

## New Asymmetric Reactions Using a Gallium Complex: A Highly Enantioselective Ring Opening of Epoxides with Thiols Catalyzed by a Gallium·Lithium·Bis(binaphthoxide) Complex

Takehiko Iida, Noriyoshi Yamamoto, Hiroaki Sasai, and Masakatsu Shibasaki\*

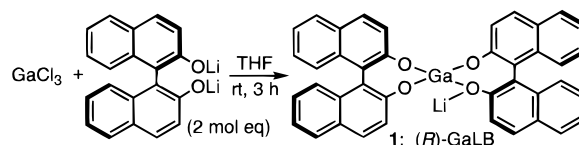
Faculty of Pharmaceutical Sciences  
University of Tokyo  
Hongo, Bunkyo-ku, Tokyo 113, Japan

Received January 27, 1997

The enantioselective ring opening of symmetrical epoxides is an attractive and quite powerful method in asymmetric synthesis.<sup>1</sup> Since a pioneering report by Whitesell,<sup>2</sup> various types of stoichiometric or catalytic asymmetric epoxide openings have been reported,<sup>3</sup> and recently Jacobsen *et al.* have realized a highly efficient catalytic asymmetric epoxide opening with Me<sub>3</sub>SiN<sub>3</sub>.<sup>3i</sup> However, only a few practical methods have been reported so far, which in general require the use of silylated compounds as nucleophiles. We became very interested in the development of catalytic asymmetric epoxide ring openings using nonsilylated nucleophiles such as RSH, HCN, and HN<sub>3</sub>.<sup>4</sup> In 1985, Yamashita and Mukaiyama reported a catalytic asymmetric epoxide opening by thiols using a zinc tartrate catalyst.<sup>3b</sup> To the best of our knowledge, this is the only useful example to obtain synthetically versatile  $\beta$ -hydroxy sulfides in an optically active form by way of an epoxide opening. Mukaiyama's catalyst, however, is still unsatisfactory in terms of broad usefulness, selectivity, and reactivity. We report herein an efficient catalytic asymmetric ring opening of symmetrical epoxides with thiols using a newly prepared asymmetric complex: gallium·lithium·bis(binaphthoxide) (**1**, GaLB).<sup>5</sup> This catalyst should also be useful for catalytic asymmetric epoxide openings with other nonsilylated nucleophiles.

We have previously succeeded in developing several heterobimetallic asymmetric complexes, in which the metals play complementary roles in activating and positioning both the electrophile and the nucleophile in a catalytic asymmetric process.<sup>6,7</sup> We envisioned that these complexes would prove to be useful for catalytic asymmetric opening of **2** with a

### Scheme 1. Preparation of (*R*)-GaLB (**1**)



nucleophile such as PhCH<sub>2</sub>SH (**3**). However, lanthanum·M<sub>3</sub>-tris(binaphthoxide) (M = Li or Na)<sup>6</sup> or aluminum·lithium·bis(binaphthoxide) (ALB)<sup>7</sup> showed only low catalytic activity to give 2-(benzylthio)cyclohexanol (**4**)<sup>3b</sup> in 1–10% yields, although modest to high enantiomeric excess (ee) values (27–86% ee) were observed. In order to develop more reactive catalysts, we then prepared new heterobimetallic asymmetric complexes using group 13 elements (B, Ga, In) other than Al. Of these, the gallium·lithium·bis[*(R)*-binaphthoxide] complex [**1**, (*R*)-GaLB], which was readily prepared from GaCl<sub>3</sub>,<sup>8</sup> (*R*)-binaphthol (2 mol equiv to GaCl<sub>3</sub>), and BuLi (4 mol equiv to GaCl<sub>3</sub>) in THF, showed a high catalytic activity for the present reaction. The structure of **1** is proposed, as shown in Scheme 1.<sup>9</sup> Although racemic **4** was obtained when THF was used as a solvent, the use of toluene gave a 40% ee of 1(*R*),2(*R*)-**4**<sup>10</sup> (87% yield) in the presence of 10 mol % of GaLB at room temperature (rt).<sup>11</sup> Interestingly, the ee of **4** gradually increased as the reaction proceeded, presumably due to the resultant decrease in concentration of remaining thiol.<sup>12</sup> In addition, by using a stoichiometric amount of **1**, compound **4** could be obtained with 88% ee in 87% yield. These results appear to indicate that an undesired ligand exchange of binaphthol for the thiol **3**<sup>13</sup> or perhaps just a Lewis acid catalyzed reaction without participation of a lithium binaphthoxide moiety, was taking place.

