ORGANIC LETTERS

2000
Vol. 2, No. 24
3773−3776

Chiral Sulfonamide Induced Enantioselective Protonation of Samarium Enolate in the Reaction of α,β-Unsaturated Ester with Ketone

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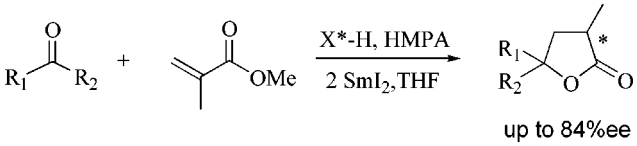
Received August 7, 2000 *(Revised Manuscript Received October 2, 2000)*

ABSTRACT



Good enantioselectivity (up to 84% ee) has been achieved in the formation of α,γ-substituted-γ-butyrolactone by the SmI_2-mediated reductive coupling of ketones with methyl methacrylate using various chiral proton sources.

Asymmetric protonation of prochiral metal enolates has been demonstrated to be a useful and promising method for the preparation of chiral carbonyl compounds and carboxylic acid derivatives bearing stereogenic centers at their α-position.[1] A number of successful approaches for asymmetric protonation of lithium enolates have been developed by many researchers.[2,3] However, there are very few examples of asymmetric protonation of samarium enolates besides the pioneering work of Takeuchi and co-workers.[4] In a previous paper,[5] we described the asymmetric synthesis of optically active α,γ-substituted-γ-butyrolactones by using the SmI_2-induced reductive coupling of ketones with a chiral methacrylate in the presence of (−)-sultam as a proton source. We wish to report herein the investigation of chiral sulfonamide induced enantioselective protonation in the reaction of ketone with achiral methyl methacrylate in a reagent-controlled manner for the synthesis of optically active α,γ-substituted-γ-butyrolactone.

It has been found that in the reaction of α,β-unsaturated esters with ketones mediated by SmI_2 as an electron-transfer agent, the presence of a proton source is essential for the formation of the γ-butyrolactones. The effect of a proton source in the reaction was examined by Fukuzawa and co-workers in 1988,[6b] and *tert*-butyl alcohol was found to give

