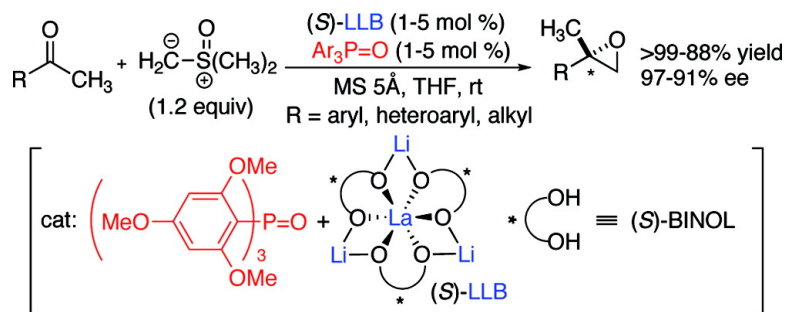


## Catalytic Asymmetric Synthesis of 2,2-Disubstituted Terminal Epoxides via Dimethyloxosulfonium Methylide Addition to Ketones

Toshihiko Sone, Akitake Yamaguchi, Shigeki Matsunaga, and Masakatsu Shibasaki

*J. Am. Chem. Soc.*, **2008**, 130 (31), 10078-10079 • DOI: 10.1021/ja803864p • Publication Date (Web): 10 July 2008

Downloaded from <http://pubs.acs.org> on February 8, 2009



### More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

[View the Full Text HTML](#)



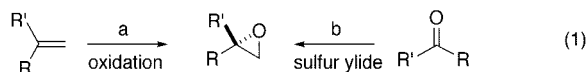
## Catalytic Asymmetric Synthesis of 2,2-Disubstituted Terminal Epoxides via Dimethyloxosulfonium Methylide Addition to Ketones

Toshihiko Sone, Akitake Yamaguchi, Shigeki Matsunaga,\* and Masakatsu Shibasaki\*

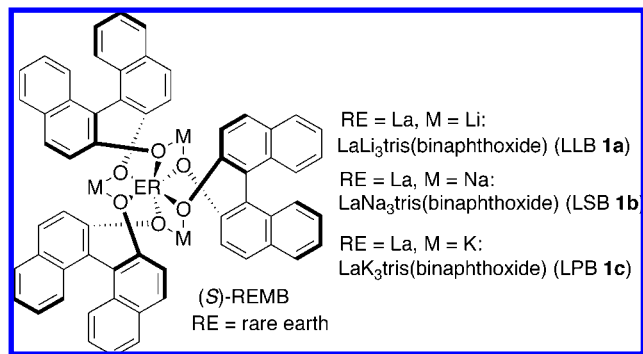
Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Received May 22, 2008; E-mail: mshibasa@mol.f.u-tokyo.ac.jp; smatsuna@mol.f.u-tokyo.ac.jp

Optically active epoxides are versatile building blocks for the synthesis of biologically active natural and unnatural compounds. Although various useful catalytic asymmetric epoxidation methods have been reported,<sup>1</sup> 2,2-disubstituted terminal epoxides remain particularly challenging target compounds. Catalytic asymmetric epoxidations of geminally disubstituted terminal unfunctionalized alkenes (eq 1, path a) have been studied using enzymes,<sup>2</sup> chiral metal and organo-catalysts,<sup>3</sup> but the enantioselectivity, yield, and/or substrate generality of these reactions are not satisfactory.



Considering the importance of 2,2-disubstituted epoxides as key building blocks for valuable chiral tertiary alcohols, a new strategy to synthesize chiral 2,2-disubstituted terminal epoxides is highly desirable.<sup>4,5</sup> Herein, we report an alternative approach based on Corey–Chaykovsky epoxidation<sup>6</sup> of ketones (eq 1, path b). A La–Li<sub>3</sub>-tris(binaphthoxide) (LLB **1a**, Figure 1) complex with an Ar<sub>3</sub>P=O additive (Ar = 2,4,6-trimethoxyphenyl) promoted the addition of dimethyloxosulfonium methylide to ketones, giving 2,2-disubstituted terminal epoxides in >88–99% yield and 91–97% ee.



