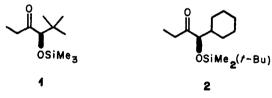
## ACYCLIC STEREOSELECTION. 35. EFFECT OF CATION ON DIASTEREOFACIAL SELECTIVITY IN ALDOL REACTIONS OF A CHIRAL $\sim$ -SILYLOXY KETONE.<sup>1</sup>

Clayton H. Heathcock\* and Simeon Arseniyadis<sup>2</sup> Department of Chemistry, University of California Berkeley, California 94720

**Abstract:** By an appropriate choice of cation, three of the four possible aldols from the reactions of the chiral  $\alpha$ -silyloxy ketone 1 with aldehydes may be obtained. The <u>Z</u> lithium enolate provides 6, the <u>Z</u> boron enolate gives 7, and the <u>E</u> magnesium enolate affords 8.

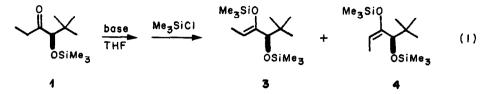
Some time ago we reported the preparation and a study of the aldol reactions of the chiral  $\alpha$ -silyloxy ketone 1.<sup>3</sup> Compound 1 was found to show modest diastereofacial selectivity in the reactions of its lithium enolate with prochiral aldehydes and high diastereofacial selectivity, with mutual kinetic resolution, in its reactions with several chiral aldehydes.<sup>3-5</sup> Masamune and coworkers have carried out independent investigations of double asymmetric induction in the aldol reaction,<sup>6</sup> introduced the related ketone 2, demonstrated that its dialkylboron enolates show excellent diastereofacial selectivity,<sup>7</sup> and employed the enantiomerically-homogeneous form of 2, prepared in three simple steps from mandelic acid, in an elegant total synthesis of 6-deoxyerythronolide B.<sup>8,9</sup>



In this Letter, we report the results of a study of the effect of cation on the stereochemistry of the aldol reactions of 1.

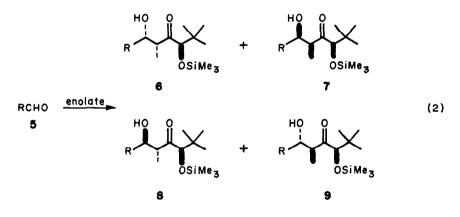
The lithium enolate of 1 was prepared by addition of the ketone to a solution of lithium diisopropylamide in tetrahydrofuran (THF) at -78 <sup>o</sup>C. Addition of trimethylsilyl chloride (TMSCl) and workup in the conventional manner

provided a 96:4 mixture of  $\underline{Z}$  and  $\underline{E}$  enolsilanes 3 and 4 (eq 1).



Treatment of 1 with bromomagnesium isopropylcyclohexylamide in THF at -30  $^{\circ}$ C, followed by silylation with TMSC1 gave the <u>Z</u> and <u>E</u> enolsilanes in a ratio of 9:91 (eq 1).<sup>10</sup> The di-<u>n</u>-butylboron enolate of 1, presumably <u>Z</u>, was prepared by reaction of the ketone with di-<u>n</u>-butylboron triflate and diethylisopropylamine in methylene chloride.<sup>11</sup>

Aldol reactions of the lithium and boron enolates of 1 were carried out by literature procedures.<sup>4,7</sup> The magnesium enolate reactions were carried out in THF (0.3 M enolate, 0.33 M aldehyde) at -78 °C for 20 min; reaction was quenched by the addition of aqueous sodium bicarbonate at -78 °C. The aldehydes employed were isobutyraldehyde (5a) and benzaldehyde (5b). The four diastereomeric aldols that may be produced from 1 and an aldehyde are shown in eq 2. Results



**a**: R = i - Pr, **b**: R = Ph

of the investigation are summarized in Table 1. Stereostructures of the four aldols in the benzaldehyde series (6b-9b) were determined in the following manner. The structure of 6b, the major isomer obtained in the lithium enolate reactions has been assigned previously.<sup>4</sup> On the basis of Masamune's work with the related ketone  $2,^7$  we have assigned the major isomer obtained in the boron

Stereoch	emistry of	E Reaction	of Keton	e 1 with	h Aldehy	ydes (1	Eq 2)
Config.			P	Product Composition			Yield,
Enolate	<u>Z:E</u>	Aldehyde	6	7	8	9	ß
Lithium	96:4	 5a	88	12	0	0	70
Lithium	96:4	5b	84	16	0	0	75
Magnesium	9:91	5a	11	11	64	14	72
Magnesium	9:91	5b	10	10	70	10	70
Boron	a	5a	10	90	0	0	70
Boron	a	5b	7	93	0	0	70

