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Lanthanide Trifluoromethanesulfonate-Catalyzed Asymmetric Aldol Reactions in Aqueous Media

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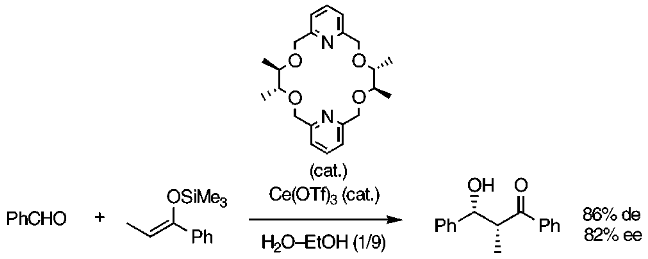
ABSTRACT



Catalytic asymmetric aldol reactions catalyzed by lanthanide trifluoromethanesulfonates in aqueous media have been realized for the first time using a chiral crown ether.

Lewis acid-catalyzed reactions are one of the most powerful methods in modern synthetic chemistry.[1] Among the many Lewis acids developed so far, lanthanide trifluoromethanesulfonates (lanthanide triflates, Ln(OTf)$_3$) have received much attention because of their strong Lewis acidity and unique properties.[2] In particular, their water-tolerance nature has led to development of Lewis acid-catalyzed reactions in aqueous media.[3] These reactions have a great advantage compared with conventional Lewis acid-mediated reactions in dry organic solvents, because tedious procedures to remove water from the solvents, substrates, and catalysts are not necessary. Furthermore, Ln(OTf)$_3$ can be easily recovered after the reaction is completed, and reused. This type of aqueous reaction was first demonstrated by us in Yb(OTf)$_3$-catalyzed aldol reactions of silyl enol ethers with formaldehyde in aqueous THF.[4] Since then, Ln(OTf)$_3$ has been used for numerous reactions including carbon−carbon bond-forming reactions and other transformations. However, catalytic asymmetric reactions using Ln(OTf)$_3$ in aqueous solvents have not been reported. Here we report the first example of Ln(OTf)$_3$-catalyzed asymmetric aldol reactions in aqueous media.[5−7]

The most important feature in designing a chiral ligand for Ln(OTf)$_3$ for reactions in aqueous media is its binding property to lanthanide cations. A ligand with strong coordinating ability often leads to reduction of the Lewis acidity

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(1) Santell, M.; Pons, J.-M. *Lewis Acids and Selectivity in Organic Synthesis*; CRC Press: Boca Raton, FL, 1995.

(2) Kobayashi, S. In *Lanthanides: Chemistry and Use in Organic Synthesis*; Kobayashi, S., Ed.; Springer: Berlin, 1999; p 63.

(3) (a) Kobayashi, S. *Synlett* **1994**, 689. (b) Kobayashi, S. In *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blacky Academic and Professional: London, 1998; p 262. (c) Kobayashi, S.; Manabe, K.; Nagayama, S. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000.

(4) Kobayashi, S. *Chem. Lett.* **1991**, 2187.

(5) 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.* In press.

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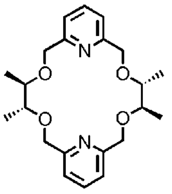
of the metal cations and, as a result, to low yields of the desired products. On the other hand, weaker binding ability of the ligand results in generating free metal cations coordinated by solvent molecules instead of the ligand. This leads to a decrease in the enantioselectivity of the products by competition between the chiral Lewis acid- and achiral, free Lewis acid-catalyzed pathways. This problem has to be solved by finding a chiral ligand which has strong binding ability *and* does not significantly reduce the Lewis acidity of Ln(OTf)$_3$. Quite recently, we have reported that a combination of Pb(OTf)$_2$ and a chiral crown ether can be used as a chiral Lewis acid catalyst in asymmetric aldol reactions in aqueous media.[5d] In these reactions, the chiral crown ether was found not to reduce the reaction rate despite its good binding ability to the Pb cation. Therefore, in the course of searching for effective chiral ligands for Ln(OTf)$_3$, we decided to screen various chiral crown ethers.[8]