We hypothesized that the use of more sterically hindered thiols such as **5** might prevent such undesired side reactions. As hoped, the reaction of **2** with **5** in the presence of GaLB (10 mol %) afforded **12** with 98% ee even at rt, albeit only in 35% yield.<sup>14</sup> After many attempts, we were pleased to find that the addition of MS 4A (0.2 g/mmol of **2**) was extremely effective in enhancing the reaction rate,<sup>15,16</sup> with **12** being obtained in 80% yield without reduction of ee (Table 1, entries 1–2). GaLB catalysis was found to be applicable to a wide range of symmetrical epoxides; epoxides with functional groups (**6–8**)<sup>17</sup> and epoxides fused to five-membered rings (**9** and **10**) underwent

(1) For a recent review on the enantioselective ring opening of symmetrical epoxides, see: Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron* **1996**, *52*, 14361–14384.

(2) Whitesell, J. K.; Felman, S. W. *J. Org. Chem.* **1980**, *45*, 755–756.  
(3) (a) Plum, H.; Wynberg, H. *Rec. J. R. Neth. Chem. Soc.* **1984**, *103*, 36–37. (b) Yamashita, H.; Mukaiyama, T. *Chem. Lett.* **1985**, 1643–1646. (c) Yamashita, H. *Chem. Lett.* **1987**, 525–528. (d) Su, H.; Walder, L.; Zhang, Z.; Scheffold, R. *Helv. Chim. Acta* **1988**, *71*, 1073–1078. (e) Chan, A. S. C.; Coleman, J. P. *J. Chem. Soc., Chem. Commun.* **1991**, 535–536. (f) Hayashi, M.; Kohmura, K.; Oguni, N. *Synlett* **1991**, 774–776. (g) Nugent, W. A. *J. Am. Chem. Soc.* **1992**, *114*, 2768–2769. (h) Asami, M.; Ishizaki, T.; Inoue, S. *Tetrahedron: Asymmetry* **1994**, *5*, 793–796. (i) Martínez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897–5898. (j) Cole, B. M.; Shimizu, K. D.; Krueger, C. A.; Harrity, J. P. A.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1668–1671.

(4) Quite recently Jacobsen has reported that the (salen)Cr ring opening functions with HN<sub>3</sub> through a (salen)Cr bimetallic transition state. See: Hansen, K. B.; Leighton, J. L.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 10924–10925.

(5) This paper describes the first detailed study of GaLB (**1**), including the preparation procedure. Only one example of Michael reaction using **1** is included in ref 6b.

(6) For discussions concerning the multifunctional activities of heterobimetallic asymmetric catalysts, see: (a) Sasai, H.; Arai, T.; Satow, Y.; Houk, K. N.; Shibasaki, M. *J. Am. Chem. Soc.* **1995**, *117*, 6194–6198. (b) Arai, T.; Yamada, Y. M. A.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *Chem. Eur. J.* **1996**, *2*, 1368–1372.

(7) (a) Arai, T.; Sasai, H.; Aoe, K.; Okamura, K.; Date, T.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 104–106 and references cited therein. (b) Arai, T.; Bougauchi, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1996**, *61*, 2926–2927.

(8) GaCl<sub>3</sub> was purchased from Kojundo Chemical Laboratory Co., Ltd., 5-1-28, Chiyoda, Sakato, Saitama 350-02, Japan (fax +81-492-84-1351).

(9) For **1**: <sup>13</sup>C NMR (THF, external D<sub>2</sub>O was used to obtain lock signal)  $\delta$  121.0, 121.3, 124.0, 125.2, 126.3, 127.0, 127.3, 128.4, 134.6, 157.4; FAB-MS *m/z* 653 and 651 (M<sup>+</sup> + Li), 646 and 644 (M<sup>+</sup>). The <sup>13</sup>C NMR spectrum of GaLB was similar to that of ALB, the structure of which has been unequivocally determined by X-ray crystallography. See: refs 6b and 7a.

(10) The absolute configuration of **4** was determined by comparison with the specific rotation reported in ref 3b.

