Catalytic Asymmetric Aldol Reactions in Aqueous Media Using Chiral Bis-pyridino-18-crown-6–Rare Earth Metal Triflate Complexes

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Abstract: Catalytic asymmetric aldol reactions in aqueous media have been developed using $Pr(OTf)_3$ and chiral bis-pyridino-18-crown-6 **1**. In the asymmetric aldol reaction using rare earth metal triflates $(RE(OTf)_3)$ and **1**, slight changes in the ionic diameters of the metal cations greatly affected the diastereo- and enantioselectivities of the products. The substituents (MeO, Br) at the 4-position of the pyridine rings of the crown ether did not significantly affect the selectivities in the asymmetric aldol reaction, although they affected the binding ability of the crown ether with RE cations and the catalytic activity of $Pr(OTf)_3$– crown ether complexes. From X-ray structures of $RE(NO_3)_3$–crown ether complexes, it was found that they had similar structures regardless of the RE cations and the crown ethers used. Accordingly, the binding ability of the crown ether with the RE cation and the catalytic activity of the complex are important for attaining high selectivity in the asymmetric aldol reaction. Various aromatic and α,β-unsaturated aldehydes and silyl enol ethers derived from ketones and a thioester can be employed in the catalytic asymmetric aldol reactions using $Pr(OTf)_3$ and **1**, to provide the aldol adducts in good to high yields and stereoselectivities. In the case using the silyl enol ether derived from the thioester, 2,6-di-*tert*-butylpyridine significantly improved the yields of the aldol adducts.

Introduction

Asymmetric aldol reactions provide one of the most powerful tools for constructing optically active β-hydroxy carbonyl compounds.[1] In the past two decades, various enantioselective aldol reactions have been developed to pursue efficiency in obtaining these chiral compounds. Among them, catalytic asymmetric aldol reactions of aldehydes with silyl enol ethers (the Mukaiyama aldol reaction[2]) mediated by chiral Lewis acids have been elaborated into the most powerful and efficient asymmetric aldol methodology.

In recent years, organic reactions in aqueous media have attracted a great deal of attention.[3] These reactions have several advantages as compared to reactions under dry conditions, which are required in many conventional synthetic procedures. For example, while it is necessary to dry solvents and substrates vigorously before use for many reactions in dry organic solvents,

such drying is unnecessary for reactions in aqueous media. Moreover, water is no doubt cheap, safe, and clean as compared to organic solvents, and unique reactivity and selectivity which are not attained under dry conditions are often observed in aqueous reactions. Because water is a "solvent" in living organisms, studies on organic reactions in aqueous media may lead to a real understanding of life and nature; particularly, chiral catalysts which work well in aqueous media may become models of enzymes.

In the course of our investigations to develop new synthetic reactions in aqueous media, we have reported lanthanide triflates $(Ln(OTf)_3)$-catalyzed aldol reactions of aldehydes with silyl enol ethers in aqueous THF.[4] Since then, not only $Ln(OTf)_3$ but also $Sc(OTf)_3$ and $Y(OTf)_3$ were shown to be useful for the reactions. The most characteristic feature of these rare earth metal triflates $(RE(OTf)_3)$ is that they act as water-compatible Lewis acids in aqueous solvents, and they have been regarded as new types of Lewis acids.[5] $RE(OTf)_3$ are strong Lewis acids because of the hard character of their metal cations and the strong electron-withdrawing effect of the trifluoromethanesulfonyl group, and

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(1) For reviews on asymmetric aldol reactions, see: (a) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352. (b) Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; Vol. 3, p 998. (c) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095. (d) Gröger, H.; Vogl, E. M.; Shibasaki, M. *Chem.-Eur. J.* **1998**, *4*, 1137. (e) Nelson, S. G. *Tetrahedron: Assymmery* **1998**, *9*, 357.
(2) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1012.
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(4) (a) Kobayashi, S. *Chem. Lett.* **1991**, 2187. (b) Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3590.
(5) (a) Kobayashi, S. *Synlett* **1994**, 689. (b) Kobayashi, S. In *Lanthanides: Chemistry and Use in Organic Synthesis*: Kobayashi, S., Ed.; Springer: Berlin, 1999; p 63. (c) Kobayashi, S. *Eur. J. Org. Chem.* **1950**, *15*, 5. (d) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. *Chem. Rev.* **2002**, *102*, 2227.
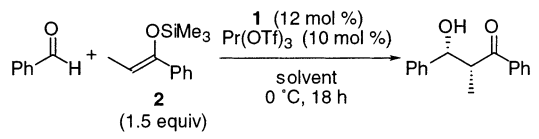
many useful reactions are catalyzed by RE(OTf)$_3$ in aqueous media as well as in dry organic solvents.[5] Only catalytic amounts of the triflates are enough to complete the reactions in most cases. Furthermore, RE(OTf)$_3$ can be easily recovered after the reactions and reused without loss of activity.

Despite these synthetic utilities of RE(OTf)$_3$, there had been no successful example of asymmetric reactions using chiral RE(OTf)$_3$ as chiral Lewis acid catalysts (catalytic asymmetric reactions) in aqueous media. Catalytic asymmetric reactions, especially carbon−carbon bond-forming reactions, in aqueous media have been a subject of current importance, while only limited examples have been reported so far.[6] Therefore, we undertook the development of catalytic asymmetric reactions using RE(OTf)$_3$ in aqueous media,[7] and we have recently developed the first example of RE(OTf)$_3$-catalyzed asymmetric aldol reactions using a chiral crown ether (**1**) in aqueous media.[8] Herein we describe the detailed studies and further improvements of the asymmetric aldol reactions in aqueous media. This work sheds light on important factors which govern the effectiveness of the catalytic system and will provide useful ideas for designing new catalysts which work efficiently in aqueous media.