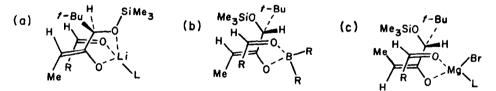
 Table 1

 eochemistry of Reaction of Ketone 1 with Aldehydes (Edited and Statemark Stress)

(a) The enolborinate geometry was not determined, but is presumed to be largely  $\underline{Z}$  on the basis of prior work (ref 7, 10).

enolate reaction structure 7. The major isomer obtained in the magnesium enolate reaction was determined to have structure 8b by single crystal x-ray analysis of the corresponding dihydroxy ketone, mp 85-86 <sup>O</sup>C.

It is interesting that three of the four possible aldols can be selected as the major product of the reaction of 1 by a simple choice of cation. As has previously been pointed out,<sup>12</sup> the stereochemistry observed in the aldol reactions of 1-lithium enolate may be explained by invoking the chelated enolate, which reacts on its less hindered <u>re</u> face (Figure 1a), while that seen in the aldol reactions of 1-boron enolate seem to result from reaction on the unchelated boron enolate, which reacts preferentially on its <u>si</u> face (Figure 1b).



**Figure 1:** (a) Approach of an aldehyde to the <u>re</u> face of the chelated Z lithium enolate of ketone 1. (b) Approach of an aldehyde to the <u>si</u> face of the unchelated Z boron enolate of ketone 1. (c) Approach of an aldehyde to the <u>si</u> face of the unchelated <u>E</u> magnesium enolate of ketone 1.

The magnesium enolate of 1 is "boron-like" in its diastereofacial preference; reaction occurs on its <u>si</u> face. However, since the major enolate has the E configuration, the predominant product is 8, rather than 7. Thus, the magnesium must not be chelated by the trimethylsilyloxy group during the aldol process (Figure 1c). 6012

**ACKNOWLEDGEMENT:** This work was supported by a research grant from the United States Public Health Service (AI15027).

## References and Notes

1. For part 34, see: Heathcock, C. H.; Uehling, D. E. J. Org. Chem., in press.

2. Current address: ICSN, CNRS, 91190 Gif Sur Yvette, France.

3. Heathcock, C. H.; Pirrung, M. C.; Buse, C. T.; Hagen, J. P.; Young, S. D.; Sohn, J. E. <u>J. Am. Chem. Soc.</u>, **1979**, <u>101</u>, 7077.

4. Heathcock, C. H.; Pirrung, M. C.; Lampe, J.; Buse, C. T.; Young, S. D. <u>J.</u> Org. Chem., 1981, <u>46</u>, 2290.

5. Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pilli, R.; Badertscher, U. <u>J.</u> <u>Org. Chem.</u>, **1985**, <u>50</u>, 2095.

6. Masamune, S.; Ali, S. A.; Snitman, D. L.; Garvey, D. S. <u>Angew. Chem. Int.</u> Ed. Engl., 1980, 19, 557.

7. Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. <u>J. Am. Chem. Soc.</u>, 1981, <u>103</u>, 1566.

8. Masamune, S.; Hirama, M.; Mori, S.; Ali, S. A.; Garvey, D. S. <u>J. Am. Chem.</u> Soc., 1981, <u>103</u>, 1568.

9. See also: Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. Angew. Chem. Int. Ed. Engl., 1985, 24, 1.

10.  $\alpha$ -Alkoxy ketones show a remarkable tendency toward formation of E enolates upon reaction with bromomagnesium isopropylcyclohexylamide. Thus, the trimethylsilyl ether of 2-hydroxy-2-methyl-3-pentanone is converted into a 67:33 mixture of E and Z enolsilanes by the same procedure. A full investigation of this phenomenon is underway.

11. (a) Fenzl, W.; Köster, R. Liebigs Ann. Chem., 1975, 1322. (b) Masamune, S.; Mori, S.; Van Horn, D.; #rooks, D. W. Tetrahedron Lett., 1979, 1665. (c) Evans, D. A.; Vogel, E.; Nelson, J. V. J. Am. Chem. Soc., 1979, 101, 6120. (d) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. J. Am. Chem. Soc., 1981, 103, 3099.

12. (a) Heathcock, C. H. "Asymmetric Reactions and Processes in Chemistry";
Eliel, E. L.; Otsuka, S., Eds.; American Chemical Society: Washington, D.C.,
1982. (b) Heathcock, C. H. "Asymmetric Synthesis, Volume 3"; Morrison, J. D.,
Ed.; Academic Press, Inc.: New York, 1984.

(Received in USA 1 August 1985)