

# A Highly Efficient Asymmetric Synthesis of Optically Active $\alpha,\gamma$ -Substituted $\gamma$ -Butyrolactones Using a Chiral Auxiliary Derived from Isosorbide

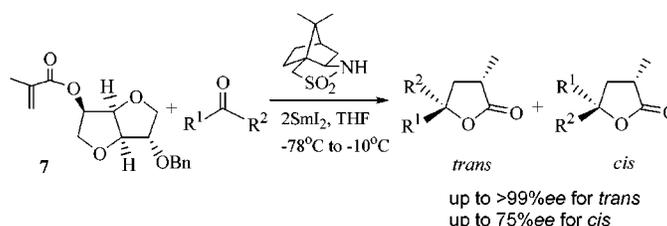
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## ABSTRACT



Using an easily accessible and inexpensive chiral auxiliary derived from isosorbide, optically active  $\alpha,\gamma$ -substituted  $\gamma$ -butyrolactones were obtained in high enantiomeric purity (up to >99% ee for *trans*) by the  $\text{SmI}_2$ -induced reductive coupling of chiral methacrylate **7** with ketones in the presence of (–)-sultam as a proton source.

Compounds bearing the substituted  $\gamma$ -butyrolactone moiety are widespread in nature and have received much interest because of their physiological properties.<sup>1</sup> Moreover, functionalized  $\gamma$ -butyrolactones are important intermediates for the synthesis of many organic compounds.<sup>2</sup> Much attention has been focused on the asymmetric synthesis of  $\gamma$ -butyrolactones.<sup>3</sup> The approach based on  $\text{SmI}_2$ -mediated reductive

radical reactions recently introduced by Fukuzawa<sup>4</sup> is one of the most facile and effective methods for preparing chiral  $\gamma$ -butyrolactones. However, there has been no report, to the best of our knowledge, concerning highly enantioselective synthesis of  $\alpha,\gamma$ -substituted  $\gamma$ -butyrolactones.<sup>5</sup> In a previous paper, we described the asymmetric synthesis of optically active  $\gamma$ -methyl- $\gamma$ -phenyl- $\gamma$ -butyrolactone using easily accessible and inexpensive chiral auxiliaries derived from

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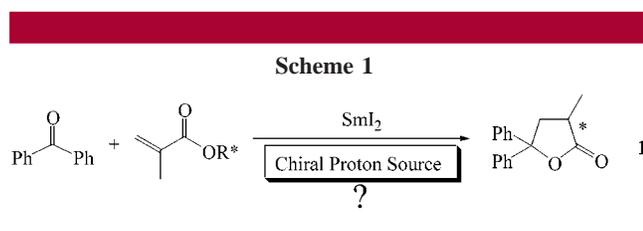
V.; Prabhakaran, J.; George, T. G. *Tetrahedron* **1997**, *44*, 15061–15068. (j) Taniguchi, N.; Uemura, M. *Tetrahedron Lett.* **1997**, *38*, 7199–7202. (k) Merlic, C. A.; Walsh, J. C. *Tetrahedron Lett.* **1998**, *39*, 2083–2086. For catalysis mediated by chiral metal complexes, see: (l) Ohkuma, T.; Kitamura, M.; Noyori, R. *Tetrahedron Lett.* **1990**, *31*, 5509–5512. (m) Doyle, M. P.; Protopopova, M. N.; Zhou, Q.-L.; Bode, J. W. *J. Org. Chem.* **1995**, *60*, 6654–6655. (n) Yu, W. Y.; Bensimon, C.; Alper, H. *Chem. Eur. J.* **1997**, *3*, 417–423. (o) Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1999**, *121*, 7708–7709. For ligand-controlled asymmetric synthesis, see: (p) Mikami, K.; Yamaoka, M. *Tetrahedron Lett.* **1998**, *39*, 4501–4504.

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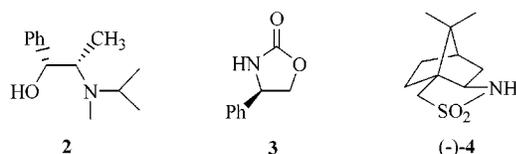
(5) During the preparation of this manuscript, a method was reported for the synthesis of *cis*- $\alpha,\gamma$ -dialkyl  $\gamma$ -lactones using chiral *sec*-dialkyl bishomopropargylic alcohols as the reactant; see: Diaz, D.; Martin, V. S.; *Org. Lett.* **2000**, *2*, 335–337.

isomannide and isosorbide.<sup>6</sup> Herein, we wish to report a new reaction system that can be easily and effectively used for the synthesis of optically active  $\alpha,\gamma$ -substituted  $\gamma$ -butyrolactones.