After many trials, we found that the use of crown ether **1**[9] realized the catalytic asymmetric aldol reaction in aqueous solvents. For example, when **1** (12 mol %) and Pr(OTf)$_3$ (10 mol %) were used, the reaction of benzaldehyde with silyl enol ether **2** in water/ethanol (1/9 (v/v)) at 0 °C for 18 h gave the desired aldol adduct in high yield (85%) with high diastereo- (*syn*/*anti* = 91/9, 82% de) and enantioselectivities (78% ee for the *syn* isomer (2*R*,3*R*)).[10] In this reaction, water plays an essential role for the high yield and selectivities. When the reaction was carried out in pure ethanol, lower yield and selectivity were observed (51% yield (16 h), 70% de, 23% ee for the *syn* isomer (2*R*,3*R*)).[11] Furthermore, the reaction in dichloromethane resulted in much lower yield and selectivity (3% yield (185 h), 28% de, 22% ee).



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With this result in hand, we next carried out a systematic evaluation of Ln(OTf)$_3$ and other rare earth metal triflates in the asymmetric aldol reaction. The diastereo- and enantioselectivities and ionic diameters[12] of the metal cations used are shown in Figure 1. The ionic diameters significantly affected the selectivity.[13] For the larger cations such as La, Ce, Pr, and Nd, both diastereo- and enantioselectivities were high.[14] The smaller cations such as Sc and Yb showed no enantioselection.

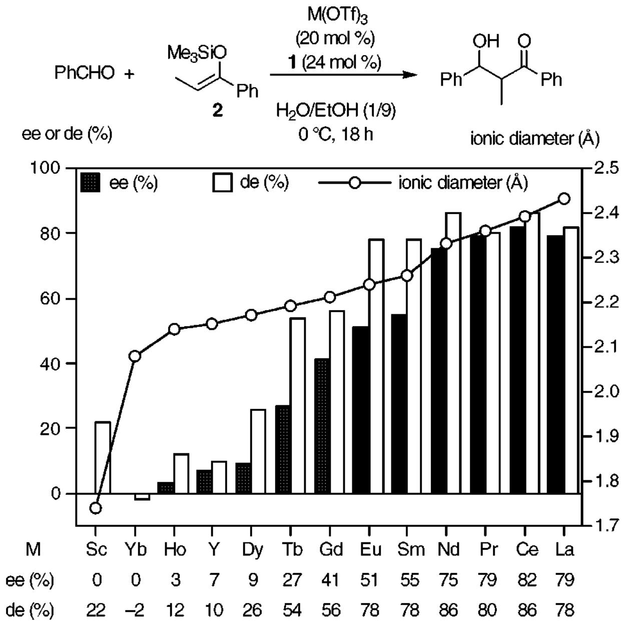

Figure 1. Enantio- and diastereoselectivities in the aldol reaction using rare earth metal triflates and ionic diameters (8-coordination for Sc, 9-coordination for other metals) of the metal cations (M^{3+}). De: (*syn*% − *anti*%); ee ((2*R*,3*R*)% − (2*S*,3*S*)%). Yields: 49−95%.

The observed selectivities suggest that, in the case of La, Ce, Pr, and Nd, only a negligible amount of metal cations which are uncomplexed with **1** exists in water/ethanol (1/9). ^{1}H NMR studies revealed the strong binding of **1** to La cations. For a 1:0.4 mixture of **1** (10 mM) and La(OTf)$_3$ in D$_2$O/CD$_3$CD$_2$OD (1/9) at 30 °C, two sets of signals which correspond to the ligand were observed in a ratio of 0.6:0.4,

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(6) Lanthanide triflate-catalyzed enantioselective Diels−Alder and 1,3-dipolar cycloaddition reactions in nonaqueous solvents have been reported. (a) Kobayashi, S.; Ishitani, H. *J. Am. Chem. Soc.* **1994**, *116*, 4083. (b) Kobayashi, S.; Kawamura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5840. (c) Markó, I. E.; Chellé-Regnaut, I.; Leroy, B.; Warriner, S. L. *Tetrahedron Lett.* **1997**, *38*, 4269. (d) Sanchez-Blanco, A. I.; Gothelf, K. V.; Jørgensen, K. A. *Tetrahedron Lett.* **1997**, *38*, 7923. (e) Nishida, A.; Yamanaka, M.; Nakagawa, M. *Tetrahedron Lett.* **1999**, *40*, 1555.