(11) A solution of GaLB was placed in a reaction vessel and concentrated *in vacuo* at rt to remove solvents. The residue was redissolved in toluene under Ar, and the mixture was used as a catalyst solution. The use of toluene gave the best results: see Supporting Information.

(12) For time-courses of ee and yield for **4**, see Supporting Information.

(13) GaLB would be regenerated as the outcome of a decrease in the concentration of **3**, since the ligand exchange seems to be a reversible reaction.

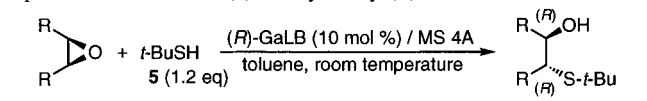
(14) Low yields were obtained even at higher temperatures.

(15) Molecular sieves (MS) 4A were dried at 180 °C for 6 h under reduced pressure prior to use.

(16) Several catalytic asymmetric reactions have been carried out successfully in the presence of MS 4A: (a) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922–1925. (b) Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimoto, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340–5345. (c) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949–3954.

(17) Compounds **6–8** were prepared from corresponding olefins by epoxidation, and the relative configuration of **7** was determined by X-ray crystallographic analysis.

(18) (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Org. Chem.* **1991**, *56*, 1296–1298.

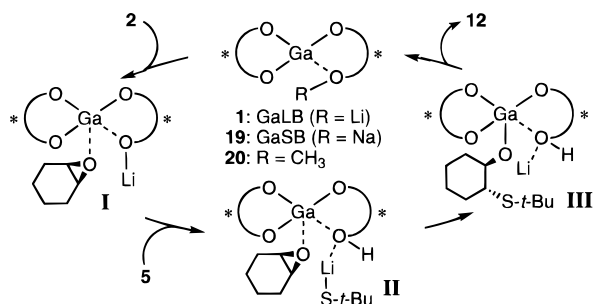
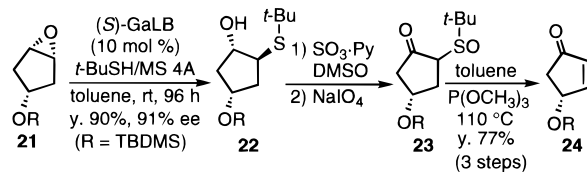
**Table 1.** Catalytic Asymmetric Ring Openings of Symmetrical Epoxides with *t*-BuSH (**5**) Catalyzed by (*R*)-GaLB with MS 4A<sup>a</sup>


entry	epoxide	MS 4A <sup>b</sup> (g)	time (h)	product	yield <sup>c</sup> (%)	ee <sup>d</sup> (%)
1		none	65	<b>12</b>	35	98
2		0.2	9	<b>12</b>	80	97
3		0.2	36	<b>13</b>	74	95
4		0.2	12	<b>14</b>	83	96
5		0.2	137	<b>15</b>	64	91
6		0.2	24	<b>16</b>	89	91
7 <sup>e</sup>		0.2	72	<b>17</b>	89	89
8		2.0	48	<b>18</b>	89	82

<sup>a</sup> The absolute configurations of the products were determined by Mosher's method.<sup>18,19</sup> <sup>b</sup> Weight per 0.1 mmol of GaLB. <sup>c</sup> Isolated yield. <sup>d</sup> All ee values were determined by chiral stationary phase HPLC. For entries 1–3 and 6, the ee values of the corresponding benzoates were determined. <sup>e</sup> Carried out at 50 °C in the presence of 30 mol % of GaLB. Mts = 2,4,6-trimethylbenzenesulfonyl.

ring opening with high ee (89–96% ee) in good yields (entries 3–7). On the other hand, however, the reaction of acyclic **11** proceeded very slowly, giving **18** in a low yield. This problem was overcome by an increase in the amount of MS 4A (2.0 g/mmol of **11**), with the reaction reaching completion in 48 h and affording **18** with 82% ee in 89% yield (entry 8). The role of MS 4A (sodium aluminosilicate) is interesting, with <sup>13</sup>C NMR spectra revealing that GaLB was transformed into GaSB (**19**)<sup>6b</sup> in the presence of large amounts of MS 4A, and in fact the use of GaSB (10 mol %) instead of GaLB gave **18** with 78% ee in 93% yield (rt, 12 h). In striking contrast to these results, the use of GaSB with the other epoxides gave very low ee values, suggesting that transformation of GaLB to GaSB did *not* take place to a significant extent under the standard reaction conditions (entries 2–6) using smaller quantities of MS 4A. Another possible role of the MS 4A may be to assist decomplexation of the product from the catalysts, resulting in an enhanced overall reaction rate.