It has been found that, in the reaction of  $\alpha,\beta$ -unsaturated esters with ketones mediated by  $\text{SmI}_2$  as an electron-transfer agent, the presence of an alcohol is essential for the formation of the  $\gamma$ -butyrolactones. The effect of a proton source in the reaction was examined by Fukuzawa and co-workers in 1988,<sup>7</sup> and *tert*-butyl alcohol was found to give the most satisfactory results. Deuterium exchange experiments confirmed the role of the alcohol as the proton donor and a proton was introduced into the  $\alpha$ -C of the lactone. So, it is desirable to construct the  $\alpha$ -C chiral center of the lactone by asymmetric protonation. Moreover, it would be interesting to study the asymmetric inductions when both chiral auxiliary and chiral proton source are present in the reaction (Scheme 1).



First, the enantioselective effect of *N*-isopropylphedrine (**2**) as the chiral proton source in the reaction of methyl methacrylate with benzophenone was examined. As a result about 9% ee (53% yield) was obtained under the optimized conditions at temperatures from  $-78$  to  $-10$  °C. Although this ee value is low, it shows that asymmetric protonation in this process is possible. Furthermore, it reveals that a samarium enolate is formed as a key intermediate in this reaction.<sup>8</sup> To increase the enantioselectivity, various chiral compounds were examined as proton sources, which resulted in moderate enantioselectivity;<sup>9</sup> some examples were shown (Figure 1). The reaction afforded 16% ee and 63% yield of



**Figure 1.**

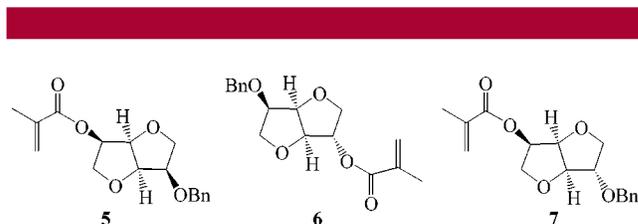
product when compound **3** was the chiral proton source. When optically active sultam ( $-$ )-**4** or ( $+$ )-**4** was employed, the enantiomeric excess was elevated to 39% [the sign of

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the product's optical rotation is ( $-$ ) or 47% [( $+$ )] and in good yield, 89% or 83%, respectively. These results clearly showed that the configuration of the product was largely determined by the stereochemistry of the proton source employed.

On the basis of the low or moderate level of enantioselectivity of the asymmetric protonation, we turned our focus on the asymmetric synthesis induced by a chiral auxiliary. Recently, our group became interested in asymmetric reactions based on the application of isomannide and isosorbide derivatives as chiral auxiliaries.<sup>6,10</sup> Isomannide and isosorbide are inexpensive, and commercially available carbohydrate derivatives, substrates **5–7** (Figure 2), were easily prepared



**Figure 2.**

from them. We first treated these substrates with benzophenone in the presence of *t*-BuOH from  $-78$  °C to room temperature. The reactions proceeded smoothly, and **7** gave the highest enantioselectivity.<sup>11</sup> It was also noticed that the reaction temperature was very important. The enantioselectivity increased when the reaction was quenched at a lower temperature; for example, the reaction of benzophenone with **7** provided lactone with 79% ee when quenched at  $-10$  °C as opposed to 60% ee when quenched at room temperature (Table 1, entries 3 and 4).

**Table 1.** Enantioselective Synthesis of  $\gamma$ -Butyrolactone **1**

entry	ester	temp	proton source	yield (%) <sup>a</sup>	ee (%) <sup>b</sup>	[ $\alpha$ ] <sub>D</sub> sign
1	<b>5</b>	$-78$ °C $\rightarrow$ rt	<i>t</i> -BuOH	51	50	(+)
2	<b>6</b>	$-78$ °C $\rightarrow$ rt	<i>t</i> -BuOH	68	8	(-)
3	<b>7</b>	$-78$ °C $\rightarrow$ rt	<i>t</i> -BuOH	55	60	(+)
4	<b>7</b>	$-78$ $\rightarrow$ $-10$ °C	<i>t</i> -BuOH	55	79	(+)
5	<b>7</b>	$-78$ $\rightarrow$ $-10$ °C	<b>2</b>	43	85	(+)
6	<b>7</b>	$-78$ $\rightarrow$ $-10$ °C	<b>3</b>	51	86	(+)
7	<b>7</b>	$-78$ $\rightarrow$ $-10$ °C	( $-$ )- <b>4</b>	66	95	(+)
8	<b>7</b>	$-78$ $\rightarrow$ $-10$ °C	( $+$ )- <b>4</b>	67	93	(+)
9	<b>7</b>	$-78$ $\rightarrow$ $-10$ °C	( $\pm$ )- <b>4</b>	60	95	(+)
10	<b>7</b>	$-78$ $\rightarrow$ $-10$ °C	TrOH	53	87	(+)

<sup>a</sup> Isolated yield. <sup>b</sup> The ee values were determined by HPLC analysis on a chiralcel AD column [detected at 254 nm; eluent, *n*-hexane/2-propanol, 80/20 (v/v)].

