ORGANIC LETTERS

2011
Vol. 13, No. 6
1576–1578

Catalytic Enantioselective Synthesis of Chiral γ-Butyrolactones

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Received January 25, 2011

ABSTRACT

A tandem catalytic asymmetric aldol reaction/cyclization of β,γ-didehydro-γ-lactones with aldehydes was achieved using chiral tin dibromide as a chiral precatalyst and sodium alkoxide as a base precatalyst. Optically active *trans*-β,γ-disubstituted γ-butyrolactones were selectively obtained in moderate to high yields with up to 99% ee from γ-aryl-substituted β,γ-didehydro-γ-butyrolactones and bulky aliphatic aldehydes.

Nonracemic γ-lactones are versatile chiral synthons for the synthesis of numerous biologically active natural products or synthetic drugs.[1] To prepare such useful synthetic intermediates, various methods have been developed.[2] Although much effort has been devoted to the enantioselective synthesis of chiral γ-lactones employing a catalytic amount of a chiral promoter,[3] to the best of our knowledge, there are no reports on the catalytic process via an aldol approach.[4] We report here a novel example of the catalytic asymmetric synthesis of optically active γ-butyrolactones from β,γ-didehydro-γ-butyrolactones through a tandem enantioselective aldol reaction/cyclization (Scheme 1).

We have previously reported the asymmetric aldol reaction[5] and the asymmetric Mannich-type reaction[6] using alkenyl trichloroacetates as masked enolates and chiral tin alkoxides as catalysts that are recycled in the presence of alcohol. These addition reactions provide the corresponding optically active β-hydroxy carbonyl compounds and β-amino carbonyl compounds with high enantiomeric excess (ee). However, these methods present the disadvantage that an alcohol is required as an additive in order to recycle the chiral tin alkoxides, in addition to the fact that unnecessary methyl or ethyl trichloroacetate is

(1) (a) Tomioka, K.; Tanaka, M.; Koga, K. *Tetrahedron Lett.* **1982**, *23*, 3401. (b) Ziegler, F. E.; Cain, W. T. *J. Org. Chem.* **1989**, *54*, 3347. (c) Arai, Y.; Kawanami, S.; Koizumi, T. *Chem. Lett.* **1990**, 1585. (d) Braun, M.; Opdenbusch, K.; Unger, C. *Synlett* **1995**, 1174. (e) Ohba, M.; Izuta, R.; Shimizu, E. *Tetrahedron Lett.* **2000**, *41*, 10251. (f) Hilborn, J. W.; Lu, Z.-H.; Jurgens, A. R.; Fang, Q. K.; Byers, P.; Wald, S. A.; Senanayake, C. H. *Tetrahedron Lett.* **2001**, *42*, 8919. (g) Ghosh, A. K.; Swanson, L. *J. Org. Chem.* **2003**, *68*, 9823. (h) Gudipati, V.; Curran, D. P.; Wilcox, C. S. *J. Org. Chem.* **2006**, *71*, 3599. (i) Biswas, K.; Aya, T.; Qian, W.; Peterkin, T. A. N.; Chen, J. J.; Human, J.; Hungate, R. W.; Kumar, G.; Arik, L.; Lester-Zeiner, D.; Biddlecome, G.; Manning, B. H.; Sun, H.; Dong, H.; Huang, M.; Loeloff, R.; Johnson, E. J.; Askew, B. C. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4764. (j) Yang, H.; Qiao, X.; Li, F.; Ma, H.; Xie, L.; Xu, X. *Tetrahedron Lett.* **2009**, *50*, 1110. (k) Ghosh, A. K.; Shurrush, K.; Kulkarni, S. *J. Org. Chem.* **2009**, *74*, 4508.

(2) For a review, see: Mulzer, J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Winterfeldt, E., Eds.; Pergamon: Oxford, 1991; Vol. 6, p 350.

