Stereoselective Aldol Condensations via Boron Enolates[1]

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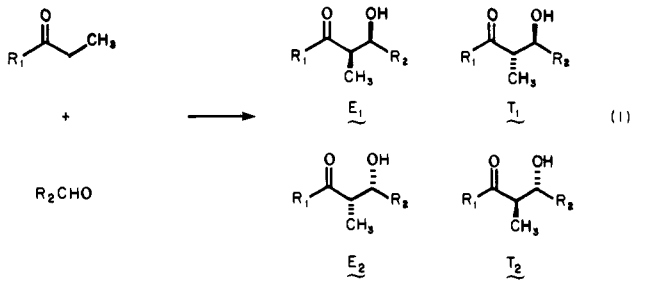
Abstract: A detailed investigation of the enolization of a variety of ketones and carboxylic acid derivatives with dialkylboryl triflates in the presence of a tertiary amine and the subsequent aldol condensations of these boron enolates was conducted. The stereochemistry of the enolates formed from acyclic ketones was found to be dependent on the structure of the ketone, the dialkylboryl triflate, and the tertiary amine. A mechanism for the enolization involving initial coordination of the boryl triflate to the ketone carbonyl with subsequent deprotonation by the amine is proposed to explain the results. The boron enolates derived from these acyclic ketones undergo aldol condensation with a number of aldehydes in good yield. Consistently good correlation was observed between the enolate geometry and the product aldol stereochemistry for these acyclic ketones regardless of the structure of the ketone or the boron ligands. However, for the boron enolate derived from cyclohexanone the aldol stereoselectivity was dependent on the boron ligands and the solvent. In this case, the use of the cyclopentylthexylboron enolate in tetrahydrofuran as solvent resulted in complete stereocontrol in the condensation. Although simple esters and amides cannot be enolized with the triflate reagents, *tert*-butyl thiopropionate was readily converted to the trans enolate. The stereoselectivity of the aldol condensations of this enolate is also dependent on the boron ligands and the solvent; again, the proper choice of these parameters allowed total stereocontrol of the condensation. It was found that carboxylic acids could be converted to the dialkylboryl enediolates, and the aldol condensations of these species were used to probe the relative reactivity of cis and trans enolates. Chiral boron enolates were studied for possible asymmetric induction in the aldol condensation. Methyl ketone enolates exhibited moderate levels of chirality transfer, while cis enolates gave only one detectable diastereoisomer. The sense of chirality transfer was proven by determination of the absolute configurations of newly created centers of asymmetry. A transition state model based on steric interactions is proposed for chirality transfer.

Introduction

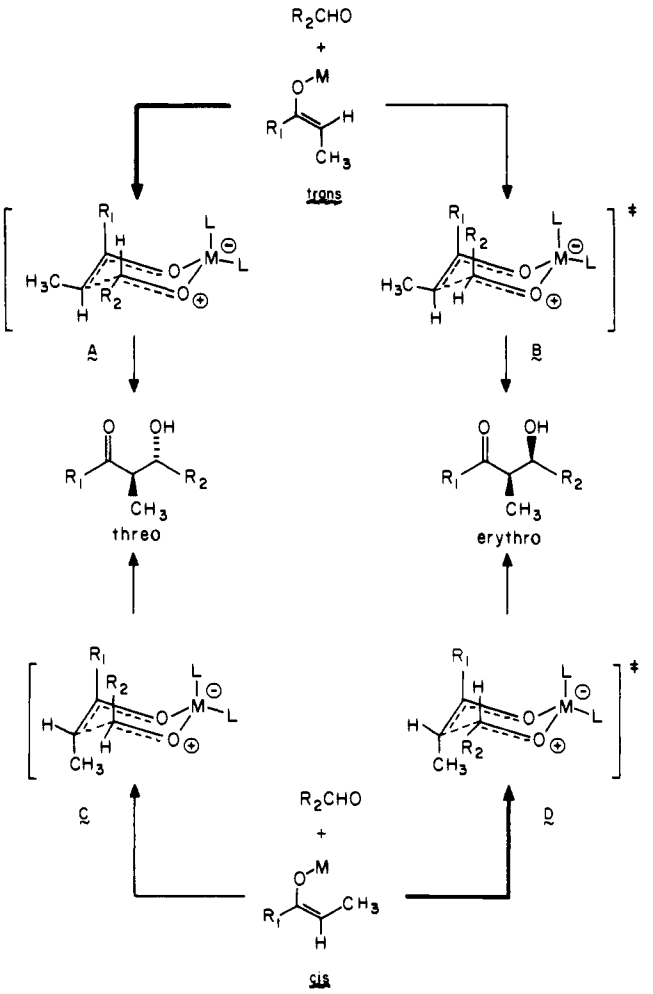
The aldol condensation is a reaction of fundamental importance in the biosynthesis of a broad range of biologically significant natural products. The recognition of both the macrolide and ionophore antibiotics as attainable targets for synthesis has been instrumental in focusing renewed interest toward the development of stereoregulated variants of this process in the laboratory.[3] Ideally, it would be significant to reveal those stereochemical issues which deal with the control of *both* reaction diastereoselection ($E_1 + E_2$ vs. $T_1 + T_2$) and enantioselection (E_1 vs. E_2 or T_1 vs. T_2) for a range of reaction substrates (eq 1).



(1)

In 1957, in conjunction with a stereochemical study of the Ivanov and Reformatsky reactions, Zimmerman and Traxler accounted for the observed aldol diastereoselection by advancing the hypothesis that the reaction proceeded via a preferred chairlike transition state involving cooperative metal ion ligation of both the enolate and carbonyl substrates (cf. Scheme I).[4] Subsequent investigations by Dubois[5] and more recently by Heathcock[6] on preformed lithium enolates have unambiguously shown that *kinetic* aldol diastereoselection is, in part, defined by enolate geometry. With regard to the pericyclic chair transition states illustrated in Scheme I, both "trans" and "cis" lithium enolates (M = Li) exhibit excellent kinetic threo and erythro product selection, re-

Scheme I



(1) Aspects of this work have been previously disclosed: (a) Evans, D. A. 15th Eurochem Conference on Stereochemistry, Burgenstock, Switzerland, April 29, 1979. (b) Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120-6123. (c) Evans, D. A.; Taber, T. R. *Tetrahedron Lett.* **1980**, 4675-4678.

(2) Abstracted from the Ph.D. Theses of J. V. Nelson and T. R. Taber.

(3) For a review of early efforts in this area see: Nielson, A. T.; Houlihan, W. J. *Org. React.* **1968**, *16*, 1-438.

(4) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920-1923.

(5) (a) Dubois, J. E.; Fort, J. F. *Tetrahedron* **1972**, *28*, 1653-1663, 1665-1675, and references cited therein. (b) Dubois, J. E.; Fellman, P. *C. R. Acad. Sci.* **1972**, *274*, 1307-1309. (c) Dubois, J. E.; Fellman, P. *Tetrahedron Lett.* **1975**, 1225-1228.

(6) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066-1081, and citations to earlier work.

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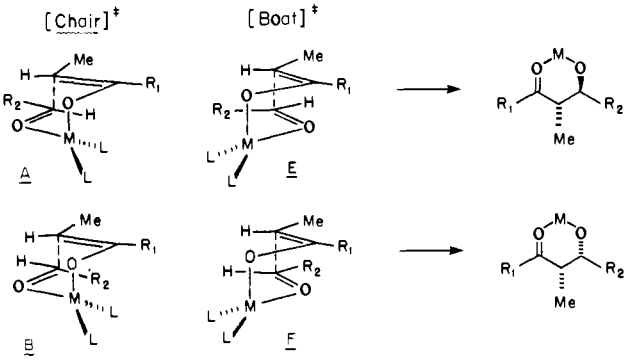
Scheme II



spectively, when the enolate ligand, R_1, is sterically demanding such as *tert*-butyl. The observation that the steric bulk of R_1 (t-C_4H_9 > i-C_3H_7 > C_2H_5 > OCH_3 > H) and the attendant aldol diastereoselection[5,6] are directly coupled is consistent with the elaborated Zimmerman model (Scheme I).[4] For example, for trans enolates transition state B is destabilized relative to A owing to $R_1 \leftrightarrow R_2$ interactions. Related trends in aldol stereoselection have been noted for magnesium,[7] zinc,[8] and aluminum[9] enolates.

At the outset of the present study the decision was made to explore the role of "metal-centered steric effects" in the kinetic aldol process.[1] Within the context of the diastereoisomeric chair transition states illustrated in Scheme I, the pseudo-1,3-diaxial $R_2 \leftrightarrow L$ interactions in transition states B and C might confer enhanced aldol diastereoselection from either enolate geometry. Given the assumption that the chair transition state geometry is preferred, it follows that both the enolate ligand, R_1, and the metal ligand, L, will contribute in a *complementary* fashion to enhanced aldol diastereoselection. It was also felt that an examination of metal ligand steric effects in the aldol process might also provide direct evidence pertaining to the actual transition state geometry (boat vs. chair). If one examines the four diastereoisomeric transition states for a given enolate geometry (Scheme II), it is projected that in the chair transition state geometries, $R_1 \leftrightarrow R_2$ and $L \leftrightarrow R_2$, steric parameters will contribute in a *complementary* fashion to destabilize B relative to A. However, for the diastereoisomeric boat transition states E and F, the enolate ligand, R_1, and the metal ligand, L, control elements will operate in a *non-complementary* fashion. Consequently, an examination of the effects of structural variation at the metal center (ML_2) *and* enolate ligand, R_1, might reveal the actual transition geometries in question. For the reasons outlined in our earlier communication,[1b] dialkylboryl enolates appeared to be excellent candidates for study. A limited number of literature cases indicated that good levels of aldol diastereoselection might be anticipated.[10] This paper reports the full details of our initial investigations into the generation of stereochemically homogeneous boron enolates and their stereoselective aldol condensations with aldehydes. The parallel investigations of Masamune[11] and Mukaiyama[12] are in accord with those made in the present study.

Results and Discussion

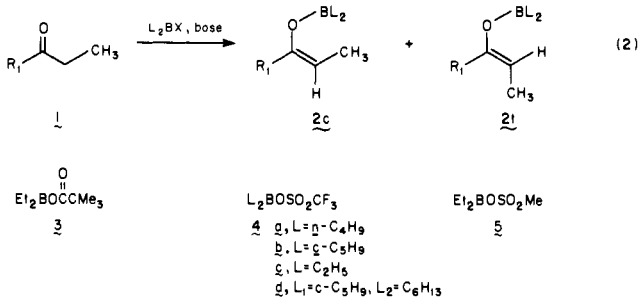
Selective Generation of Boron Enolates. A variety of published methods exist for the generation of dialkylboryl enolates.[13]

Table I. Kinetic Enolate Formation with Triflates 4a and 4b (Eq 2)

entry	1, R_1 =	4, L =	base[a]	conditions[b]	ratio 2c:2t[c,d]
A	Et	n-C_4H_9	DPEA	−78 °C, 30 min	>97:3
B	Et	n-C_4H_9	Lut	−78 °C, 30 min	69:31
C	Et	n-C_4H_9	Lut	+77 °C, 3 h[e]	(86:14)
D	Et	c-C_5H_9	DPEA	0 °C, 30 min	82:18
E	Me_2CH	n-C_4H_9	DPEA	−78 °C, 30 min	45:55
F	Me_2CH	n-C_4H_9	Lut	−78 °C, 30 min	56:44
G	Me_2CH	n-C_4H_9	Lut	+77 °C, 30 min[e]	(73:27)
H	Me_2CH	c-C_5H_9	Lut	0 °C, 30 min	42:58
I	Me_2CH	c-C_5H_9	DPEA	0 °C, 30 min	19:81
J	Me_3C	n-C_4H_9	DPEA	0 °C, 30 min[f]	25:75
K	Me_3C	n-C_4H_9	DPEA	+35 °C, 2 h	(>97:3)
L	Me_2CHCH_2	n-C_4H_9	DPEA	−78 °C, 30 min	>97:3
M	C_6H_5	n-C_4H_9	DPEA	25 °C, 1 h	>97:3
N	Me_3CS	n-C_4H_9	DPEA	0 °C, 30 min	≤5:95

[a] DPEA = diisopropylethylamine, Lut = 2,6-lutidine. [b] Except where noted, all reactions carried out in ether. [c] Enolate ratios determined on trimethylsilyl enol ethers (see text) by ^1H NMR and/or gas chromatography by comparison with independently prepared samples (cf. ref 6). [d] Values reported are kinetic ratios; those in parentheses are equilibrium values. [e] Reactions carried out in CCl_4; prolonged reaction times did not change enolate ratio. [f] Incomplete enolization of substrate noted.