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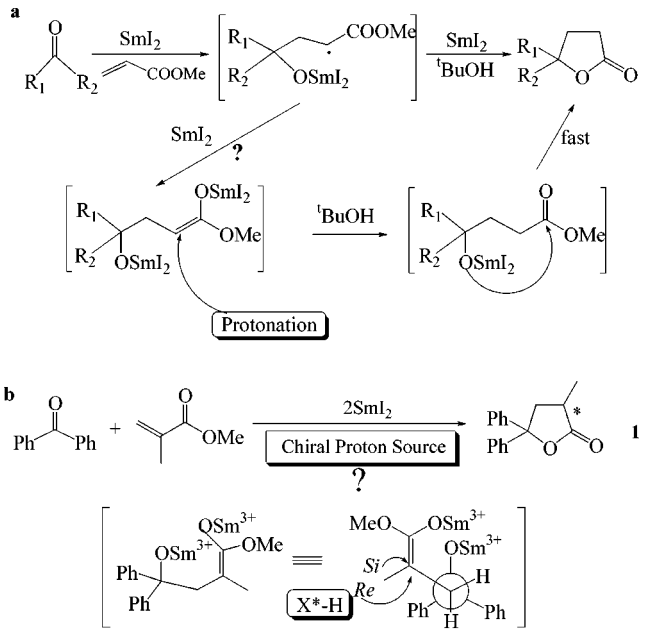
(2) For recent examples of stoichimetric enantioselective protonation of lithium enolates, see: (a) Vedejs, E.; Kruger, A. W.; Lee, N.; Sakata, S. T.; Stec, M.; Suna, E. *J. Am. Chem. Soc.* **2000**, *122*, 4602−4607. (b) Yasuhito, Y.; Yoshihiro, E.; Kazunori, O.; Kenji, K. *Tetrahedron Lett.* **2000**, *41*, 209−213. (c) Vedejs, E.; Kruger, A. W.; Suna, E. *J. Org. Chem.* **1999**, *64*, 7863−7870. (d) Asensio, G.; Cuenca, A.; Gavina, P.; Medio-Simon, M. *Tetrahedron Lett.* **1999**, *40*, 3939−3940. (e) Yanagisawa, A.; Kikuchi, T.; Watanabe, T.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2337−2343. (f) Yanagisawa, A.; Kikuchi, T.; Yamamoto, H. *Synlett* **1998**, 174−176. (g) Prat, L.; Mojovic, L.; Levacher, V.; Dupas, G.; Queguiner, G.; Bourguignon, J. *Tetrahedron: Asymmetry* **1998**, *9*, 2509−2516. (h) Martin, J.; Lansne, M.-C.; Plaquevent, J.-C.; Duhamel, L. *Tetrahedron Lett.* **1997**, *38*, 7181−7182. (i) Takahashi, T.; Nakao, N.; Koizumi, T. *Tetrahedron: Asymmetry* **1997**, *8*, 3293−3308. (j) Kosugi, H.; Hoshino, K.; Uda, H. *Tetrahedron Lett.* **1997**, *38*, 6861−6864. (k) Takahashi, T.; Nakao, N.; Koizumi, T. *Chem. Lett.* **1996**, 207−208. (l) Fuji, K.; Kawabata, T.; Kuroda, A. *J. Org. Chem.* **1995**, *60*, 1914−1915. (m) Yanagisawa, A.; Kuribayashi, T.; Kikichi, T.; Yamamoto, H. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 107−109. (n) Vedejs, E.; Lee, N.; Sakata, S. T. *J. Am. Chem. Soc.* **1994**, *116*, 2175−2176. (o) Cavelier, F.; Gomez, S.; Jacquier, R.; Verducci, J. *Tetrahedron Lett.* **1994**, *35*, 2891−2894. (p) Gerlach, U.; Haubenreich, T.; Hünig, S. *Chem. Ber.* **1994**, *127*, 1981−1988. (q) Gerlach, U.; Haubenreich, T.; Hünig, S. *Chem. Ber.* **1994**, *127*, 1989−1992. (r) Fuji, K.; Tanaka, K.; Miyamoto, H. *Tetrahedron: Asymmetry* **1993**, *4*, 247−259. (s) Yasutaka, T.; Koga, K. *Tetrahedron: Asymmetry* **1993**, *4*, 35−38. (t) Fehr, C.; Stempf, I.; Galindo, J. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1042−1044. (u) Matsumoto, K.; Ohta, H. *Tetrahedron Lett.* **1991**, *32*, 4729−4732.

10.1021/ol006429c CCC: $19.00
Published on Web 10/31/2000

the best results. Deuterium exchange experiments confirmed the proton was introduced into the α-carbon of the lactone. Although a free radical mechanism has been assumed,[6] we are interested in the possibility that the reaction may further proceed by an enolate intermediate and the methoxide anion is released via a kinetic equilibration (Scheme 1a). Therefore,

Scheme 1



it is desirable to construct the α-carbon chiral center of the γ-butyrolactones by enantioselective protonation of the samarium enolate (Scheme 1b).

In our first attempt, we examined the reaction of methyl methacrylate with benzophenone using *N*-isopropylephedrine[7] (**2**) as the chiral proton source. An enantiomeric excess of 9% was obtained under optimized conditions at temperatures from −78 to −10 °C. Although the low ee value was given at this stage, it showed that asymmetric protonation in the reaction might be possible. Furthermore, it revealed that the samarium enolate was the key intermediate in this reaction.

