SCANDIUM-CATALYZED RING-OPENING DESYMMETRIZATION OF MESO-EPOXIDES[#]

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[#]This paper is dedicated to Professor Yoshito Kishi on the occasion of his 70th birthday.

Abstract – In the presence of catalytic amounts of Sc(DS)$_3$ and chiral bipyridine ligand **1**, ring-opening desymmetrization of *meso*-epoxides with aromatic amines and indole derivatives proceeded smoothly in water without using any organic solvents to afford the corresponding adducts in high yields with high enatioselectivities. Interestingly, the Sc-caytalyzed reactions proceeded much faster in water than in dichloromethane.

INTRODUCTIOMN

The ring-opening desymmetrization of *meso*-epoxides with nucleophiles provides an efficient and powerful strategy for constructing two contiguous stereogenic centers in a single event. The reactions proceed under Lewis acidic conditions in most cases, and combinations of chiral Lewis acids and nucleophiles have been investigated.[1] On the other hand, organic reactions in water are now of great interest because water is an inexpensive, safe, and clean solvent, and unique reactivity and selectivity are often observed by using water as a solvent.[2] After discovery of water-compatible Lewis acids,[3] we have searched for chiral Lewis acids that work efficiently in aqueous media,[4] and recently a novel chiral scandium complex prepared from Sc(OTf)$_3$ and chiral bipyridine **1**[5] has been found to catalyze enantioselective hydroxymethylation reactions of silicon enolates using an aqueous formaldehyde solution (HCHO aq.).[6] While efficient chiral Lewis acid catalysis in aqueous media has been attained based on Sc for the first time, a certain amount of an organic co-solvent combined with water was needed

in these reactions.   We then decided to switch from $Sc(OTf)_3$ to $Sc(OSO_2C_{12}H_{25})_3$ $(Sc(DS)_3)$[7] to conduct the reactions in water without using any organic solvents.   While enantioselective hydroxymethylation reactions using HCHO aq. proceeded smoothly in water,[8] we also found that a chiral scandium complex prepared from $Sc(DS)_3$ and **1** was effective for ring-opening reactions of *meso*-epoxides in water.[9]   In this paper, we report highly enantioselective ring-opening desymmetrization of *meso*-epoxides with aromatic amines and indole derivatives in water.   Preliminary kinetic studies on the reactions in water and dichlomethane (DCM, as a representative of an organic solvent) are also described.

RESULTS AND DISCUSSION

Ring-opening desymmetrization of *meso*-epoxides with aromatic amines.

Chiral β-amino alcohols are often found in biologically important compounds, and catalytic enantioselective synthesis of these chiral building blocks mainly relies on asymmetric ring-opening of *meso*-epoxides.[10]   Indeed, although several examples using chiral Lewis acids are reported in literature,[11] all these reactions proceeded in organic solvents.   In the course of our investigations to extend the use of the novel chiral scandium complex[6] to other reactions in water, we decided to study asymmetric ring-opening desymmetrization of *meso*-epoxides with amines in water.[12]   We were pleased to find that the reaction of *cis*-stilbene oxide (**2a**) with aniline (**3a**) proceeded smoothly to afford the desired β-amino alcohol in 91% yield with 94% ee using 10 mol% of $Sc(DS)_3$ and 20 mol% of **1** in water (rt, 22 h).   It is noted that the ring opening reaction proceeded smoothly in water, and that no diol formation was observed.   Reducing the catalyst loading led to a decrease in conversion (5 mol%: 79% y, 94% ee; 3 mol%: 76% y, 94% ee), which could be overcome by a longer reaction time (1 mol%: 90% y, 94% ee for 30 h).   The enantioselectivity was not affected neither by reducing the ratio of the ligand to the metal from 2 to 1.2 (89% y, 91% ee) nor by the catalyst loading; indeed, the enantioselectivity was maintained even with only 0.25 mol% of the catalyst (32% y, 91% ee).   Hydrophobic interactions upon increasing the concentration of organic reactants may play a crucial role in these results.[13]   Interestingly, the reaction proceeded sluggishly without ligand **1**.   Moreover, the use of $Sc(OTf)_3$ instead of $Sc(DS)_3$ in water or water/THF gave the desired ring opening product in only poor yield.   Conducting the reaction at lower temperature (5 °C) had no effect on the enantioselectivity, whilst the conversion was significantly decreased.   On the other hand, higher temperature (40 °C) increased the reaction rate but had a detrimental effect on the enantioselectivity.

