

of General Medical Sciences) through Grant GM-29028 and by Merck Sharp and Dohme. In addition, we thank S. T. Bella of the Rockefeller University for the microanalyses and Drs. G. Furst and T. Terwilliger of the University of Pennsylvania Spectroscopic Service Centers for aid in recovering and interpreting the high-field NMR and mass spectra, respectively.

Registry No. (\pm)-1a, 82079-52-5; (\pm)-1b, 82079-53-6; (\pm)-1c, 82045-35-0; (\pm)-1d, 82079-54-7; (\pm)-3a, 82045-36-1; (\pm)-3b, 82109-85-1; 4a, 82045-37-2; 4b, 82045-38-3; (\pm)-5, 82045-39-4; (\pm)-6, 82045-40-7; (\pm)-7, 82045-41-8; 8, 6880-04-2; (\pm)-9, 82045-42-9; 10, 82045-43-0; (\pm)-11a, 82045-44-1; (\pm)-11b, 82045-45-2; (\pm)-12, isomer 1, 82045-46-3; (\pm)-12, isomer 2, 82045-47-4; (\pm)-13, isomer 1, 82045-48-5; (\pm)-13, isomer 2, 82079-55-8; (\pm)-13, isomer 3, 82079-56-9; (\pm)-13, isomer 4, 82079-57-0; (\pm)-14a, 82045-49-6; (\pm)-14b, 82079-58-1; (\pm)-15a, 82109-86-2; (\pm)-15b, 82045-50-9; 16a, 82045-51-0; 16b, 82045-52-1; 17a, 82045-53-2; 17b, 82045-54-3; (\pm)-E-19a, 82045-55-4; (\pm)-Z-19a, 82079-59-2; (\pm)-19b, 82045-56-5; 2-amino-2-methyl-1-propanol, 124-68-5.

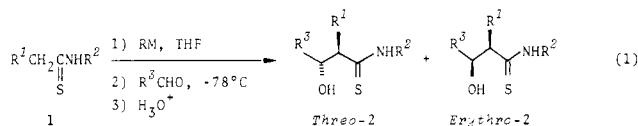
Stereoselective Generation of *Z* Secondary Thioamide Dianion: Application to Diastereoselective Aldol Condensations and Thio Claisen Rearrangements

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Aldol (β -hydroxycarbonyl) units are a characteristic structural element of numerous macrolide¹ and polyether antibiotics. This led to recent development of new synthetic methods that allow the diastereoselective generation of aldols.² Most of them utilize the enolate monoanions of a ketone, an ester, or their equivalents. The aldol condensation with dianions of carboxylic acid or its equivalent has been very scarcely studied probably owing to the low diastereoselectivity as observed for carboxylic acid³ and secondary amide dianions⁴ and considerable scarcity of dianions⁵ as well as their mechanistic complexity (vide infra).⁶ Generally the diastereoselectivity of an aldol is well correlated to the geometric purity of enolate (*E* or *Z*) and to the six-membered chairlike transition state ordering the substituent of the aldehyde in an equatorial position (see eq 1).^{7,8} In addition to these, we have



(1) (a) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem.* **1977**, *89*, 602. (b) Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683.

(2) For recent study, see: (a) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566. (b) Evans, D. A.; McGee, L. R. *Ibid.* **1981**, *103*, 2876. (c) Evans, D. A.; Bartoli, J.; Shih, T. H. *Ibid.* **1981**, *103*, 2127. (d) Meyers, A. J.; Yamamoto, Y. *Ibid.* **1981**, *103*, 4278. (e) Heathcock, C. H.; Hagen, J. P.; Tarvi, E. T.; Pirrung, M. C.; Young, S. D. *Ibid.* **1981**, *103*, 4972.

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(4) (a) Schrlitz, D. M.; Kaiser, E. M.; Hauser, C. R. *J. Org. Chem.* **1967**, *32*, 2610. (b) Majewski, M.; Mpango, G. B.; Thomas, M. T.; Wu, A.; Snieckus, V. *Ibid.* **1981**, *46*, 2029.

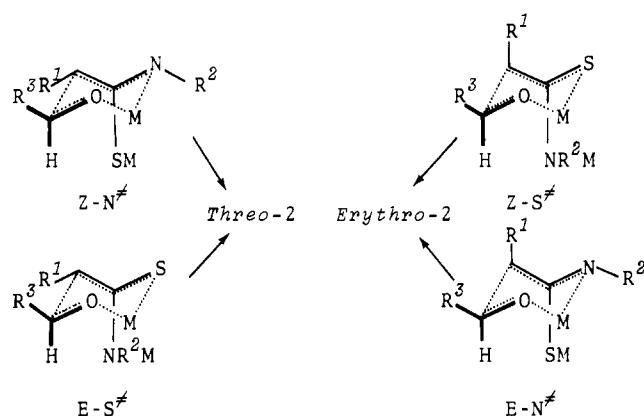
(5) Morwick, T. *Tetrahedron Lett.* **1980**, *21*, 3227.