A working model for the catalytic asymmetric epoxide opening is shown in Scheme 2. GaLB (**1**) appears to act as an asymmetric multifunctional catalyst,<sup>6</sup> with a lithium binaphthoxide moiety functioning as a Brønsted base, activating **5** and controlling the orientation of the resulting lithium thiolate by chelation. In contrast, significant enantioselectivity was not detected when **20** was used instead.<sup>20</sup> In addition, a gallium metal appears to function as a Lewis acid, activating and also controlling the orientation of **2** presumably due to coordination of an axial lone pair, allowing for the cleavage of C–O bond by backside attack (**III**). On this basis, the likely absolute configuration of **12** can be predicted to be 1(*R*),2(*R*), and in

**Scheme 2.** Working Model for the Ring Opening of Cyclohexane Oxide (**2**) with *t*-BuSH (**5**) Catalyzed by GaLB (**1**)**Scheme 3.** Catalytic Asymmetric Synthesis of **24**

fact (*R*)-GaLB did indeed give 1(*R*),2(*R*)-products (**12–18**) in every case. Since six-membered S<sub>N</sub>2-like transition states are not usually seen for epoxide opening reactions, probably due to bond angle problems, the geometry (**II**) is suggested as a working model that provides a way to correlate these results.<sup>21</sup> The alkoxide intermediate (**III**) thus produced may then abstract a proton from an acidic OH group to afford **12** and regenerate GaLB, thereby completing the catalytic cycle.

We have applied this methodology to the synthesis of **24**, an important intermediate in the synthesis of prostaglandins. As shown in Scheme 3, epoxide **21**<sup>22</sup> gave **22** with 91% ee in 90% yield by reaction with *t*-BuSH (**5**) in the presence of (*S*)-GaLB (10 mol %) and MS 4A (rt, 96 h). Oxidation of **22** gave  $\alpha$ -sulfinyl ketone **23**, and subsequent pyrolysis afforded (*R*)-**24**<sup>23</sup> in 77% overall yield.

In conclusion, we have succeeded in developing a highly efficient method for the catalytic asymmetric ring opening of symmetrical epoxides. This reaction, promoted by a new catalytic system consisting of gallium·lithium·bis(binaphthoxide) complex (**1**, GaLB) and MS 4A, can be carried out at room temperature to give  $\beta$ -hydroxy sulfides with high enantiomeric excesses. Further applications using HCN and/or HN<sub>3</sub> are under study.

**Acknowledgment.** We thank Dr. Keiichi Aoe and Mr. Hajime Hiramatsu of Tanabe Seiyaku Co., Ltd., for the determination of X-ray structure of epoxide **7** and also thank the JSPS for research fellowships for young scientists.

**Supporting Information Available:** Experimental procedures, <sup>1</sup>H and <sup>13</sup>C NMR, IR, mass spectral data for the products, preparation method for GaLB, solvent effects, and time-courses for the reaction of **2** with **3** (44 pages). See any current masthead page for ordering and Internet access instructions.

JA9702576

(19) The absolute configurations of **12** and **18** were determined as follows. For **12**, its specific rotation was compared with that of an authentic sample derived from **13**. For **18**, the specific rotation of 1,2,4-butanetriol 1,4-ditrityl ether obtained by desulfurization of **18** was compared with that of an authentic sample prepared from commercially available (*S*)-1,2,4-butanetriol.

(20) Complex **20** was prepared from GaCl<sub>3</sub>, (*R*)-binaphthol dilithium salt, and (*R*)-2-hydroxy-2'-methoxy-1,1'-binaphthalene lithium salt.

(21) A flexible complex, in which Ga–O and Li–O bonds lengthen due to partial dissociation, might enable an intramolecular S<sub>N</sub>2-like process to occur, although this is merely a hypothesis at the present time.

(22) Asami, M. *Tetrahedron Lett.* **1985**, 26, 5803–5806.

(23) [ $\alpha$ ]<sub>D</sub><sup>24</sup> +60.0° (c 0.475, CH<sub>3</sub>OH). See ref 22; [ $\alpha$ ]<sub>D</sub><sup>25</sup> +58.1° (c 1.13, CH<sub>3</sub>OH) (90% ee).