Results and Discussion

Catalytic asymmetric aldol reactions using RE(OTf)$_3$ and a chiral ligand are difficult to achieve in aqueous media, because competitive ligand exchange between a chiral ligand and water easily occurs, and this leads to a decrease in the enantioselectivity of the products by competition between the chiral Lewis acid- and achiral, free Lewis acid-catalyzed pathways. While many ligands such as aminocarboxylate type ones can coordinate to RE cations strongly in aqueous solvents,[9] these ligands also reduce the Lewis acidity of the RE cations significantly. As a result, the complexes are not sufficiently Lewis acidic to catalyze the desired reactions. To overcome this problem, a chiral ligand which coordinates to the metal cations strongly, but does not significantly reduce the Lewis acidity of RE(OTf)$_3$, is needed.[10−12] Recently, we have reported catalytic asymmetric aldol reactions in aqueous media using a combination of a chiral crown ether and Pb(OTf)$_2$.[7d] In these reactions, the chiral crown ether was found not to reduce the catalytic activity of Pb(OTf)$_2$. We assumed that use of chiral multidentate ligands such as crown
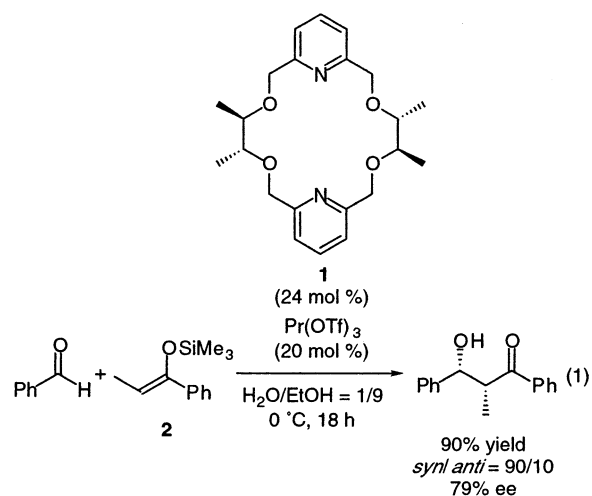
Table 1. Effect of Solvents

entry	solvent	yield (%)	*syn/anti*	ee (*syn*) (%)
1	H$_2$O/EtOH = 1/3	55	88/12	76
2	H$_2$O/EtOH = 1/9	85	91/9	78
3	H$_2$O/EtOH = 1/27	89	93/7	80
4[a]	H$_2$O/THF = 1/9	73	73/27	47
5[b]	H$_2$O/CH$_3$CN = 1/9	92	87/13	61
6[c]	EtOH	51	85/15	23
7[d]	CH$_2$Cl$_2$	4	57/43	28

[a] 31 h. [b] 112 h. [c] 16 h. [d] 35 h.

ethers would be a key to develop Lewis acid-catalyzed asymmetric reactions in aqueous media. Therefore, we decided to screen various chiral crown ethers for RE(OTf)$_3$.[13,14]

After many trials, it turned out that crown ether **1**[15−17] was effective for catalytic asymmetric aldol reactions in aqueous EtOH. For example, when **1** (24 mol %) and Pr(OTf)$_3$ (20 mol %), one of RE(OTf)$_3$, were used, the reaction of benzaldehyde with silyl enol ether **2** in H$_2$O/EtOH (1/9 (v/v)) at 0 °C for 18 h gave the desired aldol adduct in high yield with good diastereo- and enantioselectivities (eq 1).[18]

We next examined the effect of solvents in this reaction (Table 1). Use of aqueous EtOH gave good selectivities regardless of the ratios between 1/3 and 1/27 (entries 1−3), although the increased amount of water resulted in lower yield because of the comparatively rapid hydrolysis of **2** (entry 1). Lower selectivities were obtained when the reaction was carried out in aqueous THF (entry 4) or aqueous CH$_3$CN (entry 5).

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(7) We have recently reported Cu(II)- and Pb(II)-catalyzed asymmetric aldol reactions in aqueous media: (a) Kobayashi, S.; Nagayama, S.; Busujima, T. *Chem. Lett.* **1999**, 71. (b) Kobayashi, S.; Nagayama, S.; Busujima, T. *Tetrahedron* **1999**, *55*, 8739. (c) Kobayashi, S.; Mori, Y.; Nagayama, S.; Manabe, K. *Green Chem.* **1999**, *1*, 175. (d) Nagayama, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 11531.

(8) Kobayashi, S.; Hamada, T.; Nagayama, S.; Manabe, K. *Org. Lett.* **2001**, *3*, 165.

(9) Hart, F. A. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Gillard, R. D., McCleverty, J. A., Eds.; Pergamon Press: Oxford, 1987; Vol. 3, Chapter 39.

(10) Engberts et al. reported a slight ligand acceleration in an asymmetric Diels−Alder reaction in aqueous media. (a) Otto, S.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1999**, *121*, 6798. See also: (b) Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059. (c) Denmark, S. E.; Wynn, T. *J. Am. Chem. Soc.* **2001**, *123*, 6199.

(11) Although the mechanism has not been fully elucidated, Yamamoto et al. have reported that addition of a catalytic amount of triphenylphosphine accelerates an AgOTf-catalyzed allylation of benzaldehyde with allyltri-butyltin in aqueous THF. Yanagisawa, A.; Nakashima, H.; Ishiba, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 4723.

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(14) For chiral rare earth metal complexes, see: Aspinall, H. C. *Chem. Rev.* **2002**, *102*, 1807.

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(17) For preparation of crown ethers **1**, **3**−**7**, see the Supporting Information.

(18) The diastereo- and enantioselectivities of the aldol adduct were determined according to the literature method. See: Denmark, S. E.; Wong, K.-T.; Stavenger, R. A. *J. Am. Chem. Soc.* **1997**, *119*, 2333.
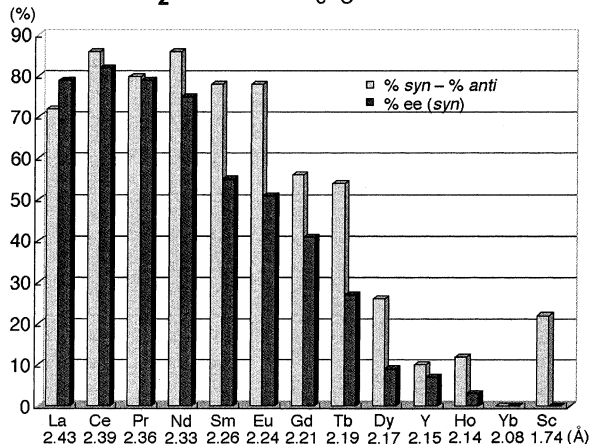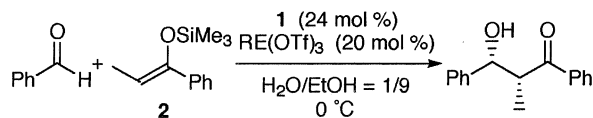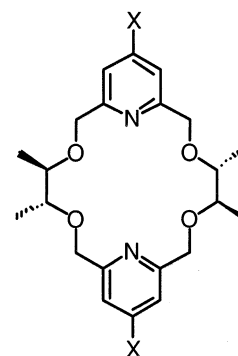
Figure 1. Enantio- and diastereoselectivities in the aldol reaction using rare earth metal triflates and **1**, and ionic diameters (8-coordination for Sc, 9-coordination for other metals) of the metal cations (RE^{3+}). Yields: 49−95%.

