3H), 6.97 (s, 4H), 6.44 (d, $J = 2.6$ Hz, 2H), 2.34 (s, 12H), 2.21 (s, 6H); MS (EI): m/z: 448 $[M+H]^+$; elemental analysis calcd for $C_{29}H_{29}N_5$: C 77.8, H 6.53, N 15.6; found: C 77.3, H 6.65, N 15.4.

$[Cu(L^H)_2](BF_4)_2$: MS (FAB): m/z: 485 $[^{63}Cu(L^H)_2]^+$, 274 $[^{63}Cu(L^H)]^+$; elemental analysis calcd for $C_{22}H_{18}B_2CuF_8N_{10}$: C 40.1, H 2.75, N 21.2; found: C 39.6, H 2.74, N 20.8; UV/Vis (MeCN): $\tilde{\nu}_{max}$ $[10^3\,cm^{-1}]$ (ε_{max} $[M^{-1}cm^{-1}]$) = 14.3 (58), 24.4 (105), 32.8 (27700), 36.7 (35100), 37.7(31900), 40.2 (44700).

$[Cu(L^{Mes})_2](BF_4)_2$: MS (FAB): m/z: 958 $[^{63}Cu(L^{Mes})_2]^+$, 510 $[^{63}Cu(L^{Mes})]^+$; elemental analysis calcd for $C_{58}H_{58}B_2CuF_8N_{10}$: C 61.5, H 5.16, N 12.4; found: C 61.3, H 5.17, N 12.3; UV/Vis (MeCN): $\tilde{\nu}_{max}$ $[10^3\,cm^{-1}]$ (ε_{max} $[M^{-1}cm^{-1}]$) = 14.4 (46), 24.0 (sh), 29.8 (25200), 30.6 (sh), 35.5 (sh), 36.6 (31100), 45.4 (sh).

$[Cu(L^{Mes})_2](ClO_4)_2$: elemental analysis calcd for $C_{58}H_{58}Cl_2CuN_{10}O_8$: C 60.2, H 5.05, N 12.1; found: C 59.4, H 5.03, N 11.9.

Crystal data for $[Cu(L^H)_2](BF_4)_2$: $C_{22}H_{18}B_2CuF_8N_{10}$, crystal dimensions $0.50 \times 0.50 \times 0.30$ mm, monoclinic, space group $P2_1$ (no. 4), $a = 8.4555(13)$, $b = 8.531(2)$, $c = 18.828(5)$ Å, $\beta = 96.639(13)^\circ$; $V = 1349.0(5)$ Å^3, $\rho_{calcd} = 1.624\,g\,cm^{-3}$; Siemens P4 diffractometer, $4 \le 2\theta \le 50^\circ$, $Mo_{K\alpha}$ radiation, $\lambda = 0.71073$ Å, $\theta/2\theta$ scans, $T = 223(2)$ K; of 3515 measured reflections, 2893 were independent and 2000 were observed with $I > 2\sigma(I)$, $-10 \le h \le 1$, $-1 \le k \le 10$, $-22 \le l \le 22$; $R = 0.048$, $wR = 0.129$, GOF = 0.972 for 388 parameters, Flack parameter = −0.02(3), $\Delta\rho_{max} = 0.59\,e\,Å^{-3}$. Crystal data for $[Cu(L^{Mes})_2](ClO_4)_2 \cdot 2CH_3NO_2$: $C_{60}H_{64}Cl_2CuN_{12}O_{12}$, crystal dimensions $0.30 \times 0.25 \times 0.25$ mm, monoclinic, space group $P2_1/c$ (no. 14), $a = 12.048(4)$, $b = 19.808(8)$, $c = 25.36(2)$ Å, $\beta = 99.92(4)^\circ$; $V = 5963(5)$ Å^3, $\rho_{calcd} = 1.426\,g\,cm^{-3}$; Rigaku AFC7R diffractometer, $5 \le 2\theta \le 50^\circ$, $Mo_{K\alpha}$ radiation, $\lambda = 0.71069$ Å, $\omega/2\theta$ scans, $T = 180(2)$ K; of 12975 measured reflections, 10518 were independent and 6041 were observed with $I > 2\sigma(I)$, $0 \le h \le 14$, $0 \le k \le 23$, $-30 \le l \le 29$; $R = 0.083$, $wR = 0.309$, GOF = 1.040 for 784 parameters, $\Delta\rho_{max} = 1.10\,e\,Å^{-3}$. The structures were solved by direct methods (SHELXTL Plus[12]) and developed by least-squares refinement against $|F^2|$ (SHELXL93[13]). All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were placed in calculated positions. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101277. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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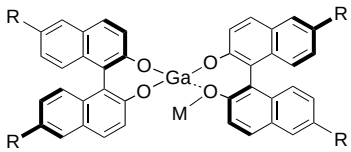
Enantioselective Ring Opening of Epoxides with 4-Methoxyphenol Catalyzed by Gallium Heterobimetallic Complexes: An Efficient Method for the Synthesis of Optically Active 1,2-Diol Monoethers**

