

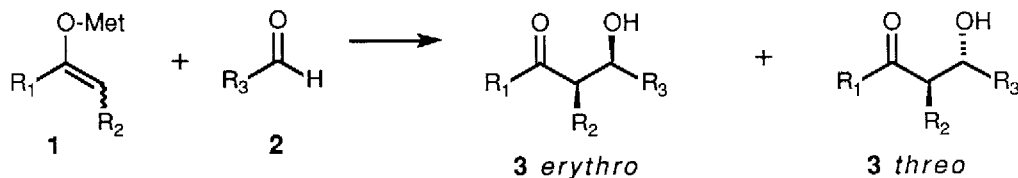
DIASTEREOSELECTIVE ALDOL REACTIONS OF CYCLOHEXANONE LITHIUM ENOLATE

Marek Majewski* and D. Mark Gleave

Department of Chemistry, University of Saskatchewan,
Saskatoon, Saskatchewan, Canada, S7N 0W0.

Summary: The aldol addition reactions of the lithium enolate of cyclohexanone with aromatic aldehydes show high kinetic *threo* selectivity.

Much research has been devoted during the last ten years to the control of relative stereochemistry in the aldol reactions.¹ A typical aldol addition results in the formation of two diastereoisomers **3** *erythro* and **3** *threo*.²



It is well established³ that, when the metal (Met) in **1** belongs to group I, II or III (lithium is the most common), the geometry of the enolate **1** correlates well with the relative stereoselectivity: *Z* enolates lead to the *erythro* aldols whereas *E* enolates yield the *threo* aldols. This correlation, which has been rationalized in terms of the cyclic transition state originally proposed by Zimmerman and Traxler,⁴ is very important in synthetic planning and also useful pedagogically.

One disconcerting exception from the above correlation has been the reaction between benzaldehyde **2a** (R₃=Ph) and cyclohexanone lithium enolate **1a** (R₁,R₂= -(CH₂)₄-; Met=Li), which, by necessity, has the *E* geometry and should therefore produce *threo* aldols predominantly. This important model reaction, often used to evaluate the effect of different conditions and reagents on aldol stereoselectivity, has been reported to be non-stereoselective, with the *erythro:threo* ratio of 48:52.⁵ This observation has been frequently cited.⁶

We were interested in the possible influence of electronic effects on stereoselectivity of the aldol reaction,⁷ and we decided to investigate the aldol additions of cyclohexanone lithium enolate with substituted aromatic aldehydes. During this work we have re-examined the reaction with benzaldehyde and found it to be *threo* selective under kinetic conditions. The results are presented below.

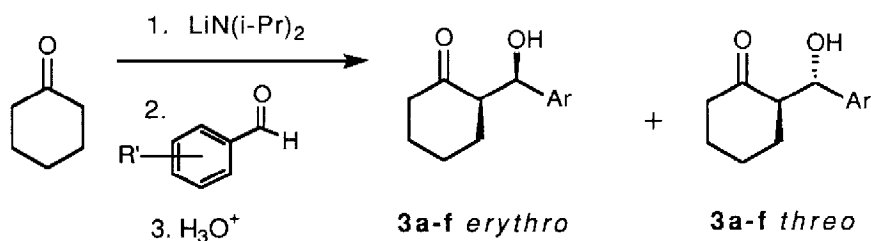


Table 1: Aldol addition of cyclohexanone Li-enolate to aromatic aldehydes.

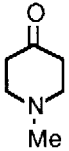
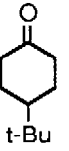
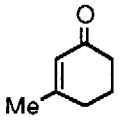
Entry	R'	Solvent	<i>threo</i> : <i>erythro</i>	isolated yield
1	H	Et ₂ O	76 : 24	84%
2	H	DME	72 : 28	50%
3	H	THF	84 : 16	75%
4	p-NMe ₂	THF	73 : 27	68%
5	p-OMe	THF	78 : 22	68%
6	p-Ph	THF	94 : 6	67%
7	m-CF ₃	THF	70 : 30	80%
8	p-CF ₃	THF	74 : 26	80%

All the reactions showed substantial *threo* selectivity.⁸ There was a small, but persistent over a large number of experiments, solvent effect: DME was the poorest solvent, both in terms of diastereoselectivity and efficiency, THF was the best. The influence of the aldehyde substituents R' was modest; 4-biphenylcarboxaldehyde (entry 6) showed the highest diastereoselectivity and both electronwithdrawing and donating substituents caused the decrease in the *erythro:threo* ratio. When a small amount of water was deliberately added to the enolate, the ratio remained unchanged. An excess of LDA (10%) did not affect the stereoselectivity, however ca.10% of bis-aldol was produced.⁹ When the n-BuLi, which was used to generate the LDA, was contaminated with large quantities of water (10 mmols of n-BuLi were treated with 7 mmols of H₂O and then used to generate 3 mmols of LDA), the aldol reaction was non-stereoselective (*threo:erythro*=1:1). Also, when 2, or more, equivalents of lithium bromide were added to

the enolate solution, the stereoselectivity was drastically reduced (*threo:erythro*=56:44).¹⁰ Interestingly, the presence of 1 equivalent of LiBr, in the form of MeLi-LiBr complex used to generate LDA, had much less effect on the selectivity (*threo:erythro*=67:33). Thus the previous observations of non-stereoselectivity in this reaction could, conceivably, be attributed to the presence of lithium salts or lithium hydroxide as impurities.