When the reaction was carried out in pure EtOH or CH$_2$Cl$_2$, much lower yield and selectivities were observed (entries 6, 7).[19] The results indicate that a certain amount of, but not too much, water is essential to attain good yield and selectivities. We discuss this effect of water later.

Effect of Metals in RE(OTf)$_3$. In the asymmetric aldol reaction using **1**, we carried out a systematic evaluation of RE(OTf)$_3$. The diastereo- and enantioselectivities in the reactions using RE(OTf)$_3$ having metal cations of various ionic diameters[20] are shown in Figure 1. It was found that the selectivities varied significantly with the ionic diameters.[21] While the larger cations such as La, Ce, Pr, and Nd gave the aldol adduct with high diastereo- and enantioselectivities, the smaller cations such as Dy, Y, Ho, Yb, and Sc gave lower selectivities. These results suggest that size-fitting between crown ether **1** and the metal cations is an important factor to attain high selectivities.

To study the effect of the electron-donating ability of the pyridine nitrogens, we prepared novel crown ethers **3**[17] and **4**[17] and also carried out a screening of the metal triflates in the aldol reactions. Crown ether **3**, which has electron-donating MeO groups at the 4-position of the pyridine rings of **1**, gave high selectivities for the larger cations and gave low selectivities for the smaller cations, as **1** did (Figure 2). On the other hand, the selectivity in the reactions using **4**, which has electron-withdrawing Br groups at the 4-position of the pyridine rings of **1**, was affected more significantly by the ionic diameters, although **4** showed a trend almost similar to that of **1** and **3** (Figure 3). As a consequence, it was found that the substituents at the 4-position of the pyridine rings of **1** did not significantly affect the variations of the selectivities in the aldol reaction, and, for larger cations such as La, Ce, and Pr, these crown ethers

(19) For effects of water in RE(OTf)$_3$-catalyzed aldol reactions, see: ref 4b.
(20) Shannon, R. D. *Acta Crystallogr.* **1976**, *A32*, 751.
(21) Size effects of rare earth metals on enantioselectivity have been observed in asymmetric reactions. For example: (a) Sasai, H.; Suzuki, T.; Itoh, N.; Arai, S.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 2657. (b) Evans, D. A.; Nelson, S. G.; Gagné, M. R.; Muci, A. R. *J. Am. Chem. Soc.* **1993**, *115*, 9800. (c) Kobayashi, S.; Ishitani, H.; Hachiya, I.; Araki, M. *Tetrahedron* **1994**, *50*, 11623. (d) Schaus, S. E.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 1001.
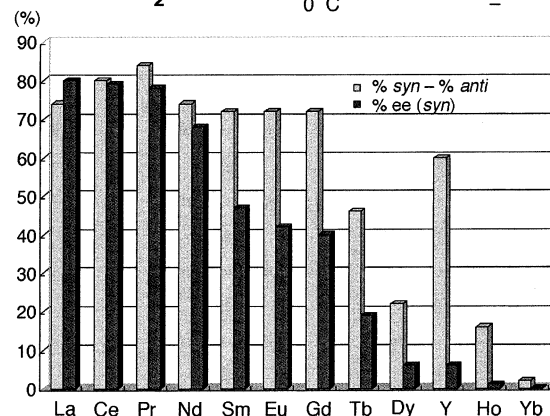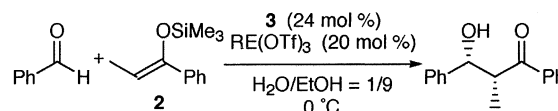
3 : X = MeO
4 : X = Br

Figure 2. Enantio- and diastereoselectivities in the aldol reaction using rare earth metal triflates and **3**. Yield: 30−89%.
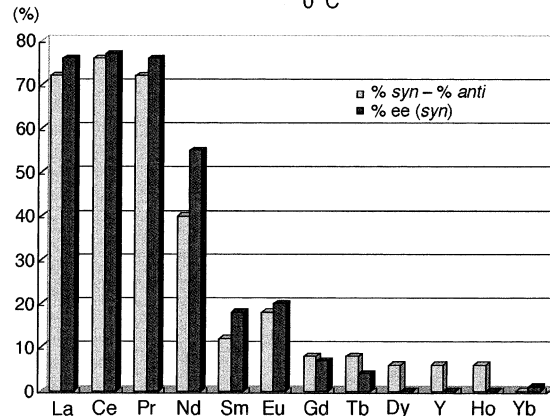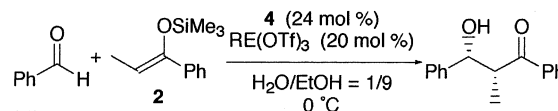

Figure 3. Enantio- and diastereoselectivities in the aldol reaction using rare earth metal triflates and **4**. Yield: 22−89%.

gave the aldol adduct with the same level of diastereo- and enantioselectivities.

Binding Ability of Chiral Crown Ethers with RE^{3+}. The observed variations of the selectivities shown in Figures 1−3 suggest that, in the case of the larger cations, they mostly exist as complexes with the crown ethers in aqueous EtOH, and that, in the case of the smaller cations, significant amounts of free

Table 2. Binding Constants of Crown Ethers (**1**, **3**, or **4**) with La^{3+} or Y^{3+}

crown ether	with La^{3+} (M^{-1})	ee (%)^b	with Y^{3+} (M^{-1})	ee (%)^b
1	6.7×10^3	79	2.5×10^2	7
3	4.3×10^5	80	7.2×10^2	6
4	3.1×10^2	76	2.6×10	−1

^{a} Determined by ^{1}H NMR in D$_2$O/C$_2$D$_5$OD (1/9) at 0 °C. ^{b} Enantioselectivity in the aldol reaction using the combination of each crown ether and metal triflate under the conditions shown in eq 1.

cations exist. To elucidate the binding ability of the crown ethers, therefore, we measured the binding constants of the crown ethers (**1**, **3**, **4**) with La^{3+}, which gave higher selectivities in the aldol reaction, and with Y^{3+}, which gave lower selectivities.