**Figure 1.** Structures of (S)-RE-M<sub>3</sub>-tris(binaphthoxide) complex (REMB, RE = rare earth), LLB **1a**, LSB **1b**, and LPB **1c**.

Initial screening of several chiral multimetallic catalysts developed in our group revealed that heterobimetallic rare earth–alkali metal RE-M<sub>3</sub>-tris(binaphthoxide) complexes (REMB, Figure 1)<sup>7,8</sup> were the most promising candidates for the addition of a sulfur ylide to ketones. Optimization studies with dimethyloxosulfonium methylide **2** and ketone **3a** using REMB complexes are summarized in Table 1. LLB **1a** promoted the reaction at room temperature in 79% yield, but the enantioselectivity was poor (entry 1, 15% ee). In the presence of MS 5Å, enantioselectivity improved to 72% ee (entry 2). Other metal combinations, such as La–Na (LSB, **1b**) and La–K (LPB, **1c**), resulted in much less satisfactory yield and enantioselectivity (entry 3, 25% yield, 14% ee, entry 4, 17% yield,

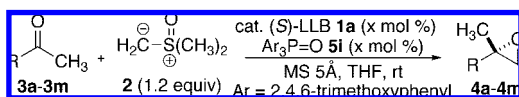
**Table 1.** Optimization of Reaction Conditions

entry	REMB 1	R: 5 (x mol %)	time (h)	yield <sup>a</sup> (%)	ee (%)	
1 <sup>b</sup>	LLB <b>1a</b>	none	48	79	15	
2	LLB <b>1a</b>	none	12	80	72	
3	LSB <b>1b</b>	none	12	25	14	
4	LPB <b>1c</b>	none	12	17	52	
5	LLB <b>1a</b>	Ph– (5)	<b>5a</b>	12	77	80
6	LLB <b>1a</b>	4-Cl-C <sub>6</sub> H <sub>4</sub> – (5)	<b>5b</b>	12	99	74
7	LLB <b>1a</b>	C <sub>6</sub> F <sub>5</sub> – (5)	<b>5c</b>	12	61	48
8	LLB <b>1a</b>	<i>n</i> Bu (5)	<b>5d</b>	12	87	75
9	LLB <b>1a</b>	cyclohexyl (5)	<b>5e</b>	12	99	76
10	LLB <b>1a</b>	2,4,6-Me <sub>3</sub> -C <sub>6</sub> H <sub>2</sub> – (5)	<b>5f</b>	12	97	75
11	LLB <b>1a</b>	4-MeO-C <sub>6</sub> H <sub>4</sub> – (5)	<b>5g</b>	12	82	77
12	LLB <b>1a</b>	2,6-(MeO) <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> – (5)	<b>5h</b>	12	84	93
13	LLB <b>1a</b>	2,4,6-(MeO) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub> – (5)	<b>5i</b>	12	98 <sup>c</sup>	96
14	LLB <b>1a</b>	2,4,6-(MeO) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub> – (10)	<b>5i</b>	12	94	95
15	LLB <b>1a</b>	2,4,6-(MeO) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub> – (15)	<b>5i</b>	12	92	92

<sup>a</sup> Yield determined by <sup>1</sup>H NMR analysis of crude mixture. <sup>b</sup> Reaction was run in the absence of MS 5Å. (R)-**4a** was obtained in major. <sup>c</sup> Isolated yield after purification by column chromatography.

