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Enantioselective ring-opening reaction of *meso*-epoxides with ArSH catalyzed by heterobimetallic Ti–Ga–Salen system

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ABSTRACT

The enantioselective ring-opening reaction of *meso*-epoxides with aryl thiols catalyzed by a chiral heterobimetallic Ti–Ga–Salen complex was realized, and the 1,2-mercapto alcohols were obtained in good yields and moderate to high enantioselectivities (up to 92% ee). A strong synergistic cooperation between different Lewis acids in the system was exhibited in the catalytic process.

The enantioselective desymmetrization of *meso*-epoxides with nucleophiles has proven to be a valuable tool for the straightforward synthesis of enantiomerically highly enriched 1,2-difunctionalized organic compounds.[1] In general, nucleophiles such as RNH_2,[2] ROH,[3] TMSCN,[4] and RN_3[5] have been widely investigated in the reaction catalyzed by various chiral catalysts.[6] However, since the first useful example reported by Yamashida and Mukaiyama using zinc tartrate as catalyst,[7a] only a few practical methods have been realized using thiols as nucleophiles so far.[7] In 1997, Shibasaki and co-workers developed a heterobimetallic Ga–Li–BINOL (GaLB) complex as highly efficient catalyst for this reaction.[7b] Hou and co-workers reported the use of Ti–Salen complex with moderate enantioselectivities.[7c] Recently, Kobayashi and co-workers[7d,e] and Schneider and co-workers[7f] reported their investigations independently using Scandium-bipyridine and Indium-bipyridine as highly enantioselective catalysts in the ring-opening reaction with excellent results. Although the asymmetric thiolysis of aromatic *meso*-epoxides gave excellent enantioselectivities in several reports, however, the aliphatic *meso*-epoxides afforded unsatisfied results except the utilization of GaLB complex.[7b]

The design and use of bimetallic complexes for asymmetric catalysis have seen significant progress and are emerging as a rapidly developing area.[8] For example, Belcokon et al. showed that a mixture of two chiral V^{V} and Ti^{IV} complexes resulted in the formation of a mixed complex which exhibited high catalytic properties derived from both homometallic species.[9] Moreover, since the successful application of the first heterometallic multifunctional catalyst in the asymmetric Michael reaction,[8a] Shibasaki et al. have developed various hetero- or homo- bimetallic complexes, such as La–Li–Pybox, Pd–La–Schiff base, Cu–Sm–Schiff base, and Ni_2–Schiff base in various reactions with excellent enantioselectivities.[10]

Recently, we reported a highly enantioselective desymmetrization of *meso*-epoxides by aryl selenols using a heterometallic Ti–Ga–Salen complex as catalyst[11] in which the catalyst displayed excellent reactivity and enantioselectivity. Herein, we wish to report the enantioselective ring-opening reaction of *meso*-epoxides with aryl thiols catalyzed by the heterobimetallic Ti–Ga–Salen complex.

The catalysts were synthesized straightforward as shown in Scheme 1. The commercially available Salen compounds (*R*,*R*)-**1** were selected as the requisite ligands. Treatment of **1** with 1 equiv of $GaMe_3$ provided monometallic complexes **2** in high yields.[12] Reactions of **2** with another equivalent of $Ti(O^{i}Pr)_4$ gave the heterobimetallic complexes **3**, which were directly used in the reactions. Using hexane as solvent, we initially tested the ring-opening of cyclohexene oxide with thiophenol at 0 °C catalyzed by the in situ prepared complex **3a** or **3b**. To our delight, the reaction gave the β-hydroxy sulfide in 76% ee and 96% chemical yield when **3b** was used, while 62% ee was obtained with **3a** (entries 1 and 2).

Utilizing **3b** as catalyst, the reaction conditions were then optimized, and the results are summarized in Table 1. Among the