First, to determine the binding constant of **1** with La^{3+}, we carried out a ^{1}H NMR study. For a 1:1.2 mixture of **1** (0.95 mM) and La(OTf)$_3$ in D$_2$O/CD$_3$CD$_2$OD (1/9) at 0 °C, two sets of signals which correspond to the crown ether were observed in a ratio of 26:74, the minor component being free **1**. The result indicated that the equilibrium between free **1** and **1** complexed with the La cation was slow on the NMR time scale, and the binding constant was calculated to be 6.7×10^3 M^{-1}. In a similar way, the binding constants of other complexes were also determined. These results were summarized in Table 2 with each selectivity in the aldol reaction using the combination of each crown ether and the metal triflate under the conditions shown in eq 1.

Table 2 shows that all of the crown ethers bind La^{3+} much more strongly than Y^{3+}. This result cleanly explains the better selectivities of La(OTf)$_3$ than those of Y(OTf)$_3$ in the aldol reactions. However, it is notable that **3** and **4** gave selectivities almost similar to that of **1**, although **3** binds La^{3+} about 60 times more strongly than does **1**, and **4** binds La^{3+} about 20 times more weakly than does **1**. Furthermore, the binding constant of **4** with La^{3+} is smaller than that of **3** with Y^{3+}, while the enantioselectivity using **4** and La(OTf)$_3$ is much higher than that using **3** and Y(OTf)$_3$. On the basis of these results, it is considered that not only binding ability but also other factors such as catalytic activity of the RE(OTf)$_3$−crown ether complex play a vital role in attaining good selectivity. Therefore, we next studied the catalytic activity of the complexes.

Initial Reaction Rates of the Aldol Reaction. To compare the catalytic activity of RE(OTf)$_3$−crown ether (**1**, **3**, **4**) complexes, the initial reaction rates of the aldol reaction of benzaldehyde with silyl enol ether **2** using Pr(OTf)$_3$ and the crown ethers (**1**, **3**, **4**) were measured. The results are shown in Figure 4. It was found that all of the crown ethers decelerated the reaction to various extents. In the absence of the crown ethers, Pr(OTf)$_3$ catalyzed the reaction at the initial rate of 1.5×10^{-4} M s^{-1}, while **1** retarded the reaction to 1.7×10^{-5} M s^{-1}. The presence of MeO groups in **3** significantly reduced the catalytic activity (2.2×10^{-6} M s^{-1}). On the other hand, in the case of **4**, the initial rate (1.0×10^{-4} M s^{-1}) was close to that in the absence of the crown ethers. In the case of **3**, MeO groups increase the electron-donating ability of the pyridine nitrogens, while Br groups decrease this ability in the case of **4**.[22] It appears that this electron donation from the pyridine
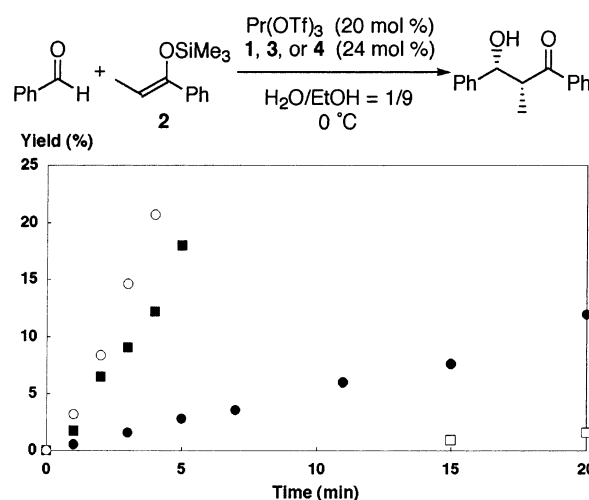
Figure 4. Initial reaction rates of the asymmetric reactions (○, Pr(OTf)$_3$; ●, Pr(OTf)$_3$ + **1**; □, Pr(OTf)$_3$ + **3**; ■, Pr(OTf)$_3$ + **4**).

nitrogens to the metal cation governs the Lewis acidity of the metal and, as a consequence, the catalytic activity of the complexes.

On the basis of these studies, the same level of enantioselectivity using crown ethers **1**, **3**, and **4** with the larger rare earth metals such as La, Ce, and Pr can be explained as follows. In the case of **1** and **3**, which have high binding ability to the metal cations, only very small amounts of free metal cations exist in the solution. Therefore, the reactions proceed mainly through a pathway catalyzed by the chiral complexes. As a consequence, **1** and **3** afforded good selectivities, while they decreased the reaction rate of the aldol reaction. On the other hand, in the case of **4**, which has relatively low binding ability, small amounts of free metal cations exist. In this case, however, the catalytic activity of the chiral complexes is close to that of the free cations. Therefore, although a certain amount of the racemic aldol adduct is produced through the pathway catalyzed by the free metal cations, the reaction still proceeds mainly through the chiral complexes-catalyzed pathway. As a consequence, a significant decrease of enantioselectivity as compared to the case of **1** or **3** was not observed.

X-ray Crystal Structures of the Complexes of RE Cation and Crown Ethers. We tried to prepare several PrX$_3$−**1** complexes with the intent of obtaining crystal structures that might elucidate the transition state model of the asymmetric aldol reactions using Pr(OTf)$_3$ and **1**. Although the complexes of RE(OTf)$_3$ with **1** could not be isolated as crystals, the complex suitable for single-crystal X-ray diffraction was obtained from Pr(NO$_3$)$_3$ and **1**.[23] The complex was found to exist as [Pr(NO$_3$)$_2$·**1**]$_3$[Pr(NO$_3$)$_6$], and a single structure for the complex of Pr with **1** was observed. The cationic moiety was shown in Figure 5. This complex has pseudo D_2 symmetry, and the Pr cation complexed with **1** is located almost in the center of the crown ring. Interestingly, the methyl groups of **1** are all in axial positions with respect to the crown ring.[24] We assume

(22) The pK_a values of pyridine, 4-methoxypyridine, and 4-bromopyridine in water at 25 °C are 5.17, 6.47, and 3.71, respectively. *Lange's Handbook of Chemistry*; Dean, J. A., Lange, N. A., Eds.; McGraw-Hill Book Company: New York, 1972; Section 5.

