **2**-mediated epoxidation of terpenes proceeded with significant facial selectivity. Thus, we decided to explore the activity of **2** for asymmetric epoxidation of styrenes (Table 3). Treatment of *trans*-stilbene with **2** (100 mol %) under the standard reaction conditions provided the corresponding chiral epoxide in 99% yield with 31% ee (entry 1).

(10) For a reference regarding the use of dimethyldioxirane for limonene epoxidation, see: Asouti, A.; Hadjiarapoglou, L. P. *Synlett* **2001**, *12*, 1847.

Enantiopurities of the chiral epoxides were determined by ^{1}H NMR spectroscopy using Eu(hfc)$_3$ as chiral shift reagent. The percentage of enantiomeric excess (% ee) was evaluated on the basis of the integration ratio of the corresponding resolved peak areas. When sub-stoichiometric quantities of **2** (20 or 50 mol %) were employed for the *trans*-stilbene epoxidation, similar ee value (~30% ee) were obtained (entries 2 and 3). At 0 °C, enantioselectivity of the *trans*-stilbene epoxidation was found to increase moderately to 36% ee (entry 4). Comparable enantioselectivities were obtained for the **2**-mediated epoxidation of *trans*-*β*-methylstyrene (26% ee) and *trans*-α-methylstilbene (35% ee) (entries 5 and 6). It was interesting to note that comparable enantioselectivity for the epoxidation of 1,2-dihydronaphthalene (37% ee) and 4-chlorostyrene (36% ee) (entries 7 and 8) was obtained under identical reaction conditions. Up to 40% ee was achieved for the **2**-mediated 4-chlorostyrene epoxidation conducted at 0 °C (entry 9). For epoxidation of α-methylstyrene, the enantioselectivity was 17% ee (entry 10). Control experiments employing *β*-cyclodextrin and **1** again gave no stereoselectivity in epoxidation of the styrenes (data not shown).

It is reported that CDs can serve as chiral templates to mediate asymmetric epoxidation via inclusion complex formation with moderate enantioselectivity using NaOCl, H_2O_2, and *t*-BuOOH as oxidants.[11] According to a report by Sakuraba and co-workers,[11d] asymmetric *trans*-*β*-methylstyrene epoxidation can be achieved by preformed crystalline CD−alkene inclusion complex with NaOCl as oxidant, and chiral epoxide was obtained in 40% ee after 4 days of reaction at 0 °C. However, no enantioselectivity was observed when the same reaction was conducted in aqueous solution. In this work, our **2**-mediated epoxidation of *trans*-*β*-methylstyrene was found to give chiral epoxide in 26% ee under aqueous CH_3CN solution (Table 3, entry 5).

Generally speaking, chiral dioxiranes give higher enantioselectivity in the epoxidation of *trans*- and trisubstituted alkenes than *cis*- and terminal alkenes.[5,6] In view of the comparable ee values being obtained for a series of styrenes, **2**-mediated styrene epoxidation would proceed through similar inclusion complexes. We reason that the phenyl ring of styrenes would be included within the CD cavity. Consistent with the results obtained from the **2**-mediated terpene oxidations, the formation of (*R*)- or (*R*,*R*)-epoxides as the major enantiomers suggests that the *Re* face of the double bond was preferentially epoxidized by the tethered dioxirane. Due to the poor water solubility of the alkenes, attempts to investigate the inclusion complex formation by 2D ROESY experiment were unsuccessful.

Experimental Section

Synthesis of *β*-Cyclodextrin Ketoester 2. α,α-Dichloromethyl methyl ether (6.1 mL, 67.5 mmol) was added dropwise to pyruvic acid (6.0 g, 67.5 mmol) in a round-bottom flask at room temperature. The reaction mixture was heated at 50 °C for 45 min. Then, the crude acid chloride was added dropwise to a solution of *β*-cyclodextrin (5.1 g, 4.5 mmol), 4-(dimethylamino)pyridine (0.11 g, 0.9 mmol), and distilled pyridine (7.5 mL) in anhydrous DMF (25 mL) at 0 °C under nitrogen atmosphere. After being stirred at room temperature for 5 h, the reaction mixture was added dropwise to acetone (400 mL) with stirring at 0 °C, and the precipitate was collected by filtration. The pale yellow precipitate was dissolved in H_2O (6 mL) and added dropwise to EtOH (300 mL) at 0 °C. The off-white precipitate collected by filtration was dissolved in H_2O (4 mL) and added dropwise to EtOH (300 mL) at 0 °C. Finally, the precipitate was filtered and dried under vacuum at 40 °C to furnish **2** (2.4 g, 2 mmol, 44% yield) as a white solid: analytical TLC (silica gel 60) (5:4:3 butanol−ethanol−water (v/v/v)), $R_f = 0.36$; mp > 250 °C; ^{1}H NMR (400 MHz, D_2O)[12] δ 5.00 (d, $J = 3$ Hz, 7H), 4.05−4.58 (m, 3H), 3.75−3.92 (m, 25H), 3.50−3.65 (m, 14H), 2.45 (s, 0.5 H, COCH_3), 1.54 (s, 2.5 H, C(OH)$_2$CH_3); ^{13}C NMR (100.6 MHz, DMSO-d_6, TMS) (ketone form of **2**) δ 191.24, 159.76, 102.30, 101.77, 101.42, 81.94, 81.38, 81.08, 72.87, 72.24, 71.87, 68.52, 64.81, 59.74, 59.36, 26.58; ^{13}C NMR (100.6 MHz, D_2O) (hydrate form of **2**) δ 172.64, 102.16, 101.80, 101.54, 92.79, 81.36, 81.25, 80.88, 73.05, 72.04, 71.78, 69.40, 64.97, 60.26, 60.03, 25.17; IR (KBr) 1734 cm^{-1}; UV/vis (H_2O) λ_{max} 255 nm; FABMS *m*/*z* 1205 (M^+, 5), 1228 (M^+ + Na, 8).

