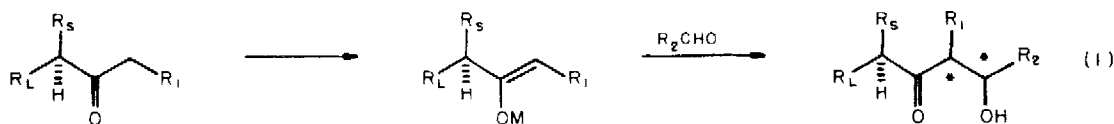


ENANTIOSELECTIVE ALDOL CONDENSATIONS VIA BORON ENOLATES.  
A STERIC MODEL FOR ASYMMETRIC INDUCTION.

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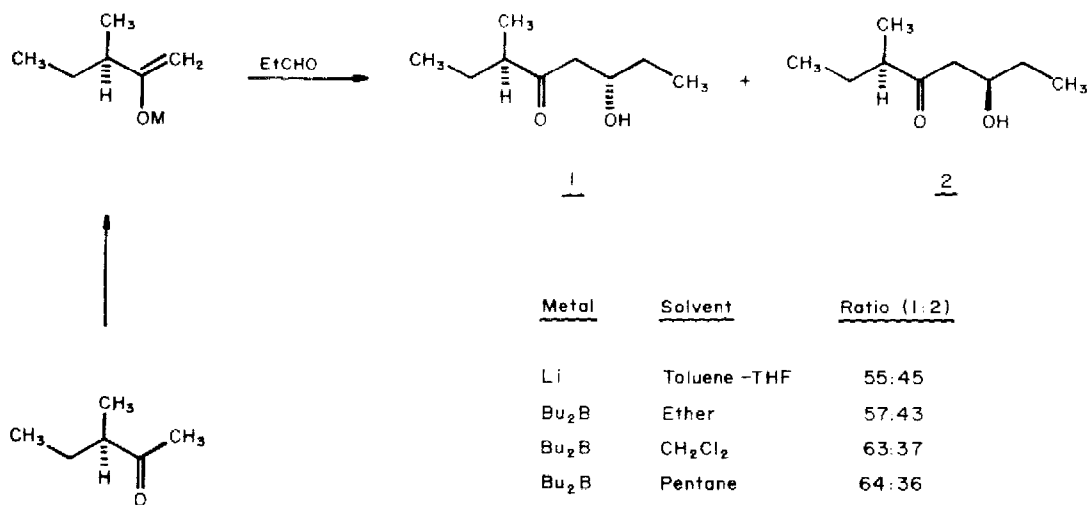
Summary: Chiral boron enolates have been shown to be effective in stereoregulated aldol condensations. A transition state model is proposed for chirality transfer.

In conjunction with efforts to develop practical approaches to the total synthesis of a broad range of natural products, considerable effort has recently been devoted to the development of stereoregulated aldol condensations.<sup>1</sup> Recent reports substantiate the importance of the metal center in rendering these reactions highly stereoselective in nature. The purpose of this communication is to report our observations on the consequence of resident enolate chirality on the stereochemical course of comparative aldol condensations with both boron and lithium enolates (eq 1).<sup>2</sup>



In 1976, Seebach documented the first example of this type of asymmetric induction for lithium enolates ( $R_1 = H$ ,  $R_S = Me$ ,  $R_L = Et$ ).<sup>2a</sup> Recently Heathcock reported enhanced diastereoselection for a more sterically biased lithium enolate ( $R_1 = Me$ ,  $R_S = OSiMe_3$ ,  $R_L = t-Bu$ ).<sup>2b</sup> It was of considerable interest to us to determine whether boron enolates would exhibit enhanced diastereoselection of the type illustrated. Accordingly, we have re-examined the aldol condensation reported by Seebach (Scheme I).<sup>2a</sup> Condensation of the lithium enolate of ( $\pm$ )-3-methyl-2-pentanone with propionaldehyde, under the reported conditions ( $-100^\circ C$ , 5 sec),<sup>2a</sup> afforded the aldol products 1 and 2 in a ratio of 55:45 as determined by analytical HPLC.<sup>3</sup> This product ratio is in excellent agreement to that reported by Seebach on the chiral ketone substrate. The dibutylboron enolate of ( $\pm$ )-3-methyl-2-pentanone was prepared in the solvents

