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Chiral zinc(II) and copper(II)-catalyzed asymmetric ring-opening reactions of *meso*-epoxides with aniline and indole derivatives

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ABSTRACT

The ring-opening reactions of *meso*-epoxides with aniline and indole derivatives proceeded smoothly in water in the presence of Zn(II) and Cu(II) surfactant-type catalysts to afford the corresponding products in moderate to high yields with good to excellent enantioselectivities. Opposite enantiomers were obtained by using Sc(III) and Zn(II) or Cu(II) with the same chiral ligand. Crystal structures of these catalysts may explain the reversal of the enantioselectivity. Some reactions were also tested in dichloromethane (DCM), and it was revealed that the reactions proceeded faster in water than in DCM. Finally, several non-linear effect experiments suggested unique structure of these chiral catalysts.

1. Introduction

Most organic reactions have been carried out in organic solvents because most organic materials are not soluble in water and most reactive species are not stable in the presence of water. This is also the case for chiral catalysts, which are often unstable in the presence of water and thus are difficult to conduct catalytic asymmetric reactions in the presence of water. On the other hand, from an environmentally point of view, recent demand is development of benign chemical processes.[1] In this context, while several types of reactions in aqueous media have been reported,[2] organic solvents are required as co-solvents to dissolve organic materials in many cases. To overcome this problem, we developed Lewis acid–surfactant-combined catalysts (LASCs) to conduct organic reactions in water as the sole solvent. Hydrophobic substrates are taken into micellous emulsions created by LASCs and the hydrophobic substrates, where reactants, substrates, and the catalyst are concentrated, and the desired reactions proceed very efficiently.[3] Very recently, we have also shown that even hydrophilic substrates can be used in this system.[3e]

Catalytic asymmetric ring-opening reactions of *meso*-epoxides provide a useful method for the synthesis of chiral 1,2-bifunctional alcohols. Based on this method, a number of protocols have been developed for the synthesis of enantiomerically enriched 1,2-azido alcohols,[4] 1,2-amino alcohols,[5] 1,2-diol derivatives,[6] 1,2-cyano alcohols,[7] 1,2-mercaptoalcohols,[8] 1,2-halohydrines,[9] and 1,2-seleno alcohols.[10] Our group has mainly contributed to this field by exploiting efficient asymmetric reactions in water, and reported the first examples of chiral scandium and bismuth-catalyzed ring-opening reactions of *meso*-epoxides with aniline derivatives in water. We have also developed the first catalytic asymmetric ring-opening reactions of *meso*-epoxides with indole derivatives in water. In the course of our investigations to develop more efficient catalysts in water, we have discovered unique catalysis of zinc(II) and copper(II). We describe zinc(II) and copper(II) catalyzed asymmetric ring-opening reactions of *meso*-epoxides with aniline and indole derivatives in water.

2. Results and discussion

At the outset, we carried out the ring-opening reaction of *meso*-epoxide **1** with aniline in the presence of various metal surfactant-combined catalysts in water (Table 1). Sc(III), Zn(II), and Cu(II) catalysts gave the desired product **4a** in good to excellent yields with good to excellent enantioselectivities (entries 1, 7, 8). It is noted that opposite enantiomers were obtained by using Sc(III) and Zn(II) or Cu(II) with the same chiral ligand; while Sc(III) gave one enantiomer of the product, Zn(II) or Cu(II) gave the opposite enantiomer of the product. On the other hand, the reactions also proceeded in dichloromethane (DCM), and the Sc(III) and Zn(II) catalysts gave the desired product in 85% and 60% yields with 93% and 90% ees, respectively, although Cu(II) catalyst was not so effective.

We then carefully examined the reaction of *cis*-stilbene oxide (**1**) with aniline in the presence of 5 mol % of the Zn(II) or Cu(II) catalysts and 6 mol % of chiral bipyridine **3** in water and DCM at room

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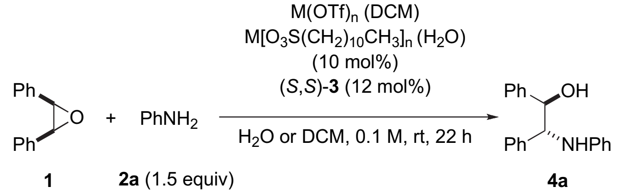
Table 1
Ring-opening reaction of *meso*-epoxide **1** with aniline



Entry	M	*n*	In H_2O		In DCM	
			Yield[a] (%)	ee[b] (%)	Yield[a] (%) **1**	ee[b] (%)
1	Sc	3	87	95 (1*S*,2*S*)	85	93 (1*S*,2*S*)
2	Y	3	9	62 (1*S*,2*S*)	—	—
3	Yb	3	27	82 (1*S*,2*S*)	—	—
4	In	3	6	32 (1*S*,2*S*)	—	—
5	Mn	2	6	81 (1*S*,2*S*)	—	—
6	Ni	2	Trace	—	—	—
7	Cu	2	82	80 (1*R*,2*R*)	18	80 (1*R*,2*R*)
8	Zn	2	97	92 (1*R*,2*R*)	60	90 (1*R*,2*R*)
9	Ag	1	Trace	—	—	—

[a] Isolated yield.
[b] ee was determined by chiral HPLC analysis.

temperature. It is noted that $Zn[O_3S(CH_2)_{10}CH_3]_2$ or $Cu[O_3S(CH_2)_{10}CH_3]_2$ and **3** in water gave higher yields than $Zn(OTf)_2$ or $Cu(OTf)_2$ and **3** in DCM. In addition, $Zn[O_3S(CH_2)_{10}CH_3]_2$ or $Cu[O_3S(CH_2)_{10}CH_3]_2$ and **3** in water showed higher reactivity than $Zn(OTf)_2$ or $Cu(OTf)_2$ and **3** in DCM (Fig. 1).

