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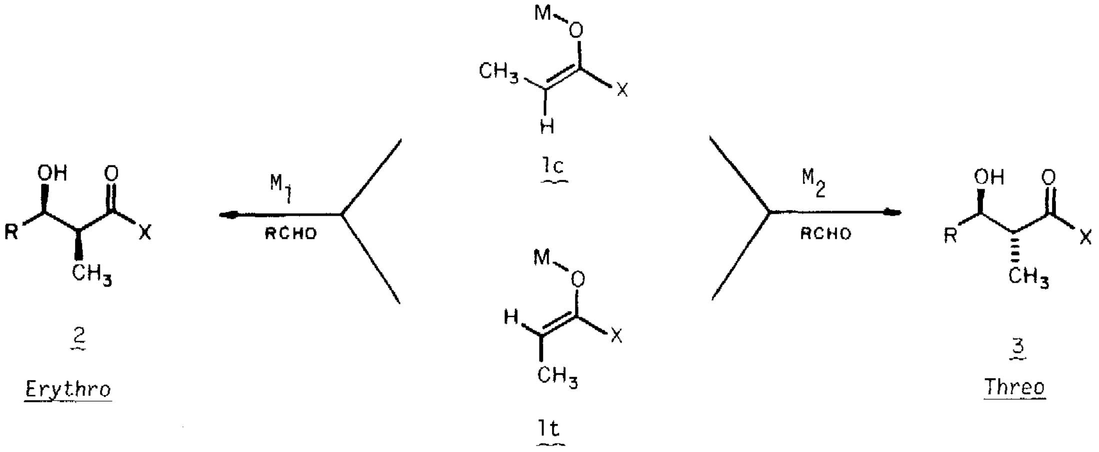
ALDOL DIASTEREOSELECTION *VIA* ZIRCONIUM ENOLATES.
PRODUCT-SELECTIVE, ENOLATE STRUCTURE INDEPENDENT CONDENSATIONS.

D. A. Evans and L. R. McGee
Contribution No. 6258 from the Laboratories of Chemistry
California Institute of Technology
Pasadena, California 91125

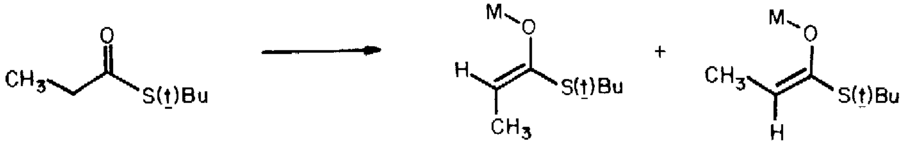
Summary: Both (*E*)- and (*Z*)-zirconium enolates have been shown to undergo selective kinetic aldol condensation to give mainly *erythro*-β-hydroxy ketones, esters and amides.

It is now well established that highly diastereoselective kinetic aldol condensations can be executed if the appropriate steric control elements are incorporated into the metal enolate.[1,2] For lithium enolates, where the enolate substituent, X, is sterically demanding or for boron enolates (M = BR_2), aldol product stereochemistry is *strongly* coupled to enolate geometry (*e.g.* 1c → 2, 1t → 3). For such metals, the stereoselective synthesis of a given enolate can be a major challenge. In order to circumvent this problem *we have undertaken to develop product selective aldol condensations which are independent of enolate geometry*.



In this communication we wish to disclose our observations on the *erythro*-product-selective aldol condensations of *cis* and *trans*-biscyclopentadienylchlorozirconium enolates 1c and 1t (M_1 = Cp_2ZrCl) with aldehydes.[3] In this study the zirconium enolates were conveniently prepared from the corresponding lithium enolates by ligand exchange with Cp_2ZrCl_2.

The following control experiments demonstrated that loss of enolate geometry was *not* significant during the lithium-zirconium exchange. Enolization of *tert*-butyl thiopropionate (4) with lithium diisopropylamide (LDA) in THF (-78°C) followed by a chlorotrimethylsilane quench afforded a ratio **5b**:**6b** = 90:10 as determined by gas chromatography.[4] Analogous enolization of **4** with LDA followed by the addition of a THF solution of Cp_2ZrCl_2 afforded the zirconium enolates **5c** and **6c**. Although this enolate mixture could not be directly silylated, treatment of the mixture of **5c** and **6c** successively with _n_-butyllithium and chlorotrimethylsilane afforded enolsilanes in a ratio **5b**:**6b** = 88:12. It was thus concluded that $\geq$98% retention of enolate geometry accompanied the metal exchange.