Under the optimized conditions (1 mol% of $Sc(DS)_3$ and 1.2 mol% of **1** in water), we next examined other substrates (Table 1).   Sterically hindered anilines such as *N*-methylaniline (**3b**) maintained high yields and led to a further increase in enantioselectivity to 96% ee (Table 1, entry 2).   The ring-opening with an

electron-rich amine such as *o*-anisidine (**3c**) proceeded with slightly improved enantioselectivity and yielded the desired product, which could be easily converted into the free 1,2-amino alcohol (entry 3). α-Naphthylamine (**3d**) also reacted smoothly to provide the amino alcohol in high yield with high enantioselectivity. Similarly, α-naphthylamine bearing a functional group such as 1-amino-4-bromo naphthalene (**3e**) gave the desired product, which could be further transformed to introduce other functional groups (entry 5). On the other hand, benzylamine and other aliphatic amines did not yield the desired products. Aromatic *cis*-epoxides, *cis*-4,4'-dimethylstilbene oxide **2b** and *cis*-1,2-dinaphtylethylene oxide **2c** reacted with aniline to furnish 1,2-amino alcohols in good yields with high enantioselectivity (entries 6 and 7). Aliphatic epoxides, *cis*-1,6-diphenyl-3-hexene oxide (**2d**) and *cis*-5-decene oxide (**2e**), reacted with aniline under otherwise identical reaction conditions to afford the desired products in good to high yields with good enantioselectivity (entries 8 and 9). In general, even a trace amount of water exerts a detrimental effect on yield and enantioselectivity, and only few examples of enantioselective Lewis acid-catalyzed reactions in water without using any organic solvents have been reported.[14] To the best of our knowledge, this is to date the first example of an asymmetric epoxide ring-opening in water.[15]

Table 1. Asymmetric Ring-opening of *meso*-Epoxides with Aromatic Amines

Entry	Epoxide	Amine	Yield (%)	Ee (%)
1	**2a**	**3a**	89	91
2	**2a**	**3b**	88	96
3	**2a**	**3c**	81	93
4	**2a**	**3d**	83	91
5	**2a**	**3e**	85	86
6	**2b**	**3a**	81	90
7	**2c**	**3a**	75	91
8	**2d**	**3a**	61	60
9	**2e**	**3a**	89	71

