

Catalytic Asymmetric Synthesis of 2,2-Disubstituted Oxetanes from Ketones by Using a One-Pot Sequential Addition of Sulfur Ylide**

Toshihiko Sone, Gang Lu, Shigeki Matsunaga,* and Masakatsu Shibasaki*

The catalytic enantioselective syntheses of epoxides has been studied intensively over the last three decades.^[1] In striking contrast, there are few reports on the catalytic enantioselective synthesis of higher analogues—oxetanes. Oxetanes have recently gained attention as attractive, stable, small, and less lipophilic molecular modules for drug discovery.^[2] Considering the wide applicability of oxetane units in medicinal chemistry, organic synthesis, and material science,^[2–5] the development of synthetic methods for making a diverse array of oxetanes, especially optically active oxetanes, is highly desirable. Highly enantioselective syntheses of 2-monosubstituted oxetanes, involving the asymmetric reduction of 3-haloketones using chiral reagents or catalysts and subsequent cyclization, have been reported.^[4] However such strategies are not applicable to the synthesis of 2,2-disubstituted oxetanes. Previously reported methods for chiral 2,2-disubstituted oxetanes required a lengthy multistep synthetic route.^[5] Herein, we describe a straightforward one-pot catalytic asymmetric synthesis of 2,2-disubstituted oxetanes from ketones. A $\text{LaLi}_3\text{tris}(\text{binaphthoxide})$ complex (LLB ((S)-**1a**), Figure 1) with an $\text{Ar}_3\text{P}=\text{O}$ additive ($\text{Ar}=2,4,6\text{-trimethoxyphenyl}$) promoted the successive addition of dimethyloxosulfonium methylide to ketones and intermediate epoxides. Chiral amplification was observed in the second step to afford oxetanes with greater than 99.5–99% *ee*, an enantiomeric excess higher than that of the intermediate epoxides.

Initially, we screened chiral catalysts suitable for the reaction of readily available racemic 2,2'-disubstituted epoxide **2a** with dimethyloxosulfonium methylide (**3**).^[6] Among the catalysts screened, rare earth/alkali metal/binol heterobimetallic complexes (REMB; binol = 2,2'-dihydroxy-1,1'-binaphthyl)^[7] gave the most promising results for a kinetic resolution.^[8–10] The results of the optimization studies are summarized in Table 1. (S)-LLB ((S)-**1a**) promoted the

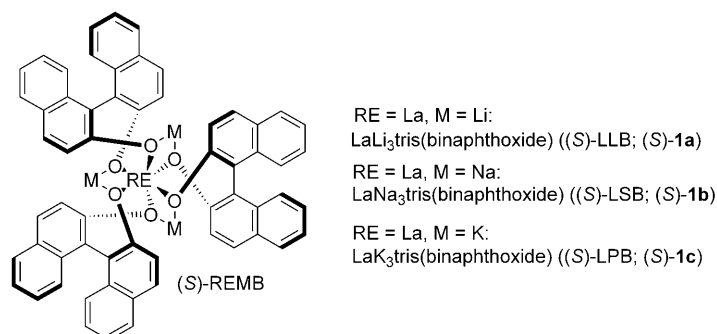


Figure 1. Structures of (S)-RE- M_3 -tris(binaphthoxide) complexes (REMB, RE = rare-earth metal).

reaction of epoxide **2a** with ylide **3** to afford (R)-oxetane **4a** in 16% yield and 24% *ee* (Table 1, entry 1). No reaction proceeded in the absence of (S)-LLB under otherwise identical conditions at 45°C (Table 1, entry 2).^[11] Both (S)-LSB ((S)-**1b**) and (S)-LPB ((S)-**1c**; Figure 1) afforded only trace amounts, if any, of oxetane **4a** (Table 1, entries 3 and 4). We then examined the effects of achiral additives, which are useful for modifying the chiral environment of REMB complexes.^[12] NaI, which is effective in the Corey–Chaykovsky cyclopropanation of enones and α,β -unsaturated *N*-acylpyrroles,^[13] was not at all effective (Table 1, entry 5) for generating oxetanes. In contrast, phosphine oxides, which are effective in the Corey–Chaykovsky epoxidation of ketones,^[14] increased both the reactivity and selectivity of the reaction.^[15] Among the phosphine oxides screened (Table 1, entries 6–9), $\text{Ar}_3\text{P}=\text{O}$ **5d** ($\text{Ar}=2,4,6\text{-trimethoxyphenyl}$) afforded the best results, giving oxetane **4a** in 30% yield and 59% *ee* (Table 1, entry 9, $k_{\text{rel}}=5.0$).^[16] Selectivity was additionally improved by changing the reaction solvent from THF to either THF/toluene (1:1, Table 1, entry 10, $k_{\text{rel}}=7.5$) or THF/*n*-hexane (1:1, Table 1, entry 11, $k_{\text{rel}}=7.7$). By increasing the catalyst loading to 10 mol %, oxetane **4a** was obtained in 41% yield and 73% *ee* after 48 hours (Table 1, entry 12, $k_{\text{rel}}=10.4$). In entry 12 of Table 1, (R)-**2a** was recovered in 42% *ee*. (R)-**2b**, having an alkyl substituent, was also applicable under the same reaction conditions, and oxetane **4b** was obtained in 43% yield and 78% *ee* (Table 1, entry 13, $k_{\text{rel}}=14.6$).

