Pergamon

Tetrahedron Letters, Vol. 35, No. 20, pp. 3329-3332, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0574-H

Anti-Selective Asymmetric Aldol Reactions. Enantioselective Synthesis of *anti*-α,β-Dihydroxy Phenyl Ester Derivatives

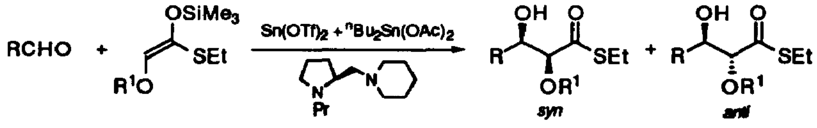
Shū KOBAYASHI* and Takashi KAWASUJI

Department of Applied Chemistry, Faculty of Science,
Science University of Tokyo (SUT), Kagurazaka, Shinjuku-ku, Tokyo 162

Abstract: In the presence of a chiral tin(II) Lewis acid, the silyl enol ether derived from (E)-phenyl α-*t*-butyldimethylsiloxyacetate reacted with aldehydes to afford the corresponding *anti*-aldol adducts, *anti*-α,β-dihydroxy ester derivatives, in high yields with high diastereo- and enantioselectivities.

Optically active 1,2-diol units are often observed as key structures of natural products such as macrolides, polyether antibiotics and carbohydrates, etc. Recently, several enantioselective dioxyosmylations of olefins have been developed to realize practical preparations of some optically active 1,2-diols in high enantiomeric excesses.[1] However, in these methods, basic carbon skeletons must be constructed before the asymmetric oxidations, and preparation of optically active *anti*-1,2-diols still remains as a limitation.

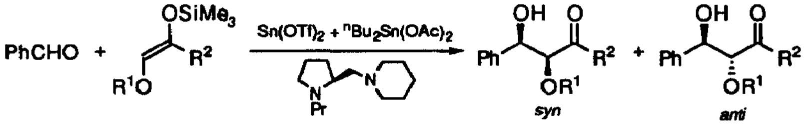
We have recently shown alternative approaches to the synthesis of optically active 1,2-diol units: the asymmetric aldol reaction of the silyl enol ethers derived from α-alkoxy thioesters with aldehydes by using a chiral tin(II) Lewis acid.[2] According to this method, both diastereomers of optically active α,β-dihydroxy thioester derivatives can be prepared in high selectivities by simply choosing the protective group of the alkoxy parts of the silyl enol ethers.



R^1 = TBS, 46-93% yield, *syn*/*anti* = 88/12-97/3, *syn* aldol = 82-94%ee
R^1 = Bn, 59-88% yield, *syn*/*anti* = 9/91- 1/99, *anti* aldol = 95-98%ee

In the course of our investigation to develop more efficient asymmetric reactions as well as to clarify the origin of the high diastereo- and enantioselectivities, we carefully examined the asymmetric aldol reaction of various silyl enol ethers[3] and found a unique effect due to the ester parts of the silyl enol ethers. In this paper, we report the *anti*-selective aldol reaction of the silyl enol ether derived from the phenyl ester derivatives with aldehydes. Some consideration of the origin of the diastereo- and enantioselectivities in this reaction is also described.

Unique selectivities were observed when the silyl enol ether derived from phenyl α-*t*-butyldimethylsiloxyacetate (**1**)[4] was reacted with benzaldehyde in the presence of tin(II) triflate, (S)-1-propyl-2-[(1-piperidin-1-yl)methyl]pyrrolidine, and dibutyltin diacetate. While the *syn*-aldol adduct was obtained in the reaction of the silyl enol ether derived from S-ethyl α-*t*-butyldimethylsiloxyethanethioate under the same reaction conditions,[2a)] the *anti*-aldol adduct was preferentially obtained in the reaction of **1**.



