

Chiral Scandium-catalyzed Highly Stereoselective Ring-opening of *meso*-Epoxides with Thiols

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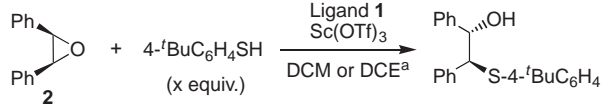
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The desymmetrization of *meso*-epoxides with thiols proceeded smoothly in dichloromethane or dichloroethane in the presence of a catalytic amount of a chiral scandium complex consisting of $\text{Sc}(\text{OTf})_3$ and chiral bipyridine **1**, to afford the corresponding sulfides in high yields with high enantioselectivities.

The ring-opening desymmetrization of *meso*-epoxides with nucleophiles provides a powerful and efficient strategy for constructing two contiguous stereogenic centers in a single event. In general, the reactions proceed under Lewis acidic conditions, and combinations of chiral Lewis acids and nucleophiles such as amines and alcohols have been investigated.¹ However, the use of thiols as nucleophiles is still relatively unexplored and only a few examples have been reported.² Recently, we have developed a novel chiral scandium complex prepared from $\text{Sc}(\text{OTf})_3$ and chiral bipyridine **1**, that catalyzes enantioselective hydroxymethylation reactions of silicon enolates using an aqueous formaldehyde solution.³ We also reported that a chiral scandium complex prepared from $\text{Sc}(\text{OSO}_3\text{C}_{12}\text{H}_{25})_3$ ($\text{Sc}(\text{DS})_3$) and **1** was effective for ring-opening reactions of *meso*-epoxides in water with aromatic amines, aromatic *N*-heterocycles, and an alcohol.^{4,5} Interestingly, some thiols also worked well using $\text{Sc}(\text{DS})_3$ and **1** in water (Scheme 1).⁵ As an extension of this work, we further investigated the desymmetrization of *meso*-epoxides by ring opening with thiols, and found that efficient reactions also proceeded not only in water but also in organic solvents. In this paper, we report the highly enantioselective ring-opening of *meso*-epoxides with thiols catalyzed by a chiral scandium complex.⁶

First, we selected the reaction of *cis*-stilbene oxide (**2**) with 4-*t*-butylbenzenethiol as a model, and several reaction conditions were examined (Table 1). The reaction proceeded in moderate yield with high enantioselectivity in dichloromethane (DCM) at room temperature in the presence of $\text{Sc}(\text{OTf})_3$ (10 mol %) and chiral bipyridine **1** (12 mol %) (Entry 1).⁸ The yield was improved without loss of enantioselectivity using an excess amount of the thiol (3.0 equiv., Entries 2 and 3). It should

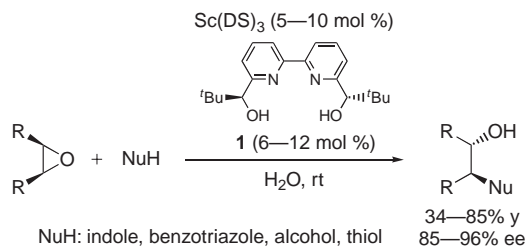
Table 1. Optimization of reaction conditions

							
Entry	X	Sc/Lig	Time/h	Temp/°C	Conc/M	Yield/%	ee/%
1	1.5	10/12	7	rt	0.2	42	92
2	3	10/12	7	rt	0.2	74	94
3	3	10/12	12	rt	0.2	87	95
4	1.5	10/12	7	40	0.4	78	92
5	1.5	5/6	7	40	0.4	84	93

^aDCM (dichloromethane) at rt and DCE (dichloroethane) at 40 °C.

be noted that no desired product was obtained when $\text{Sc}(\text{OTf})_3$ was used alone as a catalyst under the conditions (without **1**).⁹ On the other hand, when the reaction was carried out at 40 °C in dichloroethane (DCE), the same levels of yield and enantioselectivity were obtained even using a slight excess of the thiol (1.5 equiv.) and a smaller amount of the chiral scandium catalyst (Entries 4 and 5). It is noteworthy that the use of 5 mol % of the catalyst also gave the desired product in high yield with excellent enantioselectivity (Entry 5).