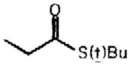
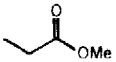
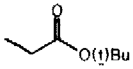
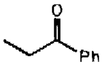
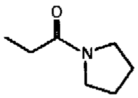
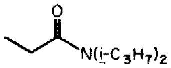


4 **5** **6**

a, M = Li
b, M = $SiMe_3$
c, M = $ZrClCp_2$

Table I summarizes the comparative lithium and zirconium aldol condensations of six carbonyl substrates with benzaldehyde. Where possible, the comparative lithium aldol results recently reported by Heathcock[2a] are included. Entries A-C represent enolates with predominant "_trans_"-geometry **1t**, while entries D-F provide examples of "_cis_"-enolates **1c**. In all cases, the zirconium enolates exhibited good to excellent kinetic _erythro_ diastereoselection. The high _erythro_ product selection for amide enolates (entries E, F) appears to be general for a range of aldehydes (Table II).

Table I. Metal Enolate Condensations With Benzaldehyde.

Entry	Substrate	Enolate Ratio **1c**:**1t**	Product Ratios (M)[a] **2**:**3** (Li)	**2**:**3** (Zr)	% Yield (Zr)
A		10:90	63:37	93:7	70
B		5:95[b]	52:48 (62:38)[b]	87:13	80
C		5:95[b]	37:63[b] (49:51)	72:28	[c]
D		>98:2[b]	82:18 (88:12)[b]	90:10	62
E	 **7**	>95:5[d]	60:40	95:5	80
F	 **8**	81:19[b]	61:39 (63:37)[b]	>98:2	87

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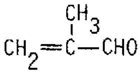
[a] Aldol product ratios analyzed by ^{1}H NMR, ^{13}C NMR, GLC. [b] Ref. 2a. [c] Not determined. [d] ^{13}C NMR spectrum of ^{13}MeCH=C(OLi)N(CH_2)$_4$ exhibited only one methyl resonance.

Table II. Condensations of the Zirconium Enolates of Amides 7 and 8 With Representative Aldehydes.

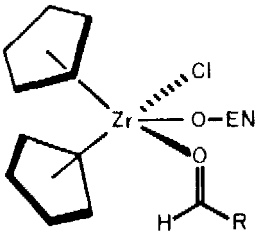
Aldehyde	Aldol Product Ratios (2:3)[a,b]	
	X = $-N(CH_2)_4$	X = $-N(\underline{i}-C_3H_2)_2$
$\underline{n}-C_3H_7CHO$	94:6	98:2
$\underline{i}-C_3H_7CHO$	95:5	97:3
 $CH_2{=}C(CH_3){-}CHO$	90:10	95:5

[a] Ratios determined by gas chromatography. [b] Yields in all cases were 80-90% of isolated products.

For the preparation and aldol condensations of the zirconium enolates reported herein the following general procedure was followed: To a 0.1 molar solution of 1.1 equiv of LDA in 4:1 THF-hexane at -78°C was added 1.0 equiv of carbonyl substrate. After 30 min, 1.1 equiv of a 0.16 $\underline{M}$ solution of Cp_2ZrCl_2 in THF was added and the resultant zirconium enolate was allowed to form between -78°C and room temperature (30 min). After re-cooling to -78°C 0.9 to 1.1 equiv of aldehyde was added, stirred 1 h, and the reaction was quenched with saturated aqueous ammonium chloride. After filtration, the product was extracted into methylene chloride, dried (Na_2SO_4), and concentrated in vacuo. Aldol diastereoisomer ratios were determined by NMR and/or gas chromatography.[5] In the comparative lithium aldol condensations, the lithium enolates were treated with 1.1 equiv of aldehyde followed by an NH_4Cl quench after 4-5 sec according to the reported procedure.[2a]

That these conditions result in kinetic ratios was shown by monitoring the product ratio after quenching at -78°C for times ranging from a few seconds to several hours with no change observed. Additionally, a crossover experiment with p-chlorobenzaldehyde showed no crossover for esters and amides and only 20% crossover with t-butyl thiopropionate after 30 min at room temperature.[6]