R1	R2	Yield/%	*syn*/*anti*	ee/%
TBS	SEt	86	88/12	90 (*syn*)
TBS	OPh (**1**)	95	6/94	92 (*anti*)

In order to clarify the origin of the unique selectivities as well as to develop efficient synthetic reactions for the preparation of *anti*-diol units, several reaction conditions were screened, and the results are shown in Table 1. While the reactions using (S)-1-alkyl-2-[(1-piperidin-1-yl)methyl]pyrrolidines (**2**-**4**) proceeded with high selectivities, the yields and selectivities were low when (S)-1-methyl-2-[(N-1-naphthylamino)methyl]pyrrolidine (**5**) was used. In general, it was found that the chemical yields were lower in the reaction of **1** except in the case of benzaldehyde. In order to increase the reactivity of the silyl enol ether, we prepared new silyl enolate **6** from p-methoxyphenyl α-*t*-butyldimethylsiloxyacetate. As expected, the reactivities were greatly improved without decreasing the selectivities, and several examples are shown in Table 2. In most cases, the desired *anti*-aldol adducts were obtained in high yields with high diastereo- and

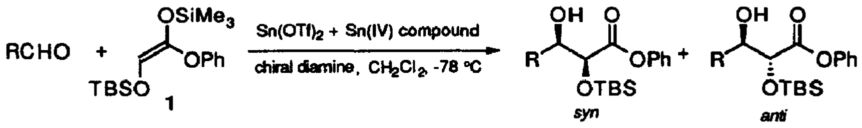
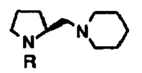


Table 1. *Anti*-Selective Asymmetric Aldol Reaction of **1**

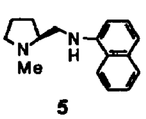
aldehyde	chiral diamine	Sn(IV)	yield/%	*syn*/*anti*	ee/%(*anti*)
PhCHO	**2**	OAc	87	6/94	90
PhCHO	**2**	F	83	3/97	90
PhCHO	**3**	F	51	3/97	93
PhCHO	**4**	F	54	3/97	95
PhCHO	**5**	F	66	53/47	32
	**2**	OAc	61	7/93	96
	**2**	F	40	<2/>98	95

Sn(IV) compound: F = ^{n}Bu$_3$SnF; OAc = ^{n}Bu$_2$Sn(OAc)$_2$

chiral diamine:



2 R = Me **4** R = Pr
3 R = Et



5

enantioselectivities. While a high enantioselectivity was obtained in the reaction of **6** with propionaldehyde, a rather low diastereoselectivity was observed. Trimethylsilylpropynal also worked well to give the adduct, a synthetically useful compound having 1,2-*anti*-diol units and an acetylene group, in good selectivities.[5]

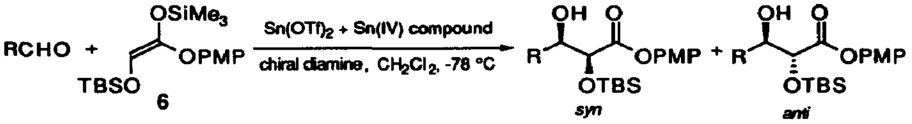
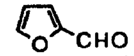
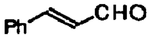


Table 2. *Anti*-Selective Asymmetric Aldol Reaction of **6**

aldehyde	chiral diamine[a]	Sn(IV)[a]	yield/%	*syn/anti*	ee/%(*anti*)
PhCHO	**2**	OAc	95	6/94	92
PhCHO	**2**	F	64	5/95	85
PhCHO	**3**	OAc	91	9/91	93
PhCHO	**4**	OAc	90	10/90	94
	**2**	OAc	92	3/97	94
	**2**	OAc	87	2/98	95
	**2**	OAc	91	7/93	95
Me_3Si—≡—CHO	**2**	OAc	93	22/78	91
C_2H_5CHO	**2**	OAc	31	31/69	84

a) See Table 1.
PMP = p-Methoxyphenyl

Further information about the origin of the selectivities was obtained by examining the effect of the ester part on the selectivities (Table 3). Interestingly, the reactions proceeded with *syn* preference when silyl enol ethers having ethyl ester or S-phenyl ester parts were used. For *anti*-selective reactions, the phenyl ester part (both the oxygen and the phenyl group) is essential.[6]