Several *meso*-epoxides and thiols were then subjected to this system (Table 2). Benzenethiols having electron-donating and electron-withdrawing groups worked well in the reaction in the presence of 10 mol % of $\text{Sc}(\text{OTf})_3$ -**1** to afford the corresponding sulfides in high yields and with excellent enantioselectivities (Entries 1–4). In particular, *cis*-stilbene oxide (**2**) reacted with 4-chlorobenzenethiol to provide the desired product in 97% ee (Entry 4). The absolute configuration of the product in Entry 3 was determined after oxidizing to the corresponding sulfone (compared the optical rotation of the sulfone with that in literature).¹⁰ Furthermore, not only reactions using benzenethiols proceeded smoothly but those involving less reactive alkyl thiols (Entry 5) also worked well to give the desired adducts in good yields with excellent enantiomeric excesses. As for the scope of the *meso*-epoxide, other *cis*-stilbene oxide derivatives also reacted well to give the corresponding sulfides in good to high yields with excellent enantioselectivities (Entries 6–8). In the reaction of *cis*-stilbene oxide derivative **3** with 4-*t*-butylbenzenethiol, epoxide **3** was consumed after 4 h at room temperature, however some side reactions occurred with the result that the yield of the desired sulfide was decreased (Entry 6). Notably however, the reaction of *cis*-stilbene oxide derivative **4** with 4-*t*-butylbenzenethiol proceeded relatively slowly but without side reactions at room temperature, to afford the desired product in high yield with excellent enantiomeric excess (Entry 8). While the reactions proceeded smoothly at room temperature in most



Scheme 1. Sc-catalyzed desymmetrization of *meso*-epoxides in water.

Table 2. Ring-opening of *meso*-epoxides with thiols

$ \begin{array}{c} R^1 \\ \diagup \\ R^1-O \\ \diagdown \\ R^1 \end{array} + R^2SH \xrightarrow[\text{DCM, rt, time}]{\text{Ligand } \mathbf{1} \text{ (12 mol \%)} \\ \text{Sc(OTf)}_3 \text{ (10 mol \%)}} \begin{array}{c} R^1 \\ \diagup \\ OH \\ \diagdown \\ R^1-SR^2 \end{array} $					
Entry	Epoxide	R ²	Time/h	Yield/%	ee/%
1		4- <i>t</i> -BuC ₆ H ₄	12	87	95
2	2	4-MeOC ₆ H ₄	12	79	95
3	2	C ₆ H ₅	12	84	90 ^a
4	2	4-ClC ₆ H ₄	12	76	97
5	2	PhCH ₂	12	68	96
6		4- <i>t</i> -BuC ₆ H ₄	4	64 (69) ^b	91 (94) ^b
7	3	4-ClC ₆ H ₄	12	53	93
8		4- <i>t</i> -BuC ₆ H ₄	18	86	96
9		4- <i>t</i> -BuC ₆ H ₄	24	41	50

^aThe absolute configuration of the product was determined to be 2*S*,3*S* (see text). ^b0 °C for 7 h.

cases, it is possible to conduct the reaction at 0 °C to afford the desired compound in higher enantiometric excess (Entry 6 in parenthesis). It should be noted that excellent levels of enantioselectivity have been attained in the ring-opening desymmetrization of *cis*-stilbene oxide derivatives with thiols by using a relatively simple chiral catalyst prepared from Sc(OTf)₃ and chiral bipyridine **1**. In contrast, *cis*-2,3-epoxybutane (**5**) reacted with 4-*t*-butylbenzenethiol to afford the corresponding sulfide in moderate yield with moderate enantiomeric excess (Entry 9). We confirmed that in this case a background reaction (without the catalyst) is competitive with the enantioselective process and that this undesired non-catalyzed pathway decreased the enantioselectivity. A trial to suppress the undesired pathway and to improve the enantioselectivity is now under investigation.

A typical experimental procedure is described for the desymmetrization of *cis*-stilbene oxide **2** with 4-*t*-butylbenzenethiol. Sc(OTf)₃ (19.7 mg, 0.04 mmol) and chiral bipyridine ligand (*S,S*)-**1** (15.8 mg, 0.048 mmol) in DCM (0.8 mL) were stirred for 10 min at room temperature. To this solution, an epoxide (0.4 mmol) in DCM (0.8 mL) and a thiol (1.2 mmol) in DCM (0.4 mL) were successively added. The mixture was stirred at the same temperature for 4–24 h. Water was added to quench the reaction, and the product was extracted with DCM. After usual work-up, the crude product was purified by preparative TLC on silica gel to afford the desired sulfide. The enantioselectivity of the product was determined by HPLC analysis using a chiral column.

