

**ACYCLIC STEREOSELECTION. 27. SIMPLE DIASTEREOSELECTION  
 IN THE LEWIS ACID MEDIATED REACTIONS OF ENOLSILANES WITH ALDEHYDES.<sup>1</sup>**

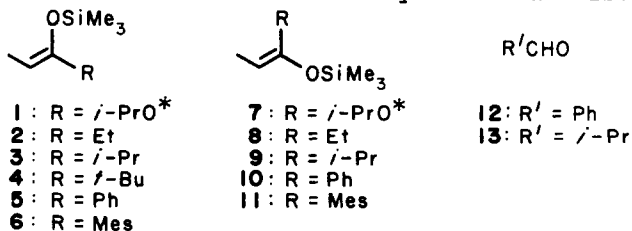
Clayton H. Heathcock\*, Kathleen T. Hug and Lee A. Flippin<sup>2</sup>

Department of Chemistry, University of California  
 Berkeley, California 94720

**Abstract:** The Lewis acid mediated reactions of enolsilanes 1-11 with benzaldehyde and isobutyraldehyde have been investigated. With the exception of compound 4, essentially no stereoselectivity is observed.

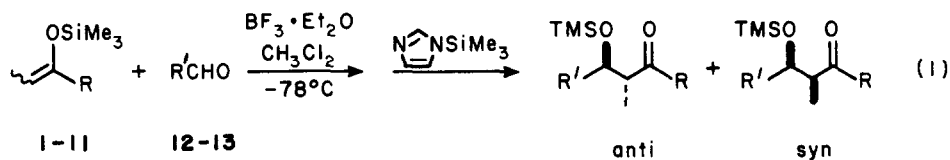
The stereochemistry of reaction of various preformed metal enolates with aldehydes has been well-studied.<sup>3</sup> Much less is known about simple diastereoselection in the related reaction of enol ethers with aldehydes under conditions of acid catalysis. The little information that is available comes from a single study by Chan and coworkers, who investigated the TiCl<sub>4</sub>-mediated reactions of E and Z enolsilanes derived from ethyl propionate with benzaldehyde,<sup>4</sup> from a study by Noyori and coworkers of the trimethylsilyl triflate-catalyzed reactions of enolsilanes with acetals,<sup>5</sup> and from Reetz and coworkers, whose studies have concerned mainly the Lewis acid-mediated reactions of enolsilanes with α- and β-alkoxy aldehydes.<sup>6</sup> These studies reveal no consistent pattern. In the Chan work<sup>4</sup> it was found that the Z enolsilane derived from ethyl propionate is unselective, giving anti/syn ratios in the range 2:1 to 1:1. However, the corresponding E enolsilane was found to be much more selective, giving anti/syn ratios of 3:1 to >100:1.<sup>7</sup> On the other hand, for the acetal reactions, Noyori and coworkers report syn-selectivity, regardless of enolsilane geometry; syn/anti ratios of 2:1 to 32:1 are reported.<sup>8</sup> Reetz and coworkers report that the Z enolsilane 5 reacts with chiral α-alkoxy aldehydes to give both excellent simple diastereoselection (syn) and high diastereofacial selectivity (chelation-controlled).<sup>6</sup>

To further examine this point, we have carried out an investigation of the reactions of enolsilanes 1-11 with benzaldehyde (12) and isobutyraldehyde (13)

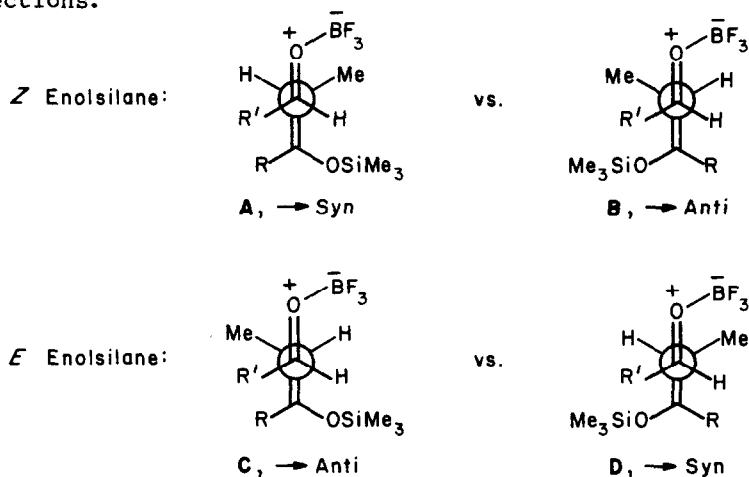


\*In these cases the *i*-butyldimethylsilyl ether was used.