In light of these results, the possibility of preparing chiral  $\gamma$ -butyrolactones via double asymmetric induction was

explored employing both chiral substrate **7** and a chiral proton source. As shown in Table 1, when compounds **2** and **3** were used as the chiral proton sources, better results were obtained as expected, and the enantiomeric excesses were 85% and 86%, respectively. Surprisingly, when (–)-**4** was employed, the reaction also provided **1** with very high ee (95%, entry 7). The configuration of the main product induced only by chiral proton source (–)-**4** (see above) was different from that induced only by chiral substrate **7**, a result we did not expect. An equally high enantiomeric excess (93% ee) was obtained when (+)-**4** was used as the chiral proton source (entry 8). These results led to the suggestion that the enantioselectivity of the reaction may be unrelated to double asymmetric induction. To confirm this consideration, the use of racemic sultam [(±)-**4**] was examined. A high degree of enantioselectivity was attained (95% ee, entry 9), similar to that with the achiral sterically bulky trityl alcohol (entry 10). These two results supported the idea that double asymmetric induction was not exerted in this reaction. Moreover, in all cases, we found that the configurations of the main products were the same (entries 3–10). Thus, it can be concluded that the enantioselectivity of the reaction was strongly controlled by the stereochemistry of the chiral substrate and that the chirality of the proton source was not a factor. In addition, the results suggest that chelation of samarium atom and the oxygen atoms in the substrate may play an important role in the asymmetric induction. The exact transition-state model and mechanistic explanation of this study remain unclear at this time.

The success in synthesis of highly optically active **1** prompted us to extend this new reaction system to the preparation of  $\gamma$ -butyrolactones with two chiral centers, the  $\alpha$ -C and the  $\gamma$ -C. Treatment of chiral methacrylate **7** with unsymmetrical ketones under optimized conditions<sup>12</sup> for several hours afforded the isomeric *trans* and *cis* lactones, which could be separated by column chromatography. Table 2 summarizes the results of the asymmetric coupling reaction. The *trans* products of chiral  $\alpha,\gamma$ -substituted  $\gamma$ -butyrolactones were obtained with high ee values in all cases; extremely high ee values (>99%) were achieved with acetophenone and propiophenone (entries 1 and 2). When  $\alpha$ -tetralone was used, *trans* and *cis* spiro lactones **13** were obtained with very good enantiomeric excesses (entry 6). The configuration of

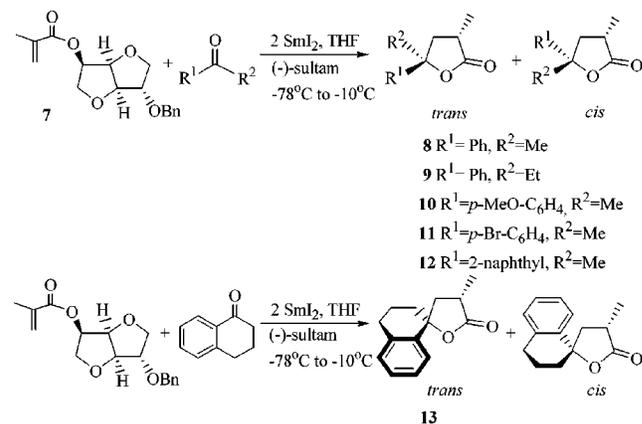
(8) For a review of asymmetric protonation of enolates and enols, see: (a) Fehr, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2566–2587. For examples of asymmetric protonation of samarium enolates, see: (b) Takeuchi, S.; Miyoshi, N.; Ohgo, Y. *Chem. Lett.* **1992**, 551–554. (c) Takeuchi, S.; Ohira, A.; Miyoshi, N.; Mashio, H.; Ohgo, Y. *Tetrahedron: Asymmetry* **1994**, *5*, 1763–1780. (d) Nakamura, Y.; Takeuchi, S.; Ohira, A.; Ohgo, Y. *Tetrahedron Lett.* **1996**, *37*, 2805–2808. (e) Nakamura, Y.; Takeuchi, S.; Ohgo, Y.; Yomaoka, M.; Yoshida, A.; Mikami, K. *Tetrahedron Lett.* **1997**, *38*, 2709–2712. (f) Takeuchi, S.; Nakamura, Y.; Ohgo, Y.; Curran, D. P. *Tetrahedron Lett.* **1998**, *39*, 8691–8694.