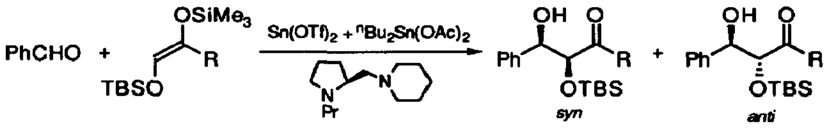


Table 3. Effect of Ester Groups

R	Yield/%	*syn/anti*	ee/% (*syn,anti*)
SEt	86	88/12	90, 65
SPh	12	69/31	88, 62
OPh	87	6/94	nd, 92
OEt	91	75/25	11, 43

nd = not determined

In summary, novel *anti*-selective asymmetric aldol reactions have been developed using a chiral tin(II) Lewis acid. The phenyl ester part of the silyl enol ether employed is essential to obtain the selectivities, and in combination with the previous reported method, it now becomes possible to prepare both *syn*- and *anti*-diol units with construction of new carbon-carbon bonds, by simply choosing the ester parts of the silyl enol ethers.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan.

References and Notes

(1) (a) Crispino, G. A.; Jeong, K. -S.; Kolb, H. C.; Wang, Z. -M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785. (b) Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1993**, *115*, 12579, and references cited therein.

(2) (a) Mukaiyama, T.; Uchiro, H.; Shiina, I.; Kobayashi, S. *Chem. Lett.* **1990**, 1019. (b) Mukaiyama, T.; Shiina, I.; Kobayashi, S. *ibid.* **1991**, 1901.

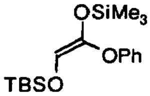
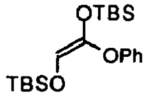
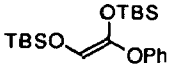
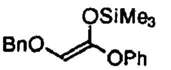
(3) Kobayashi, S.; Kawasuji, T. *Synlett* **1993**, 911.

(4) H. Yamamoto et al. reported catalytic asymmetric aldol reactions of the ketene silyl acetals derived from acetic acid or propionic acid phenyl esters with aldehydes. Furuta, K.; Maruyama, T.; Yamamoto, H. *Synlett* **1991**, 439. See also, Kiyooka, S.; Kaneko, Y.; Kume, K. *Tetrahedron Lett.* **1992**, *33*, 4927; Parmee, E. R.; Tempkin, O.; Masamune, S.; Abiko, A. *J. Am. Chem. Soc.* **1991**, *113*, 1041.

(5) A typical experimental procedure is described for the reaction of **6** with benzaldehyde: To a suspension of tin(II) triflate (0.4 mmol) in dichloromethane (0.5 ml) were added chiral diamine **2** (0.48 mmol) in dichloromethane (0.5 ml) and dibutyltin diacetate (0.44 mmol) successively at room temperature. The mixture was stirred for 30 min at rt and then cooled to -78 °C. Dichloromethane solutions (0.5 ml each) of **6** (0.4 mmol) and benzaldehyde (0.36 mmol) were successively added and the mixture was stirred for 20 h. Sat. aqueous sodium hydrogen carbonate was added to quench the reaction, and after a usual work up, p-methoxyphenyl 2-*t*-butyldimethylsiloxy-3-hydroxy-3-phenylpropanate was obtained in 95% yield (*syn*/*anti* = 6/94). The enantiomeric excess of the *anti* aldol was determined to be 92% by using Daicel CHIRALCEL OD.

(6) The effects of the geometry, substituents on the silicon, and the α-alkoxy part of the silyl enol ethers of the phenyl esters are summarized in Table 4 (tin(II) triflate, chiral diamine **2**, dibutyltin diacetate; dichloromethane, -78 °C).

Table 4. Effect of the Silyl Enol Ethers

silyl enol ether	Yield/%	*syn*/*anti*	ee/% (*syn*,*anti*)
	87	6/94	nd, 90
	72	4/96	nd, 89
	26	79/21	3, 82
	91	29/71	66, 78

nd = not determined

(*Received in Japan* 21 *January* 1994)