Takehiko Iida, Noriyoshi Yamamoto, Shigeki Matsunaga, Hee-Gweon Woo, and Masakatsu Shibasaki*

The enantioselective ring opening of achiral epoxides by nucleophilic addition is an attractive method, which is invaluable in asymmetric synthesis.[1] We reported recently an asymmetric ring opening reaction of epoxides with *t*BuSH that is catalyzed by a Ga-Li-bis(binaphthoxide) complex (GaLB) in the presence of 4-Å molecular sieves (Scheme 1).[2] The high enantioselectivity of these reactions prompted us to



(*R*)-GaLB: R = H, M = Li (*R*)-GaLB*: R = ≡—SiEt$_3$, M = Li
(*R*)-GaSB: R = H, M = Na (*R*)-GaHB : R = H, M = H

Scheme 1. Proposed structures of Ga-M-bis(binaphthoxide) (GaMB) and of Ga-Li-bis((6,6′-(triethylsilyl)-ethynyl)binaphthoxide) (GaLB*).

investigate the possible use of other nucleophiles. Oxygen nucleophiles are interesting candidates since their reaction with achiral epoxides provides an effective route to valuable chiral building blocks such as 1,2-diol derivatives.[3] Quite recently Jacobsen et al. reported the enantioselective ring opening of symmetrical epoxides with carboxylic acids, and an efficient kinetic resolution of racemic terminal epoxides with water by using a (salen)Co^{III} catalyst (salen = *N,N′*-bis(salicylidene)ethylenediamine dianion).[4] However, this type of reaction has not been realized so far with alcohols or phenols. Herein we report the development of a catalytic enantioselective ring opening of epoxides with 4-methoxyphenol by utilizing gallium heterobimetallic complexes.

Hydroxyarene derivatives, such as 4-chlorophenol, 2,4-dinitrophenol, and 4-methoxyphenol, were first examined as nucleophiles for the epoxide opening reaction [Eq. (1)]

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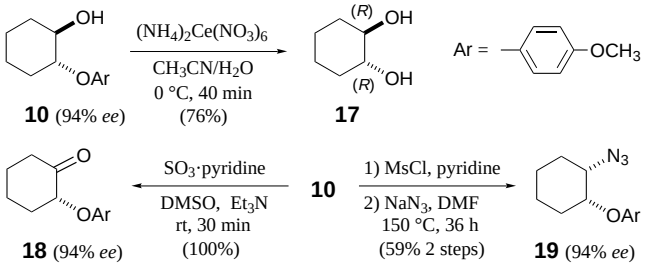
because the corresponding aryl ether products can be converted easily into 1,2-diols.[5] Of these hydroxyarenes, 4-methoxyphenol (**1**) showed an aptitude for the reaction with cyclohexene oxide (**3**) in the presence of (*R*)-GaLB (20 mol%) and 4-Å molecular sieves (toluene, 50 °C) (Table 1 entry 2) to give 1,2-diol monoether **10** in 48% yield (93% *ee*). The absolute configuration of (*1R,2R*)-**10** was determined by identifying the sense of the specific optical rotation of the corresponding 1,2-diol **17**;[6] this was readily obtained in 76% yield by treatment with ammonium cerium(IV) nitrate (CAN)[7] (Scheme 2). GaLB catalysis was found to be applicable to a wide range of unfunctionalized and functionalized symmetrical epoxides (Table 1) affording: **9** (86% *ee*), **11** (67% *ee*), **12** (87% *ee*), **13** (80% *ee*), and **14** (90% *ee*), although the yields were only modest to passable (31–75%, entries 1 and 3–6). These reduced yields can probably be ascribed to an undesired ligand exchange of **1** for 1,1′-binaphthol, thus resulting in the formation of side products.[8]



Scheme 2. Transformations of **10** into the optically active 1,2-diol **17**, ketone **18**, and azide **19** (yields are given in parentheses); DMSO = dimethyl sulfoxide, DMF = *N,N*-dimethylformamide, MsCl = methanesulfonyl chloride.