Nonetheless, only two procedures have been developed which involve the direct enolization of carbonyl substrates.[10b,14] Köster has reported that ethyl ketones **1** (R_1 = C_2H_5, i-C_3H_7, C_6H_5, c-C_6H_{11}) react at elevated temperatures (85–110 °C) with triethylborane under the catalytic influence of **3** to give enolates **2c** and **2t** (L = Et) under presumed equilibrating conditions[10b] (eq 2). Mukaiyama has recently disclosed that the dibutylboryl



(2)

trifluoromethanesulfonate (**4a**), in the presence of either 2,6-lutidine (Lut) or diisopropylethylamine (DPEA), rapidly enolizes ketones in ethereal solvents at low temperature (≥−78 °C). Stereoselective enolate formation was not addressed in this study.[14] In conjunction with the present investigation, the issue of selective enolate generation via the boryl triflate reagents **4** was undertaken. Substrate and reaction variables which include the influence of carbonyl ligand (R_1), boron ligand (L), base, and solvent have been examined. The boryl triflate reagents **4a–c** were prepared from the corresponding trialkylborane (L_3B) and trifluoromethanesulfonic acid in high yield as air- and moisture-sensitive distillable liquids in direct analogy with literature precedent.[12,15]

The general procedure for enolate formation involved reaction of equimolar quantities of ketone or thioester **1** and boryl triflate **4** in the presence of 1.1 equiv of tertiary amine base in anhydrous ether at temperatures ranging from −78 to 25 °C depending upon the particular carbonyl substrate. The precipitation of insoluble ammonium triflate in ethereal and hydrocarbon solvents accompanied enolate formation. Attempts to directly transform the

(7) Fellmann, P.; Dubois, J. E. *Tetrahedron* **1978**, *34*, 1349–1357.
(8) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310–3324.
(9) (a) Jeffrey, E. A.; Meisters, A.; Mole, T. *J. Organomet. Chem.* **1974**, *74*, 365–372, 373–384. (b) Maruoka, K.; Hashimoto, S.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 7705–7707.
(10) (a) Mukaiyama, T.; Inomata, K.; Muraki, M. *J. Am. Chem. Soc.* **1973**, *95*, 967–968. (b) Fenzl, W.; Köster, R. *Justus Liebigs Ann. Chem.* **1975**, 1322–1338. (c) Fenzl, W.; Köster, R.; Zimmerman, H. J. *Ibid.* **1975**, 2201–2210.
(11) (a) Masamune, S.; Mori, S.; Van Horn, D.; Brooks, D. W. *Tetrahedron Lett.* **1979**, 1665–1668. (b) Hirama, M.; Masamune, S. *Ibid.* **1979**, 2225–2228. (c) Van Horn, D. E.; Masamune, S. *Ibid.* **1979**, 2229–2232. (d) Hirama, M.; Garvey, D. S.; Lu, L. D.-L.; Masamune, S. *Ibid.* **1979**, 3937–3940.
(12) Inoue, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174–178.
(13) (a) Tufariello, J. J.; Lee, L. T. C.; Wojtkowski, P. *J. Am. Chem. Soc.* **1967**, *89*, 6804–6805. (b) Pasto, D. J.; Wojtkowski, P. *Tetrahedron Lett.* **1970**, 215–218. (c) Hooz, J.; Linke, S. *J. Am. Chem. Soc.* **1968**, *90*, 5936–5937. (d) Brown, H. C.; Rogič, M. M.; Rathke, M. W.; Kabalka, G. W. *Ibid.* **1968**, *90*, 818–820. (e) Inomata, K.; Muraki, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1807–1810.
(14) Mukaiyama, T.; Inoue, T. *Chem. Lett.* **1976**, 559–562.
(15) Trofimenko, S. *J. Am. Chem. Soc.* **1969**, *91*, 2139–2140.

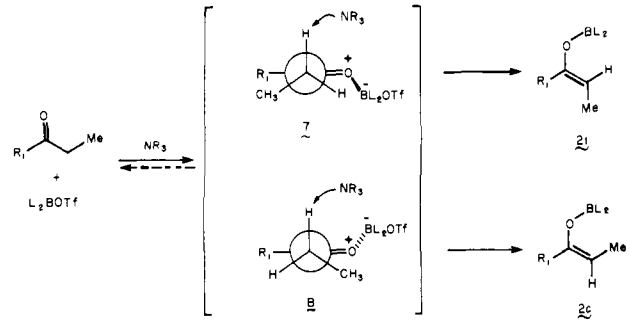
resultant boron enolates (**2c**, **2t**) to enol derivatives which could be more conveniently analyzed led to the unanticipated observation that these nucleophiles did *not* react cleanly with either chlorotrimethylsilane or acetic anhydride. This problem was circumvented by conversion of the **2c**–**2t** mixtures to the analogous lithium enolates with ≥2 equiv of butyl- or methyllithium[16] followed by derivatization with chlorotrimethylsilane. The derived trimethylsilyl enol ethers were compared with independently prepared samples which have been previously characterized.[6] The only ambiguity in enolate stereochemical assignment was that for the enolsilane derived from *tert*-butyl thiopropionate (**6**) (Table I, entry N). The enolate stereochemistry in this system was assigned in analogy to that observed for the related propionate esters since the major enol silane isomer derived from **6** had the same stereochemistry as that derived from enolization with lithium diisopropylamide (−78 °C, THF; 10:90).[17] Table I summarizes the variable reaction and substrate parameters which were studied. Boron enolates **2c** and **2t** were found to be configurationally stable at 25 °C for as long as 2 h in the presence of the DPEA·HOTf and at 0 °C (30 min) in the presence of Lut·HOTf. At elevated temperatures (77 °C, CCl_4) complete enolate equilibration (**2c** ⇌ **2t**) could be achieved (entries C and G). As anticipated, enolate equilibrium is reached more rapidly in the presence of the stronger acid, Lut-HOTf. With the exception of entries C, G, and K, all reported enolate ratios are presumed to be kinetically controlled (Table I).

The data in Table I reveal a number of significant trends which bear on the enolization mechanism. Entries A and B illustrate the importance of increased amine steric hindrance in maximizing kinetic selection in the deprotonation process. Relative to the influence of the boron ligand (L), a comparison of the enolate ratios derived from the use of triflates **4a** (L = *n*-C_4H_9) and **4b** (c-C_5H_9) on 3-pentanone (entries A, D) and isopropyl ethyl ketone (entries E, I) as informative. With a given base (DPEA), the more hindered boryl triflate **4b** exhibits enhanced kinetic selection for trans enolate formation. These observations parallel those noted by Masamune and co-workers.[11b] As anticipated, the more hindered triflate (**4b**) is less reactive in the enolization process than either **4a** or **4c**, and reactions with this reagent must be carried out at 0 °C (entry D). No significant differences in reaction stereoselection were noted between the dibutyl- and diethylboryl triflates **4a** and **4c**, and the pyrophoric nature of **4c** renders it less attractive as a reagent. Finally, for a given amine base (DPEA) and triflate (**4a**), ketone substrates **1** (R_1 = Et, Me_2CH, Me_3C) exhibit a qualitative *decrease* in cis-enolate kinetic selection with *increased* steric requirements of R_1 (entries A, E, J). In addition to the studies noted above which were carried out in ether, it was found that a range of other solvents could be employed with equal facility (CCl_4, $CHCl_3$, CH_2Cl_2, C_6H_6, C_5H_{12}) with only *minor* variations in *kinetic* enolate selection. However, those solvents which solubilize the ammonium triflate were generally employed to effect enolate equilibration at elevated temperatures (entries C, G, K). Solvent effects in the aldol condensation of these enolates, however, were found to be significant (cf. Tables III, V–VII) and will be discussed in the following sections.

In addition to the observations noted above, additional experiments which could have a bearing on the enolization mechanism were carried out. An examination of the ^1H NMR spectra ($CDCl_3$) of equimolar solutions of boryl triflate **4a** and both ,6-lutidine and diisopropylethylamine (DPEA) revealed 1:1 complexation between the two reagents (eq 3). Complexation

$$Bu_2B{-}OTf + R_3N \rightleftharpoons Bu_2\overset{-}{B}{-}\overset{+}{N}R_3 \quad (3)$$
$$\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\quad OTf$$

Scheme III



was complete within minutes with lutidine and in 30 min with the more hindered base at 25 °C. The ^{11}B NMR spectrum of the complex was indicative of a tetracoordinate species.[18] Our observations that other less hindered nitrogen bases such as pyridine, Dabco, DBU, and tetramethylguanidine are totally ineffective in the enolization process could be attributed to the *irreversible* amine–borane complexation.[19]

To account for all observations pertaining to kinetic deprotonation, the mechanistic model in Scheme III is proposed. (A) Trans and cis enolates **2t** and **2c** are derived from deprotonation of syn and anti complexes **7** and **8**, respectively. (B) Deprotonation tends to be the rate-determining step rather than complexation. (C) All factors being equal (R_1 = Et), e.g., **7** = **8**, anti deprotonation (**8** → **2c**) is preferred over syn deprotonation (**7** → **2t**) with hindered bases.

Assumption A is based upon allylic strain arguments and related observations in hydrazone deprotonation.[20] Assumption B is consistent with both the substrate studies (Table I) and the product selection as a function of base structure. Finally, assumption C must be proposed to explain the high cis-enolate stereoselection for 3-pentanone and related systems. By inspection, the transition states for syn and anti deprotonation (cf. **7** vs. **8**) could well be influenced by amine steric hindrance. With hindered bases (DPEA), deprotonation of the anti complex **8** could well be preferred on steric grounds (Table I, entry A). However, with less hindered amines the relative rates of deprotonation of the syn and anti complexes could be attenuated. The observation that *tert*-butyl thiopropionate (**6**) forms predominately the trans enolate (**2t**:**2c** ≥ 95:5) is consistent with the expectation that **7** (R_1 = *S*-*t*-Bu) might be expected to be more stable than **8** (R_1 = *S*-*t*-Bu) based upon analogous geometrical preferences for related onium ions.[21] This model for enolization appears to be internally consistent with the above observations that the relative stabilities of syn and anti boryltriflate carbonyl complexes could be an important consideration in the kinetic enolization process. It should be pointed out that the actual structures of the carbonyl–boron complexes remain undefined. The conclusions drawn from the deprotonation studies in Table I must be tempered by the observation by Masamune that for thioester **1** (R_1 = SC_6H_5) and 9-BBN triflate (Et_2O, 0 °C, DPEA) selective cis-enolate (**2c**) formation must be inferred from the stereochemical outcome of the resultant aldol condensation.[11d]

One other potentially attractive method was briefly explored for the stereoselective synthesis of boron enolates (eq 4). It was found that trimethylsilyl enol ethers react rapidly with the boryl triflate reagents to give boron enolates in high yield. However,

(16) Pasto, D. J.; Wojtkowski, P. W. *J. Org. Chem.* **1971**, *36*, 1790–1792. For related studies see: Negishi, E.; Idacavage, M. J. *Tetrahedron Lett.* **1979**, 845–848.

(17) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868–2877. For related studies on the enolization of **6** with lithium diisopropylamide see: Evans, D. A.; McGee, L. R. *Tetrahedron Lett.* **1980**, 3975–3978.

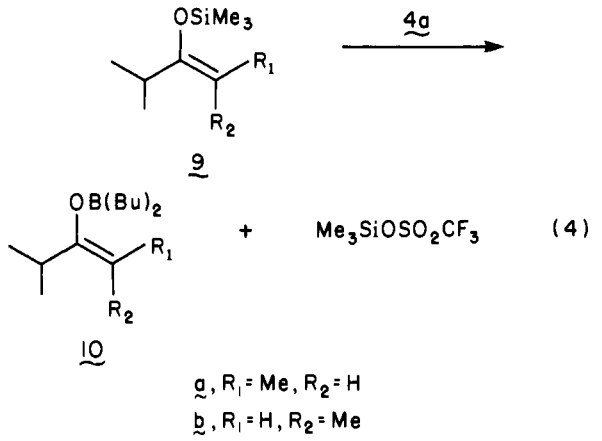
(18) Experiments carried out by L. R. McGee.

(19) Mukaiyama[12] has noted that triethylamine is a suitable base.

(20) Bergbreiter, D. E.; Newcomb, M. *Tetrahedron Lett.* **1979**, 4145–4148. Jung, M. E.; Shaw, T. J.; Fraser, R. R.; Banville, J.; Taymaz, K. *Ibid.* **1979**, 4149–4152. Davenport, K. G.; Eichenauer, H.; Enders, D.; Newcomb, M.; Bregbreiter, D. E. *J. Am. Chem. Soc.* **1979**, *101*, 5654–5659.

(21) This conclusion is drawn from the observed stabilities of isomeric dioxolenium ions and protonated thioesters. Borch, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5303–5305. Olah, G. A.; Ku, A. T. *J. Org. Chem.* **1970**, *35*, 331–335.

(22) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324–2336.