(7) For reviews on catalytic asymmetric aldol reactions, see: (a) Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; p 997. (b) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352.

(8) For reviews on complexation of lanthanides with macrocyclic ligands, see: (a) Fenton, D. E.; Vigato, P. A. *Chem. Soc. Rev.* **1988**, *17*, 69. (b) Alexander, V. *Chem. Rev.* **1995**, *95*, 273.

(9) Bradshow, J. S.; Huszthy, P.; McDaniel, C. W.; Zhu, C. Y.; Dalley, N. K.; Izatt, R. M.; Lifson, S. *J. Org. Chem.* **1990**, *55*, 3129.

(10) The de and ee 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.

(11) For effects of water in Ln(OTf)$_3$-catalyzed aldol reactions, see: Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3590.

(12) Shannon, R. D. *Acta Crystallogr.* **1976**, *A32*, 751.

(13) Size effects of lanthanides 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) Schaus, S. E.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 1001. See also ref 6a.

(14) Other aldehydes also gave good to high selectivities in the presence of Pr(OTf)$_3$ (10 mol %) and **1** (12 mol %) in water/ethanol (1/9) at −10 °C. *p*-Anisaldehyde: 83% yield, 86% de, 75% ee (*syn*). 1-Naphthaldehyde: 92% yield, 76% de, 72% ee (*syn*). Cinnamaldehyde; 77% yield, 56% de, 76% ee (*syn*). 3-Phenylpropanal: 53% yield, 34% de, 47% ee (*syn*). Reactions of other silyl enolates with benzaldehyde also proceeded with good selectivities. (*Z*)-3-Trimethylsiloxy-2−pentene: 53% yield, 62% de, 68% ee (*syn*). (*E*)-1-*tert*-Butylthio-1-trimethylsiloxypropene: 33% yield, 86% de, 73% ee (*syn*). It is noteworthy that Pr(OTf)$_3$ can be easily recovered after extraction of organic materials from the aqueous layer with an organic solvent and evaporation of water. Ligand **1** was easily separated from other organic products by silica gel chromatography.

indicating that the equilibrium between free **1** and **1** complexed with the La cation is slow on the NMR time scale and that almost all the La cations bind to **1**. When the amount of $La(OTf)_3$ was increased to 1.2 equiv relative to **1**, free **1** was scarcely observed. Further evidence for the strong binding was obtained from an experiment where the $Pr(OTf)_3$-catalyzed reaction of benzaldehyde with **2** was carried out in the presence of a large excess of **1**. When the amount of **1** was doubled from 24 to 48 mol % at 0 °C, almost the same enantioselectivity (80% ee (*syn*)) was observed, indicating that the complexation of **1** with the Pr cation had already reached saturation. On the other hand, when $Gd(OTf)_3$ (20 mol %) was used, the increase of the amount of **1** from 24 to 48 mol % resulted in an increase in the selectivities (from 56 to 82% de, from 41 to 50% ee), confirming the insufficient binding of **1** to the less effective metal cations.

