

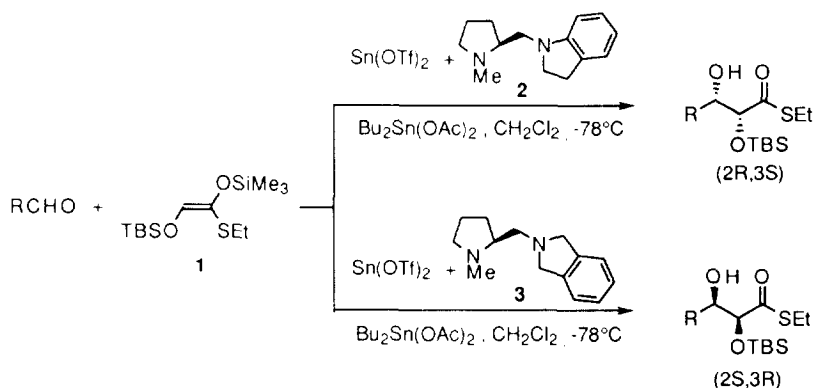
Chiral Tin(II) Lewis Acid-Mediated Enantioselective Aldol Reactions: Synthesis of Both Enantiomers Using Similar Types of Chiral Sources¹

Shū Kobayashi* and Mineko Horibe

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

Abstract: Chiral tin(II)-Lewis acid-mediated aldol reactions of various enolates with an aldehyde were investigated by using chiral diamine **2**. Based on these reactions, both enantiomers of aldol adducts were prepared using similar types of chiral sources.

In the field of asymmetric synthesis, the preparation of both enantiomers in high selectivities is one of the most fundamental and important goals.² Although traditional methods have required sources of enantiomeric precursors, auxiliaries, or catalysts, both enantiomers of the sources are often hard to obtain (for example, alkaloids, amino acids, sugars, etc.). As a solution to this problem, we have previously shown that both enantiomers including 1,2-diol units can be prepared with almost perfect stereochemical control by using similar types of chiral sources in the aldol reactions of silyl enol ether **1** with aldehydes (Scheme 1).³ While the aldol adduct with a 2R, 3S absolute configuration was obtained by using chiral diamine **2**, the



Scheme 1.

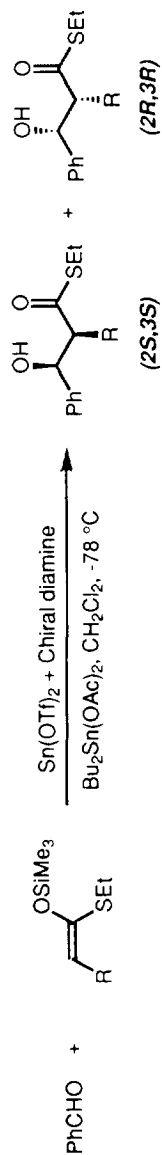
aldol adduct with the reverse absolute configuration (2*S*, 3*R*) was produced by using chiral diamine **3**. After testing several chiral diamines, the unique selectivities were found to be dependent on chiral diamine **2**. We then evaluated the function of **2** using several enolates other than **1**, and the results are summarized in this report.

When 1-ethylthio-1-trimethylsiloxypropene **4** was treated with benzaldehyde in the presence of tin(II) triflate, chiral diamine **2**, and Bu₂Sn(OAc)₂ in dichloromethane at -78 °C, the corresponding aldol adduct was obtained in a 90% yield (*syn/anti* = 93/7), and the enantiomeric excess of the *syn* adduct was 30% with a 2*R*, 3*R* configuration. Although the enantioselectivity was moderate, the absolute configuration of the major adduct was the reverse of that obtained using most chiral diamines derived from L-proline.⁴ The selectivity was improved when chiral diamine **5** was used. Furthermore, we found that the α -substituent of the silyl enol ether influenced the enantioselectivity when chiral diamine **5** was used, and that larger alkyl groups gave better results. On the other hand, excellent *syn* selectivities and enantioselectivities with a reverse absolute configuration were obtained by using chiral diamine **6** (Table 1).⁴

