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A Novel Chiral Lead(II) Catalyst for Enantioselective Aldol Reactions in Aqueous Media

Satoshi Nagayama and Shū Kobayashi*

Graduate School of Pharmaceutical Sciences
The University of Tokyo, CREST
Japan Science and Technology Corporation (JST)
Hongo, Bunkyo-ku, Tokyo 113-0033 Japan

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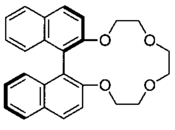
Catalytic asymmetric reactions provide one of the most efficient methods for the preparation of optically active compounds.[1] While several excellent chiral catalysts have been developed recently, most of them have to be used in strictly anhydrous organic solvents although organic reactions in aqueous media leading to benign chemical synthesis are now of great interest.[2] This is probably due to the instability of many catalysts and intermediates in the presence of even a small amount of water. To address this issue, we have continued fundamental research on organic reactions in aqueous media.[3] In this paper, we report the design and synthesis of a novel chiral lead(II) catalyst that can be used in asymmetric aldol reactions in aqueous media. A general idea for designing chiral catalysts in aqueous media is also proposed.

Catalytic asymmetric aldol reactions are one of the most powerful carbon−carbon bond-forming methodologies that afford synthetically useful chiral β-hydroxy ketones and esters.[4] Chiral Lewis acid-catalyzed reactions of silyl enol ethers with aldehydes (the Mukaiyama reaction)[5] are among the most convenient and promising, and several successful examples have been reported since the first chiral tin(II)-catalyzed reactions appeared in 1990.[6] However, the use of aprotic anhydrous solvents as well as low reaction temperatures (−78 °C) has been needed in almost all successful cases.[7] To perform catalytic asymmetric aldol reactions successfully in aqueous media,[8] two problems to be addressed were assumed. First, many cations (Lewis acids) hydrolyze very easily in water. To overcome this problem, we screened various cations and have found that rare earths and some other cations such as Fe^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Pb^{2+} are stable and work as Lewis acid catalysts in water.[3g] The second issue is the instability of chiral ligand-coordinated metal complexes in water. Since many chiral ligand-coordinated metal complexes are decomposed rapidly in water, we decided to utilize muticoordination system and to select chiral crown ethers as chiral ligands.

Chiral crown ethers **1**−**3** were synthesized according to the literature methods,[9] and combination with metals was examined on the basis of ionic diameters of cations[10] and the hole size of the crown ethers.[9,11] Chiral catalysts were prepared by mixing metal compounds and the crown ethers and were tested in a model aldol reaction of the (*Z*)-silyl enol ether of propiophenone (**4**) with benzaldehyde in water−ethanol (1:9) at 0 °C. The results are summarized in Table 1. When $Cu(OTf)_2$ or $Zn(OTf)_2$ was combined with **1**,[12] the aldol reaction proceeded smoothly to afford the corresponding adduct in high yield albeit no chiral induction was observed. According to the diameters and the hole size, we next examined the combination of $Sc(OTf)_3$ or $Yb(OTf)_3$ and **2**.[13] Although these rare earth metal triflates are known to be excellent Lewis acid catalysts in aqueous media,[14] no chiral induction was detected in the model aldol reaction. We then studied the use of AgOTf or $Pb(OTf)_2$ and **3**.[15] While no chiral induction was observed using AgOTf−**3**, it was exciting to find that the aldol reaction proceeded smoothly using $Pb(OTf)_2$−**3** to afford the corresponding adduct in 62% yield with high *syn*-selectivity (*syn*/*anti* = 90/10) and that the enantiomeric excess of the *syn*-adduct was 55%. It should be noted that the hole size of the crown ether is essential because no chiral induction was observed in the same model aldol reaction using the combination of $Pb(OTf)_2$ and **1** or **2**. It was also found that the counteranions of lead (II) strongly influenced the selectivity. While the same level of enantioselectivity was obtained by using $Pb(ClO_4)_2$ and **3**, lower enantiomeric excesses (ee's) were observed when $Pb(NO_3)_2$ or $Pb(SbF_6)_2$ and **3** were used. When $Pb(BF_4)_2$, $Pb(PF_6)_2$, or PbF_2 was employed, the model aldol reactions proceeded sluggishly.



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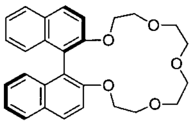

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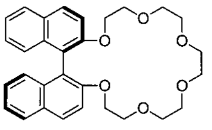

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The effect of solvents was then examined.[16] The aldol reaction proceeded most efficiently in a water−alcohol solution. 2-Propanol was the best alcohol, and much lower yield and selectivities were obtained when the reaction was carried out in dichloromethane. In pure water (without alcohols), lower yield and selectivities were also observed, while the diastereo- and enantioselectivities were improved in the presence of a surfactant.[17] Other substrates were also successfully used in this system (Pb-

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(12) Ionic diameters of Cu^{2+} and Zn^{2+} are 144 pm and 148 pm, respectively.[10] The hole size of 12-crown-4 was reported to be 120−150 pm. Vögtle, F. *Supramolecular Chemistry: An Introduction*; John Wiley & Sons: Chichester, 1989.

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(15) Ionic diameters of Ag^{+} and Pb^{2+} are 252 pm and 240 pm, respectively.[10] The hole size of 18-crown-6 was reported to be 260-320 pm.

(16) Details are shown in Supporting Information.