After several attempts,[9] we found that the use of GaLB*, prepared from (*R*)-6,6′-bis((triethylsilyl)ethynyl)binaphthol, improved the yields of the ring opening reactions. The reason for this may be that GaLB* has a higher stability than GaLB with respect to ligand exchange.[10] Thus **10** was obtained in 60% yield without reduction of enantiomeric excess (Table 1, entry 2 in parenthesis). In addition, **9** and **12** were obtained in good yields with 89% *ee* and 92% *ee*, respectively (Table 1, entries 1 and 4 in parentheses). As shown in Scheme 2, **10** could not only be converted into 1,2-diol **17** but also into α-aryloxyketone **18** and β-aryloxy azide **19** without any reduction of its optical purity.

Achiral reactions of epoxides with oxygen nucleophiles are not well-known, and the epoxide opening with hydroxyarenes under common basic or acidic conditions seems to be difficult. Actually, the reaction of **3** with **1** at 50 °C did not proceed at all in the presence of catalytic and/or stoichiometric amounts of bases such as *n*BuLi, NaO*t*Bu, KO*t*Bu, K_2CO_3, and Cs_2CO_3. Likewise, the addition of Lewis acids such as $BF_3 \cdot Et_2O$ and $ZnCl_2$ was also ineffective for the reaction. In contrast to these results, the GaLB complex showed prominent catalytic activity as mentioned above. A model for the GaLB-catalyzed epoxide-opening reaction is shown in Scheme 3. GaLB is a heterobimetallic complex[11] composed of a lithium binaphthoxide moiety and a central gallium atom. The former appears to function as a Brønsted base by activating and controlling the orientation of **1**, and the latter seems to act as a Lewis acid by activating and controlling the orientation of **3**, thereby enabling an enantioselective ring opening of **3** with **1**.[12] Furthermore, the addition of 4-Å molecular sieves,

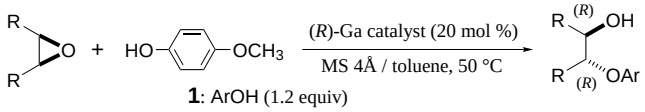
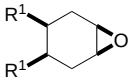
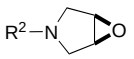
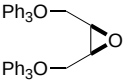


Table 1. Catalytic enantioselective epoxide ring opening with 4-methoxyphenol (**1**) promoted by gallium heterobimetallic complexes in the presence of 4-Å molecular sieves

Entry	Epoxide		Product		GaLB			GaSO		
				t [h]	yield [%]	ee [%]	*t* [h]	yield [%]	ee [%]	
1		**2**	**9**	72	75	86	4	77	54	
			(72)[a]	(73)[a]	(89)[a]					
2		**3**	**10**	72	48	93	4	73	56	
			(72)[a]	(60)[a]	(94)[a]	(4)[b]	(61)[b]	(51)[b]		
3		**4**	**11**	72	31	67	4	67	58	
4		**5**	**12**	72	70	87	24	90	55	
			(72)[a]	(69)[a]	(92)[a]					
5[c]		**6**	**13**	96	34	80	48	83	43	
6[d]		**7**	**14**	160	51	90	19	44	34	
7		**8**	**15**	72	[e]	[e]	7	75	50	
8[f]		**3**	**16**	–	–	–	4	75	61	

[a] Values in parentheses show the results of the GaLB* catalyzed reaction. [b] 5 mol% GaSO was used. [c] $R^1 = CH_2OSiPh_2tBu$. [d] R^2 = 2,4,6-Trimethylbenzenesulfonyl; 30 mol% GaLB was used. [e] No reaction. [f] 4-Methoxy-1-naphthol was used instead of **1**.

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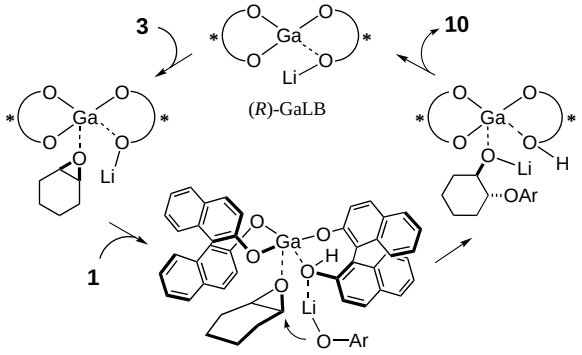
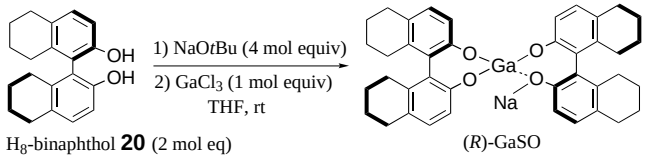


Scheme 3. Model for the GaLB-catalyzed ring opening of cyclohexene oxide (**3**) with 4-methoxyphenol (**1**).

which might assist the decomplexation of **10** from the catalyst, was extremely effective in enhancing the reaction rate: The reaction of **3** in the absence of the molecular sieves (50 °C, 73 h) afforded **10** in only 5% yield but with 95% *ee*.