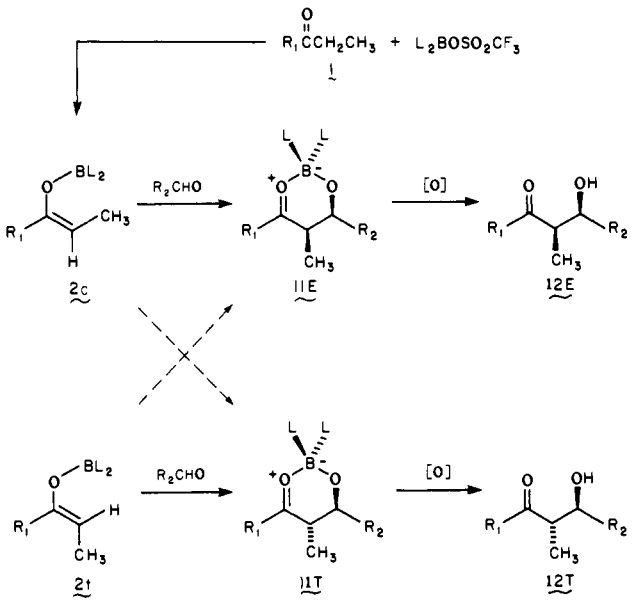


this exchange process is accompanied by a *significant* loss in product stereochemistry as judged by the resultant aldol condensation experiments (vide infra). Subsequent to this study, Kuwajima has reported that these exchange reactions appear to be stereospecific in nature.[23] The low diastereoselection observed by us was due to a nonstereoselective aldol process initiated by the byproduct trimethylsilyl triflate. This exchange method could prove to be useful in the synthesis of boron enolates which are inaccessible via the triflate reagents.[24]

Stereoselective Aldol Condensations. The initial set of aldol condensation conditions was similar to those reported by Mukaiyama (Et_2O, −78 °C, DPEA)[14] with either dibutyl- or dicyclopentylboryl triflates **4a** and **4b**. The derived ketol borate complexes **11E** and **11T** (Scheme IV) were oxidized to the erythro and threo ketols **12E** and **12T** by one of two procedures. For some substrates the reported buffered hydrogen peroxide procedure[14] was found adequate; however, for more sensitive substrates such as thioesters, the oxidant MoO_5·py·HMPT (MoOPH)[25] was found to be superior. In order to ensure that the aldol diastereoisomer ratios **12E**:**12T** reflected the kinetic product ratios, several aldol *ate*-complex stability studies were carried out. Treatment of **11E** (R_1 = Et, R_2 = Ph; E:T ≥ 97:3), formed from **12E** with triflate **4a**, under the conditions of both aldol condensation and subsequent oxidative isolation resulted in recovery of the ketol **12E** with *no* loss in stereochemistry. The ate-complex **11E** (R_1 = Et, R_2 = Ph) exhibited no tendency to isomerize in refluxing ether (3 h) even in the presence of 0.3 equiv of DBU. Some isomerization was noted (**11E**:**11T** = 63:37), however, in refluxing toluene (1.0 h, 0.3 equiv of DBU). We surmise that this equilibration is not proceeding via retro-aldolization, but by acid–base deprotonation of the "ate" complex. It was found that the above equilibration procedure was not synthetically viable for the production of the thermodynamically more stable threo aldol chelates owing to the intervention of other side reactions. Related stability studies on the cyclohexanone aldol adducts **14E** and **14T** also ensured that kinetic product ratios were obtained.

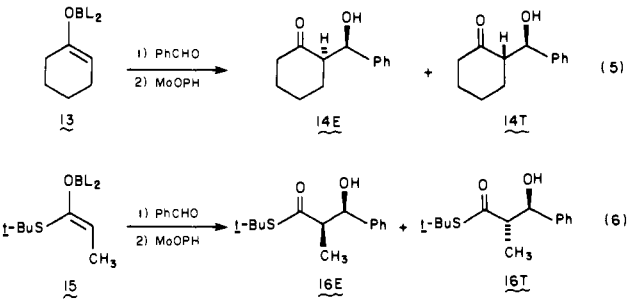
From the data in Table II, in which reaction solvent and temperature (Et_2O, −78 °C) variables were held constant, there is a consistently good correlation between enolate geometry and product aldol stereochemistry. For the 3-pentanone cis enolate (**2c**, R_1 = Et), the aldol diastereoselection ratio, **12E**:**12T**, corresponds to the enolate ratio **2c**:**2t** within experimental error for not only benzaldehyde, but also the aliphatic aldehydes (entries A, B, C, D, G). Both α-methacrolein and tiglic aldehyde (entries E, F) were somewhat less stereoselective. Similar trends were also observed with the thioester **6** (entries S–X). Another significant conclusion can be drawn from the data on the effects of

Scheme IV



the boron ligand, L, on aldol diastereoselection. For three enolates (R_1 = Et, *i*-C_3H_7, *t*-BuS), the change in boron ligand from *n*-butyl to cyclopentyl results in only a minor (≤5%) enhancement reaction selectivity (entries A, G; J, K; S, T). On the other hand, it is apparent that, in the majority of cases, boron ligand structure plays a *significant* role in the enolization process (Table I).

Based upon the excellent aldol diastereoselection observed with the acyclic carbonyl substrates, it was surprising to observe that the cyclohexanone enolate (L = *n*-C_4H_9) condensation (Et_2O, −78 °C) with benzaldehyde (eq 5) exhibited relatively low stereose-



lection (**14E**:**14T** = 33:67). Accordingly, enolates **13** and **15** were chosen to study the interplay of both solvent effects and boron ligand structure on reaction stereoselection (Table III).

For a given boron ligand there is a small but consistent improvement in aldol diastereoselection when less polar solvents are employed. This trend is observed for both enolates **13** and **15**. In subsequent studies we have found that aldol diastereoselection in methylene chloride is comparable to that observed in pentane, and the former is frequently the solvent of choice (cf. Table V). Assuming that these reactions proceed via the pericyclic aldol mechanism (Scheme I), the less polar solvents could well result in "transition state compression", thereby enhancing those steric parameters which appear to regulate diastereoselection. The solvent effects noted above have also been found to be significant in enolate chirality transfer (vide infra). In an effort to further enhance aldol selection for enolate **13**, we prepared the sterically demanding thexylcyclopentylboryl triflate **4d** from the corresponding boron hydride[26] and TfOH. In view of our earlier results, the high diastereoselection observed with this mixed ligand was gratifying.

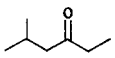
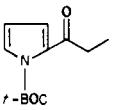
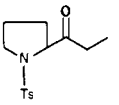
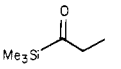
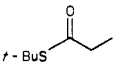
(23) Kuwajima, I.; Kato, M.; Mori, A. *Tetrahedron Lett.* **1980**, 4291–4294.

(24) The triflate reagents are ineffective in the formation of both ester and amide enolates.

(25) (a) Schmitt, G.; Olbertz, B. *J. Organomet. Chem.* **1978**, *152*, 271–279. (b) Mimoun, M.; Seree de Roch, L.; Sajus, L. *Bull. Chim. Soc. Fr.* **1969**, 1481–1492.

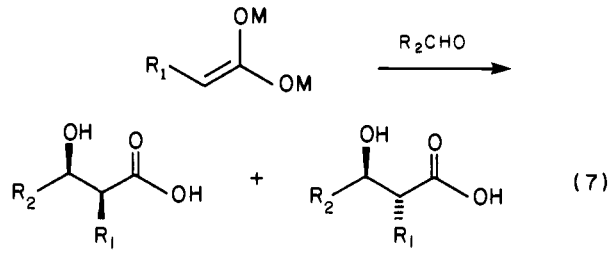
(26) (a) Brown, H. C.; Negishi, E. *J. Am. Chem. Soc.* **1972**, *94*, 3567–3572. (b) Brown, H. C.; Pfaffenberger, D. *Ibid.* **1967**, *89*, 5475–5477.

Table II. Kinetic Aldol Condensations With Representative Aldehydes at −78 °C (Scheme III)

entry	$R_1C(=O)-CH_2CH_3$	$R_2C(=O)-H$	L_2BOTf[a]	enolization T, °C	ratio[b] 2c:2t	ratio[c] 12E:12T	yield, %[d]
A		C_6H_5-CHO	n-C_4H_9	−78	>97:3	>97:3	77
B		C_6H_5-CHO	n-C_4H_9[e]	−78	69:31	72:28	76
C		n-C_3H_7-CHO	n-C_4H_9	−78	>97:3	>97:3	65
D		i-C_3H_7-CHO	n-C_4H_9	−78	>97:3	>97:3	61
E		CH_2=C(CH_3)-CHO	n-C_4H_9	−78	>97:3	92:8	68
F		(E)-CH_3CH=C(CH_3)-CHO	n-C_4H_9	−78	>97:3	93:7	65
G		C_6H_5-CHO	c-C_5H_9	0	82:18	84:16	(86)
H		C_6H_5-CHO	n-C_4H_9	−78	>99:1	>97:3	82
I		C_6H_5-CHO	c-C_5H_9	0		84:16	(85)
J		C_6H_5-CHO	n-C_4H_9	−78	45:55	44:56	65
K		C_6H_5-CHO	c-C_5H_9	0	19:81	18:82	(87)
L		C_6H_5-CHO	n-C_4H_9	+35	>99:1	>97:3	65
M		C_6H_5-CHO	n-C_4H_9	+25	99:1	>97:3	82
N		C_6H_5-CHO	n-C_4H_9	−78		>97:3	70
O		i-C_3H_7-CHO	n-C_4H_9	+25		90:10	60
P		i-C_3H_7-CHO	c-C_5H_9[f]	+25		87:13	57
Q		C_6H_5-CHO	n-C_4H_9	−78		19:81	53
R		C_6H_5-CHO	c-C_5H_9	0		35:65	(68)
S		C_6H_5-CHO	n-C_4H_9	0	≤5:95	10:90	75
T		C_6H_5-CHO	c-C_5H_9	0	≤5:95	5:95	(90)
U		n-C_3H_7-CHO	n-C_4H_9	0	≤5:95	10:90	67
V		i-C_3H_7-CHO	n-C_4H_9	0	≤5:95	9:91	63
W	6	CH_2=C(CH_3)-CHO	n-C_4H_9	0	≤5:95	12:88	65
X		(E)-CH_3CH=C(CH_3)-CHO	n-C_4H_9	0	≤5:95	18:82	61

[a] In all cases diisopropylethylamine (DPEA) was used as the base and enolization was carried out in ether for 30 min except for entries M and N where a reaction time of 60 min was employed. [b] Data derived from Table I. [c] Aldol ratios determined by ^1H NMR or ^{13}C NMR. [d] Values reported are for isolated yields. Values in parentheses were determined by ^1H NMR. [e] Lutidine was employed as the base. [f] The reaction solvent was ether-CH_2Cl_2.

A significant body of literature has been devoted to an examination of enediolate aldol stereoselection (eq 7).[4,27] Although



(7)

our earlier attempts to enolize alkyl esters (methyl propionate) had not been successful, it was found that dialkylboryl propionates ($L_2BOCOEt$) are readily enolized by DPEA and triflates **4a** and **4b**. The addition of propanoic acid to 2 equiv of triflate and DPEA (Et_2O, 0 °C) resulted in the formation of enediolates **17a** and **17b** (R = CH_3), respectively (Scheme V). Both enolates were subjected to aldol condensation under the usual conditions (Et_2O, −78 °C). Enediolate **17a** (R = CH_3) afforded a ratio **18a**:**19a** = 35:65 while **17b** (R = CH_3) exhibited moderately greater threo diastereoselection (**18a**:**19a** = 20:80). Under similar conditions, the enediolate **17a** (R = OCH_2Ph) derived from benzyloxyacetic acid afforded *exclusively* the aldol stereoisomer **19b** in 85% yield.

Table III. Aldol Condensation of **13** and **15** with Benzaldehyde (Eq 5 and 6). Solvent and Ligand Effects

entry	enolate	L_1L_2BOTf[a]	solvent	ratio[b] E:T	yield, %[c] (E + T)
A	13	L_1, L_2 = n-C_4H_9	ether	33:67	71
B	13	L_1, L_2 = n-C_4H_9	pentane	17:83	100
C	13	L_1, L_2 = c-C_5H_9	ether	32:68	(74)
D	13	L_1, L_2 = c-C_5H_9	pentane	15:85	80
E	13	L_1 = c-C_5H_9, L_2 = C_6H_{13}[d]	CH_2Cl_2	6:94	68
F	13	L_1 = c-C_5H_9 (4d), L_2 = C_6H_{13}[d]	THF	<4:96	94 (73)
G	15	L_1, L_2 = n-C_4H_9(4d)	pentane[e]	5:95	92
		L_1, L_2 = c-C_5H_9	pentane[e]	≤5:95	84

[a] All reactions employed DPEA as base and were carried out at −78 °C. [b] Ratios determined by ^1H NMR. [c] Values refer to yields determined by ^1H NMR; those in parentheses were isolated. [d] 2,3-Dimethyl-2-butyl (thexyl). [e] For the comparative experiments in ether, see Table II, entries S and T.

Confirmation of the aldol stereochemistry in both cases was achieved by trans fragmentation with dimethylformamide dimethyl acetal to the trans and cis olefins **20** and **21**.[28,29] From the

(27) (a) Mulzer, J.; Segner, J.; Brüntrup, G. *Tetrahedron Lett.* **1977**, 4651–4654. (b) Mulzer, J.; Brüntrup, G.; Finke, J.; Zippel, M. *J. Am. Chem. Soc.* **1979**, *101*, 7723–7725, and references cited therein.

(28) (a) Hara, S.; Taguchi, H.; Yamamoto, H.; Nozaki, H. *Tetrahedron Lett.* **1975**, 1545–1548. (b) Vogel, E. Ph.D. Dissertation, ETH Zurich, 1978. (c) Fráter, G. *Helv. Chim. Acta* **1979**, *62*, 2825–2828. (d) Mulzer, J.; Brüntrup, G. *Tetrahedron Lett.* **1979**, 1909–1912.

