

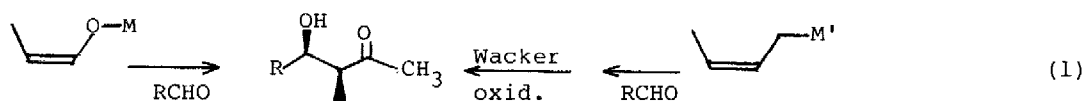
## ZIRCONIUM ENOLATES AS A NEW ERYTHRO-SELECTIVE ALDOL CONDENSATION REAGENT

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**Summary:** Zirconium enolates, prepared from lithium enolates and bis(cyclopentadienyl)zirconium dichloride, undergo a facile aldol condensation with aldehydes to give predominantly the erythro product regardless of the geometry of the starting enolates.

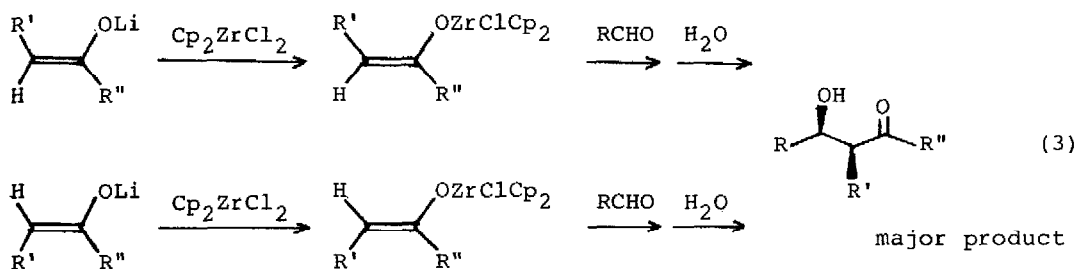
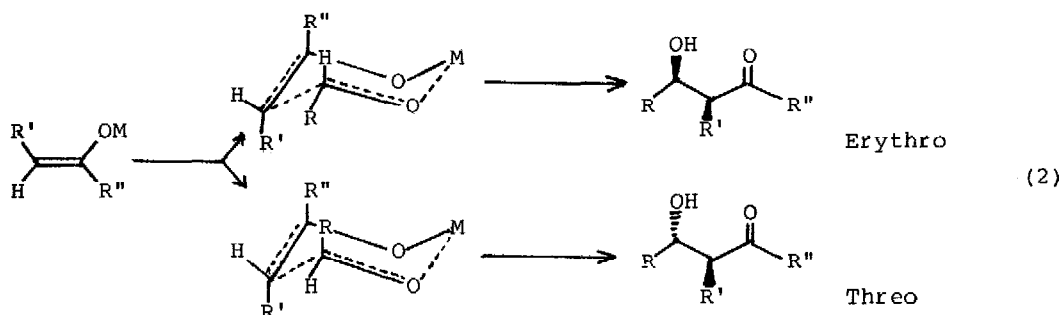
The ever-increasing interest in the chemistry of macrolide antibiotics has led to a continuing search for a new methodologies for erythro-selective synthesis of  $\beta$ -hydroxycarbonyl compounds.<sup>1</sup> The hitherto known solution to this problem is to use the addition reaction of metal enolates<sup>2</sup> or 2-alkenyl-metal derivatives to aldehydes<sup>3</sup> (eq 1).



M = Li, Mg, Zn, B, Al, Si, Sn<sup>4</sup>

M' = Li, B, Al, Sn

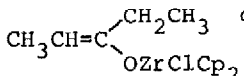
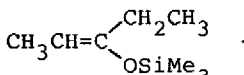
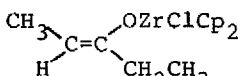
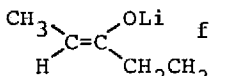
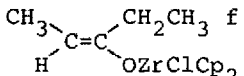
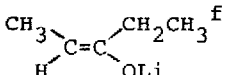
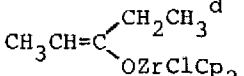
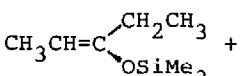
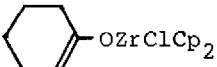
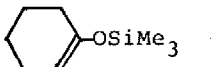
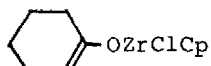
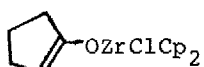
It is amply demonstrated that, for kinetically controlled reactions, the erythro isomer is the favored product from Z-enolates (eq 2), while the threo isomer ordinarily predominates from E-enolates.<sup>5</sup> Under thermodynamic control, the threo product is favored irrespective of the geometry of the starting enolates. As apparent from eq 2, the presence of a bulky substituent (R'') at the  $\alpha$ -position, as well as the stereochemically pure (Z)-geometry, is inherently required to obtain the erythro product. We now report that a totally new approach to the stereoselection via zirconium enolates, in which the erythro-selective condensation is realized with fair good selectivity regardless of



the geometry of the starting materials (eq 3).