(eq 1). This group of eleven enolsilanes includes five diastereomeric pairs. Reactions were carried out in methylene chloride at  $-78^{\circ}\text{C}$ ;  $\text{BF}_3$ -etherate, stannic chloride, and titanium tetrachloride were employed as Lewis acids. Data are presented in Table 1.



As shown in the Table, there is essentially no stereoselectivity with any of the enolsilanes studied, except the *t*-butyl derivative 4. We believe that the results are in best accord with an open transition state, for two reasons. First, enolsilane 4 shows high anti-selectivity, while the analogous lithium and magnesium enolates react with even higher syn-selectivity. Since the latter reactions almost certainly proceed via a cyclic transition state,<sup>3</sup> it follows that the enolsilane reactions probably do not. Second, the fact that similar stereorations are observed with  $\text{BF}_3$ ,  $\text{SnCl}_4$ , and  $\text{TiCl}_4$  suggests that the Lewis acid is not intimately involved with the silyloxy group in the transition state for the reaction. The data may be explained with the aid of the following Newman projections.



We start with the assumption that the Lewis acid occupies a coordination site on the aldehyde oxygen *cis* to the hydrogen<sup>6e,11</sup> and that the presence of this ligand destabilizes gauche transition states A and D. Further destabilizing interactions are R:R in transition states A and C and R:OSiMe<sub>3</sub> in transition

**TABLE 1**  
Diastereomer Ratios in the Reactions of Enolsilanes  
with Aldehydes (Eq 1)

Entry	Enolsilane	Aldehyde	Lewis Acid	Z/E Ratio	% Yield	Isomer Ratio, anti/syn <sup>j</sup>
1	1	12	SnCl <sub>4</sub>	100:0 <sup>a</sup>	42	63:37
2	2	12	BF <sub>3</sub> ·Et <sub>2</sub> O	100:0 <sup>b</sup>	62	40:60
3	3	12	BF <sub>3</sub> ·Et <sub>2</sub> O	97:3 <sup>c</sup>	57	44:56
4	3	13	BF <sub>3</sub> ·Et <sub>2</sub> O	97:3 <sup>c</sup>	83	44:56 <sup>e,k</sup>
5	3	13	SnCl <sub>4</sub>	97:3 <sup>c</sup>	70	45:55 <sup>k</sup>
6	3	13	TiCl <sub>4</sub>	97:3 <sup>c</sup>	68	54:46 <sup>k</sup>
7	4	12	BF <sub>3</sub> ·Et <sub>2</sub> O	100:0 <sup>d</sup>	95	>95:5
8	4	12	SnCl <sub>4</sub> <sup>d</sup>	100:0 <sup>d</sup>	72	>95:5
9	4	12	TiCl <sub>4</sub> <sup>d</sup>	100:0 <sup>d</sup>	53	>95:5
10	4	13	BF <sub>3</sub> ·Et <sub>2</sub> O	100:0 <sup>d</sup>	84	>95:5 <sup>e</sup>
11	4	13	SnCl <sub>4</sub>	100:0 <sup>d</sup>	60	>95:5
13	4	13	TiCl <sub>4</sub>	100:0 <sup>d</sup>	65	>95:5
14	5	12	BF <sub>3</sub> ·Et <sub>2</sub> O	100:0 <sup>d</sup>	63	53:47
15	6	12	SnCl <sub>4</sub>	100:0 <sup>f</sup>	62	72:28
16	7	12	SnCl <sub>4</sub>	11:89 <sup>a</sup>	48	70:30
17	8	12	BF <sub>3</sub> ·Et <sub>2</sub> O	14:86 <sup>g</sup>	52	43:57
18	9	12	BF <sub>3</sub> ·Et <sub>2</sub> O	0:100 <sup>c</sup>	71	65:35
19	9	13	BF <sub>3</sub> ·Et <sub>2</sub> O	0:100 <sup>c</sup>	77	30:70 <sup>e,k</sup>
20	9	13	SnCl <sub>4</sub>	0:100 <sup>c</sup>	81	42:58 <sup>k</sup>
21	9	13	TiCl <sub>4</sub>	0:100 <sup>c</sup>	73	34:66 <sup>k</sup>
22	10	12	BF <sub>3</sub> ·Et <sub>2</sub> O	0:100 <sup>h</sup>	52	70:30
23	11	12	SnCl <sub>4</sub>	7:93 <sup>i</sup>	70	72:28