Scheme V

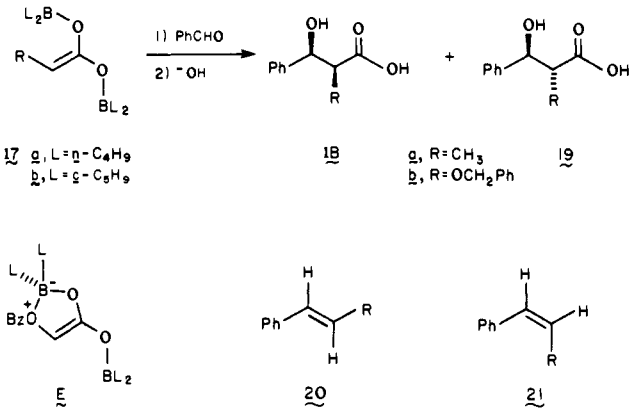
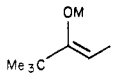


Table IV. Influence of Metal Center on Kinetic Aldol Reactions with Benzaldehydes

entry	enolate	metal (M)	erythro:threo
A		Li	>98:2[c]
		MgBr	>97:3[d]
		$B(C_4H_9)_2$	>97:3
B		Li	88:12[c]
		$B(C_4H_9)_2$	>97:3
C		Li[a]	80:20
		$B(C_4H_9)_2$	>97:3
D		Li[b]	60:40
		$B(C_4H_9)_2$	5:95
E		Li	48:52[c]
		$Al(Et)_2$	50:50[e]
		$B(C_5H_9)C_6H_{13}$	4:96

[a] Prepared from the (Z)-silylenol ether and methyllithium (ref 5c). [b] Prepared from 6 and LDA (THF); enolate ratio, 9:91; condensation carried out for 5 s. [c] Reference 6. [d] Reference 5b. [e] Reference 9b.

propionate aldol mixture (**18a**:**19a** = 20:80), this procedure afforded the ratio **20a**:**21a** = 20:80 while the hydroxy acid **19b** was observed to give exclusively the cis olefin **21b** (**20b**:**21b** ≤ 3:97). Since our earlier studies have demonstrated that boron enolate geometry *strongly* correlates with product stereochemistry, enediolate **17** can be employed directly to compare cis vs. trans boron enolate reactivity (k_{cis}:k_{trans} ≃ **18**:**19**) via internal competition. These experiments imply that trans propionate enolates, and presumably trans ethyl ketone enolates (cf. **2t**) exhibit somewhat *greater* reactivity (factor of 2–4) than the corresponding cis isomers.[30] These observations are in marked contrast to those of Dubois[5c] who observed that the trans lithium enolate derived from 3-pentanone reacted by a factor of 7–8 more slowly than the corresponding cis isomer. These differential rate effects could be interpreted in terms of diastereoisomeric transition state steric effects;[6] alternatively, differing levels of aggregation of the two lithium enolates could also account for the observed rate differences. The markedly enhanced aldol stereoselection which was observed for the benzyloxyacetic acid enediolate **17a** (R = OCH_2Ph) can be rationalized by invoking internal complexation (cf. E, Scheme V) between the *Z* boron and benzyloxy substituents.[30] Further studies on the boron enediolate systems are in progress and will be reported in due course.

Table IV summarizes the results of five kinetic metal enolate condensations with benzaldehyde. The influences of the metal

(29) The analogous trans fragmentations were also carried out with azodicarboxylate, Ph_3P; however, the yields in this reaction were inferior to the alternate method employed.[28]

(30) More detailed studies on boron enediolate condensations are currently in progress and will be reported shortly.

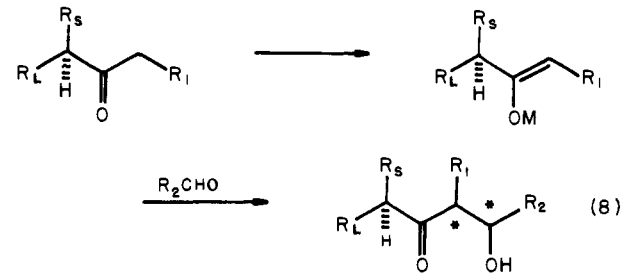
Table V. Metal-Dependent Aldol Condensations of Enolate 23 with Propanal (Eq 9)

entry	metal (M)	solvent	condensation[a] T, °C	ratio[b,c] 24:25
A	Li	THF-C_7H_8	−100	57:43[d]
B	Li	THF-C_7H_8	−100	55:45
C	Li	THF-C_7H_8	−78	53:47
D	$(n\text{-}C_4H_9)_2B$	pentane	−78	64:36
E	$(n\text{-}C_4H_9)_2B$	CH_2Cl_2	−78	63:37
F	$(n\text{-}C_4H_9)_2B$	ether	−78	57:43

[a] Reaction times were as follows: A, B, 15 min; C, 5 s; D–F, 30 min, 1 h at 0 °C. [b] Ratios were determined by analytical HPLC. [c] Yields for entries A, B = 65% (distilled); C–F = 81 ± 2% (unpurified). [d] Ratio determined by Seebach (±2%).[32]

center, M, and enolate ligand, R_1, on aldol stereoselection are readily accommodated by the general transition-state model (Scheme I). For cis enolates, when R_1 is large (entry A), transition state C, is strongly destabilized relative to D by $R_1 \leftrightarrow R_2$ interactions, and erythro diastereoselection is uniformly high. As the enolate ligand R_1 is decreased in size, the combination of steric effects of both R_1 and the metal center ($R_1 \leftrightarrow R_2$ and $R_2 \leftrightarrow L$) become important in maintaining erythro selectivity (entries B, C). Related arguments hold for trans enolates relative to transition state B. The *complementary* metal ligand and enolate ligand (R_1) control elements in the aldol process strongly support the contention that the preferred transition states possess the chair rather than boatlike geometry (cf. Scheme II).

Aldol Diastereoselection via Chiral Enolates. An important aspect of the aldol process pertains to the influence of resident chirality in the enolate in the aldol bond construction process (eq 8). It would be instructive to develop transition state models which



(8)

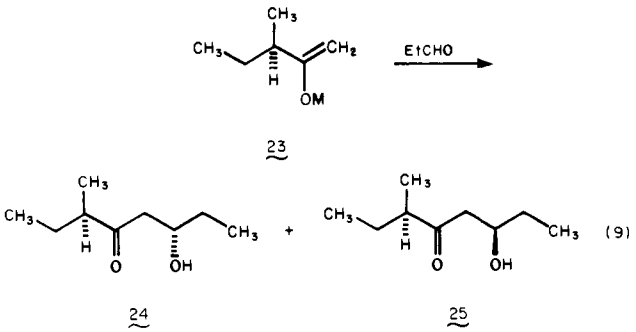
correlate the steric effects of ligands R_S (small) and R_L (large) with the sense of chirality transfer to the newly generated centers of asymmetry. Related generalizations for α-substituted chiral aldehydes are well recognized[31] (Cram's rule) and are of considerable value in stereoselective synthesis. 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).[32] Recently, Heathcock has reported enhanced diastereoselection for a more sterically biased lithium enolate (R_1 = Me, R_S = $OSiMe_3$, R_L = *t*-Bu).[33] It was of considerable interest to us to determine whether boron enolates would exhibit enhanced diastereoselection of the type illustrated. Accordingly, we have reexamined the aldol condensation reported by Seebach between the enolate derived from (±)-3-methyl-2-pentanone (**22**) and propanal (eq 9).[1b,34] Condensation of the lithium enolate **23** (M = Li) with propanal under the reported conditions (−100 °C, 15 min) afforded aldol diastereoisomers **24** and **25** (55:45) (Table V, entry B) in a ratio which was in excellent agreement with that reported by Seebach (**24**:**25** = 57:43 ± 2%, entry A). The analogous dibutylboryl enolate **23** was prepared in the indicated solvents (DPEA) and subjected to the same reaction. As anticipated from our earlier

(31) Cram, D. J.; Abd Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828–5835, 5851–5859.

(32) Seebach, D.; Ehrig, V.; Teschner, M. *Justus Liebigs Ann. Chem.* **1976**, 1357–1369.

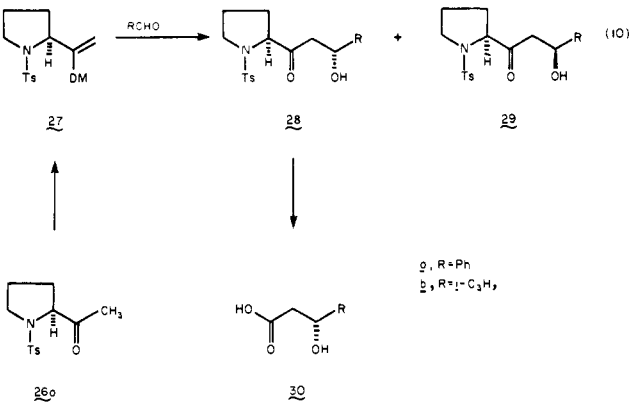
(33) Heathcock, C. H.; Pirrung, M. C.; Buse, C. T.; Hagen, J. P.; Young, S. D.; Sohn, J. E. *J. Am. Chem. Soc.* **1979**, *101*, 7077–7079.

(34) Although the *R* ketone enolate **23** has been illustrated for reasons of clarity in comparison, Seebach carried out his study on the *S* isomer.



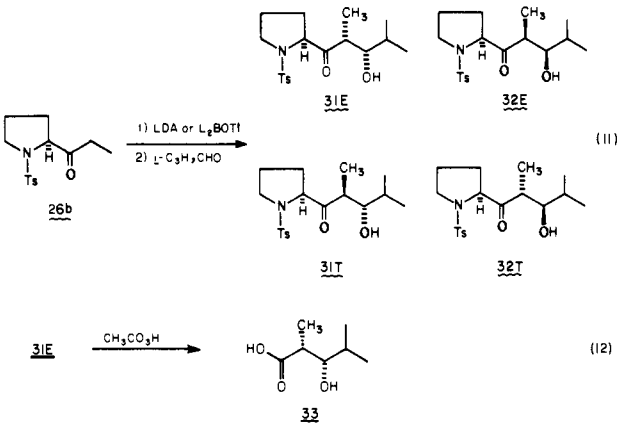
studies on solvent effects, the highest degree of asymmetric induction was observed in pentane (**24**:**25** = 64:36). Comparable results were obtained in methylene chloride which is probably the general solvent of choice for such reactions.

In an analogous study, the comparative aldol condensations of the lithium and boron enolates of the *S* ketones **26a** and **26b**, synthesized from (*S*)-proline, were carried out with representative aldehydes (eq 10 and 11). The comparative lithium (LDA) and



boron enolates **27** afforded the aldol condensation products **28a,b** and **29a,b** upon reaction with benzaldehyde and isobutyraldehyde. The diastereoisomeric aldol adducts **28** and **29** were cleanly separated by preparative HPLC, and the major aldol diastereoisomer (**28a** and **28b**) from each experiment was subjected to Baeyer–Villiger oxidation to give the optically pure β-hydroxy acids (*R*)-**30a**, $[\alpha]_D$ +21° (c 0.0148, EtOH) and (*R*)-**30b**, $[\alpha]_D$ +40.5° (c 0.0063, $CHCl_3$) whose absolute configurations have been established previously.[35,36] The condensation reactions summarized in Table VI for enolate **27** reveal trends parallel to those observed for 3-methyl-2-pentanone (**22**) (Table V). If R_S = CH_2 and R_L = TsN in enolate **27**, the sense of chirality transfer to the newly generated carbinol carbon is the same as that observed for enolate **23** (R_S = CH_3, R_L = Et).

The comparative aldol condensations of **26b** were next studied to determine the influence of methyl substitution on the enolate (eq 11). The rather surprising results are summarized in Table VII. The erythro/threo ratios (**31E** + **32E**:**31T** + **32T**) were determined by ^{13}C NMR,[37] and the ratio of erythro diastereoisomers (**31E**:**32E**) was determined by both ^{13}C NMR and analytical HPLC. The erythro diastereoselection determined under kinetic (Table II, entries O, P) as well as potentially equilibrating (Table VII, entry B) conditions for boron enolate formation indicated that a preponderance of the cis enolate was formed in both instances. Analysis of the unpurified boron enolate aldol reaction (entry B, 100% yield) revealed the presence of a *single* erythro



diastereoisomer along with 9% of a stereochemically undefined threo product (**31T** and/or **32T**). Direct crystallization of the reaction mixture afforded a 57% yield of the stereochemically homogeneous erythro aldol adduct **31E**, $[\alpha]_D$ −92.5° (c 0.0294, $CHCl_3$). The absolute configuration of **31E** was determined by nonregioselective Baeyer–Villiger oxidation to the enantiomerically pure (2*R*,3*S*)-β-hydroxy acid **33**, $[\alpha]_D$ +10.5° (0.0921, $CHCl_3$), whose absolute configuration has been unambiguously determined in this laboratory.[38]

We surmise that the enhanced chirality which has been observed in this instance via simple methyl substitution (cf. ketones **26a** and **26b**) in the cis configuration will prove to be general, and we have already made parallel observations with other chiral methyl and *cis*-ethyl ketone enolates in unrelated systems.[38] Our ability to study the nature of chirality transfer with the trans enolate derived from **26b** was thwarted by all attempts to prepare the requisite enolates.

