

Communications

Enantioselective Ring Opening of *Meso*- and Racemic Epoxides with Phenyl Lithium Catalyzed by Chiral γ -Amino Alcohols Derived from α -D-Xylose

Byung Tae Cho* and Sung Hye Shin

Department of Chemistry, Hallym University, Chunchon, Kangwon-Do 200-702, Korea. *E-mail: btcho@hallym.ac.kr
Received June 2, 2006

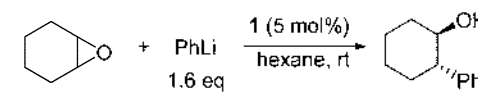
Key Words : Catalytic enantioselective ring opening reaction. Phenyllithium, Cyclohexene oxide, Cyclopentene oxide, *cis*-2,3-Epoxybutane

Enantioselective desymmetrization of symmetrical epoxides is one of the most attractive and useful methods to obtain optically active compounds, since the reaction can generate two contiguous stereogenic centers from an achiral starting material.^{1,2} A number of the asymmetric desymmetrization reaction by the ring opening of the epoxides with a wide variety of nitrogen, sulfur, oxygen, halogen, and cyano nucleophiles have been reported.² However, only two examples have been reported for the ring opening reactions with carbon nucleophile, such as chiral Schiff bases and salens-catalyzed reaction³ and stoichiometric chiral ligand-mediated reaction by organolithiums.⁴ During the course of study on developing new chiral catalysts for the reaction, we found that chiral 1,2-*O*-isopropylidene-5-deoxy-5-dialkyl-amino- α -D-xylofuranones (**1**)⁵ (Figure 1) derived from α -D-xylose played a role as effective catalysts for such reaction. Herein we wish to report the results of the desymmetrization reaction using these catalysts.

As a model system, the enantioselective ring opening reaction of cyclohexene oxide with phenyllithium was chosen. We initially investigated the efficacy of catalysts **1a-j** possessing different kinds of amine substituents at the 5-position of the xylofuranose ring. The reaction was carried out by adding the epoxide to a mixture of 1.6 equiv. of

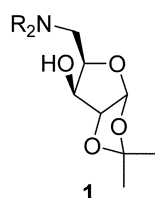
phenyllithium and 0.05 equiv of **1** in hexane at room temperature, which provided (*1R,2S*)-2-phenylcyclohexanol with moderate to good chemical yields and enantioselectivities (Table 1). The enantioselectivity of product alcohol was determined by HPLC analysis using Chiralcel OD-H column. Of the catalysts examined, **1j**^{5b} afforded the best result to be found as 71% ee (entry 10, Table 1). Next, we examined the loading effect of the catalyst on enantioselectivity by varying only the amount of catalyst **1j** for the same reaction. As shown in Table 2, the use of 5 mol% of **1j** provided to be the best. Increasing the amount of **1j** from 5 to 25 mol% did not significantly affect the enantioselectivity, which was 71% ee with 5 mol%, 71% ee with 10 mol% and 25 mol% (entries 1-4). The desymmetrization reactions for cyclopentene oxide and *cis*-2,3-epoxybutane, with PhLi using 5 mol% of **1j** as the catalyst gave (*1R,2S*)-2-phenylcyclopentanol with 79% ee and (*2R,3S*)-3-phenyl-2-butanol with 54% ee (entries 5-6).⁶ Other symmetrical oxides, such as *cis*-3,4-epoxy-1,4-dibenzoyloxybutane and 3-phenyloxetane, did not undergo the ring opening reaction with PhLi under the

Table 1. Enantioselective Ring Opening of Cyclohexene Oxide with PhLi Catalyzed by **1**



Run	Cat	Time (h)	Yield (%) ^a	% ee ^b
1	1a	24	65	46
2	1b	24	62	50
3	1c	30	60	61
4	1d	24	64	22
5	1e	30	80	40
6	1f	30	72	59
7	1g	30	66	53
8	1h	30	63	52
9	1i	30	65	48
10	1j	24	79	71

^aIsolated yield obtained after a flash column chromatography. ^bDetermined by HPLC analysis using a 25 cm of Chiralcel OD-H column.