## Scheme I

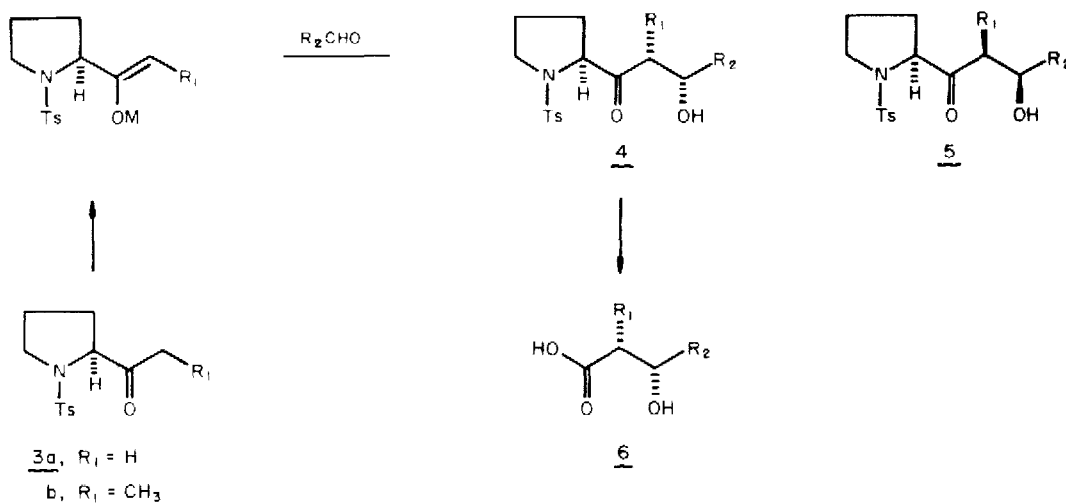


indicated (Scheme I) and condensed with propionaldehyde according to the reported procedure<sup>1b</sup> (-78°C, 30 min). It is noteworthy that the observed diastereoselection with the boron enolate is comparable in ether to that observed with lithium and slightly enhanced in nonpolar solvents. We have previously noted improved erythro-threo diastereoselection with similar solvent changes in our earlier study.<sup>1b</sup>

In a related study, the chiral ketones 3a, mp 59-60.5 °C,  $[\alpha]_D = -155.6^\circ$  (CHCl<sub>3</sub>, C = 0.0447 g/mL), and 3b, mp 73-74.5°C,  $[\alpha]_D = -157.8^\circ$  (CHCl<sub>3</sub>, C = 0.0203 g/mL), prepared from *S*-(-)-proline were examined in analogous aldol condensations (Scheme II). The lithium enolates derived from 3a and 3b (LDA) were condensed with the indicated aldehydes under "kinetic" conditions (-78°C, 5 sec) and compared to the analogous dibutylboron enolate condensations (-78°C, 30 min).<sup>1b</sup> Product diastereoisomer ratios 4:5 were determined by analytical HPLC and <sup>13</sup>C NMR spectroscopy. After chromatographic separation, the absolute configurations of 4a (R<sub>2</sub> = Ph), mp 162-163°C,  $[\alpha]_D = -90.9^\circ$  (CHCl<sub>3</sub>, C = 0.0444 g/mL) and 4a (R<sub>2</sub> = *i*-C<sub>3</sub>H<sub>7</sub>), oil,  $[\alpha]_D = -115.3^\circ$  (CHCl<sub>3</sub>, C = 0.0075 g/mL), were determined by oxidation (CH<sub>3</sub>CO<sub>3</sub>H, Na<sub>2</sub>HPO<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 25°C) to 6a (R<sub>2</sub> = Ph),  $[\alpha]_D = +21.0^\circ$  (EtOH, C = 0.0148 g/mL) and 6a (R<sub>2</sub> = *i*-C<sub>3</sub>H<sub>7</sub>),  $[\alpha]_D = +40.5^\circ$  (CHCl<sub>3</sub>, C = 0.0063 g/mL) whose absolute configurations have been established.<sup>4</sup> Erythro-adduct 4b (R<sub>2</sub> = *i*-C<sub>3</sub>H<sub>7</sub>) was purified by direct crystallization (57%), mp 155.5-156.5°C,  $[\alpha]_D = -92.5^\circ$  (CHCl<sub>3</sub>, C = 0.0294 g/mL). The absolute configuration of 4b (R<sub>2</sub> = *i*-C<sub>3</sub>H<sub>7</sub>) was determined by non-regioselective Baeyer-Villiger oxidation, as described above (45°C, 72 h), to give the enantiomerically pure 2(R),3(S)-*β*-hydroxyacid 6b (R<sub>2</sub> = *i*-C<sub>3</sub>H<sub>7</sub>),  $[\alpha]_D = +10.5^\circ$  (CHCl<sub>3</sub>, C = 0.0921 g/mL) whose absolute configuration has been unambiguously determined.<sup>5</sup>

As summarized in the Table, asymmetric induction during the aldol process is clearly influenced by the metal center with enhanced chirality transfer being observed with the boron enolates in nonpolar solvents. The boron enolate derived from 3a exhibited modest asymmetric

