Metal-controlled Reversal of Enantioselectivity in Catalyzed Asymmetric Ring-opening Reactions of *meso*-Epoxides in Water

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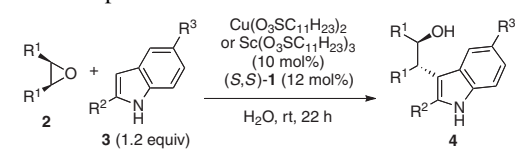
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Reversal of enantioselectivity in Cu–chiral bipyridine catalyzed asymmetric ring-opening reactions of *meso*-epoxides with indole and aniline derivatives was observed compared to Sc–chiral bipyridine catalyzed reactions, where the same chiral ligand was used. It was revealed from X-ray crystal structural analysis that a square pyramidal structure for the Cu(II) complex and a pentagonal bipyramidal structure for the Sc(III) complex were formed, which could explain the reversal of the enantioselectivity.

Organic reactions in water are currently of great interest. Water is an inexpensive, clean, and non-toxic solvent, and plays an important role in environmentally benign chemical synthesis.[1] In addition, unique reactivity and selectivity can often be observed in water.[2] Although there have been great advances in asymmetric catalysis, it is still difficult to perform asymmetric catalysis in water since most catalysts decompose rapidly in the presence of water.[3] To address this issue we have proposed a new concept using Lewis acid/chiral multicoordinated ligand combinations.[4] For example, we developed Pb(II)–chiral crown ether[4a] and Ln(III)–chiral crown ether[4b] complexes as catalysts for asymmetric Mukaiyama aldol reactions in aqueous media.[5] In these complexes, six heteroatoms coordinate to metals to stabilize the complexes in the presence of water. Moreover, water also coordinates to the metals assisting counter ion dissociation thus increasing Lewis acidity of the complexes. It should be noted that such complexes did not show any catalytic activity as Lewis acids in organic solvents. It was reasoned that the six heteroatoms worked as Lewis bases coordinating the metal thus decreasing the Lewis acidity of the complexes significantly. In the course of our investigation to expand this concept further directed toward truly efficient asymmetric catalysis in water, we envisioned that if metals were combined with multicoordinated ligands, multiple coordination forms could be possible depending on the metals employed, and unique reactivity and stereochemical outcomes might be expected by judicious choice of metals. In this paper, we show such examples in chiral metal-catalyzed enantioselective ring-opening of *meso*-epoxides in water.

Catalytic enantioselective ring-opening of *meso*-epoxides with indoles provides an efficient synthesis of optically active indole derivatives. We have recently shown that chiral Sc-catalyzed ring-opening of *meso*-epoxides with indole derivatives in water.[6] Sc(OSO$_3$C$_{12}$H$_{25}$)$_3$ (Sc(DS)$_3$)[7]–chiral bipyridine ligand **1**[8] was found to be an efficient catalyst; in the Sc–**1** complex, a pentagonal bipyramidal structure in which the bipyridine and the hydroxy groups of **1** coordinate to Sc^{3+} in a tetradentate manner was suggested by X-ray crystal structural analysis.[5a]

Table 1. Cu- and Sc-catalyzed asymmetric ring-opening reactions of *meso*-epoxides with indoles


Entry	R^1	R^2	R^3	Cu		Sc	
				Yield/%	ee/%	Yield/%	ee/%
1	Ph	H	H	80	96[a]	69	−92[b]
2	Ph	H	OMe	78	92	80	−92
3	Ph	H	Me	81	92	72	−95
4	Ph	H	Br	58	90	59	−91
5	Ph	Me	H	77	92	58	−85
6	2-Naphthyl	H	H	53	85	57	−88
7	4-MeC$_6$H$_4$	H	H	48	87	46	−84
8	4-BrC$_6$H$_4$	H	H	82	92	65	−94

[a] 1*S*,2*S*. [b] 1*R*,2*R*.

We thought that if another metal salt that formed a pyramidal structure where the bipyridines and one of the two hydroxy groups of **1** coordinated to the metal in a tridentate manner was used, the reaction course might be changed and different selectivity might be obtained.