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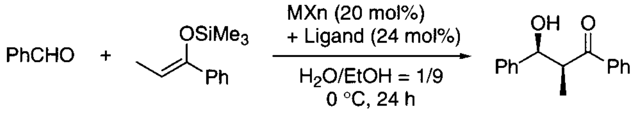
Table 1. Effect of Metal−Ligand Combinations[a]



MXn	ligand	yield (%)	*syn*/*anti*	ee (%)[a]
$Zn(OTf)_2$	**1**	88	69/31	2
$Cu(OTf)_2$	**1**	86	87/13	0
$Sc(OTf)_3$	**2**	75	52/48	1
$Yb(OTf)_3$	**2**	74	63/37	1
AgOTf	**3**	61	75/25	5
$Pb(OTf)_2$	**3**	62	90/10	55
$Pb(OTf)_2$	**1**	78	89/11	0
$Pb(OTf)_2$	**2**	92	89/11	0

[a] ee of *syn*-adduct.

$(OTf)_2$−**3**, 20 mol %; water−2-propanol (1:4.5), 0 °C).[18] In the reactions with **4**, the results are as follows: *p*-chlorobenzaldehyde (74% yield, *syn*/*anti* = 82:18, 62% ee (*syn*)); hexanal (82% yield, *syn*/*anti* = 92:8, 80% ee (*syn*)); 1-nonanal (79% yield, *syn*/*anti* = 90:10, 82% ee (*syn*)); isovaleraldehyde (99% yield, *syn*/*anti* = 94:6, 87% ee (*syn*)); 2-methylpropionaldehyde (65% yield, *syn*/*anti* = 90:10, 78% ee (*syn*)); 2-thiophenecarboxaldehyde (67% yield, *syn*/*anti* = 90:10, 75% ee (*syn*)). The reaction also proceeded smoothly using 10 mol % of $Pb(OTf)_2$−**3** (88% yield, *syn*/*anti* = 93/7, 85% ee (*syn*) in the reaction of isovaleraldehyde with **4**). It should be noted that good to high yields and high levels of diastereo- and enantioselectivities were obtained at 0 °C in aqueous media and that even aliphatic aldehydes worked well under these reaction conditions. In the reaction of benzaldehyde with the silyl enolate derived from *(S)*-ethyl propanethioate, 51% yield was obtained with *syn*/*anti* = 93/7 (47% ee (*syn*)).[19]

The key to this catalytic asymmetric aldol reaction is a novel chiral lead(II) catalyst. The solid-state structure of $Pb(OTf)_2$−**3** was determined by single-crystal X-ray diffraction (Figure 1).[16,20] The lead atom is coordinated by the six oxygens of the crown ether, two triflates, and one water. A characteristic point is that one Pb−O bond (310.9 pm) is much longer than others.[21] The oxygen atom is directly connected to the binaphthyl ring of **3**, and the long length is ascribed to the dihedral angle between the two naphthalene rings of **3**, which create an excellent asymmetric environment in the lead(II) catalyst. The high selectivities obtained would be explained by assuming that the water coordinating to lead(II) is replaced by aldehydes under the reaction conditions[3g] and that silyl enolates attack the aldehydes to afford the (2*S*,3*S*)-adduct.[22]

Finally, a preliminary kinetic study was performed in the following two systems: $Pb(OTf)_2$−**3**-catalyzed aldol reaction in water−ethanol (1:4.5) and $Pb(OTf)_2$-catalyzed achiral reaction in the same solvent system.[16] It was very interesting to find that almost comparable reaction rates between the above two systems were observed. In addition, the same levels of diastereo- and enantioselectivities were obtained during the reaction course in the $Pb(OTf)_2$−**3**-catalyzed reactions. These results indicate that suitable combinations of metal-chiral crown ether complexes provide promising chiral catalysts in aqueous media.

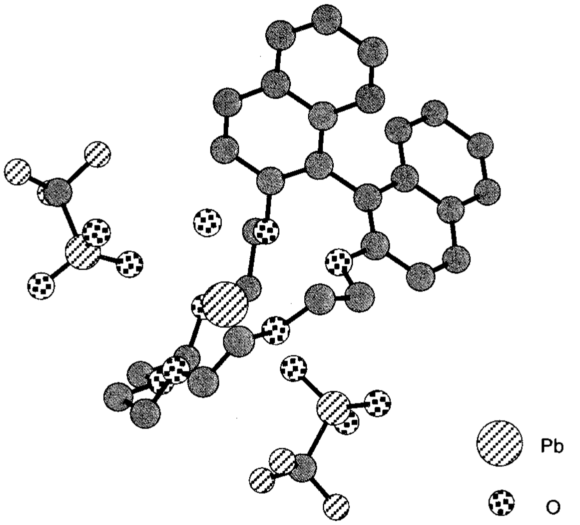


Figure 1. $Pb(OTf)_2$-crown ether **3** (X-ray).

In summary, we have developed $Pb(OTf)_2$−crown ether **3** as an efficient chiral catalyst for asymmetric aldol reactions in aqueous media. To the best of our knowledge, this is the first example of a chiral crown-based Lewis acid[23] that can be successfully used in catalytic asymmetric reactions. It should be noted that the novel chiral catalyst was successfully used in aqueous media. The catalyst has been characterized by X-ray diffraction, and its unique structure as a chiral catalyst has been revealed. A kinetic study has shown potential utility of these types of chiral catalysts which can be employed in aqueous media. Investigations along this line are now in progress in our laboratory.

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Supporting Information Available: Experimental details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Experimental procedures are described in Supporting Information. $Pb(OTf)_2$ was recovered quantitatively by simple extraction, and chiral crown ether **3** was also recoverable. The authors are grateful to Mr. Tomoaki Hamada (The University of Tokyo) for his technical support.

(19) Although the reaction conditions have not been optimized, this is the first example of the catalytic asymmetric aldol reaction of a silyl enolate derived from a thioester (water-sensitive enolate). For other substrates, higher yields and selectivities were obtained in most cases compared to those in the previous report.[8]

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