(23) The reaction of benzaldehyde with **2** in the presence of Pr(NO$_3$)$_3$ (20 mol %) and **1** (24 mol %) in H$_2$O/EtOH (1/9) at 0 °C for 18 h afforded the aldol adduct in 59% yield with good selectivities (*syn/anti* = 88/12 and 69% ee (*syn*)).

(24) The complex of 2,3,11,12-tetramethyl-18-crown-6 and Ca(NO$_3$)$_2$ or KSCN adopts similar comformation. (a) Dyer, R. B.; Metcalf, D. H.; Ghirardelli, R. G.; Palmer, R. A.; Holt, E. M. *J. Am. Chem. Soc.* **1986**, *108*, 3621. (b) Aoki, S.; Sasaki, S.; Koga, K. *Tetrahedron Lett.* **1989**, *30*, 7229.
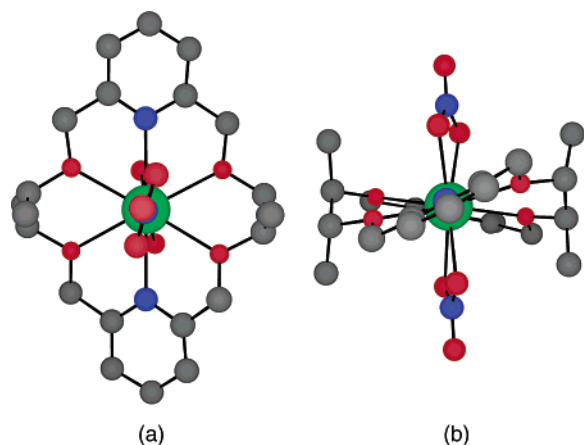
Figure 5. $[Pr(NO_3)_2 \cdot \mathbf{1}]^+$ moiety in the X-ray structure of $[Pr(NO_3)_2 \cdot \mathbf{1}]_3[Pr(NO_3)_6]$. Hydrogen atoms are omitted for clarity. (a) Top view. (b) Side view.

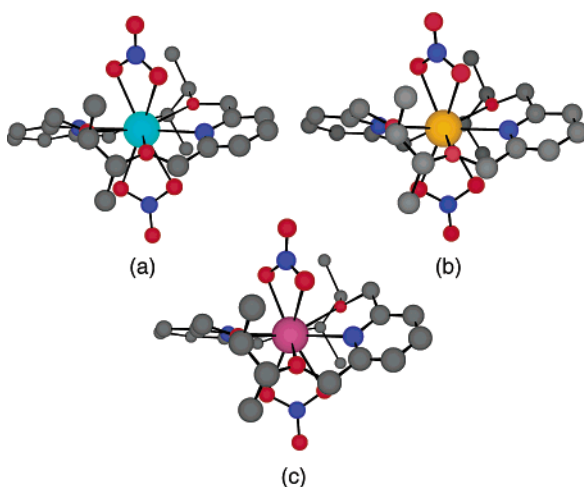**Figure 6.** X-ray structures of complexes of **1**. (a) $[Ce(NO_3)_2 \cdot \mathbf{1}]^+$ moiety in the X-ray structure of $[Ce(NO_3)_2 \cdot \mathbf{1}]_3[Ce(NO_3)_6]$. (b) $[Gd(NO_3)_2 \cdot \mathbf{1}]^+$ moiety in the X-ray structure of $[Gd(NO_3)_2 \cdot \mathbf{1}](NO_3)$. (c) $[Y(NO_3)_2 \cdot \mathbf{1}]^+$ moiety in the X-ray structure of $[Y(NO_3)_2 \cdot \mathbf{1}](NO_3)(EtOH)$.

that this conformation of the crown ring is crucial to create an effective chiral environment around the Pr cation. It is also likely that one or two of the nitrate anions are dissociated in aqueous media and that aldehydes to be activated coordinate in place of the nitrate anion.

We also obtained the X-ray crystal structures of the complexes of Ce, Gd, and Y cations with **1** as shown in Figure 6. It is noted that the structures of these complexes are very similar to each other, and that, in all of the complexes, the methyl groups are in axial positions. While all of the complexes adopt almost identical conformation, the rms (root-mean-square) deviation from the least squares plane fitted to four oxygen atoms and two nitrogen atoms of the crown ether ring becomes larger (for Ce, 0.323 Å; for Pr, 0.339 Å; for Gd, 0.403 Å; for Y, 0.436 Å) as the ionic diameter of the center metal cation becomes smaller. This deviation from the planar structure for the smaller cations may cause a slight strain to the crown ring and may be responsible for the lower binding constant of **1** with Y^{3+}.

X-ray crystal structures of the complexes of crown ethers **3** and **4** with $Pr(NO_3)_3$ were also obtained (Figure 7). In the structures of these complexes, no particular difference from $Pr(NO_3)_3-\mathbf{1}$ was observed. Again, all of the methyl groups adopt axial orientation. The average lengths of Pr−O (nitrate) bonds