Given the reasonable postulate that the aldol condensation proceeds via a pericyclic process,[4] two reasonable diastereoisomeric transition states, T_1 and T_2, which accommodate *minimal* nonbonded interactions with the aldehyde are illustrated in Scheme VI for methyl ketone and cis enolates (R_1 = 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 ↔ Bu < R_L ↔ 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 = *t*-Bu, R_S = $OSiMe_3$, R_1 = Me) exhibit good diastereoselection of the type under discussion where the preferred aldol diastereoisomer **34** is the postulated product.[33] A predictive model for trans enolates may well involve additional transition state 1,3-allylic strain considerations between R_1 and the chiral center. Additional experiments will be required to clarify this point.

Experimental Section

Infrared spectra were recorded on a Beckman 4210 spectrophotometer. ^1H magnetic resonance spectra were recorded on a Varian Associates EM-390 (90 MHz) spectrometer and are reported in parts per million from internal tetramethylsilane on the δ scale. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), coupling constant (Hz), integration, and interpretation. ^{13}C magnetic resonance spectra were recorded on a JEOL-FX-90Q (22.5 MHz) spectrometer and are reported in parts per million from tetramethylsilane on the δ scale. Multiplicities are reported using the format given above. Mass spectra were recorded on a Dupont 21-492B spectrometer by the California Institute of Technology Microanalytical Laboratory. Combustion analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, Mich.

Analytical gas–liquid chromatography was carried out on a Varian Aerograph Model 1400 gas chromatograph, equipped with a flame ionization detector, using a 6 ft × 0.125 in. stainless steel column packed

(35) Cohen, S. G.; Weinstein, S. Y. *J. Am. Chem. Soc.* **1964**, *86*, 725–728. The reported rotation for (*R*)-**30a** was $[\alpha]_D$ +21.1° (1.9%, EtOH).

(36) Büchi, G.; Crombie, L.; Godin, P. J.; Kaltenbronn, T. S.; Siddalingaiah, K. S.; Whiting, D. A. *J. Chem. Soc.* **1961**, 2843–2860. The reported rotation for (*R*)-**30b** was +26.4° (*c* 0.021, $CHCl_3$); however, independent enantioselective syntheses of both (*R*)-**30b**, $[\alpha]_D$ +40.5° (*c* 0.0063, $CHCl_3$) and (*S*)-**30b**, $[\alpha]_D$ −40.0° (0.0464, $CHCl_3$) in our laboratory (T. Shih, D. A. Evans, unpublished results) indicate that the reported rotation is low.

(37) Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *44*, 4294–4299.

(38) Evans, D. A.; McGee, L. R.; Shih, T., unpublished results.

Table VI. Metal-Dependent Condensation of Enolate 27 with Representative Aldehydes (Eq 10)

entry	metal (M)	solvent	RCHO	condensation[a] T, °C	ratio[b,c] 28:29
A	Li	ether	PhCHO	−78	45:55
B	Li	ether	i-C_3H_7CHO	−78	54:46
C	$(n\text{-}C_4H_9)_2B$	CH_2Cl_2	PhCHO	−78	83:17
D	$(n\text{-}C_4H_9)_2B$	ether	PhCHO	−78	74:26
E	$(c\text{-}C_5H_9)_2B$	ether	PhCHO	0	69:31
F	$(n\text{-}C_4H_9)_2B$	CH_2Cl_2	i-C_3H_7CHO	−78	74:26
G	$(n\text{-}C_4H_9)_2B$	ether	i-C_3H_7CHO	−78	72:28

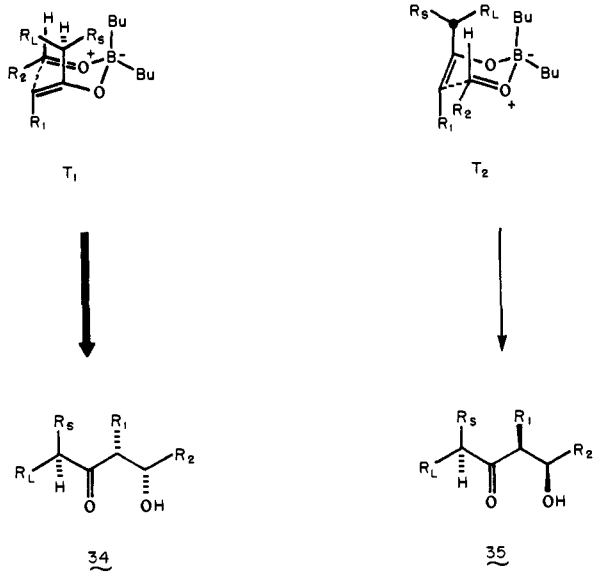
[a] Reaction times were as follows: A, B, 5 s; C, D, F, G, 30 min, 1.0 h at 0 °C; E, 90 min. [b] Ratios determined by analytical HPLC. [c] Yields for entries D, G = 77% (isolated); other yields 77 ± 14% (unpurified).

Table VII. Aldol Condensation of 26b with Isobutyraldehyde (Eq 11)

entry	metal (M)[a]	solvent	condensation[b] T, °C	ratio[c] E:T	ratio[d] 31E:32E
A	Li	THF	−78	78:22	70:30
B	$(n\text{-}C_4H_9)_2B$	CH_2Cl_2	−78	91:9	≥97:3
C	$(c\text{-}C_5H_9)_2B$	ether–CH_2Cl_2	−78	87:13	≥97:3

[a] For entry A, LDA employed for enolate formation; for entry B, enolate formed from DPEA at 45 °C; for entry C, enolate formed at 25 °C. [b] Reaction times as follows: A, 5 s; B, C, 30 min, 1 h at 0 °C. [c] Erythro-threo ratios determined by ^{13}C NMR, ref 37. [d] Erythro diastereoisomer ratios determined by ^{13}C NMR and HPLC.

Scheme VI



with 10% Carbowax 20M on 60–80 mesh Chromosorb W. Preparative gas–liquid chromatography was performed on a Varian Aerograph Model 90-P gas chromatograph using a 6 ft × 0.25 in. copper column packed with 10% SE-30 on 40–60 mesh Chromosorb W support. Medium-pressure chromatography was performed using EM Laboratories LoBar silica gel 60 prepacked columns on a Chromatronix MPLC apparatus equipped with a Fluid Metering Inc. Model RP lab pump. Analytical HPLC was performed on a Water's Associates Model ALC 202/401 high-pressure liquid chromatograph equipped with a Model 6000 pump and ultraviolet and refractive index detectors.

Optical rotations were recorded on a Perkin-Elmer 141 polarimeter at the sodium D line.

When necessary, solvents and reagents were dried prior to use. Diethyl ether and tetrahydrofuran were distilled from benzophenone ketyl. Pentane and chloroform were filtered through activity I alumina. Methylene chloride, diisopropylethylamine, 2,6-lutidine, and 2,4-lutidine were distilled from calcium hydride. Benzaldehyde, n-butyraldehyde, and isobutyraldehyde were distilled and stored at 0 °C. Methacrolein and tiglic aldehyde were distilled immediately prior to use. Chlorotrimethylsilane was distilled from quinoline immediately prior to use. Propionyltrimethylsilane was prepared by the procedure of Heathcock[6] and co-workers. The method of Vedejs[39] and co-workers was used for the preparation of MoO_5·pyridine·HMPT(MoOPH). n-Butyllithium was titrated by the procedure of Watson and Eastham.[40] All other reagents were used as received.

Preparation of Dialkylboryl Trifluoromethanesulfonates. General Considerations on Handling and Storage. The dialkylboryl triflates are extremely air- and moisture-sensitive reagents which must be transferred and stored under a scrupulously maintained argon atmosphere. With proper handling the reagents can be stored for several months without any significant decomposition. Although the dialkylboryl triflates often become yellow or orange upon storage, this discoloration had no significant effect on the yields of subsequent reactions. The trifluoromethanesulfonic acid[41] used in the procedures below was obtained from a freshly opened bottle and was not purified before use; partially used bottles which have been opened more than a few weeks should be avoided.

Diethylboryl Trifluoromethanesulfonate (4c). To 13.1 g (0.133 mol) of triethylboron[42] under argon at 0 °C was added 20.0 g (0.133 mol) of trifluoromethanesulfonic acid dropwise over 25 min. After the addition, the pale brown solution was stirred for 30 min at room temperature and then distilled (54–55 °C, 24 mm) to yield 26.0 g (90%) of diethylboryl triflate as a colorless, pyrophoric liquid; ^{13}C NMR ($CDCl_3$) δ 118.4, 14.1, 6.5. This reagent offered no advantages in reactivity or selectivity over di-n-butylboryl triflate which is more easily handled because of its greater stability.

Di-n-butylboryl Trifluoromethanesulfonate (4a). The reagent was prepared by the procedure of Mukaiyama[12] with the following important cautionary note. If the trifluoromethanesulfonic acid (1 equiv) and tributylborane (1 equiv) are combined (25 °C) as advertised, in some instances a short induction period preceding a rapid exotherm results. To avoid this potentially hazardous situation, it is recommended that 1–2 mL of the trifluoromethanesulfonic acid be added to the tributylborane, and the reaction mixture warmed (ca. 50 °C) until butane evolution is observed. The balance of the acid may be added *dropwise* while maintaining the reaction temperature between 25 and 50 °C. After stirring for 30 min (25 °C) the boryl triflate 4a was isolated in 80–90% yields via short-path distillation, bp 60 °C (2.0 mm); ^{13}C NMR ($CDCl_3$) δ 118.1, 25.1, 21.5, 13.6.

Dicyclopentylboryl Trifluoromethanesulfonate (4b). To 14.9 g (68 mmol) of tricyclopentylboron[43] at room temperature under argon was added 10.2 g (68 mmol) of trifluoromethanesulfonic acid dropwise with intermittent cooling to maintain the reaction temperature at approximately room temperature. The deep orange solution was stirred for 30 min at room temperature and was then distilled (70–72 °C (1 mm)) to yield 18.3 g (90%) of the air-sensitive boryl triflate as a colorless liquid: ^{13}C NMR (CCl_4) δ 118.0, 30.4, 26.9, 25.5. Dicyclopentylboryl triflate was stored at 0 °C.

Cyclopentylthexylboryl Trifluoromethanesulfonate (4d). A solution of 1.25 mL (12 mmol) of 9.6 M borane–methyl sulfide complex and 1.01 g (12 mmol) of 2,3-dimethyl-2-butene was stirred under argon for 2 h at 0 °C. After the addition of 10 mL of tetrahydrofuran, the solution was cooled to −30 °C and 0.82 g (12 mmol) of cyclopentene was rapidly added. The solution was stirred 1 h at −30 to 25 °C and cooled to −78 °C; 1.65 g (11 mmol) of trifluoromethanesulfonic acid was added dropwise (hydrogen evolved with foaming). After the addition the solution was stirred at −78 °C for 1 h and at −60 °C for 15 min. The reagent was then ready for use in subsequent reactions; it was not isolated.

General Procedures for the Formation of Boron Enolates. Kinetic Generation of Boron Enolates. To a stirred solution of amine (1.1–1.2 equiv) and dialkylboryl triflate (1.1 equiv) in the indicated solvents (2–3 mL/mmol of substrate) at the indicated temperatures (≤25 °C) under an argon atmosphere was added the substrate (1.0 equiv) dropwise. For reactions in ether and pentane, the progress of the reaction could be monitored by the formation of a white precipitate of ammonium triflate. After the indicated time period the dialkylboron enolate was ready for subsequent reactions.

Equilibration of Boron Enolates. After kinetic enolization at 0 °C for 5 min the mixture was heated at reflux for 2–3 h. The dialkylboron enolate solution was then ready for subsequent reactions. The choice of amine and solvent is dependent upon the structure of the ketone. While sterically hindered ketones, such as *tert*-butyl ethyl ketone, can be equilibrated by diisopropylethylammonium triflate in ether, simpler ke-

(39) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188–196.
(40) Watson, S. L.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165–168.
(41) Purchased from Aldrich Chemical Co.
(42) Purchased from Ventron/Alfa Inorganics.
(43) Brown, H. C.; Subba Rao, B. C. *J. Am. Chem. Soc.* **1959**, *81*, 6423–6428.

tones, such as diethyl ketone, require use of the more acidic 2,6-lutidinium triflate in carbon tetrachloride for equilibration (see text for additional details). No precipitate was observed when chlorinated hydrocarbons were used as solvents owing to the solubility of ammonium triflates in these solvents.

Silylation of Boron Enolates. To a 0.5 M solution of boron enolate in ether at −78 °C under an argon atmosphere was added *n*-butyllithium (3.3 equiv). After 15 min, chlorotrimethylsilane (3.3 equiv) was added and the solution allowed to warm to room temperature where a white precipitate formed. The mixture was partitioned between brine and pentane and the brine extracted once with pentane; the combined pentane extracts were washed successively with saturated aqueous sodium bicarbonate and brine, dried (Na_2SO_4), and concentrated in vacuo to afford the crude trimethylsilyl enol ethers. Yields in this reaction exceeded 100% owing to the presence of boron-derived side products. The enol ethers were analyzed by comparison with authentic samples[6] using gas–liquid chromatography or ^1H NMR (although the spectrum was complicated by the side products the olefin region was clean).