After optimization of the reaction conditions, we surveyed substrate scope of several *meso*-epoxides and aniline derivatives using Zn(II) or Cu(II) as a catalyst (Table 2). While stilbene oxide derivatives showed good selectivities with various aniline derivatives (entries 1–8, 13–20), alkyl epoxide derivatives gave only moderate selectivities (entries 9–12, 21). It is interesting to find that $Cu(OTf)_2$ had almost no activity in DCM, but that $Zn(OTf)_2$ catalyzed the *meso*-epoxides ring-opening reactions in DCM (entries 22–29). The reactions proceeded slower in DCM than in water, while the desired products were obtained with good selectivities.

Next, we carried out the ring-opening reactions of *meso*-epoxides with indole derivatives using Sc(III), Zn(II), and Cu(II) catalysts in water and DCM (Table 3). Nitrogen-containing heterocycles and their derivatives are well-known structures in natural products and medicines.[11,12] The synthesis of chiral *N*-heteroaromatic derivatives in optically active form is especially important in this area. Gratifyingly, Sc(III) and Cu(II) gave the product in good yields with excellent enantioselectivities in water. In this reaction, enantiofacial selectivities between Sc(III) and Cu(II) were reversed, and the reaction proceeded sluggishly in the presence of Zn(II). On the other hand, when the reaction was carried out in DCM, only $Cu(OTf)_2$ gave the desired product in moderate yield with high enantioselectivity. We then examined several reaction conditions with the Cu(II) catalyst in water (Table 4). As for the equivalents of indole, 1.2 equiv gave the best yield and selectivity (entry 2). The concentration was found to give almost no influence on yield and selectivity (entries 2, 4–6). The yield dropped when the catalyst loading decreased (entries 2, 7–9). When 2 mol % of the catalyst was used, the desired product was obtained in 73% yield with 90% ee.

The reaction of *cis*-stilbene oxide (**1**) with indole (**5a**) also proceeded in the presence of 5 mol % of $Cu(OTf)_2$ catalysts and 6 mol % of chiral bipyridine **3** in DCM. While the reaction rate in DCM was almost the same as that in water (Fig. 2), the enantioselectivity was higher in water than in DCM.

Several examples of *meso*-epoxide ring-opening reactions with indole derivatives are shown in Table 5. In cases of stilbene oxide (**1**) with substituted indoles, the reactions proceeded smoothly in most cases to afford the corresponding indole adducts in moderate to good yields with excellent enantioselectivities (entries 3–6). As for *meso*-epoxides, aromatic ones reacted with indole (**5a**) to afford the desired compounds in moderate yields with good selectivities (entries 7–9). However, alkyl epoxide derivatives showed poor reactivity (entries 10, 11). On the other hand, when the reactions were conducted in DCM, the rates were slower than those in water, and the reaction mixtures were messy. In some cases, only a trace amount of the desired product was obtained (entries 15, 17, and 18).

To obtain information on the chiral Cu complex, X-ray crystal structural analysis was performed. Single crystals suitable for X-ray analysis were obtained from a (*S,S*)-**3**–$CuBr_2$ complex (Fig. 3). The complex adopts square pyramidal structure in which two pyridines and one hydroxyl group of **3** coordinated to copper in a tridentate manner. Formation of this structure may be a key for obtaining high enantioselectivity. In addition, difference of the structure between chiral scandium[2c] and copper may cause the difference of absolute configurations of the products.

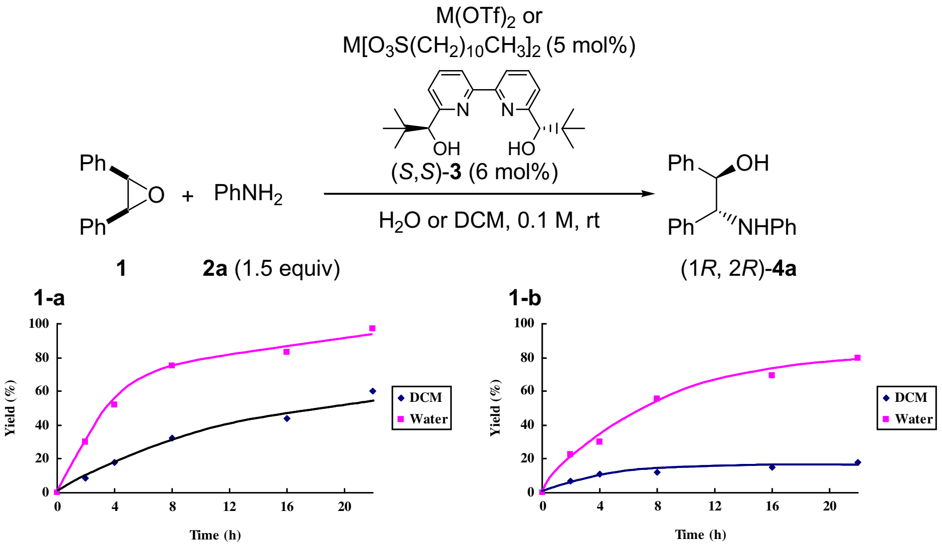


Figure 1. Plot of yield versus time for the ring-opening reactions of *cis*-stilbene oxide (**1**) with aniline (**2a**) in the presence of Zn(II) catalyst (**1–a**) or Cu(II) catalyst (**1–b**) and **3** in water (pink) and DCM (blue).