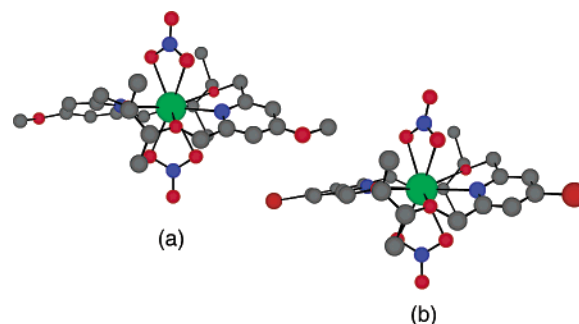**Figure 7.** X-ray structures of complexes of $Pr(NO_3)_3$: (a) $[Pr(NO_3)_2 \cdot \mathbf{3}]^+$ moiety in the X-ray structure of $[Pr(NO_3)_2 \cdot \mathbf{3}]_3[Pr(NO_3)_6]$; (b) $[Pr(NO_3)_2 \cdot \mathbf{4}]^+$ moiety in the X-ray structure of $[Pr(NO_3)_2 \cdot \mathbf{4}]_3[Pr(NO_3)_6](EtOH)$.
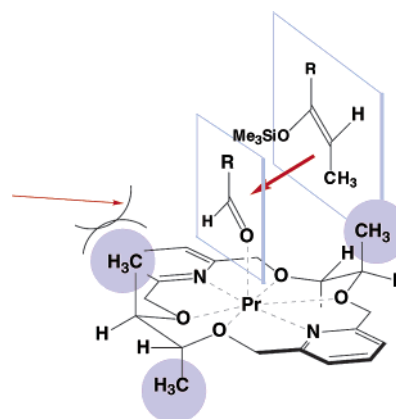

Figure 8. Assumed transition state model in the asymmetric aldol reaction using $Pr^{3+}-\mathbf{1}$.

in the complexes of **1**, **3**, and **4** are 2.541, 2.572, and 2.531 Å, respectively. It is noteworthy to mention that the order of the lengths (**3** > **1** > **4**) should reflect the Lewis acidity of the Pr cation, the complex of **4** being the most Lewis acidic because of electron-withdrawing Br groups.

From the X-ray analysis mentioned above, it was found that the structures of complexes were not affected significantly by the center metal cations and the crown ethers. Accordingly, the influences of the metal cations and the crown ethers upon the selectivities in the asymmetric aldol reactions cannot be explained by the difference in the complex structure. As mentioned earlier, therefore, the main factors which affect the selectivities should be the differences in the binding ability and the catalytic activity of the complexes.

On the basis of these X-ray structures, we propose a transition state model which can explain the absolute configuration of the favored enantiomer in the asymmetric aldol reaction, as shown in Figure 8. When an aldehyde coordinates to the Pr cation complexed with **1** in the fashion shown in Figure 8, the *si* face of the coordinated aldehyde carbonyl is shielded by the methyl substituent of **1**, allowing nucleophilic attack of **2** predominantly from the *re* face. The axial methyl substituent may also control the diastereoselectivity by making the orientation of the silyl enol ether less sterically congested. The (2R,3R)-adduct is considered to be formed selectively in this manner.

Effect of Substituents of Crown Ethers. To attain higher selectivity in the $Pr(OTf)_3$-catalyzed aldol reaction, we synthesized novel crown ethers **5**[17] and **6**,[17] which have ethyl and phenyl groups, respectively. Unfortunately, when the aldol reactions of benzaldehyde with **2** were examined using **5** and **6**

Scheme 1. Reversal of the Sense of Enantioselection
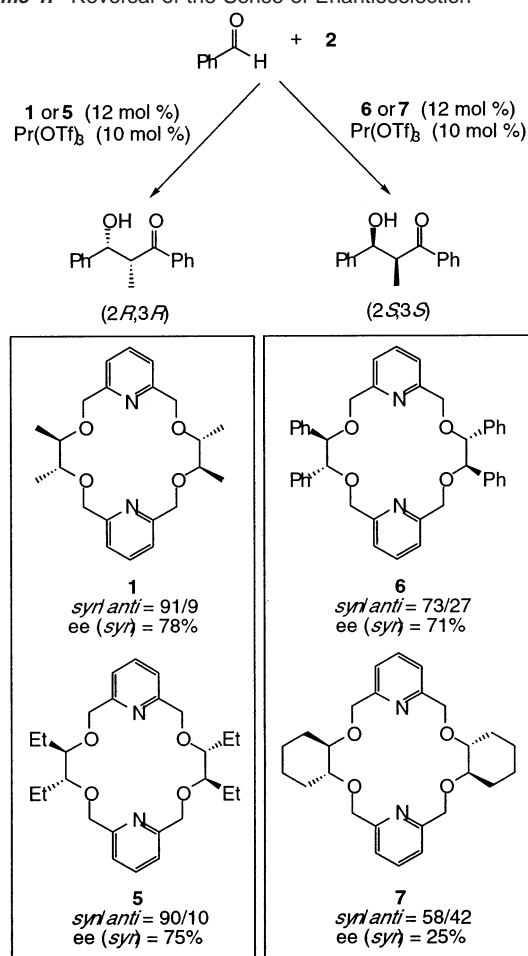
(Scheme 1), improvement of the selectivities was not attained. However, it was found that crown ether **6** afforded the enantiomer opposite to the favored one which **1** afforded. While **1** and **5** afforded the (2R,3R)-adducts selectively, **6** afforded the (2S,3S)-adduct selectively. This unexpected reversal of the sense of enantioselection is considered to be caused by conformational difference of the crown rings. In the case of **6**, the phenyl groups would be in equatorial positions,[25,26] and as a consequence the geminal hydrogen atoms would be in axial positions. It is likely that these hydrogen atoms now shield the *re* face of the aldehyde carbonyl from the nucleophilic attack of **2**. In fact, crown ether **7**,[17] which has cyclohexane rings and hydrogen atoms which are locked in axial positions, also afforded the (2S,3S)-adduct, although the selectivities were lower.

Effect of Water. The reactions in pure EtOH and CH_2Cl_2 gave lower yields and selectivities than those in aqueous EtOH, as shown in Table 1. It is apparent that water plays an essential role for attaining good yield and selectivities in this reaction.[27]

(25) In the 2:1 complex of NH_3BH_3 with *meso*-2,3,11,12-tetraphenyl-18-crown-6, the phenyl groups are in equatorial positions. In the 1:1 complex of NH_3BH_3 with (2R,3R,11R,12R)-2,3,11,12-tetraphenyl-18-crown-6, one pair of vicinal phenyl groups is axial, while the other pair is equatorial. Allwood, B. L.; Shahriari-Zavareh, H.; Stoddart, J. F.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1984**, 1461.