(6) Mulzer, J.; Brüntrup, G.; Finke, J.; Zippel, M. *J. Am. Chem. Soc.* **1979**, *101*, 7723.

(7) (a) Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120. (b) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2.

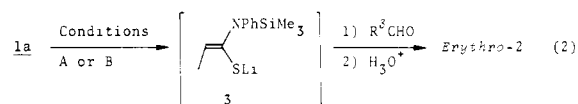
(8) For aldol condensation of a zirconium enolate and an enolate with a gegenion with no chelating ability, an acyclic, a pseudochair, or a boat transition state is proposed: (a) Evans, D. A.; McGee, L. R. *Tetrahedron Lett.* **1980**, *21*, 3975. (b) Noyori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1981**, *103*, 2106. See also ref 2d.

Scheme I



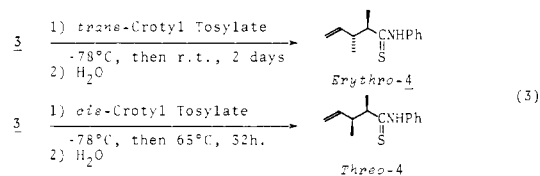
to consider another factor in the cases of enolate dianion, i.e., the selectivity for the coordination of the aldehyde oxygen to two kinds of metals, as exemplified with secondary thioamide dianion in Scheme I.

Nothing is known about the stereochemistry of dianions,⁴ and first the stereochemistry of secondary thioamide dianions is examined as follows (eq 2): the lithium enolate of *N*-(trimethylsilyl)-*N*-phenylthiopropionamide (**3**),⁹ generated either by treatment with 2 equiv of *n*-BuLi (0 °C, 1 h in THF) followed by *N*-alkylation with 1 equiv of trimethylsilyl chloride (0 °C, 1 h, condition A) or by sequential treatment with 1 equiv of *n*-BuLi (0 °C, 1 h in THF), 1 equiv of trimethylsilyl chloride (0 °C, 1 h, selective *N*-silylation^{9b}), and 1 equiv of *n*-BuLi (-78 °C, 1 h) (condition B), was treated with isobutyraldehyde (-78 °C, 1 min) to provide *erythro*-2 (*R*¹ = CH₃, *R*² = C₆H₅, *R*³ = (CH₃)₂CH) selectively [*erythro*-2/*threo*-2 = 94:6 in 97% yield (condition A); 92:8 in 99% yield (condition B)] (see eq 2). These parallel results



suggest that the secondary thioamide dianion possesses the *Z* configuration (condition A), provided that no isomerization takes place during the *N*-silylation of the secondary thioamide dianion,¹⁰ because it has been already established that the enolate generated from *tert*-thioamide¹¹ (condition B) possesses the *Z* configuration and provides *erythro* aldols selectively.

So that further insight into the structure of dianion, especially its geometric purity, could be gained, **3** was treated with *trans*- and *cis*-crotyl tosylates and subjected to the thio Claisen rearrangement conditions (*trans*, room temperature, 40 h; *cis*, THF reflux 32 h). From *trans*- and *cis*-crotyl tosylates were obtained *erythro*- and *threo*-*N*-phenyl-2,3-dimethylthio-4-pentenoylamides (**4**) in 51% and 50% yields, respectively (eq 3).¹² This stereo-



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(10) In a strict sense we are unable to preclude the minor possibility of isomerization during silylation. However, there are many precedents that indicate that the alkylation with trimethylsilyl chloride is a kinetic process. (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. (b) Chan, T. H.; Aida, T.; Lau, P. W. K.; Gorys, V.; Harpp, D. N. *Tetrahedron Lett.* **1979**, 4029.

(11) Tamaru, Y.; Harada, T.; Nishi, S.; Mizutani, M.; Hioki, T.; Yoshida, Z. *J. Am. Chem. Soc.* **1980**, *102*, 7806.