In summary, we have developed a ring-opening desymmetrization of *meso*-epoxides with thiols using a chiral scandium

complex. The scandium complex consisting of Sc(OTf)₃ and chiral bipyridine **1**, that was recently shown as an efficient catalyst in asymmetric hydroxymethylation using an aqueous formaldehyde solution, was also found to be effective in this asymmetric reaction, and various sulfides were obtained in high yields with high enantioselectivities. Recently, we have also reported desymmetrization ring-opening of *meso*-epoxides with thiols in water using Sc(OTf)₃ and chiral bipyridine **1** as a catalyst.⁵ Compared with these reactions, while the present reactions in an organic solvent gave the same levels of yields and enantioselectivities, it was revealed from our preliminary comparison experiments that the reaction rates in organic solvents were lower than that in water. Further investigations to clarify scope and limitation, kinetics, and reaction environments in these systems (in both water and organic solvents) are now in progress.

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References and Notes

- a) M. C. Willis, *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765. b) D. M. Hodgson, A. R. Gibbs, G. P. Lee, *Tetrahedron* **1996**, 52, 14361. c) E. N. Jacobsen, M. H. Wu, in *Comprehensive Asymmetric Catalysis*, ed. by E. N. Jacobsen, A. Pfaltz, H. Yamamoto, Springer-Verlag, Berlin, **1999**, Vol. 3, p. 1309.
- a) T. Iida, N. Yamamoto, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1997**, 119, 4783. b) M. H. Wu, E. N. Jacobsen, *J. Org. Chem.* **1998**, 63, 5252. c) J. Wu, X.-L. Hou, L.-X. Dai, L.-J. Xia, M.-H. Tang, *Tetrahedron: Asymmetry* **1998**, 9, 3431.
- S. Ishikawa, T. Hamada, K. Manabe, S. Kobayashi, *J. Am. Chem. Soc.* **2004**, 126, 12236.
- S. Azoulay, K. Manabe, S. Kobayashi, *Org. Lett.* **2005**, 7, 4593.
- M. Boudou, C. Ogawa, S. Kobayashi, *Adv. Synth. Catal.*, in press.
- Recently, Schneider et al. reported ring opening of *meso*-epoxides with alcohols and amines catalyzed by a chiral scandium complex in an organic solvent. C. Schneider, A. R. Sreekanth, E. Mai, *Angew. Chem., Int. Ed.* **2004**, 43, 5691.
- a) C. Bolm, M. Zehnder, D. Bur, *Angew. Chem., Int. Ed.* **1990**, 29, 205. b) C. Bolm, M. Ewald, M. Felder, G. Schlingloff, *Chem. Ber.* **1992**, 125, 1169.
- A chiral bismuth complex consisting of Bi(OTf)₃ and chiral bipyridine **1** also catalyzed enantioselective ring-opening desymmetrization of *meso*-epoxides. a) C. Ogawa, S. Azoulay, S. Kobayashi, *Heterocycles* **2005**, 66, 201. For a reference to the bismuth catalyst see: b) S. Kobayashi, T. Ogino, H. Shimizu, S. Ishikawa, T. Hamada, K. Manabe, *Org. Lett.* **2005**, 7, 4729.
- Some side reactions occurred under the conditions. Crotti et al. reported that lanthanide triflates such as Yb(OTf)₃-catalyzed aminolysis of epoxides effectively. a) M. Chini, P. Crotti, L. Favero, F. Macchia, M. Pineschi, *Tetrahedron Lett.* **1994**, 35, 433. For lanthanide triflates and scandium triflate as water- and amine-compatible Lewis acids, see: b) S. Kobayashi, M. Sugiura, H. Kitagawa, W. W.-L. Lam, *Chem. Rev.* **2002**, 102, 2227. c) S. Kobayashi, *Eur. J. Org. Chem.* **1999**, 15. d) S. Kobayashi, *Synlett* **1994**, 689.
- S. Nakamura, R. Nakagawa, Y. Watanabe, T. Toru, *J. Am. Chem. Soc.* **2000**, 122, 11340.