2a   **2b**   **2c**   **2d**   **2e**

3a   **3b**   **3c**   **3d**   **3e**
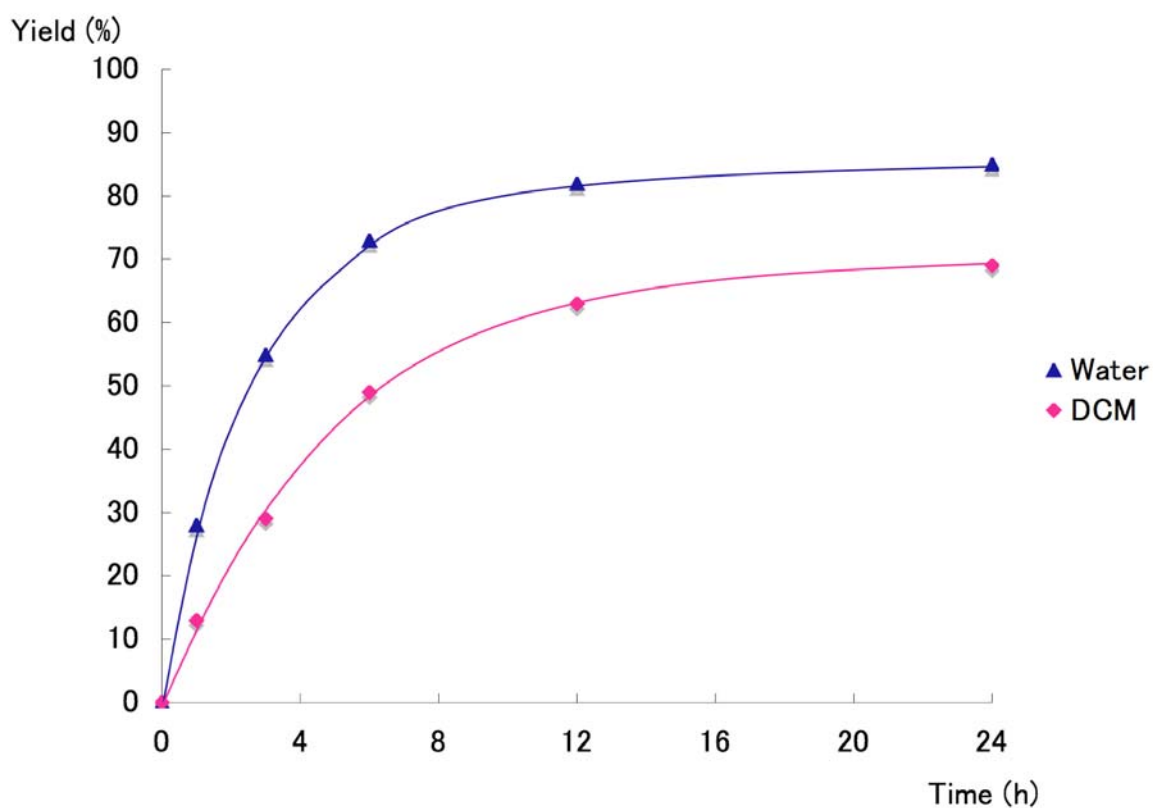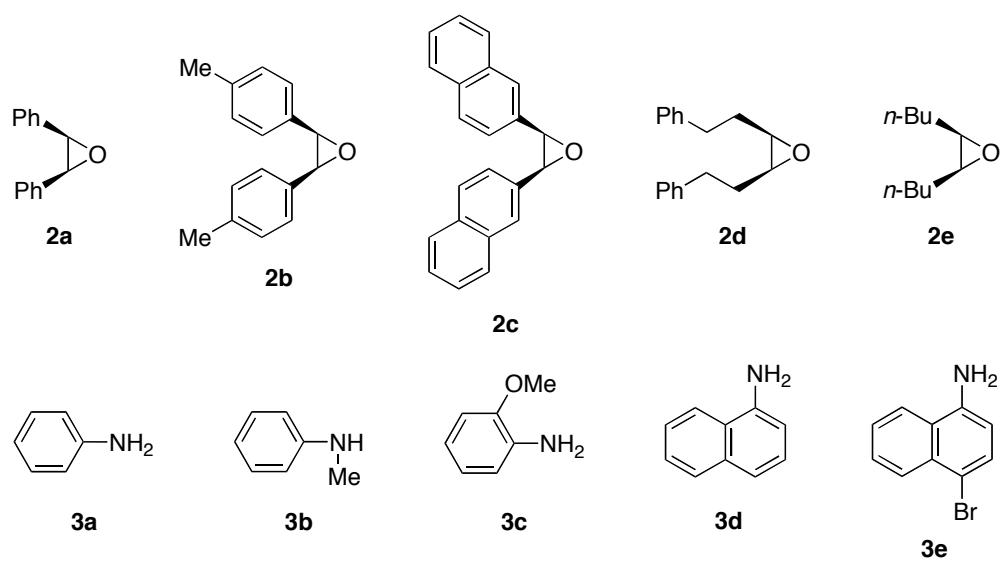
Figure 1. Plot of yield versus time for the ring-opening of *cis*-stilbene oxide (**2a**) with aniline (**3a**) in the presence of 1 mol% of Sc(DS)$_3$ and 1.2 mol% of **1** in water (blue) and 1 mol% of Sc(OTf)$_3$ and 1.2 mol% of **1** in DCM (red) at rt.

Finally, *cis*-stilbene oxide (**2a**) was treated with aniline (**3a**) in the presence of 1 mol% of Sc(OTf)$_3$ and 1.2 mol% of **1** in DCM at rt for 22 h. The reaction proceeded to afford the desired β-amino alcohol in 85% yield with 74% ee. It is noted that Sc(DS)$_3$ and **1** in water gave higher yield and enantioselectivity than Sc(OTf)$_3$ and **1** in DCM. In addition, preliminary kinetic experiments have demonstrated that Sc(DS)$_3$ and **1** in water gave higher reactivity than Sc(OTf)$_3$ and **1** in DCM (Figure 1).

Thus, we have established the first catalytic, enantioselective addition of aromatic amines to *meso*-epoxides employing Sc(DS)$_3$-**1** in water without using any organic solvents. Chiral β-amino alcohols were prepared in mostly high yields with excellent enantioselectivities. It is noted that the use of water as a solvent gave a higher yield and enantioselectivity than that of DCM.

Ring-opening desymmetrization of *meso*-epoxides with indole derivatives.