Table I. Aldol Reaction of Secondary Thioamide Dianions^a

entry	secondary thioamide		aldehyde (R ³)	metal	ratio of 2 ^b (threo:erythro)	yield, % ^c
	R ¹	R ²				
1 (1a)	CH ₃	C ₆ H ₅	CH ₃	Li	69:31	95
2 (1a)	CH ₃	C ₆ H ₅	(CH ₃) ₂ CH	Li	88:12	95
3 (1a)	CH ₃	C ₆ H ₅	C ₆ H ₅	Li	62:38	97
4 (1b)	(CH ₃) ₂ CH	C ₆ H ₅	(CH ₃) ₂ CH	Li	93:7	92
5 (1b)	(CH ₃) ₂ CH	C ₆ H ₅	C ₆ H ₅	Li	69:31	99
6 (1c)	C ₆ H ₅	CH ₃	(CH ₃) ₂ CH	Li	78:22	84
7 (1c)	C ₆ H ₅	CH ₃	(CH ₃) ₂ CH	Mg	98:2	98
8 (1c)	C ₆ H ₅	CH ₃	C ₆ H ₅	Li	71:29	75
9 (1c)	C ₆ H ₅	CH ₃	C ₆ H ₅	Mg	94:6	92
10 (1d)	C ₆ H ₅	CH ₂ CH ₂ OCH ₃	C ₆ H ₅	Li	94:6	95
11 ^d (1d)	C ₆ H ₅	CH ₂ CH ₂ OCH ₃	C ₆ H ₅	Mg	97:3	93

^a For the structures of **1** and **2**, see eq 1. For reaction conditions, see footnote 13. ^b The ratio was determined by high-pressure liquid chromatography (Waters Associates 1-ft μ -Porasil column, (75-85):(25-15) hexane-EtOAc eluent). ^c Combined (erythro, threo) isolated yield by column chromatography (silica gel, benzene-EtOAc gradient). ^d Owing to poor solubility of dimagnesium salt, this experiment was carried out in 6 times dilution at -18 °C (dry ice, CCl₄).

specificity indicates the very high (more than 97%) geometric purity of **3** and hence of the dianion.

Despite the high geometric purity of the dianion, the aldol showed poor selectivity in favor of a threo product (entries 1-6 and 8, Table I),^{13,14} suggesting that the aldehyde oxygen coordinated to the Li-N metal (a transition-state (Z)-N⁺) in a slight preference to the Li-S metal (a transition-state (Z)-S⁺, Scheme I). This preference might be attributed to a partial ionic character of the Li-N bond owing to an efficient 2p π -2p overlap compared with a 2p π -3p overlap of the Li-S bond.

So that this idea could be verified, the following two experiments were undertaken, which were intended to amplify the difference of the bonding nature between N- and S-metal bonds. The first is the reaction with dimagnesium salts,¹³ which might render the N-Mg bond more dissociated than the S-Mg bond on the basis of HSAB principle.¹⁵ Indeed, this proved to be the case, and threo selection was greatly improved as is apparent in the comparison of entries 7 with 6 and 9 with 8. The second attempt is the use of NCH₂CH₂OCH₃ in place of N-CH₃ in the expectation of dissociation of the N-metal bond by a coordination of the ether oxygen to the metal bound to a nitrogen atom. This also proved to work nicely, and high threo selection was achieved irrespective of the kind of metal used (entries 10 and 11, Table I). The stereochemistry of the products was determined by ¹H and ¹³C NMR¹⁶ spectroscopies; in the ¹H NMR spectra carbinol resonances appeared as $J_{\text{threo}}(5-8 \text{ Hz}) > J_{\text{erythro}}(2-3 \text{ Hz})$,¹⁷ just as with other aldols.

In conclusion this paper reports the first example of aldol reactions utilizing dianions derived from secondary thioamides, which are shown to be of Z configuration. The most important results described here are that the dianion, under suitable conditions, i.e., Mg²⁺ as gegenion, affords a threo aldol, while the monoanion, conveniently generated by selective N-silylation of dianion, affords an erythro aldol in high selectivities. The full

scope of the stereospecific thio Claisen rearrangement will be reported in due course.¹⁸