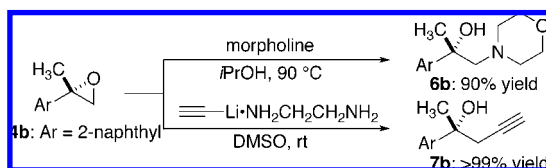
52% ee). Many trials to improve the enantioselectivity revealed that the addition of achiral phosphine oxide **5** was effective. In the presence of 5 mol % of Ph<sub>3</sub>P=O **5a**, **4a** was obtained in 80% ee (entry 5). Among the various types of phosphine oxides screened (entries 5–13),<sup>9</sup> Ar<sub>3</sub>P=O **5i** (Ar = 2,4,6-trimethoxyphenyl) was the best, giving **4a** in 98% isolated yield and 96% ee after 12 h (entry 13). A molar ratio of LLB **1a**:Ar<sub>3</sub>P=O **5i** = 1:1 was sufficient to achieve high enantioselectivity (entries 13–15).

The optimized reaction conditions using an LLB **1a**:Ar<sub>3</sub>P=O **5i** = 1:1 mixture were applicable to various ketones (Table 2). Aryl methyl ketones **3a–3h** gave epoxides in >93–99% yield and 92–97% ee (entries 1–8). Ketones **3c–3e** with an electron-withdrawing substituent at either the *para*-, *meta*-, or *ortho*-positions gave epoxides in high yield and enantioselectivity (entries 3–5). The broad generality of aryl methyl ketones is synthetically useful because the methods for producing chiral 2-aryl-2-methyl terminal epoxides in high enantioselectivity are limited to biocatalytic kinetic resolution approaches.<sup>4b,c</sup> It is noteworthy that pyridyl methyl ketone **3i** and alkyl methyl ketones **3j–3m** were also applicable and afforded epoxides in >88–99% yield and 91–96% ee (entries 9–13). Catalyst loading was successfully reduced to 2.5 and 1 mol %, and good enantioselectivity was maintained (entries 14 and 15). To demonstrate the synthetic utility of epoxides, transformations of products into chiral tertiary alcohols were investigated (Scheme 1). Ring opening of epoxide with an amine nucleophile proceeded in isopropanol at 90 °C, giving β-amino *tert*-alcohol **6b** in 90% yield. Reaction with alkynyl lithium reagent also proceeded regioselectively and afforded **7b** in >99% yield.

**Table 2.** Catalytic Asymmetric Synthesis of 2,2-Disubstituted Terminal Epoxides from Various Methyl Ketones<sup>a</sup>

entry	ketone 3: R	epoxide	cat. 1a/5i (x mol %)	time (h)	yield (%) <sup>b</sup>	ee (%)
1	Ph	<b>3a</b> <b>4a</b>	5	12	98	96
2	2-naphthyl	<b>3b</b> <b>4b</b>	5	12	97	96
3	4-Cl-C <sub>6</sub> H <sub>4</sub>	<b>3c</b> <b>4c</b>	5	12	>99	94
4	3-Cl-C <sub>6</sub> H <sub>4</sub>	<b>3d</b> <b>4d</b>	5	12	>99	94
5	2-Cl-C <sub>6</sub> H <sub>4</sub>	<b>3e</b> <b>4e</b>	5	12	96	95
6	4-F-C <sub>6</sub> H <sub>4</sub>	<b>3f</b> <b>4f</b>	5	12	94	97
7	4-EtO <sub>2</sub> C-C <sub>6</sub> H <sub>4</sub>	<b>3g</b> <b>4g</b>	5	12	94	94
8 <sup>c</sup>	4-Me-C <sub>6</sub> H <sub>4</sub>	<b>3h</b> <b>4h</b>	5	12	97	92
9	3-pyridyl	<b>3i</b> <b>4i</b>	5	12	97	92
10	PhCH <sub>2</sub> CH <sub>2</sub>	<b>3j</b> <b>4j</b>	5	12	99	93
11	<i>n</i> -octyl	<b>3k</b> <b>4k</b>	5	12	>99	93
12 <sup>c</sup>	cyclohexyl	<b>3l</b> <b>4l</b>	5	12	88 <sup>d</sup>	96
13	EtO <sub>2</sub> C-(CH <sub>2</sub> ) <sub>3</sub> -	<b>3m</b> <b>4m</b>	5	12	>99	91
14	2-naphthyl	<b>3b</b> <b>4b</b>	2.5	18	96	94
15	2-naphthyl	<b>3b</b> <b>4b</b>	1	60	96	92