Since the indole framework is widely represented in natural substances and medicinal compounds,[16] development of an efficient method for generation of chiral *N*-heteroaromatic derivatives in optically active form, in particular these incorporating indolic architectures, is a challenging and important facet of this research area.[17] To date, although several catalytic, regioselective ring-opening of racemic epoxides[18] or chiral aromatic epoxides[19] with indole derivatives have been described, only one protocol for highly selective addition of indole derivatives to *meso*-stilbene oxide in *tert*-butyl methyl ether has been reported.[20]

Our preliminary experiment was performed using *cis*-stilbene oxide (**2a**) and indole (**4a**) as model reagents. It was found that the reaction proceeded smoothly in water (0.5M) at rt for 5 h to give the desired alcohol in 50% yield with 96% ee in the presence of catalytic amounts of Sc(DS)$_3$ and **1**. Running the reaction at higher concentration (1.0 M) increased the yield dramatically while maintaining a high level of enantioselectivity (85% y, 93% ee). It should be noted that the same reaction using Sc(OTf)$_3$ instead of Sc(DS)$_3$ in dichloromethane proceeded sluggishly under the conditions. On the other hand, neither increasing the amount of nucleophile nor lengthening the reaction time resulted in further improvement of the yield or the selectivity. Thus, the desymmetrization of **2a** with **4a** was carried out with 5 mol% of Sc(DS)$_3$ and 6 mol% of **1** in water as the sole solvent, affording the desired alcohol in 85% yield with 93% ee.

It is noteworthy that this reaction could be performed under air without epimerisation of the product or loss of reactivity (Table 2, entry 1). As the next step, other epoxide and indole derivatives were examined under the optimized conditions. The electron-rich 5-methoxyindole (**4b**) allowed to maintain

very high enantioselectivity and yield (entry 2), although a slight decrease in the yield and the enantioselectivity was observed for the 5-methylindole derivative **4c** (entry 3). The sterically hindered 2-methylindole (**4d**) gave, as expected, lower yield, although enantioselectivity was high (entry 4). Use of the more electron-deficient 5-bromoindole (**4e**) gave the corresponding alcohol in good yield with high enantioselectivity (entry 5). The *meso*-epoxides, *cis*-4,4'-dimethylstilbene oxide (**2b**) and *cis*-4,4'-dibromostilbene oxide **2f** reacted with **4a** and **4b** to afford the desired products in good yields with high enantioselectivity (entries 6-8).

Table 2. Asymmetric Ring-opening of *meso*-Epoxides with Indole Derivatives.

Entry	Epoxide	Indole	Yield (%)	Ee (%)
1	**2a**	**4a**	85 (85)[a]	91 (93)[a]
2	**2a**	**4b**	75	92
3	**2a**	**4c**	71	85
4	**2a**	**4d**	63	85
5	**2a**	**4e**	59	90
6	**2b**	**4a**	62	86
7	**2f**	**4a**	59	93
8	**2f**	**4b**	56	92