The results are summarized in the Table 1. As is evident from entries 3 and 5, the zirconium enolates addord predominantly erythro product irrespective of the geometry of enolates. The relatively low stereoselection in entry 3 may be due to the presence of polar solvent, HMPT<sup>6</sup>; actually we have made such an observation in other metal enolate systems. There might be a possibility that the geometrical integrity of the starting lithium enolates disappears during the reaction with Cp<sub>2</sub>ZrCl<sub>2</sub> to give predominantly the (Z)-zirconium enolate in both cases. However, such a possibility is eliminated, since the cyclohexyl and cyclopentyl enolates with the fixed (E)-geometry again afford preferentially erythro product (entries 9-12). Consequently, the present reaction presumably does not involve a conventional cyclic transition state (eq 2), instead may proceed through an acyclic transition state.<sup>7</sup> Regardless of the precise mechanism, the present development offers a new methodology in the chemistry of enolates. We are now extending this work to the chemistry of allylic zirconium derivatives.

Table 1. Erythro-Selective Aldol Condensation via Zirconium Enolates<sup>a</sup>

Entry	Enolate	Aldehyde	Erythro (%) <sup>b</sup>	Threo (%) <sup>b</sup>	Yield <sup>c</sup>
1	 <sup>d</sup>	C <sub>6</sub> H <sub>5</sub> CHO	83	17	90
2	 + TiCl <sub>4</sub> <sup>e</sup>	C <sub>6</sub> H <sub>5</sub> CHO	50	50	85
3	 <sup>f</sup> (E/Z=8/92) <sup>g</sup>	C <sub>6</sub> H <sub>5</sub> CHO	67	33	86
4	 <sup>f</sup> (E/Z=8/92)	C <sub>6</sub> H <sub>5</sub> CHO	44	56	60
5	 <sup>f</sup> (E/Z=86/14) <sup>g</sup>	C <sub>6</sub> H <sub>5</sub> CHO	88	12	70
6	 <sup>f</sup> (E/Z=86/14)	C <sub>6</sub> H <sub>5</sub> CHO	30	70	30
7	 <sup>d</sup>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> CHO	75	25	85
8	 + TiCl <sub>4</sub> <sup>h</sup>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> CHO	55	45	80
9	 <sup>d</sup>	C <sub>6</sub> H <sub>5</sub> CHO	72	28	90
10	 + TiCl <sub>4</sub> <sup>h</sup>	C <sub>6</sub> H <sub>5</sub> CHO	36 (23) <sup>8</sup>	64 (69) <sup>8</sup>	90
11	 <sup>f</sup>	C <sub>6</sub> H <sub>5</sub> CHO	64	36	75
12	 <sup>f</sup>	C <sub>6</sub> H <sub>5</sub> CHO	74	26	82

<sup>a</sup> All reactions were carried out on 1 mmol scale. Zirconium enolates were

prepared by the addition of a THF solution of  $\text{Cp}_2\text{ZrCl}_2$  to a THF solution of lithium enolates at  $-78^\circ\text{C}$ . Aldehydes were then added and the reaction was quenched by  $\text{MeOH-H}_2\text{O}$  after 30 min at this temperature except where otherwise indicated. <sup>b</sup> Determined by  $^1\text{H}$  NMR spectra in entries 1-6 and 9-12, and by Glpc (CW 6000, 2m) in entries 6 and 7. <sup>c</sup> Isolated yield, based on aldehydes, through a column of silica gel. <sup>d</sup> The lithium enolate was prepared from the corresponding trimethylsilyl enole ether and  $n\text{-BuLi}$  at  $0^\circ\text{C}$ . <sup>e</sup> The method of ref 8 was used and the reaction was quenched at  $0^\circ\text{C}$ . <sup>f</sup> The lithium enolate was prepared via the deprotonation of the corresponding ketone by using  $\text{LiTMP}$ .<sup>9</sup> <sup>g</sup> We make a speculation that the ratio of E/Z does not change during the formation of the zirconium enolate. <sup>h</sup> The reaction was quenched at  $-78^\circ\text{C}$  via the procedure of ref 8.

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#### References and Notes

- 1) For review articles, see a) P. A. Bartlett, *Tetrahedron*, **36**, 3 (1980); b) S. Masamune, *Aldrichimica Acta*, **11**, 23 (1978).
- 2) For example, T. Inoue and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **53**, 174 (1980). See also ref 3 and references cited therein.
- 3) H. Yatagai, Y. Yamamoto, and K. Maruyama, *J. Am. Chem. Soc.*, **102**, 4548 (1980).
- 4) We are now investigating the stereoselection via tin enolates, and the results will be reported shortly.
- 5) In the absence of a coordinating cation (M), three products are obtained from (Z)-enolates; R. Noyori, K. Yokoyama, J. Sakata, I. Kuwajima, E. Nakamura, and M. Shimizu, *J. Am. Chem. Soc.*, **99**, 1265 (1977); W. A. Kleschick, C. T. Buse, and C. H. Heathcock, *ibid.*, **99**, 247 (1977).
- 6) Very low stereoselection is observed in protic media; P. Fellmann and J. E. Dubois, *Tetrahedron*, **34**, 1349 (1978).
- 7) S. Murata, M. Suzuki, R. Noyori, *J. Am. Chem. Soc.*, **102**, 3248 (1980).
- 8) T. Mukaiyama, K. Banno, K. Narasaka, *J. Am. Chem. Soc.*, **96**, 7503 (1974).
- 9) Z. A. Fataftah, I. E. Kopka, M. W. Rathke, *J. Am. Chem. Soc.*, **102**, 3959 (1980). Note Added in Proof. At the first symposium on synthetic organic chemistry held at Kyoto on September 12, we learned that the similar results were obtained by Prof. D. A. Evans. We thank him for mutual discussion.

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