To increase the enantioselectivity, various chiral compounds including chiral alcohols, chiral amides, and chiral amino alcohols were examined as proton sources. The selected examples are shown below (Figure 1); the yield and

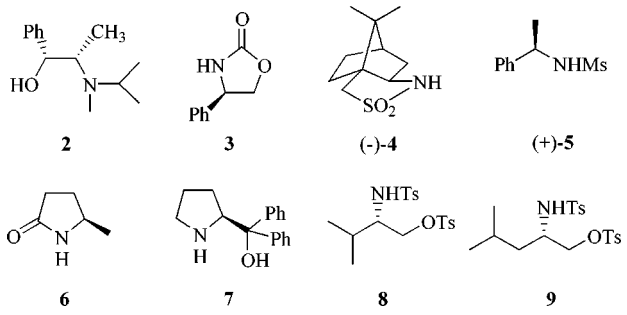
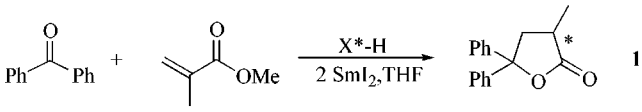


Figure 1.

enantiomeric excess of the product **1** obtained by the protonation are summarized in Table 1. Low or moderate enantioselectivity was observed for all chiral proton sources

Table 1. Enantioselective Protonation for Preparing α-Methyl-γ,γ-diphenyl-γ-butyrolactone



entry	chiral proton source	yield[a] (%)	ee[b] (%)	$[\alpha]_D$ sign
1	**2**	53	9	(+)
2	**3**	63	16	(+)
3	(−)-**4**	89	39	(−)
4	(+)-**4**	83	47	(+)
5	(−)-**5**	60	36	(−)
6	(+)-**5**	62	41	(+)
7	**6**	47	23	(+)
8	**7**	78[c]	22	(+)
9	**8**	41	48	(+)
10	**9**	92[c]	24	(+)
11[d]	**8**	78[c]	56	(+)
12[d]	(+)-**4**[e]	60[c]	67	(+)
13[d]	(+)-**5**[e]	68[c]	58	(+)
14[d]	**9**[e]	79[c]	46	(+)

[a] Isolated yield unless otherwise noted. [b] The ee values were determined by HPLC analysis on a Chiralcel AD column [detected at 254 nm; eluent: *n*-hexane/isopropyl alcohol = 80/20 (v/v)]. [c] Isolated yield based on starting material recovery. [d] 2.0 equiv of HMPA was added in the reaction. [e] >95% of the chiral proton source was recovered by chromatography.

(3) For recent examples of catalytic enantioselective protonation of lithium enolates, see: (a) Yanagisawa, A.; Watanebe, T.; Kikuchi, T.; Yamamoto, H. *J. Org. Chem.* **2000**, *65*, 2979−2983. (b) Aboulhoda, S. J.; Reiners, I.; Wilken, J.; Hénin, F.; Martens, J.; Muzart, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1847−1850. (c) Riviere, P.; Koga, K. *Tetrahedron Lett.* **1997**, *38*, 7589−7592. (d) Aboulhoda, S. J.; Letinois, S.; Wilken, J.; Reiners, I.; Hénin, F.; Martens, J.; Muzart, J. *Tetrahedron: Asymmetry* **1995**, *6*, 1865−1868. (e) Yanagisawa, A.; Kikichi, K.; Watanabe, T.; Kuribayashi, T.; Yamamoto, H. *Synlett* **1995**, 372−374. (f) Fehr, C.; Galindo, J. *Helv. Chim. Acta* **1995**, *78*, 539−552. (g) Aboulhoda, S. J.; Hénin, F.; Muzart, J. Thorey, C.; Behnem, W.; Martens, J.; Mehler, T. *Tetrahedron: Asymmetry* **1994**, *5*, 1321−1326. (h) Fehr, C.; Stempf, I.; Galindo, J. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1044−1046.