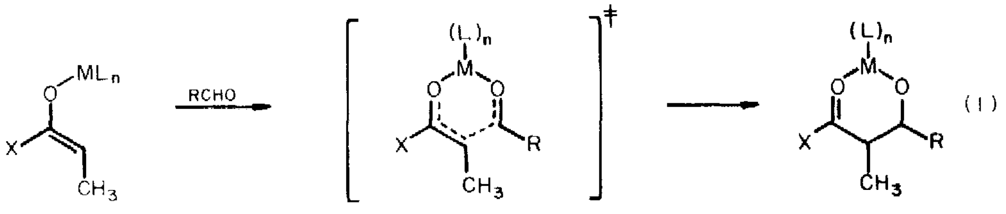
Theory predicts that the 16-electron zirconocenes have a vacant oribital which lies in the X-Zr-X plane.[7] The 16-electron bent-sandwich complexes of zirconium and titanium might be expected to form aldehyde-enolate chelates possessing the geometry 9. Little X-ray data



O–Zr–O ca. 60-80°

9

exists for 18-electron bent-sandwich complexes; however, an estimate of the O-Zr-O angle in **9** of 60-80° is not unreasonable.[8] If one accepts the premise that metal enolate-derived aldol condensations proceed *via* the pericyclic transition state **10** (eq 1) originally proposed by Zimmerman,[9] *significantly* different preferred transition state conformations could be expected as a result of O-M-O bond angle changes. Although detailed speculation as to the origin of the observed *erythro* product from either enolate is premature, we speculate that the *trans*-zirconium enolates **1t** are reacting preferentially *via* *pseudo*-boat transition states while the corresponding *cis*-enolates **1c** preferentially proceed *via* *pseudo*-chair transition states. Relevant steric factors which result in boat *vs* chair transition state selection originate from the sterically demanding cyclopentadienyl ligands and their interaction with the enolate substituents (CH_3 and X). The utility of zirconium enolates in highly enantioselective aldol condensations will be reported shortly.



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References and Notes

1. (a) D.A. Evans, E. Vogel, and J.V. Nelson, *J. Am. Chem. Soc.*, **101**, 6120 (1979); (b) H. Hirama, D.S. Garvey, L.D.L. Lu, and S. Masamune, *Tetrahedron Lett.*, 3937 (1979) and earlier references; (c) T. Inoue and T. Mukaiyama, *Bull. Chem. Soc., Jpn.*, **53**, 174 (1980).
2. (a) C.H. Heathcock, C.T. Buse, W.A. Kleschick, M.C. Pirrung, J.E. Sohn, and J. Lampe, *J. Org. Chem.*, **45**, 1066 (1980) and references cited therein; (b) M.C. Pirrung, C.H. Heathcock, *ibid.*, **45**, 1727 (1980).
3. J. Schwartz and co-workers have recently reported an example of a cyclopentanone zirconium enolate condensation with formaldehyde: J. Schwartz, M.J. Loots, and H. Kosugi, *J. Am. Chem. Soc.*, **102**, 1333 (1980).
4. The assignment of the structure **5** to the major enolate formed with LDA has been made by the analogy to the observations of Ireland and co-workers: R.E. Ireland, R.H. Mueller, and A.K. Willard, *J. Am. Chem. Soc.*, **98**, 2868 (1976).
5. *Erythro* and *threo*-stereochemical assignments were made by both ^1H and ^{13}C-NMR. Satisfactory spectral data and elemental analyses were obtained for all compounds reported.
6. C.A. Kingsbury, *J. Org. Chem.*, **37**, 102 (1972).
7. J.W. Lauher and R. Hoffmann, *J. Am. Chem. Soc.*, **98**, 1729 (1976).
8. (a) G. Fachinetti, C. Floriani, F. Marchetti, and S. Merlino, J. Chem. Soc., Chem. Commun., 522 (1976); (b) For comparison, the Cl-Zr-Cl of 97° has been determined in Cp_2ZrCl_2: K. Prout, *et al.*, *Acta Cryst.*, **B30**, 2290 (1974).
9. H.E. Zimmerman and M.D. Traxler, *J. Am. Chem. Soc.*, **79**, 1920 (1957).

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