General Procedures for the Aldol Condensation of Dialkylboron Enolates. To a solution of the dialkylboron enolate at −78 °C under an argon atmosphere was added the aldehyde (nonenolizable: 1.0 equiv, neat; enolizable: 1.2–1.5 equiv, solution in 2–3 mL of solvent/mmol of aldehyde). The mixture was then stirred for 30 min at −78 °C and 1 h at 0 °C.

Hydrogen Peroxide Workup. The reaction was quenched by addition to pH 7 phosphate buffer. The mixture was extracted twice with ether and the combined ether extracts were washed with brine and concentrated in vacuo. The crude oil was then dissolved in methanol (3 mL/mmol) at 0 °C and 30% hydrogen peroxide (1 mL/mmol) added. After the mixture was stirred at room temperature for 2 h, water (5–10 mL/mmol) was added; the milky mixture was concentrated in vacuo to remove most of the methanol. The residue was extracted twice with ether and the combined ether solution was washed with 5% aqueous sodium bicarbonate and brine, dried (Na_2SO_4), and concentrated in vacuo to afford the crude aldol adducts.

MoOPH Workup. The dialkylboron alkoxides were oxidized by the addition of MoOPH (1.5 equiv), and the yellow slurry was stirred initially at 0 °C (30 min), then at room temperature (45 min). The mixture was added to 1 N aqueous sodium hydroxide and extracted with ether. The ether solution was washed with dilute brine and brine, dried (Na_2SO_4), and concentrated in vacuo to afford the crude aldol adducts.

Silylation of the Di-*n*-butylboron Enolate of 3-Pentanone (Table I, Entry B). Kinetic enolization of 0.17 g (2.0 mmol) of diethyl ketone with 0.26 g (2.4 mmol) of 2,6-lutidine and 0.60 g (2.2 mmol) of di-*n*-butylboryl triflate in 5 mL of ether at −78 °C for 30 min was followed by silylation to afford 1.1 g (>100%) of unpurified trimethylsilyl enol ether. Analytical gas–liquid chromatography indicated the ratio of **2c**:**2t** was 69:31. Assignments were made by comparison with a known mixture[6] generated by trapping the enolates formed using lithium diisopropylamide.

Silylation of the Dicyclopentylboron Enolate of 2-Methyl-3-pentanone (Table I, Entry I). Kinetic enolization of 0.20 g (2.0 mmol) of 2-methyl-3-pentanone with 0.31 g (2.4 mmol) of diisopropylethylamine and 0.66 g (2.2 mmol) of dicyclopentylboryl triflate in 5 mL of ether at 0 °C for 30 min was followed by silylation to afford 0.81 g (>100%) of unpurified trimethylsilyl enol ether. Analytical gas–liquid chromatography indicated the ratio of **2c**:**2t** was 19:81. Assignments were made by comparison with a known mixture[6] generated by trapping the enolates formed with lithium diisopropylamide.

Silylation of the Di-*n*-butylboron Enolate of 2,2-Dimethyl-3-pentanone (Table I, Entry K). Enolization and equilibration of 0.23 g (2.0 mmol) of 2,2-dimethyl-3-pentanone with 0.31 g (2.4 mmol) of diisopropylethylamine and 0.60 g (2.2 mmol) of di-*n*-butylboryl triflate in 5 mL of refluxing ether for 2 h were followed by silylation to afford 1.4 g (>100%) of unpurified trimethylsilyl enol ether. A sharp quartet for the vinyl proton appeared at δ 4.47 (lit.[6] 4.40) in the ^1H NMR spectrum for the cis enolate **2c**. Assignment was made by comparison with a known sample generated by trapping the enolate formed using lithium diisopropylamide.

Silylation of the Di-*n*-butylboron Enolate of 5-Methyl-3-hexanone (Table I, Entry L). Kinetic enolization of 0.2o g (2.0 mmol) of 5-methyl-3-hexanone with 0.31 g (2.4 mmol) of diisopropylethylamine and 0.60 g (2.2 mmol) of di-*n*-butylboryl triflate in 5 mL of ether at −78 °C for 30 min was followed by silylation to afford 1.2 g (>100%) of unpurified trimethylsilyl enol ether. A sharp quartet for the vinyl proton appeared at δ 4.43 in the ^1H NMR spectrum for the cis enolate **2c**.

Silylation of the Di-*n*-butylboron Enolate of Propiophenone (Table I, Entry M). Kinetic enolization of 0.27 g (2.0 mmol) of propiophenone with 0.31 g (2.4 mmol) of diisopropylethylamine and 0.60 g (2.2 mmol) of di-*n*-butylboryl triflate in 5 mL of ether at room temperature for 1 h was followed by silylation to afford 1.3 g (>100%) of unpurified trimethylsilyl enol ether. Analytical gas–liquid chromatography indicated that only cis enol ether **2c** (<1% trans) was present. Assignment was made by comparison with an authentic sample[6] generated by trapping the enolate formed with lithium diisopropylamide. A sharp quartet for the vinyl proton appeared at δ 5.31 in the ^1H NMR spectrum.

Silylation of the Di-*n*-butylboron Enolate of *S*-*tert*-Butyl Propanethioate (Table I, Entry N). Kinetic enolization of 0.15 g (1.0 mmol) of *S*-*tert*-butyl propanethioate with 0.14 g (1.1 mmol) of diisopropylethylamine and 0.30 g (1.1 mmol) of di-*n*-butylboryl triflate in 5 mL of ether at 0 °C for 30 min was followed by silylation to afford 0.95 g (>100%) of unpurified trimethylsilyl enol ether. A sharp quartet for the vinyl proton appeared at δ 5.25 in the ^1H NMR spectrum for the trans enolate **2t**. In samples containing cis enolate **2c**, an additional signal appeared at δ 5.21 (q). Assignments were made by comparison with known mixtures generated by trapping the enolates formed using lithium diisopropylamide in analogy to the work of Ireland[17] et al.

***erythro*-1-Hydroxy-2-methyl-1-phenyl-3-pentanone (Table II, Entry A).** Kinetic enolization of 0.52 g (6.0 mmol) of 3-pentanone with 0.85 g (6.6 mmol) of diisopropylethylamine and 1.81 g (6.6 mmol) of di-*n*-butylboryl triflate in 15 mL of ether at −78 °C for 30 min was followed by aldol condensation and hydrogen peroxide workup with 0.64 g (6.0 mmol) of benzaldehyde to yield 1.01 g (88%) of colorless oil. No threo aldol adduct **12T** was detected by ^1H NMR of the unpurified product; vide infra. The product was chromatographed at medium pressure over silica gel (hexane:ethyl acetate, 8:1) to afford 0.89 g (77%) of erythro aldol adduct **12E** as a colorless oil: IR (CCl_4, 5%) 3605, 3500, 2985, 2969, 1705, 1695, 696 cm^{-1}; ^1H NMR (CCl_4) δ 7.17 (s, 5, aromatic), 4.80 (d, J = 3 Hz, 1, erythro C*H*OH), 3.19 (s, 1, OH), 2.65 (m, 1, COCH–), 2.21 (m, 2, $-COCH_2-$), 0.98 (d, 3, $-CHCH_3$), 0.89 (t, 3, $-CH_2CH_3$). Authentic[6] threo adduct gave rise to an additional signal at δ 4.48 (d, J = 8 Hz, threo C*H*OH). These spectra are identical with those reported in the literature[6] for this compound.

***erythro*-5-Hydroxy-4-methyl-3-octanone (Table II, Entry C).** Kinetic enolization of 0.17 g (2.0 mmol) of 3-pentanone with 0.31 g (2.4 mmol) of diisopropylethylamine and 0.60 g (2.2 mmol) of di-*n*-butylboryl triflate in 5 mL of ether at −78 °C for 30 min was followed by aldol condensation and MoOPH workup with 0.17 g (2.4 mmol) of *n*-butyraldehyde to yield 0.22 g (69%) of a colorless oil. No threo aldol adduct **12T** was detected by ^1H NMR of the unpurified product; vide infra. The product was bulb-to-bulb distilled (130 °C (1 mm)) to afford 0.20 g (65%) of erythro aldol adduct **12E** as a colorless oil: IR (neat) 3480, 2960, 1700, 1455, 975 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.89 (m, 1, erythro C*H*OH), 2.92–2.38 (m, 4, $-COCH_2-$, –COCH–, OH), 1.65–0.82 (m, 13, aliphatic). Preparative gas–liquid chromatographic separation of a mixture of aldol products generated by lithium enolate condensation provided compounds for which assignments for the ^1H NMR spectra were made by a comparison of the carbinol protons: erythro δ 3.89 (m, J = 3 Hz) and threo δ 3.65 (m, J = 7 Hz). The coupling constants were determined by an analysis of the signal of the proton on carbon 4.

Exact mass: Calcd for $C_9H_{18}O_2$: 158.131. Found: 158.132.

***erythro*-5-Hydroxy-4,6-dimethyl-3-heptanone (Table II, Entry D).** Kinetic enolization of 0.17 g (2.0 mmol) of 3-pentanone with 0.31 g (2.4 mmol) of diisopropylethylamine and 0.60 g (2.2 mmol) of di-*n*-butylboryl triflate in 5 mL of ether at −78 °C for 30 min was followed by aldol condensation and MoOPH workup with 0.17 g (2.4 mmol) of isobutyraldehyde to yield 0.21 g (65%) of a colorless oil. No threo aldol adduct **12T** was detected by ^1H NMR of the unpurified product; vide infra. The product was bulb-to-bulb distilled (130 °C (1 mm)) to afford 0.19 g (61%) of erythro aldol adduct **12E** as a colorless oil: IR (neat) 3490, 2970, 1700, 1455, 973 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.48 (d of d, J = 3 and 8 Hz, 1, erythro C*H*OH), 2.95 (s, 1, OH), 2.71 (d of q, J = 3 and 7 Hz, 1, –COCH–), 2.50 (q, 2, $-COCH_2-$), 1.61 (m, 1, $-CH(CH_3)_2$), 1.29–0.80 (m, 12, 4 CH_3's). Threo aldol adduct, prepared via the lithium enolate, gave rise to an additional signal at δ 3.41 (t, J = 7 Hz, threo C*H*OH).

Exact mass: Calcd for $C_9H_{18}O_2$: 158.131. Found: 158.134.

***erythro*- and *threo*-5-Hydroxy-4,6-dimethyl-6-hepten-3-one (Table II, Entry E).** Kinetic enolization of 0.17 g (2.0 mmol) of 3-pentanone with 0.31 g (2.4 mmol) of diisopropylethylamine and 0.60 g (2.2 mmol) of di-*n*-butylboryl triflate in 5 mL of ether at −78 °C for 30 min was followed by aldol condensation and MoOPH workup with 0.21 g (3.0 mmol) of methacrolein to yield 0.23 g (72%) of a yellow oil. The ratio of erythro:threo aldol adducts, **12E**:**12T**, in the unpurified product was determined by ^1H NMR to be 92:8. The product was bulb-to-bulb distilled (150 °C (1 mm)) to afford 0.21 g (68%) of a colorless oil: IR (neat) 3480, 3100, 2980, 1705, 1650, 1457, 977, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.98 (m, 2, olefin), 4.36 (d, J = 3 Hz, 0.92, *erythro* C*H*OH), 4.17 (d, J = 8 Hz, 0.08, threo C*H*OH), 2.90 to 2.39 (m, 4, –COCH, $-COCH_2-$, and OH), 1.69 (s, 3, $=CCH_3$), 1.20 to 0.95 (m, 6, 2 CH_3's).

Exact mass: Calcd for $C_9H_{16}O_2$: 156.115. Found: 156.116.

***erythro*- and *threo*-5-Hydroxy-4,6-dimethyl-(*E*)-6-octen-3-one (Table II, Entry F).** Kinetic enolization of 0.17 g (2.0 mmol) of 3-pentanone with 0.31 g (2.4 mmol) of diisopropylethylamine and 0.60 g (2.2 mmol) of di-*n*-butylboryl triflate in 5 mL of ether at −78 °C for 30 min was followed by aldol condensation and MoOPH workup with 0.25 g (3.0 mmol) of tiglic aldehyde to yield 0.24 g (70%) of a yellow oil. The ratio of erythro:threo aldol adducts, **12E**:**12T**, in the unpurified product was determined by ^{1}H NMR to be 93:7. The product was bulb-to-bulb distilled (150 °C (1 mm)) to afford 0.22 g (65%) of a colorless oil: IR (neat) 3490, 2970, 1700, 1667, 1450, 970, 825 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.47 (m, 1, olefin), 4.58 (s, 1, OH), 4.24 (d, J = 5 Hz, 0.93, erythro C*H*OH), 4.11 (d, J = 9 Hz, 0.07, threo C*H*OH), 2.92 to 2.32 (m, 3, –COCH– and –$COCH_2$–), 1.60 and 1.55 (d and s, 6, =C*H*C_H_3 and =CC_H_3), 1.22 (m, 6, 2 CH_3's).

Exact mass: Calcd for $C_{10}H_{18}O_2$: 170.131. Found: 170.131.