(4) For examples of asymmetric protonation of samarium enolates, see: (a) Nakamura, Y.; Takeuchi, S.; Ohgo, Y.; Curran, D. P. *Tetrahedron* **2000**, *56*, 351−356. (b) Nakamura, Y.; Takeuchi, S.; Ohgo, Y.; Yamaoka, M.; Yoshida, A.; Mikami, K. *Tetrahedron* **1999**, *55*, 4595−4620. (c) Mikami, K.; Yamaoka, M.; Yoshida, A.; Nakamura, Y.; Takeuchi, S.; Ohgo, Y. *Synlett* **1998**, 607−608. (d) Takeuchi, S.; Nakamura, Y.; Ohgo, Y.; Curran, D. P. *Tetrahedron Lett.* **1998**, *39*, 8691−8694. (e) Nakamura, Y.; Takeuchi, S.; Ohgo, Y.; Yomaoka, M.; Yoshida, A.; Mikami, K. *Tetrahedron Lett.* **1997**, *38*, 2709−2712. (f) Nakamura, Y.; Takeuchi, S.; Ohira, A.; Ohgo, Y. *Tetrahedron Lett.* **1996**, *37*, 2805−2808. (g) Takeuchi, S.; Ohira, A.; Miyoshi, N.; Mashio, H.; Ohgo, Y.; *Tetrahedron: Asymmetry* **1994**, *5*, 1763−1780. (h) Takeuchi, S.; Miyoshi, N.; Ohgo, Y. *Chem. Lett.* **1992**, 551−554.

(5) Xu, M.-H.; Wang, W.; Lin, G.-Q. *Org. Lett.* **2000**, *2*, 2229−2232.

(6) (a) Fukuzawa, S.; Nakanishi, A.; Fujinami, T.; Sakai,S. *J. Chem. Soc., Chem. Commun.* **1986**, 624−625. (b) Fukuzawa, S.; Nakanishi, A.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1669−1675.

(entries 1−10), with sulfonamide analogues being the most efficient inductors. (1*R*)-(+)-2,10-Camphorsultam **4** and (*S*)-(+)-2-amino-3-methyl-1-butanol derivative **8** gave the best results, 47% and 48% ee, respectively (entries 4 and 9). As shown in entries 3, 4, 5, and 6, the configuration of the product was largely determined by the stereochemistry of the proton source employed; this could be explained by enantiofacial discrimination in the protonation step.

To our delight, we found that the enantioselectivity was improved in the presence of 2.0 equiv of HMPA (hexamethylphosphoramide).[4h,8,9] Comparing entries 4, 6, 9, and 10 with 11, 12, 13, and 14, the ee values were elevated by 8−20%. These results suggest that the chelation of samarium atom and the oxygen atom in the HMPA may play an important role in the asymmetric protonation process. The exact transition-state model and mechanistic explanation of this study remain unclear at this time.[10] During the experimentation, it was also found that the chiral proton sources used in the reaction can be recovered quantitatively (>95% recovery in the case of entries 12, 13, and 14) and be reused without diminishing the enantioselectivity.

To obtain higher enantiomeric excess, we focused on finding more effective chiral proton sources. Some chiral sulfonamides (Figure 2) were easily prepared from the corresponding chiral amino alcohols and applied to the reaction.

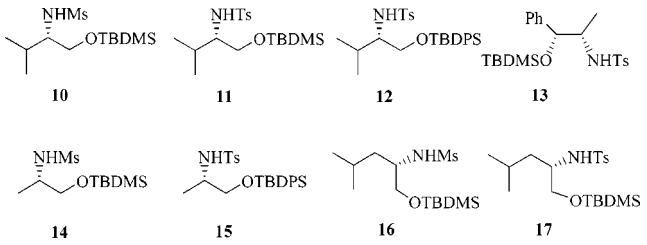


Figure 2.

As shown in Table 2, the chiral α-methyl-γ,γ-diphenyl-γ-butyrolactone was obtained with moderate to good enantiomeric excess in all cases. When **11** was used as the chiral proton source, the enantioselectivity was further improved to give the product in 84% ee as shown in entry 2. It was found that the influence of the substituents on the nitrogen atom of the amine group was important (entries 1−3 and 5−8). Moreover, increasing the size of the hydroxy protecting group led to diminished enantioselectivity (entries 2 and 3).

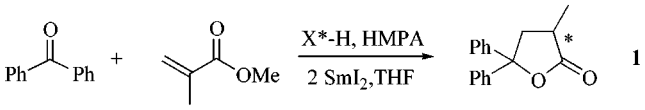
(7) It has been reported that extremely high enantioselectivity (99%) was obtained in the enantioselective protonation of a lithium enolate of a thiol ester by using *N*-isopropylephedrine as a chiral proton source, see: refs 2t and 3h.

