



## Design and Synthesis of Chiral Zn<sup>2+</sup> Complexes Inspired by Natural Aldolases for Catalytic Asymmetric Aldol Reactions

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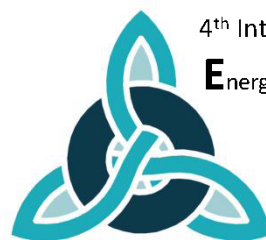
Extending carbon frameworks via a series of C–C bond forming reactions is essential for the synthesis of natural products, pharmaceutically active compounds, active agrochemical ingredients, and a variety of functional materials. Besides, the application of stereoselective C–C bond forming reactions to the one-pot synthesis of biorelevant compounds is now emerging as a challenging and powerful strategy for improving the efficiency of a chemical reaction, in which some of the reactants are subjected to successive chemical reactions in just one reactor. In this paper, we describe the design and synthesis of Zn<sup>2+</sup> complexes of optically active ligands containing cyclen (1,4,7,10-tetraazacyclododecane) and amino acids with aliphatic, aromatic, anionic, and cationic chains that mimic aldolases in stereoselective C–C bond forming reactions, especially for enantioselective aldol reactions and chemoenzymatic synthesis in aqueous solutions.<sup>1)</sup>

We carried out the aldol reaction of acetone and benzaldehydes using chiral ZnL complexes and found that chiral Zn<sup>2+</sup> complexes containing adequate hydrophobic and bulky side chains afford the aldol products in good optical yields (up to 96% ee).<sup>2a,b)</sup> The hydrophobic ZnL complex having a decyl side chain catalyzed the aldol reaction in single phase solvent systems containing HEPES buffer and a two phase system containing toluene and H<sub>2</sub>O. X-ray crystal structures of some Zn<sup>2+</sup> complexes revealed that the NH<sub>2</sub> groups in the side chain of these ZnL complexes coordinate to Zn<sup>2+</sup>, implying that the Zn<sup>2+</sup>-bound OH<sup>−</sup> of ZnL complexes (ZnL(OH<sup>−</sup>)) acts as a base to deprotonate the  $\alpha$ -proton of acetone to generate the ZnL–(enolate)<sup>−</sup> complex in these aldol reactions. We also performed the direct aldol reactions between cyclic ketones such as cyclohexanone or cyclopentanone and benzaldehydes in the presence of ZnL complex catalysts, which resulted in the formation of the corresponding aldol adducts in high chemical and optical yields. The choice of an appropriate solvent system and additive allows the preparation of either *anti*- or *syn*- aldol adducts with good diastereo- and enantioselectivity.<sup>2c)</sup>

These aldol reactions were applied to the one-pot synthesis of biorelevantly important compounds such as the optically active 1,3-diols by using a combination of the enantioselective aldol reactions catalyzed by chiral Zn<sup>2+</sup> complexes and successive reduction by the recombinant oxidoreductase system “Chiralscreen® OH”. Typical examples include the one-pot chemoenzymatic synthesis from acetone and benzaldehydes and the successive reduction with E001, which affords optically active-1,3-diols in good yields with 96% ee.<sup>2d)</sup> Using these methodologies, all of the possible stereoisomers of 1,3-diols can be obtained. These results will be presented in this paper.

1) Itoh, S. et al. *Int. J. Mol. Sci.*, **2014**, *15*, 2087-2118.

2) a) Itoh, S. et al. *Chem. Eur. J.*, **2009**, *15*, 10570-10584. b) Itoh, S. et al. *Chem. Asian J.*, **2013**, *8*, 2125-2135. c) Itoh, S. et al. *Tetrahedron Asymm.*, **2013**, *24*, 1583-1590. d) Sonoike, S. et al. *Chem. Asian J.*, **2012**, *7*, 64–74.



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