<sup>a</sup> Reaction was performed in THF (0.1 M ketone **3**) at room temperature (20–23 °C) with MS 5Å; 1.2 equiv of ylide **2** prepared from trimethylsulfoxonium chloride and NaH were used. <sup>b</sup> Isolated yield after purification by column chromatography. <sup>c</sup> Enantiomeric excess was determined after epoxide ring opening; see Supporting Information for detail. <sup>d</sup> NMR yield was >95%, but the isolated yield decreased because epoxide **4l** was volatile.

**Scheme 1.** Transformations of 2,2-Disubstituted Terminal Epoxide

In the present system, the best yield and enantioselectivity were obtained with Ar<sub>3</sub>P=O **5i** additive. The results shown in Table 1, entries 5–13, suggested that the electron-donating and coordinating MeO substituents at the 2,6-positions were key to improving enantioselectivity. <sup>31</sup>P NMR analysis of Ar<sub>3</sub>P=O **5i** alone (3.50 ppm) and Ar<sub>3</sub>P=O **5i** with LLB (16.3 ppm) indicated that Ar<sub>3</sub>P=O **5i** coordinates to LLB **1a**. We speculated that the LLB:Ar<sub>3</sub>P=O **5i** = 1:1 complex would be the active species in the present system. Electron-rich and bulky achiral additive **5i** would suitably modify the chiral environment of LLB,<sup>9,10</sup> resulting in better yield and enantioselectivity in the present reaction. Further mechanistic studies to elucidate the precise role of Ar<sub>3</sub>P=O **5i** on enantioselectivity are ongoing.

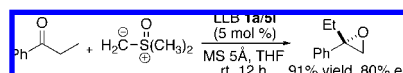
In summary, we developed a catalytic asymmetric Corey–Chaykovsky epoxidation of ketones with dimethylsulfoxonium methylide **2** using an LLB **1a** + Ar<sub>3</sub>P=O complex. The reaction proceeded smoothly at room temperature, and 2,2-disubstituted terminal epoxides were obtained in high enantioselectivity (91–97% ee) and yield (>88–99%) from a broad range of methyl ketones with 1–5 mol % catalyst loading. The use of achiral additive Ar<sub>3</sub>P=O **5i** was important to achieve high enantioselectivity. Studies to further broaden the substrate generality to other ketones, such as ethyl ketones, are ongoing.<sup>11</sup>

**Acknowledgment.** This work was supported by Grant-in-Aid for Scientific Research (S) and Grant-in-Aid for Scientific Research on Priority Areas (No. 20037010, Chemistry of Concerto Catalysis for SM) from JSPS and MEXT. We thank Dr. S. Uchiyama, Dr. H. Kakei, and Mr. S. Mouri at the University of Tokyo for technical assistance. A.Y. thanks financial support by JSPS fellowship.

**Supporting Information Available:** Experimental procedures, spectral data of new compounds, determination of absolute configurations, and <sup>31</sup>P NMR charts. This material is available free of charge via the Internet at <http://pubs.acs.org>.