(8) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 5763−5764.

(9) The enantioselectivity was lowered when 4.0 equiv of HMPA was used in the reaction. For example, with this amount of HMPA as an additive, only 13% ee was obtained in the case of protonation using **8** as the chiral proton source.

(10) Due to the high oxophilicity and high coordination number of samarium, the chiral proton source, HMPA, and solvent THF are probably coordinated to the samarium ion in the transition state.

Table 2. Synthesis of α-Methyl-γ,γ-diphenyl-γ-butyrolactone by Asymmetric Protonation[11]

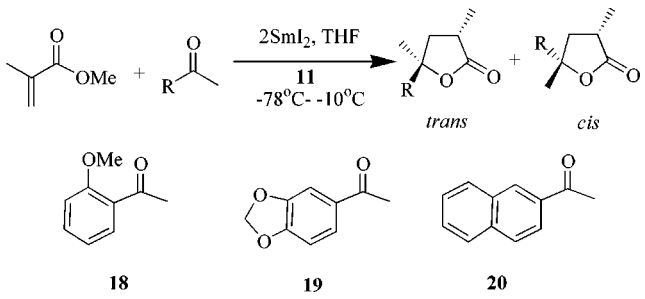


entry	chiral proton source	yield[a] (%)	ee[b] (%)	$[\alpha]_D$ sign
1	**10**	74	70	(+)
2	**11**	65	84	(+)
3	**12**	65	74	(+)
4	**13**	62	57	(+)
5	**14**	61	55	(+)
6	**15**	75	70	(+)
7	**16**	74	55	(+)
8	**17**	52	67	(+)

[a] Isolated yield based on starting material recovery. [b] The ee values were determined by HPLC analysis on a Chiralcel AD column [detected at 254 nm; eluent: *n*-hexane/isopropyl alcohol = 80/20 (v/v)].

The success in synthesis of highly optically active **1** prompted us to extend this new reaction system to the preparation of γ-butyrolactones with two chiral centers, α-C and γ-C. The unsymmetric ketones were examined in the reaction, when **11** was employed as the chiral proton source. The reaction afforded the isomeric products *trans* and *cis* lactones, which could be separated by column chromatography. Table 3 summrizes the results of the asymmetric protonation. The enantioselectivities were not as good as those of benzophenone in the reaction in the case of the two

Table 3. Synthesis of α,γ-Substituted-γ-butyrolactone by Asymmetric Protonation



ketone	yield (%)[b]	*trans*:*cis*[c]	*trans*, ee %[d]	*cis*, ee %[d]
18[a]	82	45/55	63	2
18	95	61/39	20	28
19[a]	82	42/58	4	2
19	91	56/44	17	15
20[a]	66	40/60	4	4
20	89	49/51	15	14

[a] 2.0 equiv of HMPA was added in the reaction. [b] Total isolated yields of *trans* and *cis* products. [c] The ratios of *trans*/*cis* were determined by HPLC. [d] The ee value were determined by HPLC analysis on a Chiralcel OJ, AD column (detected at 254 nm; eluent: *n*-hexane/isopropanol = 80/20 (v/v)).

ketones, except 2′-methoxyacetophenone **18**. In the case of **18**, the ee value of *trans* product was achieved to 63% in the presence of 2.0 equiv of HMPA. It suggests that the structure of the ketones also plays an important role in this reaction.

In the previous study on the absolute configuration of α,γ-substituted-γ-butyrolactones,[5] α-methyl-γ,γ-diphenyl-γ-butyrolactone, made by the reaction of benzophenone with a chiral methacrylate with an "*S*" configuration, gave a "(+)" optical rotation. Therefore, the absolute configurations of the products in Table 2, which also have "(+)" optical rotation, were according assigned as "*S*".