We then tested other silyl enol ethers and the results are summarized in Table 2. When silyl enol ether **7** was used, the reaction proceeded with *anti* preference in a moderate enantiomeric excess, and the absolute configuration of the *anti* adduct was the reverse of that obtained using chiral diamine **8**.⁵ Higher selectivities were obtained when silyl enol ether **9** was used. The *anti* adduct with a reverse absolute configuration was prepared in 93% ee by using chiral diamine **6** in the same reaction. The effect of the α -substituents of the enolates on the diastereo- and enantioselectivities is obvious from the result that only 15% ee was obtained using the silyl enol ether derived from *S*-ethyl ethanethioate. The reverse enantioselectivities were not observed in the reactions of silyl enol ethers **10-12**. It is noted that completely reversed enantioselectivities were observed between silyl enol ethers **1** and **11** by using the same chiral diamine (**2**).⁶

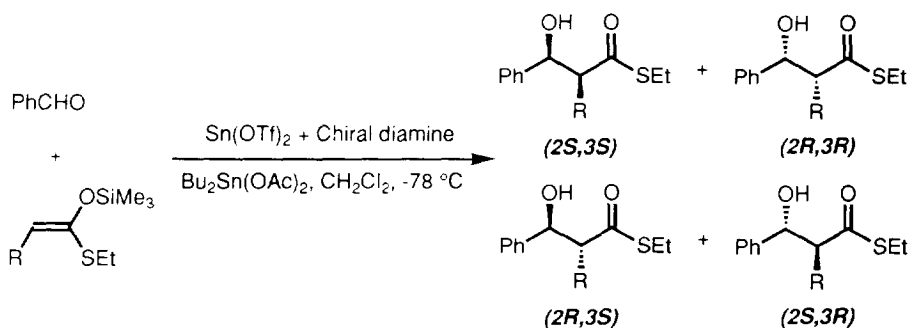
A typical experimental procedure is described for the reaction of **9** with benzaldehyde. To a suspension of tin(II) triflate (0.4 mmol) in dichloromethane (0.5 ml) were added chiral diamine **2** or **6** (0.48 mmol) in dichloromethane (0.5 ml) and dibutyltin diacetate (0.44 mmol) successively at room temperature. The mixture was then cooled to -78 °C and dichloromethane solutions (0.5 ml each) of **9** (0.4 mol) and benzaldehyde (0.27 mmol) were successively added. The mixture was stirred for 21 h, and then saturated NaHCO₃ was added to quench the reaction. After a usual work up, the crude product was chromatographed on silica gel to give *S*-ethyl 2-*S*-*t*-butyl-3-hydroxy-3-phenylpropanethioate. The diastereomers were separated⁷ and the optical purity was determined by HPLC using a chiral column.

In summary, we evaluated chiral diamine **2** in the asymmetric aldol reactions of various silyl enol ethers with an aldehyde. Both enantiomers of *syn* or *anti* adducts were prepared in the reactions of some silyl enol ethers by choosing similar types of chiral sources. In these reactions, it is postulated that the chiral tin(II) Lewis acid coordinates and activates the aldehyde, and excellent asymmetric fields are created at this stage. The findings from these

Table 1. The Asymmetric Aldol Reactions of α -Alkyl Silyl Enolates

	Yield (%)	syn/anti (%)	ee ^{a)} (%)	Yield (%)	syn/anti (%)	ee ^{a)} (%)	Yield (%)	syn/anti (%)	ee ^{a)} (%)
	90	93/7	30*	73	97/3	45*	98	99/1	66
	83	91/9	22*	84	92/8	45*	88	98/2	65
	84	94/6	27*	62	92/8	59*	85	>99/1	73
	73	97/3	17*	44	92/8	63*	86	96/4	76
							85	>99/1	>98
							97	>99/1	95
							92	>99/1	96
							77	>99/1	97

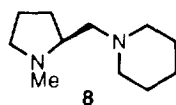
a) Major enantiomers; 2*S*, 3*S* without asterisk, and 2*R*, 3*R* with asterisk.