## Scheme 11

Table I. Aldol Condensations of Ketones  $\underline{3a}$ ,  $\underline{3b}$ .<sup>3</sup>

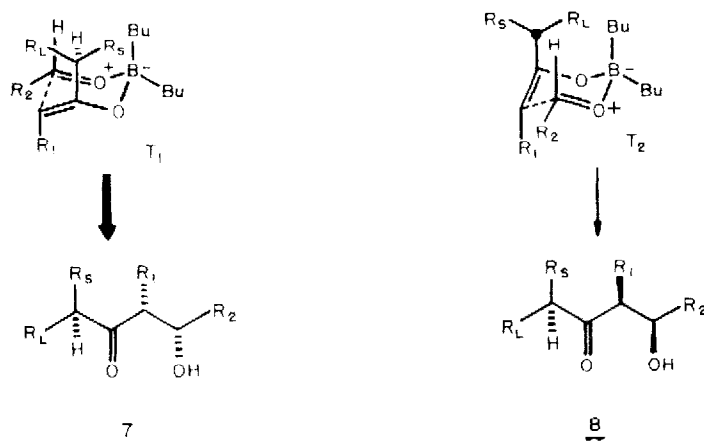
Entry	$R_1$	Metal	Solvent	$R_2CHO$	Ratio $\underline{4}:\underline{5}$ <sup>a</sup>	Yield, % <sup>b</sup>
A	H	Li <sup>c</sup>	Et <sub>2</sub> O	PhCHO	45:55	(75)
B	H	Li	Et <sub>2</sub> O	<i>i</i> -PrCHO	54:46	(75)
C	H	Bu <sub>2</sub> B <sup>d</sup>	Et <sub>2</sub> O	<i>i</i> -PrCHO	72:28	77
D	H	Bu <sub>2</sub> B	CH <sub>2</sub> Cl <sub>2</sub>	PhCHO	83:17	(80)
E	H	Bu <sub>2</sub> B	CH <sub>2</sub> Cl <sub>2</sub>	<i>i</i> -PrCHO	74:26	(91)
F	CH <sub>3</sub>	Li	THF	<i>i</i> -PrCHO	70:30	79
G	CH <sub>3</sub>	Bu <sub>2</sub> B	CH <sub>2</sub> Cl <sub>2</sub>	<i>i</i> -PrCHO	>97:3	57

a) Product ratios  $\underline{4}:\underline{5}$  determined by analytical HPLC of unpurified aldol adducts.  
 b) Isolated yields; values in parentheses refer to yields determined by NMR.  
 c) Aldol condensations carried out at  $-78^\circ\text{C}$  (5 sec). d) Condensations carried out at  $-78^\circ\text{C} \rightarrow 0^\circ\text{C}$ .

induction in methylene chloride ( $\underline{4}:\underline{5} = 3:5$ ) while the *Z*-boron enolate  $\underline{3b}$  gave a ratio of  $\underline{4}:\underline{5} \geq 32$  (Entry G). The comparative lithium enolate aldol condensations (Entries A, B, F) were less stereoselective in all cases. In the condensations of ketone  $\underline{3b}$  minor amounts of the threo-aldol products were observed (10% for boron, 20% for lithium). Our inability to efficiently generate the alternate *E*-boron enolate derived from ketone  $\underline{3b}$  thwarted attempts to examine the influence of the alternate "trans"-enolate geometry on the nature of chirality transfer in this system.

Given the reasonable postulate that the aldol condensation proceeds via a pericyclic process,<sup>6</sup> two reasonable diastereoisomeric transition states,  $T_1$  and  $T_2$ , which accommodate minimal nonbonded interactions with the aldehyde are illustrated in Scheme III for methyl ketone and cis-enolates ( $R_1 = \text{H, Me}$ ). Substituents  $R_S$  and  $R_L$  are respectively designated as "small" and "large". In those transition states involving boron, where both chelation (with  $R_S$  or  $R_L$ ) and aggregation phenomena are absent, one might expect transition state  $T_1$  to be preferred over  $T_2$  as a consequence of the influence of metal-center steric parameters ( $R_S \leftrightarrow \text{Bu} < R_L \leftrightarrow \text{Bu}$ ). All of the cases examined in this study can be interpreted to proceed preferentially through the illustrated  $T_1$ -transition state. Related studies by Heathcock with lithium enolates ( $R_L = \text{t-Bu}$ ,  $R_S = \text{OSiMe}_3$ ,  $R_1 = \text{Me}$ ) exhibit good diastereoselection of the type under discussion where the preferred aldol diastereoisomer 7 is the postulated product.<sup>2b</sup>

Scheme III



Acknowledgement. Support from the National Institutes of Health (GM-23991) is acknowledged.

#### References and Notes

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(Received in USA 14 August 1980)