Although the k_{rel} values observed in the kinetic resolution, by using racemic epoxides **2a** and **2b**, were not high (Table 1), we assumed that the selectivity was sufficient to obtain oxetanes **4** in high enantiomeric excess by a double methylene transfer starting from ketones. In our previous report, (S)-LLB ((S)-**1a**) preferentially afforded (S)-**2a** and (S)-**2b** through the addition of ylide **3** to ketones.^[14] The results shown in Table 1 suggest that (S)-**1a** preferentially promoted

[*] T. Sone, G. Lu, Dr. S. Matsunaga, Prof. Dr. M. Shibasaki
Graduate School of Pharmaceutical Sciences
The University of Tokyo
Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)
Fax: (+81) 3-5684-5206
E-mail: smatsuna@mol.f.u-tokyo.ac.jp
mshibasa@mol.f.u-tokyo.ac.jp
Homepage: http://www.f.u-tokyo.ac.jp/~kanai/e_index.html

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Table 1: Optimization studies on the kinetic resolution of racemic 2,2'-disubstituted epoxides **2** catalyzed by heterobimetallic REMB complexes.

(±)-**2a**: R = Ph
(±)-**2b**: R = *n*-octyl

Entry	Epoxide	REMB (mol %)	Additive 5 (mol %)	Solvent	<i>ee</i> of recovered 2 [%]	Yield of 4 [%] ^[a]	<i>ee</i> of 4 [%] ^[b]	<i>k</i> _{rel} ^[c]
1	2a	(<i>S</i>)-LLB (5)	none	THF	1	16	24	1.7
2	2a	none	none	THF	0	0	—	—
3	2a	(<i>S</i>)-LSB (5)	none	THF	0	trace	—	—
4	2a	(<i>S</i>)-LPB (5)	none	THF	0	trace	—	—
5	2a	(<i>S</i>)-LLB (5)	Nal (5)	THF	3	26	19	1.6
6	2a	(<i>S</i>)-LLB (5)	5a : Ph ₃ P=O (5)	THF	1	15	20	1.5
7	2a	(<i>S</i>)-LLB (5)	5b : (2,4,6-Me ₃ -C ₆ H ₂) ₃ P=O (5)	THF	2	19	23	1.7
8	2a	(<i>S</i>)-LLB (5)	5c : (2,6-(MeO) ₂ -C ₆ H ₃) ₃ P=O (5)	THF	6	19	44	2.9
9	2a	(<i>S</i>)-LLB (5)	5d : (2,4,6-(MeO) ₃ -C ₆ H ₂) ₃ P=O (5)	THF	19	30	59	5.0
10	2a	(<i>S</i>)-LLB (5)	5d (5)	THF/toluene (1:1)	16	22	72	7.5
11	2a	(<i>S</i>)-LLB (5)	5d (5)	THF/ <i>n</i> -hexane (1:1)	19	27	71	7.7
12	2a	(<i>S</i>)-LLB (10)	5d (5)	THF/ <i>n</i> -hexane (1:1)	42	41	73	10.4
13	2b	(<i>S</i>)-LLB (10)	5d (5)	THF/ <i>n</i> -hexane (1:1)	65	43	78	14.6

[a] Yield of oxetane **4** was calculated based on the amount of starting racemic epoxide (±)-**2**. Theoretical maximum yield of chiral **4** is 50%.
[b] Determined by chiral GC analysis. [c] See reference [16].