General Procedure for 2-Mediated Epoxidation Reactions (Table 1, Entry 1). To a round-bottom flask containing (*S*)-**3a** (15.4 mg, 0.1 mmol) in an aqueous Na_2·EDTA solution (4×10^{-4} M, 2 mL) was added **2** (120 mg, 0.1 mmol) at room temperature. After the reaction mixture was stirred for 5 min, CH_3CN (3 mL) and a mixture of Oxone (0.1 mmol) and $NaHCO_3$ (0.31 mmol) were added. After being stirred for 40 min at room temperature, the reaction mixture was diluted with H_2O (20 mL) and extracted with Et_2O (4 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% EtOAc in hexane) to provide a 2.5:1 mixture of epoxides *cis*-**4a** and *trans*-**4a** (14.1 mg, 85% yield based on 97% conversion) as a colorless oil. The ratio of *cis*-**4a** to *trans*-**4a** was determined by ^{1}H NMR.

General Procedure for Epoxidation Reactions Mediated by 1 and *β*-Cyclodextrin (Table 1, entry 2). To a round-bottom flask containing (*S*)-**3a** (15.4 mg, 0.1 mmol) in an aqueous Na_2·EDTA solution (4×10^{-4} M, 2 mL) was added *β*-cyclodextrin (114 mg, 0.1 mmol) at room temperature. After the reaction mixture was stirred for 5 min, a solution of **1** (10 mg, 0.1 mmol) in CH_3CN (3 mL) and a mixture of Oxone (0.1 mmol) and $NaHCO_3$ (0.31 mmol) were added. After being stirred for 40 min at room temperature, the reaction mixture was diluted with H_2O (20 mL) and extracted with Et_2O (4 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% EtOAc in hexane) to provide a 1.1:1 mixture of epoxides *cis*-**4a** and *trans*-**4a** (13.8 mg, 81% yield) as a colorless oil. The ratio of *cis*-**4a** to *trans*-**4a** was determined by ^{1}H NMR.

Experimental Procedure for NMR Titration Experiment. To a solution of **2** in D_2O (1.5 mL, 4 mM) in a NMR tube at ambient temperature was added neat (*S*)-**3a** in portions (0.2−0.8 equiv) until the change in chemical shift ($\Delta\delta$H3) of **2** was negligible. The exact mole ratios of **2**/**3a** were determined from the integration ratios of their ^{1}H NMR signals (H1 of **2** and olefinic proton of **3a**). The chemical shift (H1) of **2** was

(11) For references regarding the use of CDs as chiral templates for asymmetric epoxidation, see: (a) Banfi, S.; Colonna, S.; Julia, S. *Synth. Commun.* **1983**, *13*, 1049. (b) Hu, Y.; Harada, A.; Takahashi, S. *Synth. Commun.* **1988**, *18*, 1607. (c) Colonna, S.; Manfredi, A.; Annunziata, R.; Gaggero, N.; Casella, L. *J. Org. Chem.* **1990**, *55*, 5862. (d) Sakuraba, H.; Tanaka, Y. *Org. Prep. Proced. Int.* **1998**, *30*, 226.

(12) On the basis of the work by Pocker and co-workers, both the ketone form and hydrate form of pyruvate esters in D_2O can be observed by ^{1}H NMR spectroscopy. The chemical shift of the methyl group protons (δ ~2.4) of the ketone form is about 0.9 ppm downfield shift compared with that of the hydrate form (δ ~1.5) (see: Pocker Y.; Meany J. E.; Zadoroj, C. *J. Phys. Chem.* **1971**, *75*, 792). In this work, compared with the literature data, the singlet at δ 2.45 was assigned to be the methyl group protons of the ketone form of **2** while the singlet at δ 1.54 was assigned to be the methyl group protons of the hydrate form of **2**.

used as an internal reference as it is least affected by inclusion complex formation. A ^{1}H NMR titration curve was obtained by plotting $\Delta\delta$H3 of **2** against the mole ratios of **2** and **3a**.

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Supporting Information Available: Characterization data of **3b**−**d** and **4d**; ^{1}H NMR determination of the cis/trans ratio of terpene epoxides; ^{1}H NMR determination of the enantiomeric excess of styrene epoxides; ^{1}H and ^{13}C NMR spectra of **2** and **4d**; 2D ROESY spectrum for complex **2**/**3b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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