**Table 2.** Synthesis of Both Enantiomers

	Diamine	Yield (%)	<i>syn/anti</i>	ee (%) ^{a)}
 1	2	82	99/ 1	98 *
	3	80	99/ 1	98
 4	2	90	93/ 7	30 *
	6	85	>99/ 1	>99
 7	2	77	20/80	41 *
	8	95	6/94	92
 9	2	68	19/81	83 *
	6	80	24/76	93
 10	2	83	—	15 *
	6	52	—	92
 11	2	77	38/62	35
	2	85	95/ 5	91
 12	2	40	—	56
	2	40	—	56

a) Major enantiomers; 3S without asterisk, and 3R with asterisk.

PMP = *p*-Methoxyphenyl

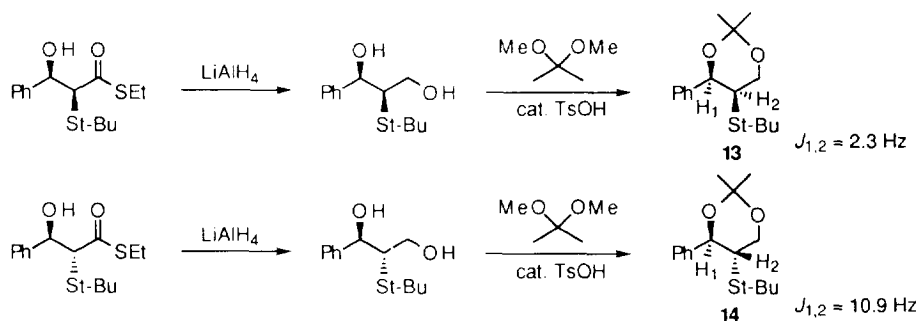


experiments now indicate that the three components, the chiral Lewis acid, aldehydes, and enolates, should all be considered in the transition states to determine the reaction course.⁸

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

References and Notes

- (1) Presented partly at Anglo-Japanese Conference on Asymmetric Synthesis, which was held at Wadham College, Oxford on July 21st-23rd, 1995.
- (2) (a) Stinson, S. C. *Chem. Eng. News* **1993**, Sept. 27, 38. (b) Narasaka, K. *Synthesis* **1991**, 1. (c) Quite recently, we developed a new method for preparation of both enantiomers by using a single chiral source and a choice of achiral ligands in the chiral lanthanide(III)-catalyzed Diels-Alder reactions. Kobayashi, S.; Ishitani, H. *J. Am. Chem. Soc.* **1994**, *116*, 4083; Kobayashi, S.; Ishitani, H.; Hachiya, I.; Araki, M. *Tetrahedron* **1994**, *50*, 11623.
- (3) Kobayashi, S.; Horibe, M. *J. Am. Chem. Soc.* **1994**, *116*, 9805.
- (4) Kobayashi, S.; Uchiro, H.; Fujishita, Y.; Shiina, I.; Mukaiyama, T. *J. Am. Chem. Soc.*, **1991**, *113*, 4247.
- (5) Kobayashi, S.; Kawasuji, T. *Tetrahedron Lett.* **1994**, *35*, 3329.
- (6) Kobayashi, S.; Hayashi, T. *J. Org. Chem.* **1995**, *60*, 1098.
- (7) The *syn*- and *anti*-adducts were converted to the corresponding ethers (**13** and **14**), respectively. The relative configuration assignments were confirmed by ¹H NMR analysis (see below).



- (8) Full accounts will be reported in near future.

(Received in UK 7 August 1995; accepted 7 September 1995)