***erythro*-1-Hydroxy-2,5-dimethyl-1-phenyl-3-hexanone (Table II, Entry H).** Kinetic enolization of 0.68 g (6.0 mmol) of 2-methyl-4-hexanone with 0.85 g (6.6 mmol) of diisopropylethylamine and 1.81 g (6.6 mmol) of di-*n*-butylboryl triflate in 15 mL of ether at −78 °C for 30 min was followed by aldol condensation and hydrogen peroxide workup with 0.64 g (6.0 mmol) of benzaldehyde to yield 1.44 g (>100%) of a pale yellow oil. No threo aldol adduct **12T** was detected by ^{1}H NMR of the unpurified product; vide infra. The product was chromatographed at medium pressure over silica gel (hexane:ethyl acetate, 8:1) to afford 1.09 g (82%) of erythro aldol adduct **12E** as a colorless oil: IR (CCl_4, 5%) 3605, 3510, 2958, 1707, 1694, 1098, 1078, 698 cm^{-1}; ^{1}H NMR (CCl_4) δ 7.23 (s, 5, aromatic), 4.88 (d, J = 4 Hz, 1, erythro C*H*OH), 3.0 (s, 1, OH), 2.64 (m, 1, –COCH–), 2.3–1.75 (m, 3, –$COCH_2$CH–), 0.98 (d, 3, –CHCH_3), 0.83 (d, 6, –CH(C_H_3)$_2$). Threo aldol adduct, from reactions using dicyclopentylboryl triflate, gave rise to an additional signal at δ 4.64 (d, J = 9 Hz, threo C*H*OH).

Exact mass: Calcd for $C_{14}H_{20}O_2$: 220.146. Found: 220.146.

***erythro*- and *threo*-1-Hydroxy-2,4-dimethyl-1-phenyl-3-pentanone (Table II, Entry J).** Kinetic enolization of 0.60 g (6.0 mmol) of 2-methyl-3-pentanone with 0.85 g (6.6 mmol) of diisopropylethylamine and 1.81 g (6.6 mmol) of di-*n*-butylboryl triflate in 15 mL of ether at −78 °C for 30 min was followed by aldol condensation and hydrogen peroxide workup with 0.64 g (6.0 mmol) of benzaldehyde to yield 1.10 g (89%) of a pale yellow oil. The ratio of erythro:threo aldol adducts, **12E**:**12T**, in the unpurified product was determined by ^{1}H NMR to be 44:56. The product was chromatographed at medium pressure over silica gel (hexane:ethyl acetate, 12:1) to afford 0.80 g (65%) of a colorless oil: IR (CCl_4, 5%) 3480, 3030, 2970, 1707, 1450, 1100, 1005, 698 cm^{-1}; ^{1}H NMR (CCl_4) δ 7.30 (s, 5, aromatic), 4.91 (d, J = 5 Hz, 0.44, erythro C*H*OH), 4.70 (d, J = 8 Hz, 0.56, threo C*H*OH), 3.40 (s, 1, OH), 3.22 to 2.46 (m, 2, –COC*H*CH and –COC*H*(CH_3)$_2$), 1.19 to 0.89 (m, 9, 3 CH_3's). These spectra are identical with those reported in the literature[6] for this compound.

***erythro*-1-Hydroxy-2,4,4-trimethyl-1-phenyl-3-pentanone (Table II, Entry L).** Enolization and equilibration of 0.68 g (6.0 mmol) of 2,2-dimethyl-3-pentanone with 0.85 g (6.6 mmol) of diisopropylethylamine and 1.81 g (6.6 mmol) of di-*n*-butylboryl triflate in 15 mL of refluxing ether for 2 h were followed by aldol condensation and hydrogen peroxide workup with 0.64 g (6.0 mmol) of benzaldehyde to yield 1.01 g (76%) of a yellow oil. No threo aldol adduct **12T** was detected by ^{1}H NMR of the unpurified product; vide infra. The product was chromatographed at medium pressure over silica gel (hexane:ethyl acetate, 8:1) to afford 0.86 g (65%) of erythro aldol adduct **12E** as a colorless oil: IR (CCl_4, 5%) 3620, 3500, 2970, 1695, 1685, 982, 698 cm^{-1}; ^{1}H NMR (CCl_4) δ 7.25 (s, 5, aromatic), 4.76 (d, J = 4 Hz, 1, erythro C*H*OH), 3.32–2.97 (m, 1, –COCH–), 3.18 (s, 1, OH), 1.02 (s, 9, –C(C_H_3)$_3$), 0.99 (s, 3, –CHCH_3). Authentic[6] threo adduct gave rise to an additional signal at δ 4.60 (d, J = 7 Hz, threo C*H*OH). These spectra are identical with those reported in the literature[6] for this compound.

***erythro*-3-Hydroxy-2-methyl-1,3-diphenyl-1-propanone (Table II, Entry M).** Kinetic enolization of 0.80 g (6.0 mmol) of propiophenone with 0.85 g (6.6 mmol) of diisopropylethylamine and 1.81 g (6.6 mmol) of di-*n*-butylboryl triflate in 15 mL of ether at room temperature for 1 h was followed by aldol condensation and hydrogen peroxide workup with 0.64 g (6.0 mmol) of benzaldehyde to yield 1.60 g (>100%) of a yellow oil. No threo aldol adduct **12T** was detected by ^{1}H NMR of the unpurified product; vide infra. The product was chromatographed at medium pressure over silica gel (hexane:ethyl acetate, 9:1) to afford 1.12 g (78%) of erythro aldol adduct **12E** as a viscous oil: IR (CCl_4, 4%) 3605, 3520, 1670, 1662, 1211, 970, 698 cm^{-1}; ^{1}H NMR (CCl_4) δ 7.95–7.75 (m, 2, aromatic), 7.55–7.0 (m, 8, aromatic), 5.05 (d, J = 3 Hz, 1, erythro C*H*OH), 3.53 (m, 1, –COC*H*–), 3.4 (s, 1, OH), 1.1 (d, 3, CH_3). Authentic[6] threo adduct gave rise to an additional signal at δ 4.92 (d, J = 9 Hz, threo C*H*OH). These spectra are identical with those reported in the literature[6] for this compound.

***erythro*-1-(1-*tert*-Butyloxycarbonyl-1-azacyclopenta-2,4-dien-2-yl)-3-hydroxy-2-methyl-3-phenyl-1-propanone (Table II, Entry N).** Kinetic enolization of 0.446 g (2.0 mmol) of 1-(1-*tert*-butyloxycarbonyl-1-azacyclopenta-2,4-dien-2-yl)-1-propanone[44] with 0.310 g (2.4 mmol) of diisopropylethylamine and 0.603 g (2.2 mmol) of di-*n*-butylboryl triflate in 5 mL of ether at −78 °C for 45 min was followed by aldol condensation and MoOPH workup with 0.22 g (2.0 mmol) of benzaldehyde to yield 0.723 g (>100%) of a light yellow oil. No threo aldol adduct **12T** was detected by ^{1}H NMR of the unpurified product; vide infra. The product was chromatographed at medium pressure over silica gel (hexane, ethyl acetate) to give 0.47 g (70%) of erythro aldol adduct **12E** as a colorless oil: IR (CCl_4) 3500, 2980, 2940, 1750, 1700, 1650, 1440, 1410, 1370, 1310, 1150, 945, 845, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.30 (broad s, 5, phenyl), 7.28–7.15 (m, 1, pyrrole), 6.78–6.70 (m, 1, pyrrole), 6.15–6.05 (m, 1, pyrrole), 5.19 (d, J = 4 Hz, 1, –CHC*H*OH), 3.64 (broad s, 1, OH), 3.40 (d of q, J = 7, 4 Hz, 1, CH_3C*H*CHOH), 1.57 (s, 9, *t*-Bu CH_3's), 1.13 (d, J = 7 Hz, 3, CH_3CH–). In the threo aldol adduct[44] the signal for CH_3CHC*H*OH (carbinol center proton) appears at δ 4.90 (d, J = 8 Hz). These spectra are identical with those reported in the literature[44] for this compound.

***erythro*- and *threo*-3-Hydroxy-3-phenyl-2-methyl-1-trimethylsilyl-1-propanone (Table II, Entry Q).** Kinetic enolization of 0.13 g (1.0 mmol) of propionyltrimethylsilane with 0.16 g (1.2 mmol) of diisopropylethylamine and 0.30 g (1.1 mmol) of di-*n*-butylboryl triflate in 5 mL of ether at −78 °C for 30 min was followed by aldol condensation and MoOPH workup with 0.11 g (1.0 mmol) of benzaldehyde to yield 0.16 g (66%) of a yellow oil. The ratio of erythro:threo aldol adducts, **12E**:**12T**, in the unpurified product was determined by ^{1}H NMR to be 19:81. The product was bulb-to-bulb distilled (150 °C (1 mm)) to afford 0.12 g (53%) of a colorless oil: IR (neat) 3460, 3030, 2960, 1635, 1450, 1250, 843, 755, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.31 (s, 5, aromatic), 5.03 (d, J = 3 Hz, 0.23, erythro C*H*OH), 4.72 (d, J = 8 Hz, 0.77, threo C*H*OH), 3.31 (m, 1, –COC*H*–), 2.8 (b, 1, OH), 0.83 (two d, 3, –CHCH_3), 0.19 (s, 9, –Si(CH_3)$_3$). Distillation resulted in a slight enrichment in the erythro adduct. These spectra are identical with those reported in the literature[6] for this compound.

***erythro*- and *threo*-*S*-(1,1-Dimethylethyl) 3-Hydroxy-2-methyl-3-phenylpropanethioate (Table II, Entry S).** Kinetic enolization of 0.29 g (2.0 mmol) of *S*-*tert*-butyl propanethioate with 0.31 g (2.4 mmol) of diisopropylethylamine and 0.60 g (2.2 mmol) of di-*n*-butylboryl triflate in 5 mL of ether at 0 °C for 30 min was followed by aldol condensation and MoOPH workup with 0.21 g (2.0 mmol) of benzaldehyde to yield 0.40 g (80%) of a yellow oil. The ratio of erythro:threo aldol adducts, **12E**:**12T**, in the unpurified product was determined by ^{1}H NMR to be 10:90. The product was bulb-to-bulb distilled (150 °C (0.5 mm)) to afford 0.31 g (75%) of a colorless oil: IR (neat) 3450, 3030, 2960, 1675, 1450, 1365, 960, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.22 (s, 5, aromatic), 5.03 (d, J = 4 Hz, 0.10, erythro C*H*OH), 4.74 (d, J = 8 Hz, 0.90, threo C*H*OH), 2.85 (m, 1, –COCH–), 2.5 (b, 1, OH), 1.48 (s, 9, –S(CH_3)$_3$), 1.03 (two d, 3, CH_3).

Exact mass: Calcd for $C_{14}H_{20}O_2S$: 252.118. Found: 252.119.

***erythro*- and *threo*-*S*-(1,1-Dimethylethyl) 3-Hydroxy-2-methylhexanethioate (Table II, Entry U).** Kinetic enolization of 0.29 g (2.0 mmol) of *S*-*tert*-butyl propanethioate with 0.31 g (2.4 mmol) of diisopropylethylamine and 0.60 g (2.2 mmol) of di-*n*-butylboryl triflate in 5 mL of ether at 0 °C for 30 min was followed by aldol condensation and MoOPH workup with 0.17 g (2.4 mmol) of *n*-butyraldehyde to yield 0.31 g (70%) of a pale yellow oil. The ratio of erythro:threo aldol adducts, **12E**:**12T**, in the unpurified product was determined by ^{1}H NMR to be 10:90. The product was bulb-to-bulb distilled (150 °C (1 mm)) to afford 0.29 g (67%) of a colorless oil: IR (neat) 3450, 2960, 1675, 1455, 1365, 960 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.8 (b, 1, OH), 3.89 (m, 0.10, erythro C*H*OH), 3.64 (m, 0.90, threo C*H*OH), 2.61 (m, 1, –COCH–), 1.49 (s, 9, –S(CH_3)$_3$), 1.27 to 0.75 (m, 10, aliphatics). Preparative gas–liquid chromatographic separation of a mixture of aldol products generated by lithium enolate condensation provided compounds for which assignments for the ^{1}H NMR spectra were made by a comparison of the carbinol protons: erythro, δ 3.89 (m, J = 3 Hz); threo, δ 3.64 (m, J = 6 Hz). The coupling constants were determined by an analysis of the signal of the proton on carbon 2.

Exact mass: Calcd for $C_{10}H_{22}O_2S$: 218.134. Found: 218.133.

***erythro*- and *threo*-*S*-(1,1-Dimethylethyl) 3-Hydroxy-2,4-dimethylpentanethioate (Table II, Entry V).** Kinetic enolization of 0.29 g (2.0 mmol) of *S*-*tert*-butyl propanethioate with 0.31 g (2.4 mmol) of diisopropylethylamine and 0.60 g (2.2 mmol) of di-*n*-butylboryl triflate in 5 mL of ether at 0 °C for 30 min was followed by aldol condensation and MoOPH workup with 0.17 g (2.4 mmol) of isobutyraldehyde to yield

(44) Sacks, C. E. Ph.D. Thesis, California Institute of Technology, 1980, pp 119–120.