a. Prepared by the method of Ireland, Mueller and Willard, *J. Am. Chem. Soc.*, **98**, 2868 (1976). b. Prepared by the method of Kuwajima, Nakamura and Hashimoto (ref. 10). c. Prepared by treatment of 2-methyl-3-pentanone with LDA and Me<sub>3</sub>SiCl; the E and Z enolsilanes were separated by preparative HPLC. d. Prepared by treatment of the appropriate ketone with LDA and Me<sub>3</sub>SiCl; only the Z enolsilane is produced. e. In this case, the aldehyde and enolsilane were premixed before addition of the Lewis acid at -78 °C. f. Prepared by treatment of ethyl mesityl ketone with potassium bis(trimethylsilylamide) and Me<sub>3</sub>SiCl in THF. g. Prepared by treatment of 3-pentanone with LTMP and Me<sub>3</sub>SiCl. h. Prepared by treatment of propiophenone with lithium bis(trimethylsilyl)amide and Me<sub>3</sub>SiCl; the resulting 70/30 mixture of Z and E isomers was separated by preparative HPLC. i. Prepared by treatment of ethyl mesityl ketone with LDA and Me<sub>3</sub>SiCl in ether. j. Unless otherwise stated, ratios were determined by 250 MHz <sup>1</sup>H NMR and 62.9 MHz <sup>13</sup>C NMR. In several cases the crude reaction product was silylated with trimethylsilylimidazole prior to analysis. k. Ratios were determined by capillary gc.

states B and D. Thus, for most of the reactions studied, there would not be a clear bias for either transition state. However, in the Z series, the anti diastereomer might be expected to predominate because of the large R:R interaction in transition state A. It has been shown by Reetz and coworkers<sup>6</sup> when the Lewis acid is forced to occupy the other ligation site on oxygen by chelation to a nearby alkoxy group, a very different stereoselectivity pattern is seen. We have made similar observations and will report fully in our full paper on the subject.

**ACKNOWLEDGEMENT:** This work was supported by a research grant from the United States Public Health Service (AI15027). We thank Mr. Mark Norman for preparing enolsilanes 3, 6, 9 and 11.

### References and Notes

1. For part 26, see C.H. Heathcock, D.L. Bai, H.-P. Märki, and K. Kees, *J. Org. Chem.*, submitted for publication.
2. Current address: Department of Chemistry, Northeastern University, Boston, MA 02115
3. For recent reviews, see (a) C.H. Heathcock in *Asymmetric Syntheses, Volume 3*, J.D. Morrison, Ed., Academic Press, 1984; (b) C.H. Heathcock in *Comprehensive Carbanion Chemistry, Vol. 2*, E. Buncl and T. Durst, Eds., Elsevier, 1984; (c) D.A. Evans, J.V. Nelson and T.R. Taber in *Topics in Stereochemistry, Volume 13*, N.L. Allinger, E.L. Eliel and S.H. Wilen, Eds., Wiley-Interscience, New York, 1982.
4. T.H. Chan, T. Aida, P.W.K. Lau, V. Gorys and D.N. Harpp, *Tetrahedron Lett.*, 4029 (1979).
5. S. Murata, M. Suzuki and R. Noyori, *J. Am. Chem. Soc.*, **102**, 3248 (1980).
6. (a) M.T. Reetz, K. Kessler, S. Schmidtberger, B. Wenderoth, and R. Steinbach, *Angew. Chem. Int. Ed. Engl.*, **22**, 989 (1983); (b) *Angew. Chem. Suppl.*, 1511 (1983); (c) M.T. Reetz, K. Kessler, and A. Jung, *Tetrahedron Lett.*, 729 (1984); (d) M.T. Reetz and K. Kessler, *J. Chem. Soc., Chem. Commun.*, 1079 (1984); (e) M.T. Reetz, *Angew. Chem. Int. Ed. Engl.*, **23**, 556 (1984); (f) M.T. Reetz, K. Kessler, and A. Jung, *Tetrahedron*, in press.
7. The reported anti/syn ratios from an 85/15 mixture of *E* and *Z* enolsilanes for benzaldehyde, hexanal, and isobutyraldehyde are 74:26, 89:11, and 92:8, respectively (ref. 4). These raw data may be corrected by the known anti/syn selectivities of the pure *Z* enolsilane, which are 2:1, 1:1, and 1:1, respectively, for the three aldehydes.
8. A close examination of the Noyori work suggests that the stereostructures of the products resulting from the reaction of ethyl *t*-butyl ketone enolsilane with benzaldehyde have been misassigned. The spectral data reported for the major isomer (see ref. 5, **Supplementary Material**) are similar to those found for the trimethylsilyl ether of the anti compound, and quite different from those found for the syn ether.<sup>9</sup>
9. C.H. Heathcock and J. Lampe, *J. Org. Chem.*, **48**, 4330 (1983).
10. I. Kuwajima, E. Nakamura and K. Hashimoto, *Organic Syntheses*, **61**, 122 (1983).
11. C.H. Heathcock and L.A. Flippin, *J. Am. Chem. Soc.*, **105**, 1667 (1983).

(Received in USA 10 November 1984)