To develop even more effective catalysts, we then prepared a number of new heterobimetallic gallium complexes with various asymmetric ligands.[13] Of these, the complexes using (*R*)-5,5′,6,6′,7,7′,8,8′-octahydrobinaphthol (**20**: H_8-binaphthol)[14] showed higher catalytic activities for the present reactions.[15] The proposed structure of the Ga-Na-bis(H_8-binaphthoxide) complex (GaSO) is shown in Scheme 4.[16]



Scheme 4. Preparation of Ga-Na-bis(H_8-binaphthoxide) (GaSO).

The reaction of **3** with **1**, catalyzed by GaSO (20 mol%), proceeded smoothly in toluene at 50 °C in only 4 h to afford **10** (73% yield) albeit in modest enantioselectivity (56% *ee*, Table 1, entry 2). Moreover, the catalytic amount of GaSO could be lowered to 5 mol% without serious reduction of reactivity; **10** was produced with 51% *ee* in 61% yield (entry 2 in parentheses). A wide range of symmetrical epoxides could be subjected to GaSO catalyzed ring opening with **1** to give good to excellent yields (except for **7**), although the enantioselectivities were only modest (43–58% *ee*). It is noteworthy that the ring opening of the acyclic substrate **8** readily proceeded in 7 h at 50 °C in the presence of GaSO (20 mol%) to afford **15** (50% *ee*, 75% yield), although the GaLB catalysis had been ineffective for **8** (Table 1, entry 7). Furthermore, the use of the sterically more hindered 4-methoxy-1-naphthol gave a slightly higher enantiomeric excess (Table 1, entry 8).

In contrast to GaLB, sodium was the most suitable alkali metal to make the heterobimetallic gallium H_8-binaphthoxide complex effective.[17] It seems likely that different Ga–O bond lengths account for the observed alkali metal ion effects. Furthermore, the GaSO and the GaLB catalysts seem to be equipped with characteristic dihedral angles of the axial biaryl groups.[18]

We have developed the first catalytic enantioselective ring opening of epoxides with hydroxyarenes using gallium heterobimetallic complexes such as GaLB, GaLB*, and GaSO, in combination with 4-Å molecular sieves. The reaction of a wide range of epoxides with 4-methoxyphenol catalyzed by GaLB afforded synthetically versatile 1,2-diol monoethers in excellent enantiomeric excess and reasonable yields. Further applications with other nucleophiles such as ROH, RNH_2, HN_3, and/or HCN, as well as experiments for further tuning the catalysts are under study.

Experimental Section

All reactions were carried out under argon.

General procedure: A mixture of powdered 4-Å molecular sieves (400 mg), dried at 180 °C under reduced pressure for 6 h prior to use, and a 0.05 M solution of (*R*)-GaLB[2] (4.0 mL, 0.20 mmol) prepared in THF:Et_2O:hexane (6:1:1) was evaporated in vacuo to remove the solvents. A solution of 4-methoxyphenol (**1**) (149 mg, 1.2 mmol) in toluene (2.0 mL) and cyclopentene oxide (**2**) (87.5 μL, 1.0 mmol) were added to the residue at room temperature, and the mixture was stirred at 50 °C for 72 h. The resultant mixture was diluted with Et_2O (30 mL) and filtered over a Celite pad to remove the molecular sieves. The filtrate was washed successively with 5% aqueous citric acid (10 mL), 1N aqueous NaOH (10 mL), saturated aqueous NH_4Cl (10 mL), and brine (10 mL), then dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by flash chromatography (SiO_2, hexane: acetone (10:1)) to afford (*1R,2R*)-**9** (157 mg, 75%) in 86% *ee* as a colorless oil; $[\alpha]_D^{25} = -36.0$ ($c = 1.08$ in $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 1.58-1.84$ (m, 4H; CH*HCH*$_2$*CH*H), 2.01–2.16 (m, 3H; C*H*HCH$_2$CH*H* overlapped with OH), 3.75 (s, 3H, CH_3), 4.28 (m, 1H, C*H*OH), 4.43 (m, 1H; C*H*Ar), 6.83 (m, 4H; Ar); ^{13}C NMR (67.8 MHz, $CDCl_3$): $\delta = 21.0$, 29.8, 32.5, 55.7, 77.2, 85.2, 114.6, 116.6, 151.9, 153.8; the enantiomeric excess of **9** was determined by HPLC analysis on a chiral stationary phase (Daicel Chiralpak AS, eluent: hexane:2-propanol (90:10)); flow-rate: 1.0 mL min^{-1}; retention time: 10.1 min for the *1S,2S* isomer and 25.5 min for the *1R,2R* isomer; detection at 254 nm).

