

THE CONDENSATION OF METHYL 2-METHYLPROPANOATE WITH CHIRAL ALDEHYDES. X-RAY CRYSTAL STRUCTURE OF (3RS,4SR) 3-HYDROXY-4-PHENYL-2,2,4-TRIMETHYLPENTANOIC ACID

Lee A. Flippin\* and Kay D. Onant†

Department of Chemistry, Northeastern University, Boston, Massachusetts 02115

**Abstract:** The lithium enolate derived from methyl 2-methylpropanoate reacts stereoselectively with 2-phenylpropanal and 2-(cyclohexyl)propanal, affording mainly the *syn* β-hydroxy ester in both cases. With 2-ethylhexanal, no selectivity was observed.

The factors which affect diastereoface selectivity in the reactions of nucleophiles with chiral aldehydes and ketones have received a great deal of study over the last three decades.<sup>1</sup> In recent years, a considerable part of this attention has been focused on the dynamics of stereocontrol in condensations of metal enolates or their equivalents with chiral, acyclic aldehydes. Several methods have emerged as powerful synthetic tools in this arena; most notably, double stereodifferentiation and mutual kinetic resolution have been successfully exploited<sup>2</sup> in condensations of certain chiral propionate equivalents with chiral aldehydes. It has recently been demonstrated that Lewis acid mediated reactions of simple enolsilanes with chiral aldehydes are often highly diastereoselective processes.<sup>3,4</sup> Unfortunately, the experimentally simple aldol techniques employing achiral metal enolates have been largely unsuccessful in this regard. Consideration of the Zimmerman-Traxler transition state models<sup>5</sup> for reactions of some lithium enolates with 2-phenylpropanal provides a good indication of the difficulty (Figure 1).

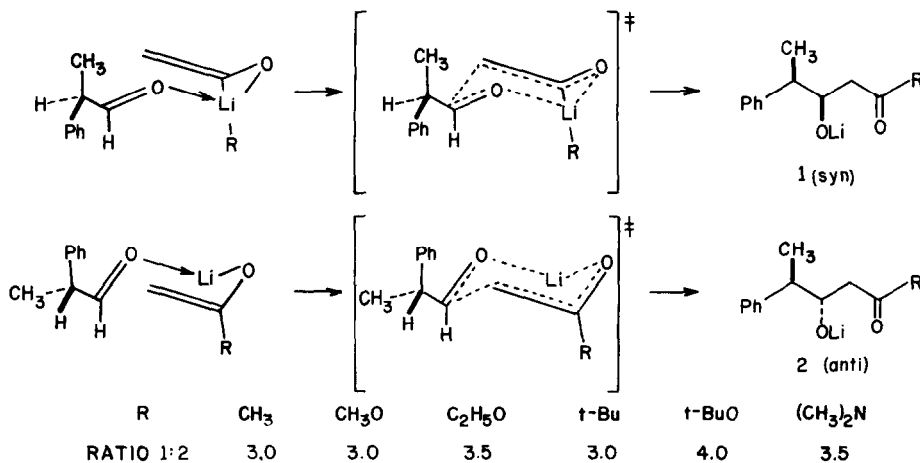
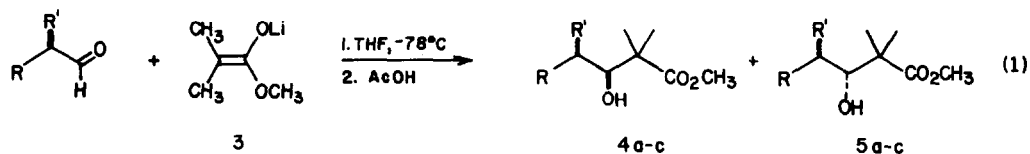


Figure 1

Thus for these simple, achiral enolates<sup>4</sup> the kinetic ratio of diastereomeric products ( $1:2$ ) is essentially independent of the nature of the remote substituent, R. Apparently the chiral center of the aldehyde interacts significantly with the methylene group of the enolate, however, because the lithium enolate from 2,2-dimethylpentan-3-one gives moderately enhanced diastereoface selectivity ( $\sim 6:1$ ) with 2-phenylpropanal.<sup>6</sup>

We wish to report our results from reactions of the preformed lithium enolate of methyl 2-methylpropanoate with several chiral aldehydes (Equation 1).