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(11) In an effort to maximize the results, other chiral auxiliaries were also surveyed. With *N*-isopropylephedrine (**2**) as chiral auxiliary, chiral  $\gamma$ -butyrolactone **1** was obtained in only 30% ee. However, **2** is a good chiral auxiliary in the synthesis of chiral 4-substituted- and *cis*-3,4-disubstituted- $\gamma$ -butyrolactones; see: note (12) of ref 4.

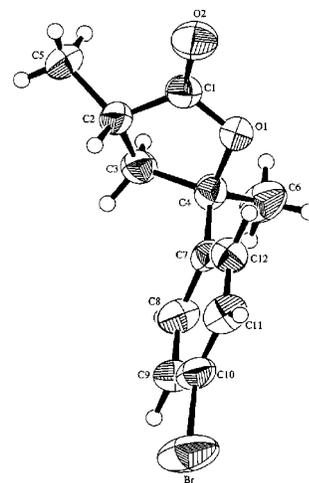
**Table 2.** Highly Enantioselective Synthesis of *trans*- $\alpha,\gamma$ -Substituted  $\gamma$ -Butyrolactones



entry	product	<i>trans/cis</i> <sup>a</sup>	<i>trans</i> ee (%) <sup>b</sup>	<i>cis</i> ee (%) <sup>b</sup>	yield (%) <sup>c</sup>
1	<b>8</b>	79/21	>99	<i>d</i>	74
2	<b>9</b>	61/39	>99	19	73
3	<b>10</b>	76/24	95	24	81
4	<b>11</b>	77/23	96	14	61
5	<b>12</b>	68/32	98	52	84
6	<b>13</b>	69/31	97	75	58

<sup>a</sup> *trans* and *cis* were confirmed by <sup>1</sup>H–<sup>1</sup>H NOESY in light of their NOE effect, and the ratio of *trans/cis* was determined by GC. <sup>b</sup> The ee values were determined by HPLC analysis on chiralcel OJ, AD column (detected at 254 nm; eluent, *n*-hexane/2-propanol, 80/20 (v/v)). <sup>c</sup> Total isolated yield of *trans* and *cis* products. <sup>d</sup> Not detected.

this type of *trans* product was solved by X-ray diffraction. Using 4'-bromoacetophenone as starting material, we obtained the corresponding product *trans*-**11** as a colorless crystal, which was recrystallized from EtOAc–hexane. The absolute configuration was then determined as (2*S*,4*R*) by X-ray crystallographic analysis of *trans*-**11**,<sup>13</sup> illustrated in Figure 3.



**Figure 3.** X-ray crystal structure of *trans*-**11**.

In summary, we have developed an efficient, novel method for the synthesis of optically active  $\alpha,\gamma$ -substituted  $\gamma$ -butyrolactones by using the SmI<sub>2</sub>-mediated coupling of ketones with a chiral methacrylate derived from isosorbide. We found that both the chiral auxiliary and the hindered proton source in this system are important features providing for the observed

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(12) Since (–)-sultam (**4**) is commercially available and not expensive, we still use it as the chiral proton source instead of (±)-sultam.

(13) Data for the X-ray structure analysis of *trans*-**11**: crystals from EtOAc–hexane, C<sub>12</sub>H<sub>13</sub>O<sub>2</sub>Br (*M<sub>r</sub>* = 269.14); colorless, prismatic; crystal dimensions 0.20 × 0.20 × 0.30 mm<sup>3</sup>; orthorhombic; space group *P*2<sub>1</sub>2<sub>1</sub>2<sub>1</sub> (#19); *a* = 8.101(3), *b* = 25.457(3), *c* = 5.886(3) Å, *Z* = 4, *V* = 1213.8(8) Å<sup>3</sup>, *F*(000) = 544.00,  $\rho_{\text{calcd}}$  = 1.473 g/cm<sup>3</sup>; *T* = 293 K;  $2\theta_{\text{max}}$  = 55.0 °C; 3348 reflections measured, 1674 were unique (*R*<sub>int</sub> = 0.066) and 1338 observed (*I* > 3σ(*I*)); Rigaku AFC7R diffractometer, Mo Kα radiation ( $\lambda$  = 0.71069 Å), graphite monochromator; Lorentz-polarization absorption correction ( $\mu$  = 33.75 cm<sup>-1</sup>). The structure was solved by Patterson methods and refined with the full-matrix least-squares method; *R* = 0.054, *wR* = 0.061; reflection/parameter ratio 9.77; residual electron density +0.74/–0.45 e Å<sup>-3</sup>.

excellent ee values of the products, >99% in some cases. Further investigations of this process to prepare other chiral  $\gamma$ -butyrolactones are in progress. Based on this new system, future work will be aimed at the asymmetric synthesis of fully substituted  $\gamma$ -butyrolactones.

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**Supporting Information Available:** General experimental details and characterization data of all new chiral lactones **1** and **8–13** are provided. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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