



## Highly Enantioselective Arylation of Symmetrical Epoxides with Phenyllithium Promoted by Chiral Schiff Bases and Salens

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**Abstract:** Cyclohexene oxide and cyclopentene oxide react with phenyllithium to give highly optically active *trans*-2-phenyl-1-cyclohexanol and -cyclopentanol in the presence of a small amount of chiral Schiff bases and salens © 1998 Elsevier Science Ltd. All rights reserved.

Enantioselective desymmetrization of symmetrical epoxides is one of attractive and useful methods to obtain optically active compounds. A number of asymmetric reactions are known which demonstrate its application to afford target molecules with high ee. There are two types of ring opening of symmetrical epoxides. One is  $\beta$ -deprotonation to provide chiral allyl alcohols and the other is the enantioselective addition of nucleophiles to give chiral *trans* 2-substituted cyclohexanols. The former was accomplished by the reaction of cyclohexene oxide, cyclopentene oxide and their derivatives with chiral lithium amide.<sup>1</sup> The latter ring opening to produce racemic compounds was attained easily by the reaction of cyclohexene oxide with Grignard reagent in the presence of copper chloride.<sup>2</sup> The first enantioselective reaction was disclosed in the reaction of cyclohexene oxide with thiols and aniline using as catalyst chiral zinc tartrates by Mukaiyama et al.,<sup>3</sup> and recently developed by Jacobsen et al and other researchers.<sup>4</sup> In this letter we want to report the first highly enantioselective ring opening arylation of cyclohexene oxide and other symmetrical epoxides with phenyllithium catalyzed by the lithium alcolates of chiral Schiff-base(A) and salen(B). We already reported that chiral Schiff base-titanium complexes are excellent catalysts for the enantioselective silylcyanation of aldehydes<sup>5</sup>, and also reactions of diketene with aldehydes to give 5-hydroxy-3-ketoesters with very high ee<sup>6</sup>.

Very recently Tomioka et al. reported the enantioselective alkylation and arylation of cyclohexene oxide with organolithiums using 2.1 equivalents of chiral ethers to the substrate to give the ring opening product with max.47% ee<sup>7</sup>. Optically active *trans* -2-aryl cyclohexanol is very useful synthons for the synthesis of a variety of optically active compounds.<sup>8</sup> We recently discovered that chiral schiff bases themselves were excellent catalysts for ring opening arylation of symmetrical epoxides such as cyclohexene oxide even in a use of catalytic amount (5 mol%). Among schiff bases A1~A7, Schiff bases (A4<sup>9</sup> and 5<sup>10</sup>) prepared from (L)-*tert*-leucinol showed excellent results (Table 1). In these reactions all products have (1*S*,2*R*) absolute configuration.

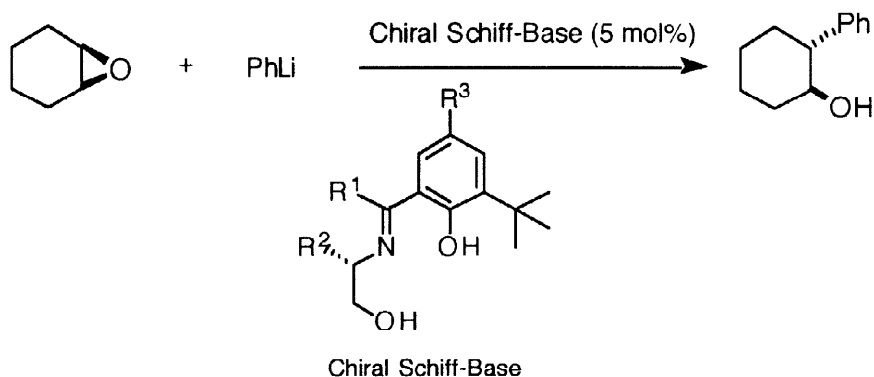


Table 1. Enantioselective ring opening reactions of cyclohexene oxide with PhLi catalyzed by chiral Schiff bases ( at r.t., in hexane).

	Schiff-Base			yield (%) <sup>a</sup>	ee (%) <sup>b</sup>
	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>		
A1	H	Me	<i>t</i> -Bu	16	12
A2	H	<i>i</i> Pr	H	80	78
A3	H	<i>i</i> Pr	<i>t</i> -Bu	100	81
A4	H	<i>t</i> -Bu	<i>t</i> -Bu	92	<b>86</b>
A5	H	<i>t</i> -Bu	H	100	<b>90</b>
A6	H	Ph	<i>t</i> -Bu	trace	-
A7	Ph	<i>i</i> Pr	<i>t</i> -Bu	16	12

<sup>a</sup>Isolated yield

<sup>b</sup>Determined by HPLC analysis (CHIRALCEL OD-H)

Typical experimental procedure is as follows: In a Schlenk tube A5 (5 mmol%) was reacted with phenyllithium(1.5 mL, 1.6 mmol in cyclohexane and ether, Kanto Chemical product) in hexane 3.0 mL at room temperature under argon atmosphere for 1 hr. Cyclohexene oxide(0.1 mL, 1.0 mmol) was added to above solution and stirred for 24 h. Ordinary work up gave the product, *trans*-2-phenyl-1-cyclohexenol in over 99% chemical yield with 90% ee. Enantioselectivity(cc %) of the product was obtained by the measurement of HPLC analysis using Chiralcel OD-H. The product is easily recrystallized from hexane to give optically pure product in good yield(mp.65°C).