Registry No. **1a**, 2955-69-3; **1a**-2Li, 82080-60-2; **1b**, 82080-61-3; **1b**-LLi, 82080-62-4; **1c**, 77130-13-3; **1c**-2Li, 82080-63-5; **1c**-Mg, 82080-64-6; **1d**, 82080-65-7; **1d**-2Li, 82080-66-8; **1d**-Mg, 82094-59-5; **threo-2a** (R³ = CH₃), 82080-67-9; **erythro-2a** (R³ = CH₃), 82080-68-0; **threo-2a** [R³ = (CH₃)₂CH], 82080-69-1; **erythro-2a** [R³ = (CH₃)₂CH], 82080-70-4; **threo-2a** (R³ = C₆H₅), 82080-71-5; **erythro-2a** (R³ = C₆H₅), 82080-72-6; **threo-2b** (R³ = (CH₃)₂CH), 82080-73-7; **erythro-2b** (R³ = (CH₃)₂CH), 82080-74-8; **threo-2b** (R³ = C₆H₅), 82080-75-9; **erythro-2b** (R³ = C₆H₅), 82080-76-0; **threo-2c** (R³ = (CH₃)₂CH), 82080-77-1; **erythro-2c** [R³ = (CH₃)₂CH], 82080-78-2; **threo-2c** (R³ = C₆H₅), 82080-79-3; **erythro-2c** (R³ = C₆H₅), 82080-80-6; **threo-2d** (R³ = C₆H₅), 82093-47-8; **erythro-2d** (R³ = C₆H₅), 82093-47-8; **3**, 82080-81-7; **erythro-4**, 82080-82-8; **threo-4**, 82080-83-9; acetaldehyde, 75-07-0; isobutyraldehyde, 78-84-2; benzaldehyde, 100-52-7; *trans*-crotyl tosylate, 76454-93-8; *cis*-crotyl tosylate, 76454-94-9.

(18) Partial support from the Ministry of Education and the Japanese Government (Grant in Aid for Special Project Research No. 56109008 and for Scientific Research C No. 56550588) is gratefully acknowledged.

Ab Initio Study of the Structure and Vibrational Frequencies of the Grignard Reagent CH₃MgCl

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Due to their importance in organic synthesis, considerable effort has been expended in characterizing Grignard reagents and possible mechanisms for their formation and reactions.¹⁻⁴ This has proven very difficult, in part, because several different species exist in the commonly employed solvents. This complexity in solution leads naturally to an interest in matrix isolation techniques which have proven valuable for the characterization of "unsolvated" intermediates and their chemical reactions. Unsolvated Grignard reagents were apparently first prepared by Skell and Girard² in 1972 but were not characterized spectroscopically until the work of Ault³ in 1980. Ault reported three or four vibrational frequencies for the products of the Mg + CH₃X (X

[†] John Simon Cuggenheim Foundation Fellow.

(1) Ashby, E. C. *Pure Appl. Chem.* **1980**, *52*, 545. Lawrence, L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1980**, *102*, 2439. Rogers, H. R.; Deutch, J. M.; Whitesides, G. M. *Ibid.* **1980**, *102*, 226 and references therein.

(2) Skell, P. S.; Girard, J. E. *J. Am. Chem. Soc.* **1972**, *94*, 5518.

(3) Ault, B. S. *J. Am. Chem. Soc.* **1980**, *102*, 4380.

(4) Matrix isolation studies of the reactions of Mg and several other metals with CH₃Br has recently been reported by Tanaka and co-workers: Tanaka, Y.; Davis, S. C.; Klabunde, K. J. *J. Am. Chem. Soc.* **1982**, *104*, 1013. These authors suggest that the reaction may require magnesium clusters.

(12) The structure of **4** is determined unequivocally by transforming each of the diastereomers to the corresponding thiol esters and comparing spectral data with those of authentic samples.¹¹ All new compounds were characterized by using IR, ¹H NMR, ¹³C NMR, and mass spectral analysis and elemental analysis.

(13) The experimental procedure is as follows: To a solution of **1** (2 mmol) in 10 mL of anhydrous THF is added 2.2 equiv of *n*-BuLi (1.6 M hexane solution) in one portion at 0 °C, and the mixture is stirred for 1 h and then cooled to -78 °C. A THF solution of aldehyde is added in one portion and quenched by addition of 1 N HCl [1:1 H₂O-THF (v/v)] after 1 min. The dimagnesium salts are prepared [with 3 equiv of *i*-PrMgBr, ambient temperature for 2 h] and reacted with aldehydes in a similar fashion.

(14) No significant change of selectivity is observed by changing the steric bulk of the N-substituent (2-methyl-, 2-methoxy-, and 2,6-dimethylphenyl). See: Pirrung, M. C.; Heathcock, C. H. *J. Org. Chem.* **1980**, *45*, 1727.

(15) Ho, T.-L. "Hard and Soft Acids and Bases Principle in Organic Chemistry"; Academic Press, New York, 1977.

(16) Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *44*, 4294.

(17) This general correlation does not hold for **2** (R¹ = (CH₃)₂CH). For example, the coupling constants of **erythro-2** and **threo-2** (R¹ = (CH₃)₂CH, R² = C₆H₅, R³ = C₆H₅) are 3.0 and 2.3 Hz, respectively.