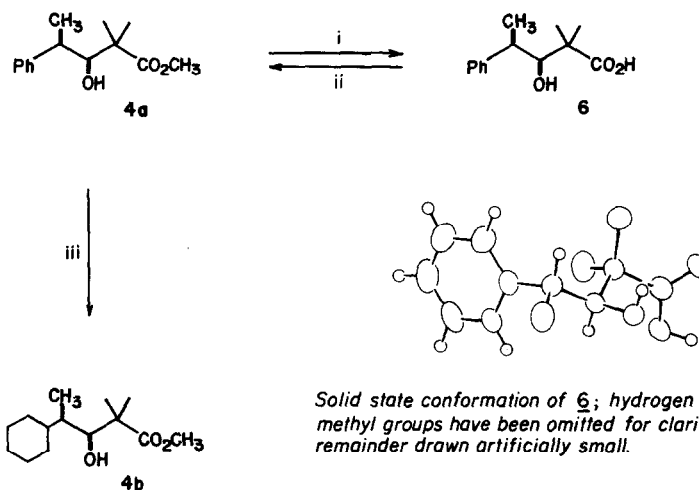


ENTRY	R	R'	RATIO 4:5 <sup>i</sup>	YIELD 4+5 <sup>ii</sup>
a	Ph	CH <sub>3</sub>	$\geq 200$	88%
b	c-C <sub>6</sub> H <sub>11</sub>	CH <sub>3</sub>	9	80%
c	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub>	CH <sub>3</sub> CH <sub>2</sub>	1	76%

<sup>i</sup> Crude product. <sup>ii</sup> Chromatographed product (silica gel; 9:1 hexanes-ethyl acetate)

The reactions were carried out according to the protocol of Heathcock, *et al.*;<sup>6</sup> that is, enolate **3** was generated by reaction of methyl 2-methylpropanoate with lithium diisopropylamide (0.5 M in THF, -78°C, 1 hr) and to this solution was added one equivalent of the appropriate aldehyde in a single portion. After 2-3 minutes the reactions were quenched at -78°C by the addition of two equivalents of glacial acetic acid and the crude products were isolated by an extractive work-up.<sup>7</sup> Notably, the reaction of enolate **3** with 2-phenylpropanal afforded a single, racemic diastereomer, **4a**, in high yield. Enolate **3** was less selective in its reaction with 2-(cyclohexyl)propanal, affording a 9:1 ratio of diastereomeric aldols, **4b** and **5b**, respectively. The reaction of enolate **3** with 2-ethylhexanal afforded a 1:1 mixture of diastereomeric aldols, **4c** and **5c**.

In order to define unambiguously the stereochemistry of **4a**, a single crystal x-ray analysis of the parent carboxylic acid, **6**, was undertaken.<sup>8</sup> Methylation of **6** under mild conditions regenerated pure **4a**. The x-ray experiment defines **4a** as the 3RS, 4SR diastereomer. Hydrogenation of **4a** gave a single aliphatic aldol that was identical in all respects to **4b** (Scheme 1).



- i) 1.1 eq KOH, 4:1 CH<sub>3</sub>OH-H<sub>2</sub>O, 25°C, 5hr, followed by aq. HCl  
 ii) Excess CH<sub>2</sub>N<sub>2</sub>, 25°C  
 iii) H<sub>2</sub> (3atm), 5% Rh-alumina, EtOH-AcOH, 25°C

Scheme 1.

## References and Notes

<sup>†</sup> Author to whom inquiries concerning the x-ray crystal structure analysis should be addressed.

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- For a recent, informative discussion of double stereodifferentiation and mutual kinetic resolution techniques in aldol chemistry, see C.H. Heathcock in "Asymmetric Synthesis, Volume 2", James D. Morrison, Ed., Academic Press, New York, 1983.
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7. Product ratios, 4:5, were determined for crude and chromatographically purified samples by analytical HPLC ( $\mu$ -porasil; 19:1 hexanes-ethyl acetate) using UV and/or RI detection. In all cases,  $^{13}\text{C}$ -NMR was used to confirm the HPLC analyses.
8.  $\text{C}_{13}\text{H}_{18}\text{O}_3$ ,  $M = 222.3$ , Orthorhombic,  $a = 30.005(2)$ ,  $b = 7.523(1)$ ,  $c = 10.904(1)$ ,  $Z = 8$ , space group  $P_{21}bcn$ . Intensity data to  $\theta = 65^\circ$  were measured using a Syntex  $P2_1$  automated diffractometer (Ni-filtered Cu-K $\alpha$  radiation ( $\lambda = 1.5418 \text{ \AA}$ ); variable speed,  $\theta/2\theta$  scans). The data with  $I \geq 2\sigma(I)$  were judged observed (1589 of 2127 unique reflections) and were used in structure solution (MULTAN80<sup>9</sup>) and refinement (anisotropic C,O; isotropic H). Convergence was reached at  $R = 0.041$ .<sup>10</sup>
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10. Atomic coordinates and derived parameters are available from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this article.

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