the reaction of (*S*)-**2a** and (*S*)-**2b** with ylide **3** to give oxetanes **4a** and **4b**. We hypothesized that chiral amplification in the second reaction between the epoxide and the ylide would occur to afford oxetanes with a higher enantioselectivity than the intermediate epoxides. Because the optimized reaction conditions for the kinetic resolution of epoxides **2** (Table 1) and the best conditions for the Corey–Chaykovsky epoxidation of ketones^[14] were the same, except for the reaction temperature and solvent, we investigated a one-pot sequential methylene-transfer process starting from ketone **6b** (Scheme 1). Catalytic asymmetric epoxidation using 5 mol% of (*S*)-**1a** in THF at room temperature produced epoxide **2b** in greater than 99% yield and 93% *ee* after 12 hours. To compensate for the low reaction rate in the second reaction, an additional 15 mol% of (*S*)-**1a** and additive **5d** were added to the reaction mixture together with an additional 1.0 equivalents of ylide **3** and *n*-hexane. The reaction mixture, including a total of 20 mol% of (*S*)-**1a**/**5d**, was then stirred at 45 °C for 72 hours to give oxetane **4b** in 88% yield and 99% *ee* upon isolation. As expected, chiral

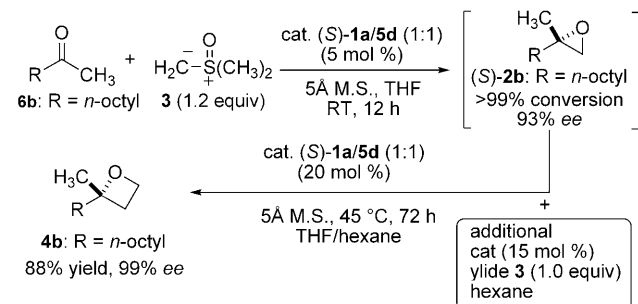
amplification was observed in the second step (93% *ee* of **2b** versus 99% *ee* of **4b**).

The substrate scope of the one-pot sequential methylene-transfer process is summarized in Table 2. With aryl methyl

Table 2: Substrate scope of oxetane **4** synthesis by a one-pot sequential addition of ylide **3** to various methyl ketones **6**.^[a]

Entry	6	R	<i>ee</i> of 2 [%]	4	Yield of 4 [%] ^[b]	<i>ee</i> of 4 [%] ^[c]
1	6a		96	4a	74	99
2	6c		96	4c	62	99
3	6d		94	4d	86	99
4	6e		97	4e	85	99
5	6b		93	4b	88	99
6	6f		93	4f	68	99
7	6g		96	4g	58	> 99.5
8	6h		97	4h	62	> 99.5

[a] Reaction was performed with 1.2 equiv of ylide **3** in THF at room temperature using 5 mol% of (*S*)-**1a**/**5d** (1:1) for the first step; for the second step, an additional 15 mol% of (*S*)-**1a**/**5d** (1:1), 1.0 equiv of ylide **3**, and *n*-hexane were added to the reaction mixture. [b] Yield of isolated oxetanes **4** (from ketones **6**) after purification by column chromatography. [c] Determined by GC or HPLC analysis.



Scheme 1. One-pot sequential addition of ylide **3** to ketone **6b** with chiral amplification.

ketones **6a** and **6c–6e**, the enantioselectivity in the first epoxidation step was 94–97% *ee*. Oxetanes **4a** and **4c–4e** were obtained in 99% *ee* and 86–62% yield after the second step, although the k_{rel} value for aryl methyl ketones was modest, as shown in Table 1.^[17] The enantioselectivity in the first epoxidation step was slightly lower for linear alkyl methyl ketones **6b** and **6f** than those for aryl methyl ketones (Table 2, entries 5 and 6, 93% *ee*). Fortunately, alkyl methyl-substituted oxetanes **4b** and **4f–4h** were also obtained in greater than 99.5–99% *ee* and 88–58% yield through chiral amplification in the second step (Table 2, entries 5–8).