Despite the strong binding of **1** to lanthanide cations such as La and Pr, **1** was found not to reduce their activity to a significant extent. Figure 2 shows the reaction profiles for the aldol reaction in the presence and absence of **1**. It should be noted that, although **1** slightly decelerated the reaction, sufficient reactivity still remained in the presence of **1**. This result is surprising because increase of the electron density of Pr by coordination of the two pyridine nitrogens of **1** seems to deactivate $Pr(OTf)_3$ significantly. Thus, the retention of the Lewis acidity is the key to realizing the asymmetric induction in the present $Ln(OTf)_3$-catalyzed aldol reactions.[15]

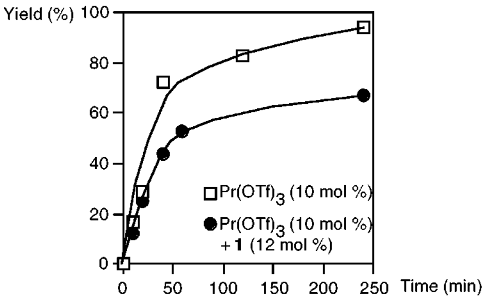

Figure 2. Reaction profiles for the $Pr(OTf)_3$-catalyzed aldol reaction of benzaldehyde with **2** in water/ethanol (1/9) at 0 °C in the absence and presence of **1**.

An X-ray crystal structure of the Pr cation and **1** was obtained for $[Pr(NO_3)_2\cdot\mathbf{1}]_3[Pr(NO_3)_6]$ (Figure 3).[16] In this structure, a single structure for the complex of Pr with **1** was observed. The Pr cation complexed with **1** is located almost in the plane of the crown ring. Interestingly, the methyl groups of **1** are all in axial positions.[17] We assume that this conformation of the crown ring is crucial to creating 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.

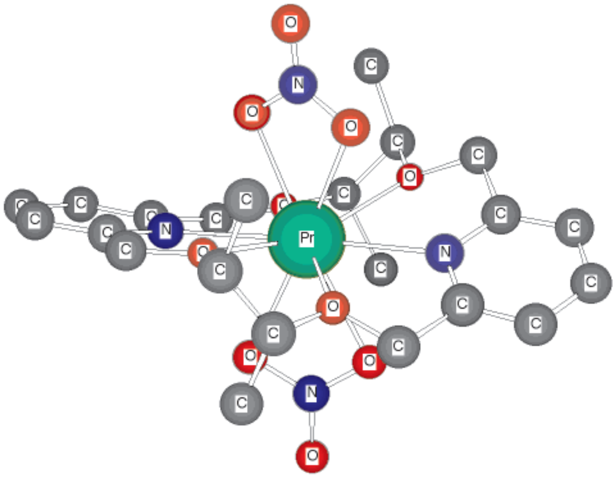

Figure 3. $[Pr(NO_3)_2\cdot\mathbf{1}]^+$ moiety in the X-ray structure of $[Pr(NO_3)_2\cdot\mathbf{1}]_3[Pr(NO_3)_6]$. Hydrogen atoms are omitted for clarity.

In conclusion, catalytic asymmetric aldol reactions using $Ln(OTf)_3$ in aqueous media have been realized for the first time. This reaction system does not need vigorous drying of the substrates and the catalyst, and $Ln(OTf)_3$ can be easily recovered. Our strategy is based on the size-fitting effects of macrocyclic ligands. In fact, slight changes in ionic diameters of the lanthanide cations greatly affected the diastereo- and enantioselectivities of the aldol adducts. Although the stereoselectivity remains to be improved further, the present work will provide a useful concept for the design of chiral catalysts which function effectively in aqueous media. Application to other $Ln(OTf)_3$-catalyzed asymmetric reactions in aqueous media on the basis of the same concept is feasible and is currently under investigation.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan.

Supporting Information Available: The general procedure of the asymmetric aldol reaction and crystallographic data for $[Pr(NO_3)_2\cdot\mathbf{1}]_3[Pr(NO_3)_6]$. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) 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 allyltributyltin in aqueous THF. Yanagisawa, A.; Nakashima, H.; Ishiba, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 4723.

(16) The reaction of benzaldehyde with **2** in the presence of $Pr(NO_3)_3$ (20 mol %) and **1** (24 mol %) in water/ethanol (1/9) at 0 °C for 18 h afforded the aldol adduct in 59% yield with 76% de and 69% ee (*syn*).

(17) The complex of 2,3,11,12-tetramethyl-18-crown-6 and $Ca(NO_3)_2$ or KSCN adopts similar conformation. (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.