Several examples of Cu–(*S*,*S*)-**1** catalyzed asymmetric ring-opening reactions of *meso*-epoxides with indoles are shown in Table 1. In most cases, the reactions proceeded well to afford the desired optically active indole derivatives in high yields with high enantiomeric excesses. Interestingly, reversal of enantioselectivities was observed between Cu- and Sc-catalyzed reactions.[9] In addition, it is noted that much lower yields of the desired compounds were obtained in organic solvents (CH$_2$Cl$_2$, THF, toluene, etc.) using Cu(OTf)$_2$– or Sc(OTf)$_3$–(*S*,*S*)-**1** as catalyst, and that the use of water as a solvent is essential for this reaction.[10]

We chose Cu(II) to investigate salts, when Cu(O$_3$SC$_{11}$H$_{23}$)$_2$–(*S*,*S*)-**1** was used as a catalyst in the reaction of *cis*-stilbene oxide (**2a**) with indole (**3a**) in water, the desired alcohol resulting from epoxide ring-opening was obtained in 80% yield with 96% ee, and the absolute configuration of the product was 1*S*,2*S*. On the other hand, Sc(O$_3$SC$_{11}$H$_{23}$)$_3$–(*S*,*S*)-**1** catalyzed the same reaction, where the same product was also obtained in high enantiomeric excess (92% ee), but the absolute configuration was reversed 1*R*,2*R*. Therefore, it is possible to obtain both enantiomers of the same product in high enantiomeric excess by selection of metal salts in combination with the same ligand (*S*,*S*)-**1** (Scheme 1).[11]

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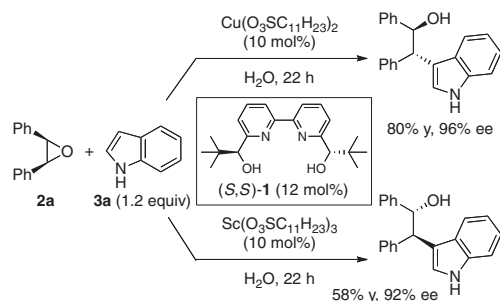
Scheme 1. Reversal of enantioselectivity in Cu- and Sc-catalyzed ring-opening reactions of *meso*-epoxides.

Table 2. Cu- and Sc-catalyzed asymmetric ring-opening reactions of *meso*-epoxides with anilines

Entry	R	Cu		Sc	
		Yield/%	ee/%	Yield/%	ee/%
1	Ph	88	91	96	−97
2	2-Naphthyl	81	90	76	−96
3	4-MeC$_6$H$_4$	78	90	85	−96
4	4-BrC$_6$H$_4$	72	91	88	−97

Furthermore, the reversal of enantioselectivity was also observed in the *meso*-epoxide ring-opening reactions with anilines. The Cu–(*S*,*S*)-**1** complex catalyzed these reactions in water to afford the corresponding β-amino alcohols in good to high yields and enantioselectivity (Table 2). It is noted that the sense of enantioselection in these reactions was again reversed compared with that obtained using the Sc–(*S*,*S*)-**1** complex as a catalyst.[12]

The reversal of enantioselectivity observed by switching metal sources, Cu(II) and Sc(III), with the same chiral ligand prompted us to further investigate the origin of the selectivity. Single crystals suitable for X-ray structure analysis were obtained from CuBr$_2$–(*S*,*S*)-**1** complex, the complex adopts a square pyramidal structure where two nitrogens and only one of the oxygens of **1** are attached to Cu(II) in a tridentate manner (Figure 1). The structure is in remarkable contrast to that of the ScBr$_3$–(*S*,*S*)-**1** analogue[5a] where two nitrogens and two oxygens of **1** are bound to Sc(III) in a tetradentate manner. This difference of the structure could explain the reversal of the enantioselectivity.[13]

In summary, we have observed reversal of enantioselectivity in Cu–chiral bipyridine catalyzed asymmetric ring-opening reactions of *meso*-epoxides with indole and aniline derivatives compared to Sc–chiral bipyridine catalyzed reactions, where the same chiral ligand was used. The key concept is use of multi-coordinated ligands combined with appropriate metals in water. X-ray crystal structural analysis of bromide analogues revealed a square pyramidal structure for the Cu(II) complex and a pentagonal bipyramidal structure for the Sc(III) complex, which could explain the reversal of the enantioselectivity. It is noted that the reactions proceeded in water and that the use of water as a solvent is essential. Investigation of the scope and limitation of this
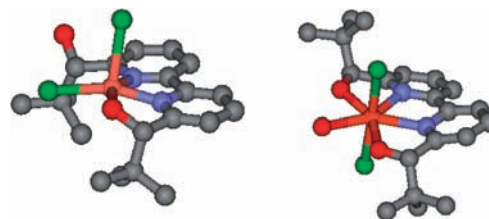

Figure 1. X-ray structure of [CuBr$_2$·**1**] (left) and [ScBr$_2$·H$_2$O·**1**]$^+$ moiety in the X-ray structure of [ScBr$_2$·H$_2$O·**1**]·Br·H$_2$O.[5a] Hydrogen atoms are omitted for clarity.

unique catalysis as well as application of this concept to other catalytic asymmetric reactions in water are now in progress.

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