(26) In the complex of $Ca(NO_3)_2$ with (2S,3S,11S,12S)-2,3,11,12-tetraphenyl-18-crown-6, all four phenyl groups are pseudoequatorial. Crosby, J.; Fakley, M. E.; Gemmell, C.; Martin, K.; Quick, A.; Slawin, A. M. Z.; Shahriari-Zavareh, H.; Stoddart, J. F.; Williams, D. J. *Tetrahedron Lett.* **1989**, *30*, 3849.
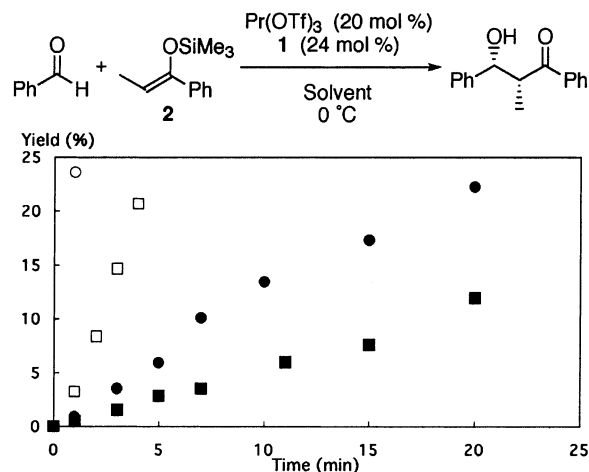
Figure 9. Initial reaction rate of the aldol reactions (○, Pr(OTf)$_3$ in EtOH; ●, **1**−Pr(OTf)$_3$ in EtOH; □, Pr(OTf)$_3$ in H$_2$O/EtOH (1/9); ■, **1**−Pr(OTf)$_3$ in H$_2$O/EtOH (1/9)).

In pure EtOH, the comparatively rapid ethanolysis of **2** caused low yield (checked by TLC). In the case of CH_2Cl_2, the reaction was very slow, probably because triflate anions coordinate to Pr^{3+} in CH_2Cl_2, reducing the Lewis acidity of Pr(OTf)$_3$ as compared to that in aqueous EtOH.

On the other hand, we assumed the reasons for low enantioselectivities in EtOH and CH_2Cl_2 as follows. It is probable that water in aqueous EtOH plays one or more of the following three roles: (1) increasing the binding ability of **1** with RE^{3+}, (2) suppressing significant loss of the Lewis acidity of RE(OTf)$_3$ by the coordination of **1**, or (3) creating an effective chiral environment of the RE^{3+}−**1** complex.

To elucidate which role(s) water plays, we first carried out the measurement of the binding constant of **1** with La^{3+} in both EtOH and CH_2Cl_2. For a 1:1.2 mixture of **1** (9.5×10^{-2} mM) and La(OTf)$_3$ in C_2D_5OD at 0 °C, the signal of free **1** was not observed.[28] Similarly, for a 1:1.2 mixture of **1** (1.1 mM) and La(OTf)$_3$ in CD_2Cl_2 at 0 °C, free **1** was not observed, either.[28] These results indicate that the binding constants of **1** with La^{3+} in C_2D_5OD and CD_2Cl_2 are much larger than that in aqueous EtOH. That is, water does not increase the binding ability of **1**.

We next carried out the measurement of the initial reaction rates of the aldol reactions using Pr(OTf)$_3$−**1** in EtOH and CH_2Cl_2. Figures 9 and 10 indicate that the initial reaction rates of these reactions are decreased by **1** more largely than that of the reaction in aqueous EtOH. It was first assumed that significant loss of the Lewis acidity by **1** decreased the enantioselectivities in the reactions in EtOH and CH_2Cl_2 because of the overwhelming, achiral Lewis acid-catalyzed pathway. However, it is likely that a very slight amount of the product is formed through the achiral Lewis acid-catalyzed pathway in these reactions, because the binding of **1** with Pr^{3+} is considered to be quantitative. Accordingly, it seems that water aids in creating an effective chiral environment of the Pr^{3+}−**1** complex, although the precise role of water is still unclear.

Catalytic Asymmetric Aldol Reactions in Aqueous Media Using Pr(OTf)$_3$ and 1. In the catalytic asymmetric aldol reaction in aqueous media using Pr(OTf)$_3$ and **1**, other aldehydes

(27) For H$_2$O-accelerated organic transformations, see: Ribe, S.; Wipf, P. *Chem. Commun.* **2001**, 299.

(28) In both C_2D_5OD and CD_2Cl_2, the equilibrium between free **1** and **1** complexed with the La cation was slow on the NMR time scale.
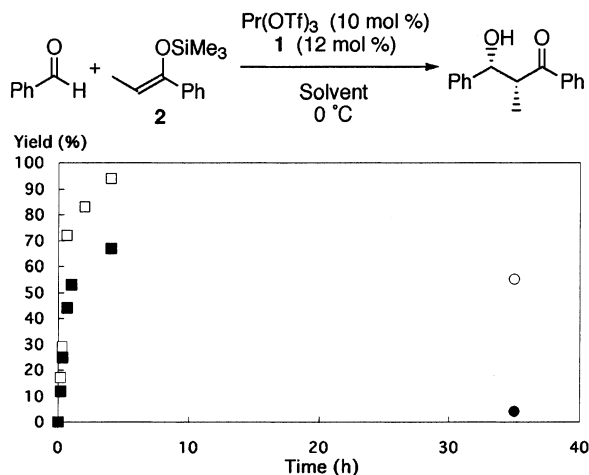
Figure 10. Profiles of the aldol reactions (○, Pr(OTf)$_3$ in CH$_2$Cl$_2$; ●, **1**−Pr(OTf)$_3$ in CH$_2$Cl$_2$; □, Pr(OTf)$_3$ in H$_2$O/EtOH (1/9); ■, **1**−Pr(OTf)$_3$ in H$_2$O/EtOH (1/9)).