In conclusion, we have developed a new simple methodology for the preparation of optically active α,γ-substituted-γ-butyrolactones via enantioselective protonation of samarium enolates. This provides not only a new strategy for construction of α-carbon chiral centers for γ-butyrolactones[12] but also a new example for studying the asymmetric protonation of samarium enolate. Various chiral proton sources were employed and studied in this reaction, and when benzokentone was employed, a good ee value of 84% was achieved. Further investigations into this process to find more effective chrial proton sources and to prepare chiral α,γ-substituted-γ-butyrolactones are currently underway in our laboratory. On the basis of this new system, future work will be aimed at the catalytic enantioselective protonation for the synthesis of optically active α-substituted-γ-butyrolactones.

Acknowledgment. This work was supported by the National Natural Science Foundation of China (297912045). We thank Zuo-Ding Ding and Min-Hua Tang for chiral HPLC analysis.

OL006429C

(11) **General procedure of the enantioselective protonation in the presence of HMPA:** To samarium metal powder (230 mg, 1.5 mmol) in a Schlenk flask was added a solution of diiodomethane (freshly distilled, 0.081 mL, 1.0 mmol) in THF (5 mL) at room temperature under nitrogen. After approximately 1 h, the color of the mixture solution turned to deep blue, indicating the formation of samarium diiodide. The solution was then cooled to −78 °C, and then a mixture of methyl methacrylate (0.5 mmol), benzophenone (0.5 mmol), and HMPA (1.0 mmol) in THF (3 mL) was added. After 5 min, to the reaction mixture was added a solution of chiral proton source (0.5 mmol) in THF (3 mL). The resulting mixture was stirred for 2 h at the same temperature and then allowed to warm slowly, the reaction was subsequently quenched at −10 °C with 5% aqueous HCl, extracted with diethyl ether, washed with aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The resulting residue was chromatographied on silica gel to afford the optically active γ-butyrolactones. Mp: 118−120 °C. $[\alpha]^{20}_D$ +10.5° (*c* 0.53, $CHCl_3$) for 41% ee {$[\alpha]^{20}_D$ +26.0° (*c* 0.495, $CHCl_3$) for 97% ee, ref 5}. FT-IR (KBr): *ν* 1774, 1451, 1304, 1230, 1191, 1167, 1039, 987, 935, 749, 707 cm^{-1}. ^1H NMR(300 MHz, $CDCl_3$): *δ* 1.27 (d, *J* = 7.0 Hz, CH_3, 3H), 2.47 (t, *J* = 12.1 Hz, 1H), 2.61−2.72 (m, 1H), 3.23 (dd, J_1 = 7.6 Hz, J_2 = 12.3 Hz, 1H), 7.26−7.46 (m, PhH, 10H) ppm. EIMS (*m*/*z*, %): 252 (M^+, 47.47), 224 (1.65), 183 (65.03), 175 (33.28), 115 (15.06), 105 (100.00), 77 (34.11), 42 (12.81). Anal. Calcd for $C_{17}H_{16}O_2$: C 80.93, H 6.39. Found: C 80.73, H 6.50.

(12) One important strategy for preparing α-substituted-γ-butyrolactone is stereoselective alkylation of lithium enolate of γ-butyrolactone, for examples, see: (a) Hanessian, S.; Murray, P. *J. Org. Chem.* **1987**, *52*, 1170−1172. (b) Chamberlin, A. R.; Dezube, M.; Reich, S. H.; Sall, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 6247−6256. (c) Yamazaki, T.; Mizutani, K.; Kiyazume, T. *J. Org. Chem.* **1993**, *58*, 4346−4359. (d) Clive, D. L. J.; Manning, H. W.; Boivin, T. L. B.; Postema, M. H. D. *J. Org. Chem.* **1993**, *58*, 6857−6873. (e) Moritani, Y.; Fukushima, C.; Ukita, T.; Miyagishima, T.; Ohmizu, H.; Iwasaki, T. *J. Org. Chem.* **1996**, *61*, 6922−6930. (f) Pellissier, H.; Michellys, P. Y.; Santelli, M. *J. Org. Chem.* **1997**, *62*, 5588−5591.