In summary, we developed a straightforward synthetic method for chiral 2,2-disubstituted oxetanes. A one-pot sequential addition of a sulfur ylide to ketones and intermediate epoxides was promoted by the heterobimetallic catalyst **1a**. Chiral amplification was observed in the second reaction of the epoxides with the sulfur ylide and was the key to affording 2,2-disubstituted oxetanes with excellent enantioselectivity (>99.5–99% *ee*). Additional trials to improve the reactivity, catalyst loading, and substrate scope of both the epoxides and ylides in the second oxetane-forming step are ongoing.^[18]

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- [1] Reviews and accounts on catalytic asymmetric epoxidations: a) E. N. Jacobsen, M. H. Wu in *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, p. 649; b) T. Katsuki in *Catalytic Asymmetric Synthesis*, 2nd ed. (Ed.: I. Ojima), Wiley-VCH, New York, **2000**, p. 287; c) C. Bonini, G. Righi, *Tetrahedron* **2002**, *58*, 4981; d) V. K. Aggarwal, C. L. Winn, *Acc. Chem. Res.* **2004**, *37*, 611; e) Q.-H. Xia, H.-Q. Ge, C.-P. Ye, Z.-M. Liu, K.-X. Su, *Chem. Rev.* **2005**, *105*, 1603; f) O. A. Wong, Y. Shi, *Chem. Rev.* **2008**, *108*, 3958.
- [2] Applications in medicinal chemistry: a) G. Wuitschik, M. Rogers-Evans, K. Müller, H. Fischer, B. Wagner, F. Schuler, L. Polonchuk, E. M. Carreira, *Angew. Chem.* **2006**, *118*, 7900; *Angew. Chem. Int. Ed.* **2006**, *45*, 7736; b) G. Wuitschik, M. Rogers-Evans, A. Buckl, M. Bernasconi, M. Märki, T. Godel, H. Fischer, B. Wagner, I. Parrilla, F. Schuler, J. Schneider, A. Alker, W. B. Schweizer, K. Müller, E. M. Carreira, *Angew. Chem.* **2008**, *120*, 4588; *Angew. Chem. Int. Ed.* **2008**, *47*, 4512.
- [3] Selected recent examples in polymer and material science: a) Y. Permana, K. Nakano, M. Yamashita, D. Watanabe, K. Nozaki, *Chem. Asian J.* **2008**, *3*, 710; b) H. Boucekif, M. I. Philbin, E. Colclough, A. J. Amass, *Macromolecules* **2008**, *41*, 1989; c) J. V. Crivello, *J. Polym. Sci Part A* **2007**, *45*, 4331.
- [4] a) M. M.-C. Lo, G. C. Fu, *Tetrahedron* **2001**, *57*, 2621, and references therein; b) K. Soai, S. Niwa, T. Yamanoi, H. Hikima, M. Ishizaki, *J. Chem. Soc. Chem. Commun.* **1986**, 1018; c) F. Bertolini, S. Crotti, V. Di Bussolo, F. Macchia, M. Pineschi, *J. Org. Chem.* **2008**, ASAP; See also, d) K. Hintzer, B. Koppenhoefer, V. Schurig, *J. Org. Chem.* **1982**, *47*, 3850.
- [5] P. H. Dussault, T. K. Trullinger, F. Noor-e-Ain, *Org. Lett.* **2002**, *4*, 4591.
- [6] E. J. Corey, M. Chaykovsky, *J. Am. Chem. Soc.* **1965**, *87*, 1353.
- [7] A review on heterobimetallic asymmetric catalysis: a) M. Shibasaki, N. Yoshikawa, *Chem. Rev.* **2002**, *102*, 2187; For selected recent examples, see: b) N. Yamagiwa, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 16178; c) N. Yamagiwa, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2004**, *116*, 4593; *Angew. Chem. Int. Ed.* **2004**, *43*, 4493; d) N. Yamagiwa, H. Qin, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 13419.
- [8] General review for nonenzymatic kinetic resolution: E. Vedejs, M. Jure, *Angew. Chem.* **2005**, *117*, 4040; *Angew. Chem. Int. Ed.* **2005**, *44*, 3974.
- [9] Kinetic resolution of 2,2-disubstituted terminal epoxides using a chiral metal catalyst is rare. For resolution with an azide nucleophile catalyzed by a (salen)Cr complex, see: a) H. Lebel, E. N. Jacobsen, *Tetrahedron Lett.* **1999**, *40*, 7303; for reviews on biocatalytic kinetic resolutions, see: b) A. Steinreiber, K. Faber, *Curr. Opin. Biotechnol.* **2001**, *12*, 552; c) A. Archelas, R. Furstoss, *Curr. Opin. Chem. Biol.* **2001**, *5*, 112.