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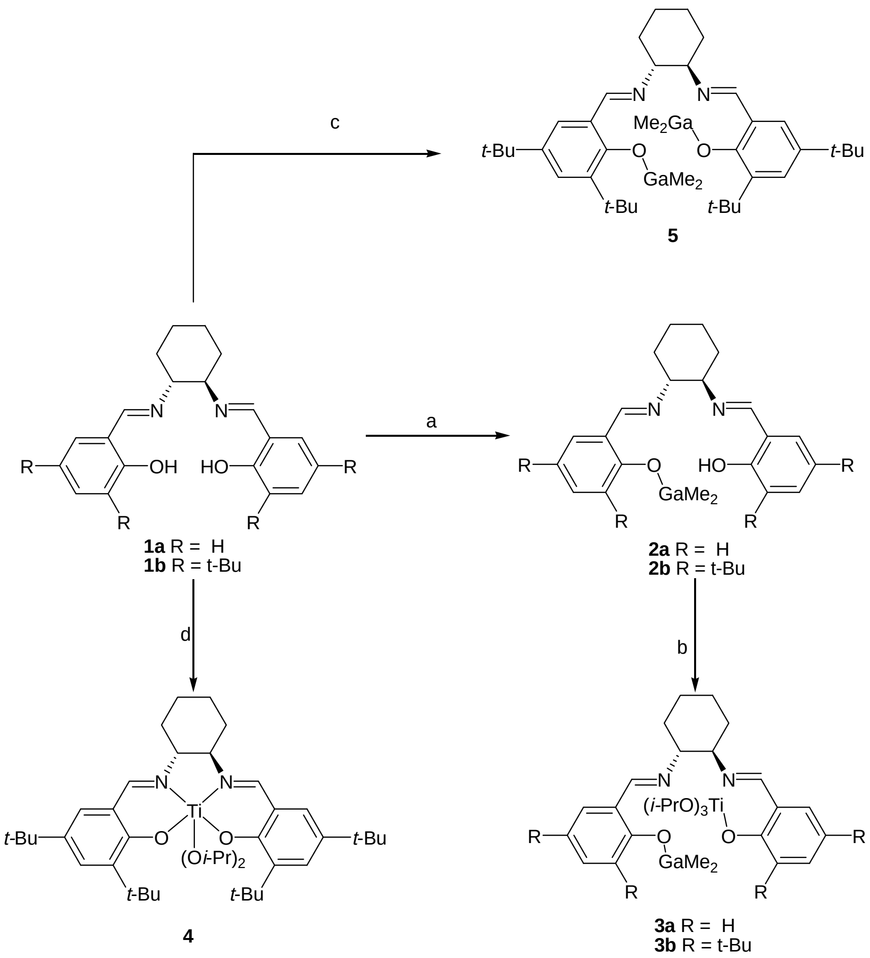
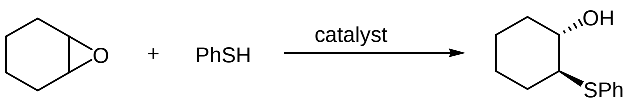


Scheme 1. Reagents and conditions: (a) $GaMe_3$, hexane, 0 °C, 1 h. (b) $Ti(O^iPr)_4$, hexane, 25 °C, 1 h. (c) $GaMe_3$ (2.1 equiv), toluene, 80 °C to reflux, 2 h. (d) $Ti(O^iPr)_4$ (1 equiv), hexane, 0 °C, 1 h.

solvents investigated, hexane was proved to be the best one in terms of the reactivity and enantioselectivity. A variation of the reaction temperature from 0 to −20 °C caused a significant increase in the ee value (entry 6), but a slight decrease was observed when the reaction was carried out at −40 °C (entry 9). Further investigation showed that there was no significant change when the amount of **3b** was decreased to 5 mol % (entry 10). The reaction still showed good results even with only 2 mol % catalyst loading (entry 11). For comparison, titanium complex **4**[7c] and homobimetallic gallium complex **5**[12] were also examined. However, complex **5** gave poor asymmetric induction (entry 8), while the cyclic titanium complex **4**, as reported by Hou et al., provided moderate enantioselectivity (entry 7).[7c] Those results demonstrated that the Ti–Ga–Salen heterobimetallic catalyst was very efficient and showed significant margins over other catalysts.

Next, the asymmetric ring-opening of a variety of *meso*-epoxides with thiophenol, 4-methyl thiophenol, and 4-chloro thiophenol were investigated under the optimized reaction conditions.[13] As shown in Table 2, it can be found that most of the reactions proceeded smoothly to furnish the β-hydroxy sulfides in high yields and moderate to high enantiomeric excesses (65–92% ee) except **8j**. We also found that cyclic *meso*-epoxides displayed better asymmetric induction than acyclic ones under the same conditions. Unfortunately, for more sterically hindered epoxides **6e** and **6f**, the results are far from satisfying (entries 9 and 10). On the other hand, the *para*-chloro or -methyl substituted thiophenol gave better results than thiophenol in terms of reactivity and selectivity. It is also worth noting that the results represent a considerable improvement comparable to the results of the reaction catalyzed by complex **4**.[7c]

Table 1
Asymmetric ring-opening reactions of cyclohexene oxide with thiolphenol[a]



Entry	Catalyst	Solvent	T (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	**3a**	Hexane	0	1	93	62
2	**3b**	Hexane	0	1	96	76
3	**3b**	Toluene	0	1	93	70
4	**3b**	Et_2O	0	1	92	63
5	**3b**	CH_2Cl_2	0	1	90	45
6	**3b**	Hexane	−20	1	96	87
7	**4**	Hexane	−20 to 40	4	93	63
8	**5**	Hexane	−20	4	72	22
9	**3b**	Hexane	−40	1	93	86
10[d]	**3b**	Hexane	−20	1	95	87
11[e]	**3b**	Hexane	−20	1	88	86

[a] Unless otherwise noted, the reaction condition: cyclohexene oxide (1 mmol), PhSH (1.2 mmol), catalyst (10 mol %).