(3) For representative examples of the catalytic enantioselective synthesis of chiral γ-lactones, see: [via hydrogenation] (a) Ohkuma, T.; Kitamura, M.; Noyori, R. *Tetrahedron Lett.* **1990**, *31*, 5509. [via C−H insertion] (b) Doyle, M. P.; van Oeveren, A.; Westrum, L. J.; Protopopova, M. N.; Clayton, T. W., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 8982. [via allylic alkylation](c) Trost, B. M.; Tanimori, S.; Dunn, P. T. *J. Am. Chem. Soc.* **1997**, *119*, 2735. [via Baeyer−Villiger oxidation](d) Bolm, C.; Luong, T. K. K.; Schlingloff, G. *Synlett* **1997**, 1151. (e) Uchida, T.; Katsuki, T. *Tetrahedron Lett.* **2001**, *42*, 6911. (f) Xu, S.; Wang, Z.; Zhang, X.; Zhang, X.; Ding, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 2840. (g) Malkov, A. V.; Friscourt, F.; Bell, M.; Swarbrick, M. E.; Kocovsky, P. *J. Org. Chem.* **2008**, *73*, 3996. [via 1,4-addition](h) Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T. *Tetrahedron: Asymmetry* **1999**, *10*, 4047. (i) Defieber, C.; Paquin, J.-F.; Serna, S.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 3873. (j) Luo, Y.; Carnell, A. J. *Angew. Chem.* **2010**, *122*, 2810. [via kinetic resolution](k) Chen, Y.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 11302. [via 1,4-hydrosilylation] (l) Hughes, G.; Kimura, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11253. (m) Lipshutz, B. H.; Servesko, J. M.; Taft, B. R. *J. Am. Chem. Soc.* **2004**, *126*, 8352.

(4) A catalytic asymmetric synthesis of chiral γ-lactones via the homoaldol approach has been reported: Burke, E. D.; Lim, N. K.; Gleason, J. L. *Synlett* **2003**, 390.

10.1021/ol200232w
Published on Web 02/24/2011

Scheme 1. Chiral Tin-Catalyzed Asymmetric Synthesis of Chiral γ-Butyrolactones

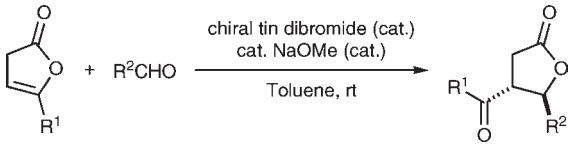
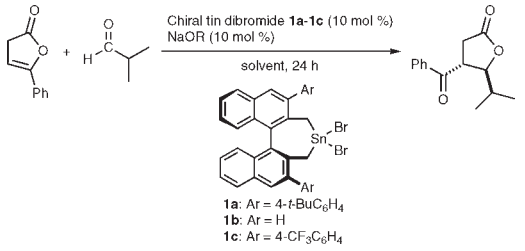


Table 1. Optimization of Tandem Catalytic Asymmetric Aldol Reaction/Cyclization[a]

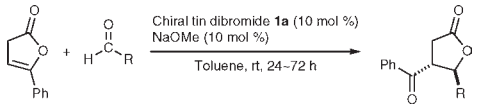


entry	chiral tin dibromide	R	solvent	temp, °C	yield, %[b]	*trans*/*cis*	ee, % (*trans*)[c]
1	**1a**	Et	THF	60	29	>99/1	60
2	**1a**	Me	THF	60	65	>99/1	78
3	**1a**	Me	*t*-BuOMe	60	63	>99/1	84
4	**1a**	Me	Toluene	60	73	>99/1	91
5[d]	**1a**	Me	Toluene	40	78	>99/1	92
6[d]	**1a**	Me	Toluene	rt	84	91/9	94
7[d]	**1b**	Me	Toluene	rt	24	99/1	30
8[d]	**1c**	Me	Toluene	rt	74	95/5	30

[a] Unless otherwise specified, the reaction was carried out using chiral tin dibromide **1a**−**1c** (10 mol %), sodium alkoxide (10 mol %), 5-phenylfuran-2(3*H*)-one (1.2 equiv), and isobutyraldehyde (1 equiv) in the specified solvent at 60 °C, 40 °C, or rt for 24 h. [b] Isolated yield. [c] The value corresponds to the *trans* isomer. Determined by HPLC analysis. [d] The reaction was performed using 1 equiv of 5-phenylfuran-2(3*H*)-one.

generated. We envisaged that if a cyclic alkenyl ester, an unsaturated lactone, could be employed as an enolate precursor in place of an acyclic alkenyl ester, the substrate would undergo the aforementioned chiral tin-catalyzed asymmetric aldol reaction with an aldehyde and the chiral tin alkoxide catalyst would be regenerated in the absence of an alcohol due to the subsequent lactonization of the resulting tin alkoxide of β-hydroxy ketones possessing an ester moiety. Thus, we attempted to react γ-substituted β,γ-didehydro-γ-butyrolactone with aldehyde utilizing chiral tin dibromide **1a** and sodium alkoxide as catalysts, and as a result, the anticipated β,γ-disubstituted γ-butyrolactone was obtained with significant asymmetric induction. For example, when a mixture of 5-phenylfuran-2(3*H*)-one (1.2 equiv) and isobutyraldehyde (1 equiv) was treated with chiral tin dibromide **1a** (10 mol %) and NaOEt (10 mol %) in THF at 60 °C for 24 h, *trans*-dihydro-4-benzoyl-5-isopropylfuran-2(3*H*)-one was obtained