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  1433-7851/98/3716-2225 $ 17.50+.50/0

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[13] The use of 10,10′-dihydroxy-9,9′-biphenanthryl,[23] 3,3′-dihydroxy-4,4′-biphenanthryl (BIPOL),[24] and α,α,α′,α′-tetraphenyl-2-methyl-2-phenyl-1,3-dioxolane-4,5-dimethanol (TADDOL)[25] gave unsatisfactory results.

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[16] GaSO was prepared in a similar manner to GaLB (from a 1:2 ratio of $GaCl_3$ and disodium H_8-binaphthoxide). This ratio was found to give the maximum reactivity and enantiomeric excess. The influence of the ratio of $GaCl_3$ and disodium H_8-binaphthoxide on the reaction of **3** with **1** at 50 °C is as follows: 1:1 (10 % yield, 30 % *ee*), 1:1.5 (53 % yield, 53 % *ee*), 1:2 (73 % yield, 56 % *ee*), 1:2.5 (65 % yield, 49 % *ee*), 1:3 (trace). The structure of GaSO is supported by positive-ion laser-desorption/ionization time-of-flight mass spectrometry (LDI-TOF; reflectron mode): *m*/*z*: 701 ([M^++Na] for ^{71}Ga).

[17] Ga-Li-bis(H_8-binaphthoxide) (39 % yield, 33 % *ee*) and Ga-K-bis(H_8-binaphthoxide) (58 % yield, 52 % *ee*) gave less satisfactory results.

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Total Synthesis of Chatancin**

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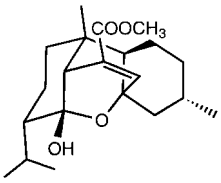
Chatancin (**1**) was discovered within a large program to screen physiologically active compounds from marine invertebrates.[1] This tetracyclic diterpene, which is isolated from a soft coral (*Sarcophyton sp.*), is an antagonist of the platelet activating factor (PAF) and thus of potential use against hypotension and respiratory, inflammatory, and cardiovascular diseases.[2] The physiological activity as well as the fact that this oxygen-bridged dodecahydrophenanthrene derivative with its unusual substitution pattern and the seven stereogenic centers has never been synthesized so far prompted us to look for a suitable stereoselective access to **1**.



chatancin **1**

We chose a protocol for the stereoselective preparation of substituted *cis*-decalinones developed in our laboratory[3] to achieve the highly stereoselective generation of four of the seven stereogenic centers of **1** starting from easily available symmetrical compounds. To develop an enantiomerically pure synthesis the third carbocycle was fashioned by attaching a small chiral side chain that is readily accessible from methyl (R)-3-hydroxyisobutyrate.[4] Thus five of the seven stereogenic centers of **1** could be established. This part of our synthetic efforts has been published earlier.[5] Starting with thymoquinone and 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene the tricyclic Diels – Alder adduct was formed, which was converted into the tetracyclic ketone (±)-**2** by stereo- and regioselective group transformations. Racemic (±)-**2** was allowed to react with (*S*)-3-lithio-2-methyl-1-benzyloxypropane to yield the diastereomeric tertiary alcohols (+)-**3** and (−)-**4** (Scheme 1). However, attempts to save chiral reagent by using only half an equivalent of the alkyllithium compound failed. This is due to a significantly higher reaction rate for the formation of the undesired diastereomer (−)-**4** than for (+)-**3**. The structure of (−)-**4** was established unambiguously by X-ray crystal structure analysis. Twofold ring opening of the diastereomeric pair (+)-**3** and (−)-**4** under acidic conditions led to the diastereomeric *cis*-decalinones (+)-**6** and (−)-**5**, respectively. Owing to the large

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