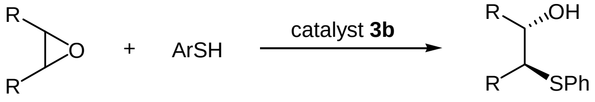
[b] Isolated yields.

[c] Determined by HPLC with a Daicel Chiralcel OD column. Absolute configurations of the major enantiomers (1*S*,2*S*) were assigned by comparison of the rotation values in the literature.

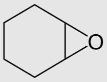
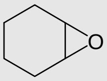
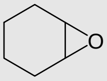
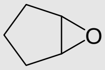
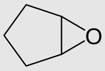
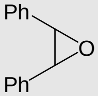
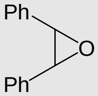
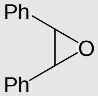
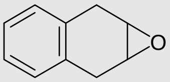
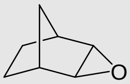
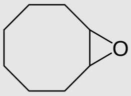
[d] 5 mol % of **3b.**

[e] 2 mol % of **3b**

Table 2
Asymmetric thiolysis of *meso*-epoxides catalyzed by **3b**[a]



6a-e **7a-c** **8a-m**

Entry	Epoxide	Ar	Product	Yield[b] (%)	ee[c] (%)
1	 **6a**	Ph	**8a**	95	84
2	 **6a**	4-Me–Ph	**8b**	95	87
3	 **6a**	4-Cl–Ph	**8c**	97	92
4	 **6b**	Ph	**8d**	96	71
5	 **6b**	4-Me–Ph	**8e**	95	82
6	 **6c**	Ph	**8f**	91	74
7	 **6c**	4-Me–Ph	**8g**	95	84
8	 **6c**	4-Cl–Ph	**8h**	90	85
9	 **6d**	Ph	**8i**	83	65
10[d]	 **6e**	Ph	**8j**	23	53
11[d]	 **6f**	Ph	**8k**	50	80

[a] Reaction conditions: epoxide (1.0 mmol), ArSH (1.2 mmol), catalyst (5 mol %), hexane (3 mL), −20 °C, 1 h.

[b] Isolated yields.

[c] Determined by HPLC with a Daicel Chiralcel OD column. Absolute configurations of the major enantiomers (1*S*,2*S*) were assigned by comparison of the rotation values in the literature or by analogy.

[d] Reaction was conducted at 0 °C for 24 h.

As mentioned in Shibasaki's report,[7b] the heterobimetallic catalyst GaLB appears to act as multifunctional catalyst, with a lithium binaphthoxide moiety functioning as a Brønsted base, activating thiol and a gallium metal function as a Lewis acid, activating and also controlling the orientation of epoxide, as a result high asymmetric induction was realized. In our case, the current catalyst system has two Lewis acid centers to activate both the epoxides and the thiols, or to control the orientation of epoxides and the nucleophiles, respectively. Considering the lower asymmetric induction of Ti–Salen (**4**) and Ga–Salen (**5**), it is most likely that the high catalytic activity of Ti–Ga–**3b** can be accounted for the two different Lewis acids should work complementally in the catalytic system. Also, ^{1}H NMR study showed that the chemical shifts of the dimethylgallium hydrogens of complex **3b** appear at a higher field (δ −0.25 and −0.36 ppm) in comparison with those of complex **2b** (δ −0.22 and −0.31 ppm), which may be due to the coordination of the oxygen in the isopropoxyl group to the gallium, as a result the change of bond angle between the Lewis acids and the substrates is probably the crucial factor.

In summary, we developed a highly enantioselective ring-opening reaction of *meso*-epoxides with aryl thiols using a heterobimetallic Ti–Ga–Salen complex as catalyst, which furnishes 1,2-mercapto alcohols in good yields (up to 97%) and high enantiomeric excesses (up to 92% ee). Both Ti and Ga metals were essential to realize high enantioselectivity. Further mechanistic studies as well as applications of this Ti–Ga heterobimetallic catalyst to other reactions are in progress.

Acknowledgments

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13. *General procedure for the ring-opening of the meso-epoxides by aromatic thiols*: GaMe$_3$ (0.05 mmol, 0.5 M in hexane) was added dropwise to 3 mL of hexane solution of ligand (*R*,*R*)-**3b** (28 mg, 0.05 mmol) under argon at 0 °C. After the solution was stirred for 1 h at room temperature, a solution of Ti(O^{i}Pr)$_4$ (0.05 mmol, 0.2 M in hexane) was then added and stirred for another 1 h to form the Ti–Ga–**3b** complex. The resultant yellow solution was cooled to −20 °C. The epoxide (1.0 mmol) and thiol (1.2 mmol) were added successively. The mixture was stirred for 1 h at the same temperature before being quenched with a saturated NH$_4$Cl solution and extracted with ether. The organic phase was dried over anhydrous sodium sulfate, and the solvent was removed. After being separated by preparative silica gel TLC, the β-hydroxy sulfide was obtained and the ee value was determined by chiral HPLC with a Daicel Chiralcel OD column.