Cyclopentene oxide and *cis*-2,3-butene oxide were also reacted with phenyllithium catalyzed by A4 to give the ring opening products in moderately high enantioselectivities (Table 2). Also chiral salens also were active catalysts for above reactions. Particularly the chiral salen B1 having two *tert*-butyl group was excellent catalyst (Table 2) but B2 had weak catalytic activity and gave the product of low ee.

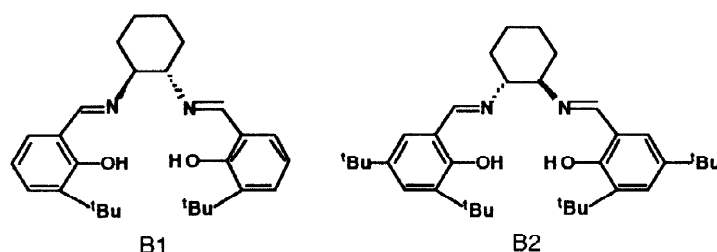


Table 2. Enantioselective ring opening reactions of symmetrical epoxides with PhLi catalyzed by chiral Schiff base A4 and chiral salen B1 ( 5 mol %)(at r.t., in hexane).

<i>cis</i> epoxide	products	chiral Schiff base A4		chiral salen B1	
		Yield (%) <sup>a</sup>	ee (%) <sup>b</sup>	Yield (%) <sup>a</sup>	ee (%) <sup>b</sup>
		53	76	34	69
		42	78	47	66
		92	86	73	80

<sup>a</sup>Isolated yield

<sup>b</sup>Determined by HPLC analysis (CHIRALCEL OD-H)

Cis-1,2-diphenylethylene oxide was not reacted with phenyllithium in the presence of both A5 and B1. Other alkyllithiums such as *n*-butyllithium and methyllithium reacted with cyclohexene oxide to give ring opening products in poor yield and low ee.

The real active catalysts for the above enantioselective reactions can be considered as lithium alkoxides, or lithium alkoates and N-lithium amides which could produce by addition of phenyllithium to imino groups of chiral Schiff base and salens.

We are working the reactions using other aryllithiums and the another types of chiral iminoalcohols now in progress.

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#### References and Notes

- Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron*, **1996**, 52, 14361-14384.
- Whitesell, J. K.; Lawrence, R. M. *Chimia* **1986**, 40, 318; Schwartz, P.; Madan, P.; Whitesell, J. K.; Lawrence, R. M. *Organic Syntheses* **1990**, 69, 1-2.
- Yamashita, H.; Mukaiyama, T. *Chem. Lett.* **1985**, 1643-1464; Yamashita, H. *Bull.Chem. Soc. Jpn.* **1988**, 61, 1213-1220.
- Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, 117, 5897-5898; Hodgson, D. M.;

- Wisdale, R. *Tetrahedron Asymmetry* **1996**, 7, 1275-1276.
5. Hayashi, M.; Miyamoto, Y.; Inoue, T.; Oguni, N. *J. Org. Chem.* **1993**, 58, 1515-1522
  6. Hayashi, M.; Inoue, T.; Miyamoto, Y.; Oguni, N. *Tetrahedron*, **1994**, 50, 4385-4398.
  7. Mizuno, M.; Kanai, M.; Iida, A.; Tomioka, K. *Tetrahedron Asymmetry*, **1996**, 7, 2483-2484  
idem, *Tetrahedron*, **1997**, 53, 10699-10708.
  8. Whitesell, J. K. *Chem. Rev.*, **1992**, 92, 953-965.
  9. Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, 119, 9913-9914.
  10. This chiral schiff base was first used in this work. <sup>1</sup>H NMR (250 Mz, CDCl<sub>3</sub>): δ 0.99 (s, 9H), 1.45 (s, 9H), 1.6 (br.s, 1H), 2.94 (dd, J=3.1Hz, 9.2Hz, 1H), 3.77 (t, J=9.2Hz, 1H), 3.94 (dd, J=3.1Hz, 9.2Hz, 1H), 6.84 (t, J=9.2Hz, 1H), 7.15 (d, J=9.2Hz, 1H), 7.36 (d, J=7.9Hz, 1H), 13.8 (br.s, 1H). [α]<sub>D</sub><sup>25</sup> = -3.8 (c 1.1, EtOH).