We also investigated the aldol reactions of lithium enolates of other six membered ring ketones with benzaldehyde. The results were consistent with the above observations (Table 2).

Table 2: Aldol reactions of lithiated cyclic ketones with benzaldehyde.

Entry	Ketone	Solvent	<i>threo</i> : <i>erythro</i>	Isolated yield
1.		THF	84 : 16	65%
2.		THF	81 : 19 ^a	63%
		Et ₂ O	75 : 25 ^a	61%
		Et ₂ O/HMPA	78 : 32 ^a	68%
3.		THF	82 : 18	77%
		Et ₂ O	76 : 24	60%

a. The ratio of *Z erythro*:*E erythro* was ca.1:1; *Z threo*:*E threo* ca.1:5.

In summary the lithium enolates of cyclohexanone and other cyclic ketones undergo the aldol reaction with benzaldehyde and substituted benzaldehydes and produce predominantly *threo* aldols in good yield. This behaviour is consistent with the rule, based on the Zimmerman-Traxler cyclic transition state model, that *E* enolates should selectively produce *threo* aldol products.

Acknowledgement: The financial support from NSERC Canada is gratefully acknowledged.

References and Footnotes:

1. For a review see: a. Evans, D. A.; Nelson, J. O.; Taber, T. R. *Top. Stereochem.* **1983**, *13*, 1-113. b. Heathcock, C. H. in "*Asymmetric Synthesis*"; **1984**; Morrison J. D., ed., vol. 3, pp. 111-212., Academic Press, New York. c. Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1-30. d. Mukayama, T. *Org. Reactions*, **1982**, *28*, 203.
2. The terms: *erythro* and *threo* are used as defined in ref. 1b, p. 113.
3. Ref. 1b, p. 119.
4. Zimmerman, H. E., and Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920; see also ref. 1b, p. 154.
5. a. House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310. b. Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. J. *Org. Chem.* **1980**, *45*, 1066.
6. *Inter alia*: a. Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120. b. Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *ibid.* **1981**, *103*, 3099. c. Imamoto, T.; Kusumoto, T.; Yokoyama, M. *Tetrahedron Lett.* **1983**, *24*, 5233. d. Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1983**, *24*, 3343. e. Morton, H. E.; Gillard, J. W.; Fortin, R.; Guindon, Y. *70th Canadian Chemical Conference*, Quebec City, **1987**, OR-49-E.
7. A substituent effect on diastereoselectivity in the reactions of tris(dialkylamino)sulfonium enolates with substituted benzaldehydes has been observed before: Noyori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1983**, *105*, 1598.
8. *Typical procedure*: A solution of LDA (2 mmol) was prepared by adding n-BuLi (2 mmol) in hexane (ca. 0.8 mL of the soln. of n-BuLi in hexane recently titrated using 2,5-dimethoxybenzyl alcohol as indicator) to diisopropylamine (2 mmol) in THF (6 mL) at 0°C and stirred for 10 min. The solution was then cooled to -78°C and cyclohexanone (2 mmol) was added via a syringe. The enolate was stirred for 30 min. at -78°C and then benzaldehyde was added (2 mmol). The reaction was quenched with saturated NH₄Cl soln. after 30s (varying the time from 5s to 120s did not affect stereoselectivity) diluted with Et₂O (ca. 20 mL), dried (MgSO₄) and the solvents were removed. The *erythro:threo* ratio was determined by NMR (300 MHz) according to the well known procedure (ref 1b, pp. 115-118.). The products were then separated by flash chromatography (SiO₂; ethyl acetate-hexane) and characterized.
9. The formation of the bis-aldol side products in this reaction is well known (ref. 5a).
10. a. Seebach recently reported that LiBr, used as an additive, played a crucial role in the regio- and stereoselectivity of the alkylation of imidazolidinones, and postulated that the structural role of this reagent is slowly beginning to emerge: Polt, R.; Seebach, D. *Helv. Chim. Acta*, **1987**, *70*, 1930. b. The influence of LiBr on the diastereoselectivity in the cyclohexanone Li-enolate case was first observed by Dr. J. W. Gillard and R. Fortin of Merck Frosst, who re-investigated our observations (we are grateful for this personal communication). c. A small effect of the addition of lithium iodide or lithium triflate on the stereoselectivity of the alkylation of enolates generated from t-butyl- δ -hydroxycarboxylates have been recently reported: Narasaka, K.; Ukaji, Y.; Watanabe, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1457.

(Received in USA 28 July 1989)