[a] The reaction was conducted under air.
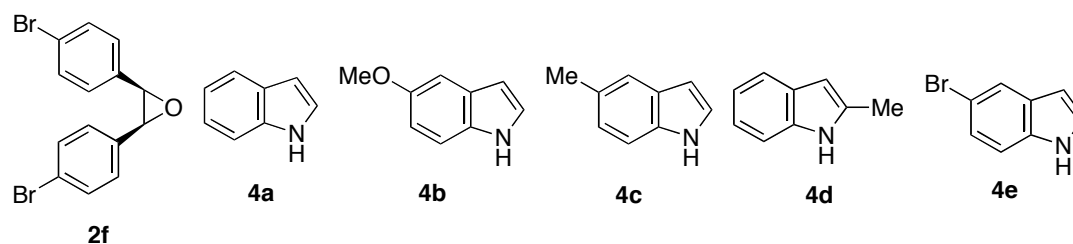
Here we also compared the reaction of *cis*-stilbene oxide (**2a**) with indole (**4a**) in water and DCM. The reaction also proceeded much faster in water than in DCM (Figure 2).
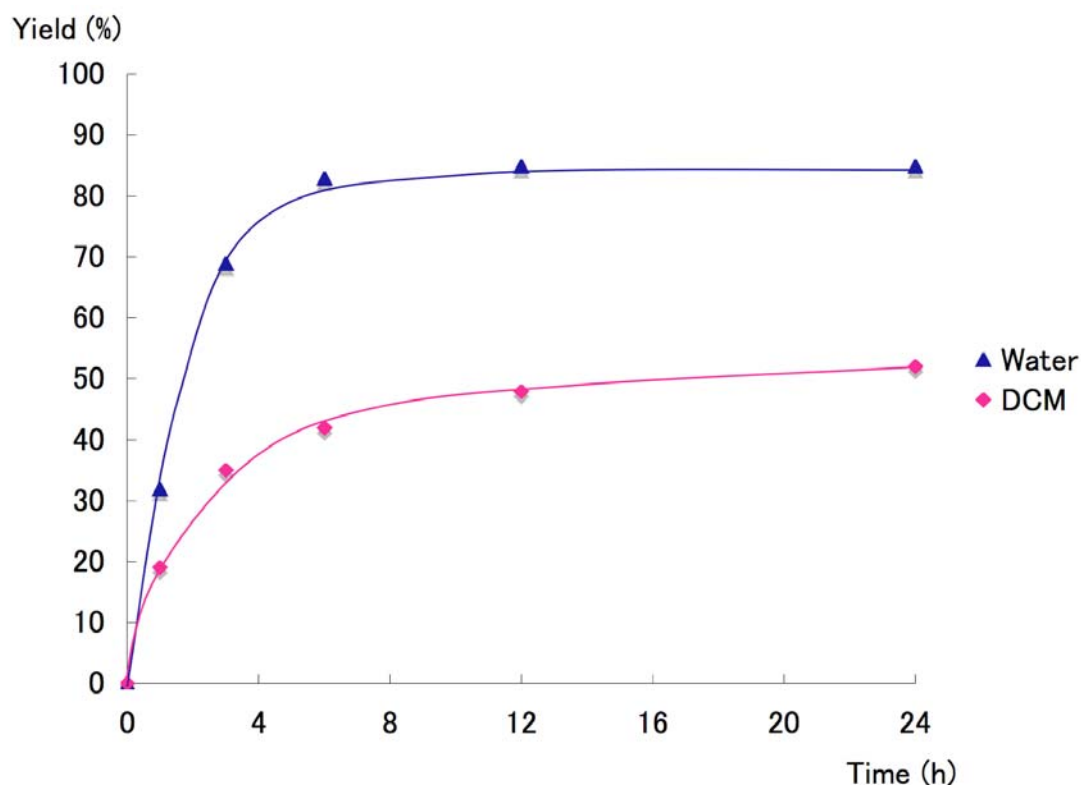
Figure 2. Plot of yield versus time for the ring-opening of *cis*-stilbene oxide (**2a**) with indole (**4a**) in the presence of 1 mol% of Sc(DS)$_3$ and 1.2 mol% of **1** in water (blue) and 1 mol% of Sc(OTf)$_3$ and 1.2 mol% of **1** in DCM (red) at rt.

CONCLUSION

We have found that ring-opening desymmetrization of *meso*-epoxides with aromatic amines and indole derivatives in water proceeded smoothly in the presence of catalytic amounts of Sc(DS)$_3$ and chiral bipyridine ligand **1**. The reactions proceeded without using any organic solvents to afford the corresponding adducts in high yields with high enantioselectivities. Interestingly, the reactions proceeded much faster in water than in dichloromethane.

EXPERIMENTAL

General Procedure for Catalytic Asymmetric Ring Opening of *meso*-Epoxides with Aromatic Amines. To Sc(DS)$_3$ (12.6 mg, 0.015 mmol) and ligand **1** (5.9 mg, 0.018 mmol) under argon was added deionised water (300 μL, 1 M concentration with respect of the epoxide). The reaction mixture was stirred for 1 h at room temperature (rt) upon which an epoxide (0.3 mmol) and an amine (0.330 mmol)

were successively added.   Vigorous stirring was continued for 30-48 h at rt.   The reaction was quenched with saturated aqueous $NaHCO_3$.   The resultant mixture was extracted with AcOEt (three times), and the combined organic layers were dried over anhydrous Na_2SO_4.   The solvents were evaporated, and the residue was purified by PTLC over silica gel using a mixture of Et_2O-hexane as eluent to give the pure amino alcohol.

General Procedure for Catalytic Asymmetric Ring Opening of *meso*-Epoxides with Indole Derivatives.   To $Sc(DS)_3$ (12.6 mg, 0.015 mmol) and ligand **1** (5.9 mg, 0.018 mmol) under argon was added deionised water (300 μL, 1 M concentration with respect of the epoxide).   The reaction mixture was stirred for 1 h at rt upon which an epoxide (0.3 mmol) and an indole derivative (0.330 mmol) were successively added.   Vigorous stirring was continued for 4-27 h at rt, and the reaction mixture was diluted with CH_2Cl_2 or AcOEt.   After phase separation, the aqueous layer was extracted with CH_2Cl_2 or AcOEt (three times).   The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure.   The resulting crude mixture was purified by PTLC using a mixture of *n*-hexane/AcOEt + 3% Et_3N as eluent (the loading zone of the silica plates were previously eluted with a mixture of *n*-hexane/AcOEt + 3% Et_3N).

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