Table 2. Tandem Catalytic Asymmetric Aldol Reaction/Cyclization with Various Aldehydes[a]



entry	R	time, h	yield, %[b]	*trans*/*cis*	ee, % (*trans*)[c]
1	3-$MeOC_6H_4$	27	68	84/16	46
2	(*E*)-PhCH=CH	24	92	77/23	51
3	*n*-C_5H_{11}	23	84	82/18	60
4	Me_2CHCH_2	25	69	82/18	60
5	Me_2CH	24	84	91/9	94
6	Et_2CH	24	55	>99/1	87
7	*c*-C_6H_{11}	24	92	67/33	93
8	*t*-Bu	72	76	>99/1	98

[a] The reaction was carried out using chiral tin dibromide **1a** (10 mol %), sodium methoxide (10 mol %), 5-phenylfuran-2(3*H*)-one (1 equiv), and aldehyde (1 equiv) in toluene at rt for 24−72 h. [b] Isolated yield. [c] The value corresponds to the *trans* isomer. Determined by HPLC analysis.

diastereoselectively in 29% yield (Table 1, entry 1).[7] The product had 60% ee. Then, we tested sodium methoxide instead of sodium ethoxide, and consequently, the first was found to be superior to the last in terms of chemical yield and enantioselectivity (entry 1 vs entry 2). In order to obtain better results, we next tried to optimize the reaction conditions. Among the solvents tested, toluene gave the highest yield and ee (entry 4 vs entries 2 and 3). Decreasing the reaction temperature further improved the chemical yield and the enantioselectivity (entries 5 and 6). Finally, the enantiomeric purity of the product reached 94% ee when the reaction was carried out at room temperature (entry 6). Although we also tested the catalytic ability of chiral tin dibromides **1b** and **1c** under the optimized reaction conditions, as a consequence, **1a** was found to be superior to **1b** and **1c** in terms of chemical yield and enantioselectivity (entry 6 vs entries 7 and 8). The reaction did not proceed at all in the presence of a chiral tin dimethoxide, generated from chiral tin dibromides **1a** (10 mol %) and sodium methoxide (20 mol %).

With the optimal reaction conditions in hand, we examined the catalytic asymmetric lactone synthesis employing various aldehydes (Table 2). A distinct decrease in the *trans*/*cis* ratio as well as the ee of the *trans* product was observed for an aromatic aldehyde and an α,β-unsaturated aldehyde (entries 1 and 2). In contrast, aliphatic aldehydes are more suitable substrates for realizing high enantioselectivity, with the exception of primary alkyl aldehydes (entries 3−8). In particular, use of a bulky aldehyde resulted in the formation of the targeted lactone with 98% ee although a longer reaction time was necessary to obtain a more satisfactory yield (entry 8).

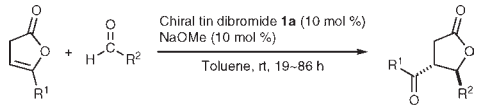
The above-mentioned results prompted us to investigate diverse γ-substituted β,γ-didehydro-γ-butyrolactones in the tandem catalytic asymmetric aldol reaction/cyclization. The results are summarized in Table 3. Not only electron-deficient but also electron-rich aromatic groups

(5) Yanagisawa, A.; Satou, T.; Izumiseki, A.; Tanaka, Y.; Miyagi, M.; Arai, T.; Yoshida, K. *Chem.—Eur. J.* **2009**, *15*, 11450.

(6) Izumiseki, A.; Yoshida, K.; Yanagisawa, A. *Org. Lett.* **2009**, *11*, 5310.

(7) Its relative stereochemistry has been unambiguously determined according to literature: Miller, R. D.; Fickes, G. N. *J. Org. Chem.* **1985**, *50*, 2375.