R₂N = Me₂N (**a**); Et₂N (**b**); ⁿBu₂N (**c**); Me₂N(CH₂)₂NMe (**d**);

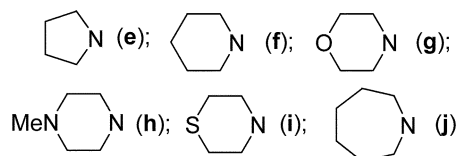














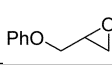
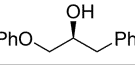


Figure 1

Table 2. Enantioselective Ring Opening of Epoxides with PhLi Catalyzed by **1j** in Hexane at Room Temperature

Run	Epoxide	Product	1j (mol%)	Yield (%) ^c	Ee (%)
1 ^a			2	70	68 ^d
2 ^a			5	79	71 ^d
3 ^a			10	78	70 ^d
4 ^a			25	70	70 ^d
5 ^a			5	66	79 ^d
6 ^a			5	60	54 ^e
7 ^b			5	40	20 ^d
8 ^b			5	32	23 ^d

^aPhLi (1.6 eq) was used; 24–30 h. ^bPhLi (0.6 eq) was used; 24 h. ^cIsolated yield. ^dDetermined by HPLC analysis using Chiralcel OD-H column (eluent: hexane/*i*PrOH = 9/1). ^eDetermined by HPLC analysis of 3,5-dinitrobenzoate of the product alcohol using Whelk O1 chiral column (eluent: hexane/*i*PrOH = 99/1).

same reaction conditions. Using the same methodology, we examined the kinetic enantioselective ring opening reaction for racemic epoxides, such as 1,2-epoxypropane and 1,2-epoxy-3-phenoxypropane. When these racemic epoxides were reacted with 0.6 equiv. of PhLi 0.05 equiv of **1j** in hexane at room temperature, the reaction provided (*R*)-3-phenyl-2-propanol with 20% ee and (*R*)-3-phenoxy-2-propanol with 23% ee (entries 7–8). The mechanism for the above reactions is unclear so far, although lithium alcoholates of **1** may be considered as the real catalysts. The reaction using other alkyl- and aryl-lithiums is currently under investigation.

In summary, we have established a new enantioselective ring opening of meso- and racemic epoxides with PhLi using

chiral γ -amino alcohols derived from α -D-xylose as chiral catalysts to provide moderate enantioselectivity.

References and Notes

- For reviews, see (a) Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry* **1991**, 2, 1. (b) O'Brien, P. J. *J. Chem. Soc. Perkin Trans. 1* **1998**, 1439. (c) Wills, M. C. *J. Chem. Soc. Perkin Trans. 1* **1999**, 1765.
- For reviews, see (a) Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron* **1996**, 52, 14361. (b) Jacobsen, E. N.; Wu, M. H. In *Comprehensive Asymmetric Catalysts*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: New York, 1999; Vol. 3, pp 1309. (c) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, 33, 421.
- Oguni, N.; Miyagi, Y.; Itoh, K. *Tetrahedron Lett.* **1998**, 39, 9023.
- Mizuno, M.; Kanai, M.; Iida, A.; Tomioka, K. *Tetrahedron* **1997**, 53, 10699.
- (a) Cho, B. T.; Kim, N. *J. Chem. Soc. Perkin Trans. 1* **1996**, 2901. (b) Cho, B. T.; Kim, N.; Khoo, J.-H. *Bull. Korean Chem. Soc.* **1996**, 17, 1.
- The reaction of cyclohexene oxide is representative. Under nitrogen atmosphere, PhLi (0.8 mL, 1.6 mmol) in cyclohexane and ether was added to **1j** (1 mL, 0.05 mmol) in hexane with stirring at room temperature. After 1 h, to the mixture was added cyclohexene oxide (1 mmol). The mixture was stirred for 30 h and then 1 mL of saturated sodium bicarbonate was added. The mixture was extracted with ether and the combined organic layer was dried over anhydrous MgSO₄. Concentration and purification with a flash silica-gel column chromatography using EtOAc/hexane (2/1) gave (1*R*,2*S*)-2-phenylcyclohexanol with 71% ee in 79% yield; M.p. 52–54 °C (lit.⁷ 57–58 °C); $[\alpha]_D^{20}$ –37.3 (*c* 1.0, PhH) {lit.⁴ $[\alpha]_D^{20}$ +47.6 (*c* 1.56, PhH), 97% ee for (1*S*,2*R*)-2-phenylcyclohexanol}; Its optical purity determined by HPLC analysis using a 25 cm of Chiralcel OD-H column (eluent: hexane/*i*PrOH = 9/1, flow rate = 0.3 mL/min) was found to be 71% ee with 1*R*,2*S* configuration (*t_R* 18.40 min for 1*S*,2*R*; *t_S* 19.67 min for 1*R*,2*S*); IR (KBr, cm⁻¹) 3312, 3287, 2932, 2920, 2853, 1493, 1446, 1061, 1051, 745; ¹H NMR (300 MHz, CDCl₃) δ 1.27–1.57 (m, 5H), 1.73–1.88 (m, 3H), 2.08–2.13 (m, 1H), 2.38–2.46 (m, 1H), 3.61–3.69 (m, 1H), 7.22–7.34 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ 25.43, 26.43, 33.66, 34.78, 53.55, 74.69, 127.01, 128.08, 128.95, 143.40.
- Huynh, C.; Derguini-Boumechal, F.; Linstrumelle, G. *Tetrahedron Lett.* **1979**, 17, 1503.