- [10] Examples of kinetic resolution using heterobimetallic complexes: a) S.-y. Tosaki, K. Hara, V. Gnanadesikan, H. Morimoto, S. Harada, M. Sugita, N. Yamagiwa, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 11776; b) H. Mihara, Y. Sohtome, S. Matsunaga, M. Shibasaki, *Chem. Asian J.* **2008**, *3*, 359.
- [11] Racemic synthesis of oxetane from ketones through the sequential addition of in situ generated sulfur ylides was reported. Oxirane ring-expansion reactions proceeded in *t*BuOH at 50°C without any promoter, but no reaction proceeded in THF neither at 45°C nor at 50°C in the absence of (S)-**1a**. K. Okuma, Y. Tanaka, S. Kaji, H. Ohta, *J. Org. Chem.* **1983**, *48*, 5133. See also reference [4c] for oxirane ring-expansion with an ylide using a chiral 2-monosubstituted epoxide.
- [12] Reviews: a) E. M. Vogl, H. Gröger, M. Shibasaki, *Angew. Chem.* **1999**, *111*, 1672; *Angew. Chem. Int. Ed.* **1999**, *38*, 1570; b) M. Shibasaki, S. Matsunaga, N. Kumagai, *Synlett* **2008**, 1583.
- [13] H. Kakei, T. Sone, Y. Sohtome, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2007**, *129*, 13410.
- [14] T. Sone, A. Yamaguchi, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2008**, *130*, 10078.
- [15] Steric and electronic modification of achiral phosphine oxides have beneficial effects in other rare-earth-metal-catalyzed asymmetric reactions: a) K. Daikai, M. Kamaura, J. Inanaga, *Tetrahedron Lett.* **1998**, *39*, 7321; b) R. Kino, K. Daikai, T. Kawanami, H. Furuno, J. Inanaga, *Org. Biomol. Chem.* **2004**, *2*, 1822; c) J. Tian, N. Yamagiwa, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2002**, *114*, 3788; *Angew. Chem. Int. Ed.* **2002**, *41*, 3636; d) N. Yamagiwa, J. Tian, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 3413; e) H. Kakei, R. Tsuji, T. Ohshima, H. Morimoto, S. Matsunaga, M. Shibasaki, *Chem. Asian J.* **2007**, *2*, 257; f) K. Hara, S.-Y. Park, N. Yamagiwa, S. Matsunaga, M. Shibasaki, *Chem. Asian J.* **2008**, *3*, 1500; g) H. Morimoto, T. Yoshino, T. Yukawa, G. Lu, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2008**, *120*, 9265; *Angew. Chem. Int. Ed.* **2008**, *47*, 9125.
- [16] The k_{rel} values in this manuscript were calculated based on the conversion and *ee* values of oxetane **4** assuming first-order kinetic dependence on **2**. Kinetic studies are required to determine accurate k_{rel} values. For discussion on the validity of the calculated values, see: J. M. Keith, J. F. Larrow, E. N. Jacobsen, *Adv. Synth. Catal.* **2001**, *343*, 5. See also Ref. [8]. In Table 1, the observed *ee* value of recovered epoxide **2a** was lower than expected on the basis of the *ee* value of oxetane **4a**, possibly because of side reaction from (R)-**2a**.
- [17] Alternatively, both the epoxidation and the ring-expansion reaction can be performed simultaneously at 45°C. The reaction of acetophenone (**6a**) at 45°C using 2.2 equivalents of ylide **3** and 20 mol % (S)-LLB from the beginning afforded oxetane **4a** in slightly lower yield (70% yield) than that of entry 1 in Table 2, but in excellent enantioselectivity (99% *ee*) after 72 hours. The

slightly lower yield and high *ee* value implied that chiral amplification worked nicely even though the enantiomeric excess of the intermediate epoxide was a little bit lower than the sequential process in Table 2.

- [18] The use of ethyl ketones is difficult at the moment because of their low reactivity in the second ring-expansion reaction and insufficient chiral amplification. For example, the reaction of propiophenone using 20 mol % of (*S*)-LLB at room temperature

gave the intermediate epoxide in 88 % *ee*. The subsequent ring-expansion reaction, however, gave the oxetane in only 26 % yield and 91 % *ee*.