Table 3. Tandem Catalytic Asymmetric Aldol Reaction/Cyclization with Various γ-Substituted β,γ-Didehydro-γ-butyrolactones and Aldehydes [a]



entry	R^1	R^2	time, h	yield, %[b]	*trans*/*cis*	ee, % (*trans*)[c]
1	4-MeC_6H_4	Me_2CH	23	83	>99/1	88
2	4-PhC_6H_4	Me_2CH	43	64	>99/1	96
3	4-FC_6H_4	Me_2CH	23	76	93/7	94
4	4-BrC_6H_4	Me_2CH	26	81	90/10	99
5	4-$MeOC_6H_4$	*t*-Bu	19	76	>99/1	99
6	4-MeC_6H_4	Me_2PhC	86	60	>99/1	98
7	2-naphthyl	Me_2PhC	22	87	>99/1	94
8	4-$MeOC_6H_4$	$(H_2C{=}CHCH_2)Me_2C$	19	65	>99/1	98
9	2-naphthyl	$(H_2C{=}CHCH_2)Me_2C$	19	82	>99/1	98

[a] The reaction was carried out using chiral tin dibromide **1a** (10 mol %), sodium methoxide (10 mol %), γ-substituted-β,γ-didehydro-γ-butyrolactone (1 equiv), and aldehyde (1 equiv) in toluene at rt for 19−86 h. [b] Isolated yield. [c] The value corresponds to the *trans* isomer. Determined by HPLC analysis.

could be used as the R^1 substituent of the lactones without reducing the isolated yields and the enantioselectivity of the *trans*-isomers, but a small amount of *cis*-isomer was observed in the case of substrates having an electron-withdrawing group (entries 3 and 4). Employment of *tert*-alkyl-substituted aldehydes as electrophiles was effective in raising the level of asymmetric induction in addition to the *trans*/*cis* ratio. In fact, as regards pivalaldehyde, 2-methyl-2-phenylpropanal, and 2,2-dimethylpent-4-enal, nearly exclusive *trans*-selectivity and excellent enantioselectivity of up to 99% ee were observed (entries 5−9). We further investigated the reactivity of a γ-methyl-substituted β,γ-didehydro-γ-butyrolactone; however, the yield of the target lactone was low because of deceleration of the lactonization.

A possible catalytic mechanism is shown in Figure 1. Initially, chiral tin dibromide **1** reacts with an equimolar amount of sodium methoxide to generate the corresponding chiral tin bromide methoxide, which is the key catalyst in the present asymmetric γ-lactone synthesis. Thus formed chiral tin bromide methoxide is then added to β,γ-didehydro-γ-butyrolactone **2** to yield chiral tin enolate **3**. Subsequent aldol reaction between chiral tin enolate **3**

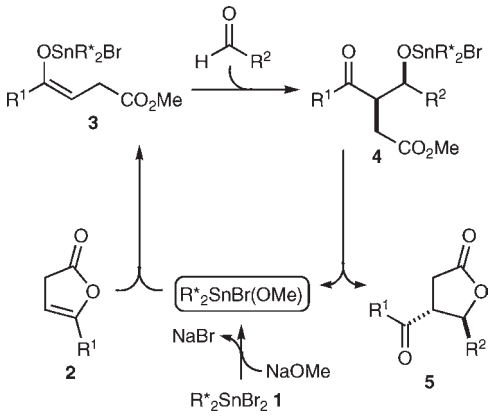


Figure 1. Plausible catalytic cycle for the tandem asymmetric aldol reaction/cyclization.

and an aldehyde gives tin alkoxide of β-hydroxy ketone **4**. Finally, tin alkoxide **4** undergoes cyclization via participation of its ester moiety to afford optically active β,γ-disubstituted γ-butyrolactone **5** with regeneration of the chiral tin bromide methoxide. The methoxycarbonyl group of intermediates **3** and **4** plays a crucial role in the catalytic cycle.

In conclusion, we have developed a novel catalytic asymmetric γ-lactone synthesis in which the enantioselective aldol reaction of γ-substituted β,γ-didehydro-γ-butyrolactone with aldehyde and the lactonization of the resulting tin alkoxide of aldol adduct take place successively. The use of in situ generated chiral tin bromide methoxide as the chiral catalyst realizes the synthesis of various nonracemic β,γ-disubstituted γ-butyrolactones with enantioselectivities of up to 99% ee.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research on Priority Area "Advanced Molecular Transformations of Carbon Resources" from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available. Experimental procedures, spectral data for products in Table 1−3. This material is available free of charge via the Internet at http://pubs.acs.org.