Table 3. Asymmetric Aldol Reactions Using Pr(OTf)$_3$ and **1**

entry	aldehyde	enolate	time (h)	yield (%)	syn/anti	ee (syn)
1	MeO–C$_6$H$_4$–CHO	**2**	18	91	92/8	75
2	o-OMe–C$_6$H$_4$–CHO	**2**	18	96	95/5	83
3	Cl–C$_6$H$_4$–CHO	**2**	18	87	90/10	83
4	naphthyl–CHO	**2**	48	96	91/9	81
5	thienyl–CHO	**2**	48	100	91/9	72
6[a]	pyridyl–CHO	**2**	48 (144	99 35	85/15 81/19	85 90)[b]
7	cinnamaldehyde	**2**	46	77	78/22	76
8	crotonaldehyde	**2**	44	70	81/19	69
9[c]	C$_6$H$_5$–CHO	OSiMe$_3$ [d]	21	53	81/19	68
10	3-phenylpropanal	**2**	176[e]	53	67/33	47

[a] 20 mol % of Pr(OTf)$_3$ and 24 mol % of **1** were used. [b] −20 °C. [c] −10 °C. [d] E/Z = 9/91. [e] 29 h at −10 °C and then 147 h at 0 °C.

and silyl enol ethers were tested, and the results are summarized in Table 3. Not only aromatic aldehydes (entries 1−6) but also α,β-unsaturated aldehydes (entries 7, 8) gave good to high yields and diastereo- and enantioselectivities. Aliphatic aldehydes such as 3-phenylpropanal were not very good substrates in the present catalytic system (entry 10).

Table 4. Asymmetric Aldol Reactions Using Pr(OTf)$_3$ and **1**

entry	aldehyde	time (h)	yield (%)	syn/anti	ee (syn)
1[b]	C$_6$H$_5$–CHO	43	63	95/5	82
2	C$_6$H$_5$–CHO	43	86	95/5	83
3	MeO–C$_6$H$_4$–CHO	116	79	96/4	83
4	pyridyl–CHO	116	62	88/12	83
5	cinnamaldehyde	88	75	87/13	78

[a] E/Z = 99/1. [b] 2,6-Di-*tert*-butylpyridine was not used.

Optically active β-hydroxy thioesters, which can be obtained in the asymmetric aldol reactions using silyl enol ethers derived from thioesters, are useful compounds because they can be precursors of various optically active alcohols with other functional groups. However, these silyl enol ethers are mostly unstable in water, and successful examples of asymmetric aldol reactions in aqueous media using these silyl enol ethers have not been reported. Indeed, when **8** was used under the same conditions as Table 3, moderate yield was obtained because of rapid hydrolysis of **8** (Table 4, entry 1). However, it was found that the addition of 2,6-di-*tert*-butylpyridine suppressed hydrolysis of **8**, affording the aldol adduct in good yield.[29] When 30 mol % of 2,6-di-*tert*-butylpyridine was used, the desired aldol adduct was obtained in 86% yield with high diastereo- and enantioselectivities (*syn/anti* = 95/5, and 83% ee[30] (*syn*)) (entry 2). The use of other aldehydes also gave good yields and selectivities (entries 3−5). These results are the first examples of catalytic asymmetric aldol reactions of silyl enol ethers derived from thioesters in aqueous media. It seems likely that the use of 2,6-di-*tert*-butylpyridine could be a versatile method for water-sensitive substrates in Lewis acid-catalyzed asymmetric reactions in aqueous media.

Summary

We have developed RE(OTf)$_3$−crown ether **1** as efficient chiral catalysts for asymmetric aldol reactions in aqueous media. To the best of our knowledge, this is the first example of catalytic asymmetric reactions using RE(OTf)$_3$ in aqueous media. Our strategy is based on the size-fitting effects of

(29) 2,6-Di-*tert*-butylpyridine was used as an additive for Lewis acid-catalyzed aldol reactions. For example: Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron* **1988**, *44*, 4275.
(30) The absolute configuration was determined to be 2*R*,3*R* after converting to the methyl ester. (a) Gennari, C.; Colombo, L.; Bertolini, G.; Schimperna, G. *J. Org. Chem.* **1987**, *52*, 2754. (b) Yamashita, Y.; Ishitani, H.; Shimizu, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2002**, *124*, 3292.

macrocyclic ligands. In fact, slight changes in ionic diameters of the metal cations greatly affected the diastereo- and enantio-selectivities of the aldol adducts. Although the substituents at the 4-position of the pyridine rings of the crown ethers did not significantly affect the selectivities in the asymmetric aldol reaction, they affected the binding ability of the crown ethers with RE cations and the reaction rates of the asymmetric aldol reaction using $Pr(OTf)_3$ and the crown ethers. Furthermore, the structures of the chiral complexes were found not to be affected significantly by the center metal cations and the crown ethers. Therefore, to attain high selectivity in the asymmetric aldol reaction, the design of a chiral crown ether, which complexes strongly with $RE(OTf)_3$ and does not decrease the Lewis acidity of $RE(OTf)_3$, is essential. In addition, the catalytic asymmetric aldol reactions using $Pr(OTf)_3$ and **1** also proceeded with good to high yields and stereoselectivities, when several aldehydes and silyl enol ethers were used. Especially in the aldol reactions using the silyl enol ether derived from a thioester, the addition of 2,6-di-*tert*-butylpyridine effectively enhanced the yields of aldol adducts. Although the stereoselectivity and the catalytic activity remain to be improved further, the present work will provide a useful concept for the designing of chiral catalysts which function effectively in aqueous media.

Experimental Section

General Procedure of the Asymmetric Aldol Reaction. To a solution of $RE(OTf)_3$ (10−20 mol %) in H_2O/EtOH (1/9, 0.1 mL) at 0 or −10 °C was added a solution of **1** (12−24 mol %) in H_2O/EtOH (1/9, 0.4 mL). A solution of an aldehyde (0.2 mmol) in H_2O/EtOH (1/9, 0.3 mL) and a solution of **2** (0.3 mmol) in H_2O/EtOH (1/9, 0.3 mL) were then added. The whole was stirred for 18 h at the same temperature. The reaction was quenched by addition of aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2 three times, dried over Na_2SO_4, and concentrated. The desired product was purified by silica gel chromatography (AcOEt/hexane 1/6).

The diastereoselectivity and the enantioselectivity of the aldol adduct formed from benzaldehyde with **2** were determined by ^{1}H NMR and HPLC analysis (Daicel Chiralpak AD, hexane/*i*-PrOH = 30/1, flow rate = 1.0 mL/min), respectively.[18]

Supporting Information Available: Experimental details for the synthesis of crown ethers **1**, **3**, **4**, **5**, **6**, and **7**, and the kinetic and binding studies, characterization data of the aldol adducts, and crystallographic data for the complexes (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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