**References**

- (1) General reviews of catalytic asymmetric epoxidations: (a) Xia, Q.-H.; Ge, H.-Q.; Ye, C.-P.; Liu, Z.-M.; Su, K.-X. *Chem. Rev.* **2005**, *105*, 1603. (b) Bonini, C.; Righi, G. *Tetrahedron* **2002**, *58*, 4981. For sulfur ylide-mediated epoxidations, see: (c) Aggarwal, V. K.; Winn, C. L. *Acc. Chem. Res.* **2004**, *37*, 611.
- (2) Enzymatic approach: (a) Dexter, A. F.; Lakner, F. J.; Campbell, R. A.; Hager, L. P. *J. Am. Chem. Soc.* **1995**, *117*, 6412. (b) Lakner, F. J.; Hager, L. P. *J. Org. Chem.* **1996**, *61*, 3923.
- (3) General reviews: (a) Jacobsen, E. N.; Wu, M. H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; p 649. (b) Katsuki, T. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; p 287. (c) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488. See also ref 1a. Geminally disubstituted terminal alkenes gave only modest enantioselectivity.
- (4) (Salen)Cr-catalyzed kinetic resolution of 2,2-disubstituted terminal epoxides using an azide nucleophile: (a) Lebel, H.; Jacobsen, E. N. *Tetrahedron Lett.* **1999**, *40*, 7303. For biocatalytic kinetic resolutions, see reviews: (b) Steinreiber, A.; Faber, K. *Curr. Opin. Biotechnol.* **2001**, *12*, 552. (c) Archelas, A.; Furstoss, R. *Curr. Opin. Chem. Biol.* **2001**, *5*, 112.
- (5) Geminally disubstituted terminal allyl alcohols are suitable substrates in Sharpless asymmetric epoxidation systems (>90% ee); see a review: Katsuki, T. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; p 621, and references therein.
- (6) (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353. For early trials of catalytic asymmetric reaction with ketone (23% ee with **3a**), see: (b) Zhang, Y.; Wu, W. *Tetrahedron: Asymmetry* **1997**, *8*, 2723.
- (7) Review of heterobimetallic rare earth–alkali metal–BINOL complexes: (a) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187. For recent selected examples, see also: (b) Tosaki, S.-y.; Hara, K.; Gnanadesikan, V.; Morimoto, H.; Harada, S.; Sugita, M.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 11776. (c) Yamagiwa, N.; Qin, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13419. (d) Mihara, H.; Sohtome, Y.; Matsunaga, S.; Shibasaki, M. *Chem. Asian J.* **2008**, *3*, 359.
- (8) For related catalytic asymmetric Corey–Chaykovsky cyclopropanation of enones with a heterobimetallic REMB-type complex, see: Kakei, H.; Sone, T.; Sohtome, Y.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 13410. In the cyclopropanation of enones, biphenyldiol ligands showed better enantioselectivity than BINOL, and mixed alkali metal La–Li<sub>2</sub>–Na–(biphenyldiol)<sub>3</sub> system gave the best enantioselectivity. In the present epoxidation of ketones, neither biphenyldiol ligand nor mixed alkali metal system gave positive effects.
- (9) Steric and electronic modification of achiral phosphine oxides have beneficial effects in other rare earth metal-catalyzed asymmetric reactions. See: (a) Kino, R.; Daikai, K.; Kawanami, T.; Furuno, H.; Inanaga, J. *Org. Biomol. Chem.* **2004**, *2*, 1822, and references therein. (b) Tian, J.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3636. (c) Yamagiwa, N.; Tian, J.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 3413. (d) Hara, K.; Park, S.-Y.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Chem. Asian J.* **2008**, Early view DOI: 10.1002/asia.200800035 and references therein.
- (10) For structural analysis of LLB and related complexes, see a review in ref 7a. See also: (a) Wooten, A. J.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2008**, *130*, 7407. (b) Wooten, A. J.; Carroll, P. J.; Walsh, P. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2549. (c) Aspinall, H. C.; Bickley, J. F.; Dwyer, J. L. M.; Greeves, N.; Kelly, R. V.; Steiner, A. *Organometallics* **2000**, *19*, 5416. (d) Di Bari, L.; Lelli, M.; Pintacuda, G.; Pescitelli, G.; Marchetti, F.; Salvadori, P. *J. Am. Chem. Soc.* **2003**, *125*, 5549.
- (11) Preliminary investigation with propiophenone gave epoxide in 91% yield and 80% ee (with 5 mol % catalyst, at rt, 12 h). Aldehydes are not suitable substrates under identical conditions. Further optimization studies are ongoing.



JA803864P