0.29 g (66%) of a pale yellow oil. The ratio of erythro:threo aldol adducts, **12E:12T**, in the unpurified product was determined by ^{1}H NMR to be 9:91. The product was bulb-to-bulb distilled (150 °C (1 mm)) to afford 0.26 g (63%) of a colorless oil: IR (neat) 3500, 2960, 1650, 1455, 1365, 960 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.51 (d of d, J = 3 and 8 Hz, 0.09, erythro C*H*OH), 3.30 (t, J = 7 Hz, 0.91, threo C*H*OH), 2.82 (s, 1, OH), 2.69 (m, J = 7 Hz, –COCH–), 1.70 (m, J = 7 Hz, 1, –C*H*$(CH_3)_2$), 1.48 (s, 9, –S$(CH_3)_3$), 1.18 (d, 3, CH_3), 0.89 (two d, 6, –CH$(CH_3)_3$).

Exact mass: Calcd for $C_{11}H_{22}O_2S$: 218.134. Found: 218.133.

***erythro*- and *threo*-S-(1,1-Dimethylethyl) 3-Hydroxy-2,4-dimethyl-4-pentenethioate (Table II, Entry W).** Kinetic enolization of 0.29 g (2.0 mmol) of *S-tert*-butyl propanethioate with 0.31 g (2.4 mmol) of diisopropylethylamine and 0.60 g (2.2 mmol) of di-*n*-butylboryl triflate in 5 mL of ether at 0 °C for 30 min was followed by aldol condensation and MoOPH workup with 0.21 g (3.0 mmol) of methacrolein to yield 0.29 g (66%) of a yellow oil. The ratio of erythro:threo aldol adducts, **12E:12T**, in the unpurified product was determined by ^{1}H NMR to be 12:88. The product was bulb-to-bulb distilled (150 °C (1 mm)) to afford 0.28 g (65%) of a pale yellow oil: IR (neat) 3460, 3080, 2960, 1675, 1455, 1365, 960, 900, 745 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.92 (m, 2, olefins), 4.37 (d, J = 4 Hz, 0.12, erythro C*H*OH), 4.14 (d, J = 9 Hz, 0.88, threo C*H*OH), 2.76 (m, 1, –COCH–), 2.49 (s, 1, OH), 1.73 (s, 3, =CCH_3), 1.50 (s, 9, –S$(CH_3)_3$), 1.13 (d, 3, CH_3).

Exact mass: Calcd for $C_{11}H_{20}O_2S$: 216.118. Found: 216.119.

***erythro*- and *threo*-S-(1,1-Dimethylethyl) 3-Hydroxy-2,4-dimethyl-4-hexenethioate (Table II, Entry X).** Kinetic enolization of 0.29 g (2.0 mmol) of *S-tert*-butyl propanethioate with 0.31 g (2.4 mmol) of diisopropylethylamine and 0.60 g (2.2 mmol) of di-*n*-butylboryl triflate in 5 mL of ether at 0 °C for 30 min was followed by aldol condensation and MoOPH workup with 0.25 g (3.0 mmol) of tiglic aldehyde to yield 0.31 g (71%) of a yellow oil. The ratio of erythro:threo aldol adducts, **12E:12T**, in the unpurified product was determined by ^{1}H NMR to be 18:82. The product was bulb-to-bulb distilled (150 °C (1 mm)) to afford 0.28 g (68%) of a colorless oil: IR (neat) 3480, 1680, 1455, 1370, 960, 830, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.47 (m, 1, olefin), 5.03 (b, 1, OH), 4.19 (d, J = 5 Hz, 0.18, erythro C*H*OH), 4.10 (d, J = 9 Hz, 0.82, threo C*H*OH), 2.72 (m, 1, –COCH–), 1.59 and 1.53 (d and s, 6, =CHC*H*$_3$, =CC*H*$_3$), 1.48 (s, 9, –S$(CH_3)_3$), 1.03 (two d, 3, CH_3).

Exact mass: Calcd for $C_{12}H_{22}O_2S$: 230.134. Found: 230.134.

***threo*-2-Phenylhydroxymethyl-1-cyclohexanone (Table III, Entry F).** Kinetic enolization of 0.98 g (10 mmol) of cyclohexanone with 1.42 g (11 mmol) of diisopropylethylamine and 11 mmol of cyclopentylthexylboryl triflate (**2c**), generated in situ, in 20 mL of tetrahydrofuran at –78 °C for 30 min was followed by aldol condensation and hydrogen peroxide workup with 1.06 g (10.0 mmol) of benzaldehyde to yield 1.92 g (94%) of a pale yellow oil. No erythro aldol adduct **14E** was detected by ^{1}H NMR of the unpurified product; vide infra. The product was chromatographed on 40 g of silica gel (hexane:ethyl acetate, 1:1) to afford 1.49 g (73%) of threo aldol adduct **14T** as a white crystalline solid, mp 73.5–76 °C: IR (CCl_4) 3540, 2943, 1697, 1450, 1129, 1043, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.2 (s, 5, aromatic), 4.6 (d, J = 8 Hz, 1, threo C*H*OH), 3.6 (b, 1, OH), 2.6–1.0 (m, 9, cyclohexyl). Authentic[6] erythro adduct gave rise to an additional signal at δ 5.31 (d, J = 3 Hz, erythro C*H*OH). The melting point and spectra of this compound are identical with those reported in the literature.[8]

***erythro*- and *threo*-3-Hydroxy-2-methyl-3-phenylpropanoic Acid (18a, 19a).** To a stirred solution of 0.57 g (4.4 mmol) of diisopropylethylamine and 1.15 g (4.2 mmol) of di-*n*-butylboryl triflate in 15 mL of ether at 0 °C under an argon atmosphere was added 0.15 g (2.0 mmol) of propanoic acid dropwise. A white precipitate appeared immediately. After 45 min the white slurry was cooled to –78 °C and 0.21 g (2.0 mmol) of benzaldehyde was added. The mixture was stirred for 30 min at –78 °C and 1 h at 0 °C. The reaction mixture was then added to saturated aqueous sodium bicarbonate and ether. After separation of the layers the organic phase was extracted with additional saturated aqueous sodium bicarbonate. The combined aqueous solution was successively acidified to pH 2 with 6 N hydrochloric acid, saturated with sodium chloride, extracted twice with ether, and dried (Na_2SO_4). Concentration of the ether solution in vacuo gave 0.31 g (87%) of clear oil: IR (neat) 3420, 2980, 1710, 1450, 1200, 1010, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.33 (s, 5, aromatic), 5.42 (s, 2, OH and CO_2H), 5.16 (d, J = 4 Hz, 0.35, erythro C*H*OH), 4.73 (d, J = 9 Hz, 0.65, threo C*H*OH), 2.79 (m, 1, –COCH–), 1.10 and 0.98 (two d, 3, CH_3). ^{1}H NMR integration afforded a ratio **18a:19a** = 35:65. The spectra of this compound are identical with those reported in the literature.[6]

***threo*-3-Hydroxy-3-phenyl-2-phenylmethoxypropanoic Acid (19b).** To a stirred solution of 0.32 g (2.4 mmol) of diisopropylethylamine and 0.60 g (2.2 mmol) of di-*n*-butylboryl triflate in 5 mL of ether at 0 °C under an argon atmosphere was added 0.17 g (1 mmol) of phenylmethoxyethanoic acid dropwise. A white precipitate appeared immediately. After 1 h the white slurry was cooled to –78 °C and 0.11 g (1.0 mmol) of benzaldehyde was added. The mixture was stirred for 30 min at –78 °C and 1 h at 0 °C. The reaction mixture was then added to saturated aqueous sodium bicarbonate and ether. After separation of the layers the organic phase was extracted with additional saturated aqueous sodium bicarbonate. The combined aqueous solution was successively acidified to pH 2 with 6 N hydrochloric acid, saturated with sodium chloride, extracted twice with ether, and dried (Na_2SO_4). Concentration of the ether solution in vacuo gave 0.23 g (85%) of a viscous colorless oil: IR (neat) 3400, 3020, 2860, 1730, 1495, 1455, 1100, 910, 735, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.27 (s and m, 10, aromatic), 6.77 (s, 2, OH and CO_2H), 4.92 (d, J = 7 Hz, 1, threo C*H*OH), 4.41 (AB q, J = 12 and 28 Hz, 2, –OC*H*$_2$C$_6$H$_5$), 4.03 (d, J = 7 Hz, 1, –C*H*CO$_2$H). The stereochemistry of this product was confirmed by dehydrative decarboxylation; vide infra. The product was characterized by conversion to a dicyclohexylammonium salt: mp 175–176 °C after recrystallization from ethyl acetate.

Anal. ($C_{28}H_{39}NO_4$): C, H, N.

(*Z*)-2-Phenylmethoxy-1-phenylethene (21b). A solution of 0.25 g (0.92 mmol) of *threo*-3-hydroxy-3-phenyl-2-phenylmethoxypropanoic acid (vide supra) and 0.66 g (5.5 mmol) of dimethylformamide dimethyl acetal in 10 mL of chloroform under a nitrogen atmosphere was stirred for 1 h at room temperature and was then heated at reflux for 7 h. The reaction mixture was concentrated in vacuo to afford an oil which was dissolved in hexane. The hexane solution was washed successively with water and brine, dried (Na_2SO_4), and concentrated in vacuo to yield 0.18 g of a yellow oil. The product was bulb-to-bulb distilled (150 °C (0.1 mm)) to afford 0.16 g (81%) of a colorless oil: IR (neat) 3030, 2940, 1645, 1487, 1445, 1365, 1090, 775, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.33 (s and m, 10, aromatic), 6.22 (d, J = 7 Hz, 1, (*Z*)-CH=C*H*O–), 5.23 (d, J = 7 Hz, 1, (*Z*)-C*H*=CHO–), 4.92 (s, 2, –OC*H*$_2$C$_6$H$_5$).

Exact mass: Calcd for $C_{15}H_{14}O$: 210.104. Found: 210.105.

Condensations of 3-Methyl-2-pentanone (22). Lithium Aldols. The lithium enolate of **22** (1.00 g, 10 mmol) was prepared and condensed with freshly distilled propionaldehyde (0.58 g, 10 mmol) according to the literature procedure.[32] The product was purified by distillation[32] to give 1.04 g (65%) of a colorless oil: IR (film) 3460, 2970, 2940, 2880, 1700, 1410, 1380 cm^{-1}; ^{1}H NMR (CCl_4) δ 3.80 (m, J = 6 Hz, 1 H, –CH$_2$C*H*OH), 3.10 (broad s, 1 H, OH), 2.60–2.20 (m, 3 H, –OCCH$_2$, –CH$_2$C*H*CO–), 1.88–1.15 (m, 4 H, 2 CH$_3$C*H*$_2$), 1.10–0.70 (m, 9 H, 3 CH$_3$'s); ^{13}C NMR (CH_2Cl_2) δ 69.1, 48.5, 47.6, 29.9, 25.9, 15.5, 11.5, 9.9. These spectral data are identical with those reported in the literature.[32]

Anal. ($C_9H_{18}O_2$): C, H.

Boron Aldols. Kinetic enolization of 0.20 g (2 mmol) of 3-methyl-2-pentanone (**22**) with 0.31 g (2.4 mmol) of diisopropylethylamine and 0.60 g (2.2 mmol) of di-*n*-butylboryl triflate in dichloromethane at –78 °C for 30 min (pentane, 60 min at 0 °C; ether, 30 min at –78 °C) was followed by aldol condensation and MoOPH workup with 0.13 g (2.2 mmol) of freshly distilled propionaldehyde to give 263 mg (83%) of a light yellow oil. A portion of the mixture was purified by distillation to give a colorless oil: IR (film) 3460, 2960, 2940, 2880, 1700, 1455, 1410, 1380 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.97 (m, J = 6 Hz, 1 H, –CH$_2$C*H*OH), 3.20 (broad s, 1 H, OH), 2.60–2.30 (m, 3 H, –OCC*H*$_2$–, –CH$_2$C*H*CO), 1.88–1.23 (m, 4 H, 2 CH$_3$C*H*$_2$), 1.20–0.80 (m, 9 H, 3 CH$_3$'s); ^{13}C NMR (CH_2Cl_2) δ 69.2, 48.5, 47.6, 29.8, 25.9, 15.5, 11.5, 9.8. These spectra are identical with the spectra above and those reported in the literature.[32]

It is an interesting sidelight that the mixture of diastereoisomers does not display any difference in the ^{13}C NMR spectrum. Thus, the diastereoisomeric ratios were determined by analytical HPLC (DuPont Zorbax Sil, 4.6 mm × 25 cm, 15% ether–hexane): k_A (major, **24**) = 6.08; k_B (minor, **25**) = 6.70. The ratio was obtained by integration of the corresponding peaks after one recycle to obtain complete separation. In this manner, the purified lithium aldol adduct was shown to be a 55:45 mixture of **24**:**25**. The unpurified boron aldol adducts were determined to be a mixture of **24**:**25** as indicated: pentane (64:36), dichloromethane (63:37), and ether (57:43). Finally, the lithium aldol condensation was repeated under "kinetic" conditions[6] at –78 °C and the ratio of **24**:**25** was found to be 53:47 (Table V).

(*S*)-(–)-*N*-4-Toluenesulfonylproline (35). The title compound was prepared from L-(-)-proline (20.0 g, 0.17 mol) and *p*-toluenesulfonyl chloride (39.0 g, 0.20 mol) according to the published procedure.[45] The oily, white solid was purified by a modification of the reported recrystallization from benzene[45a] to ensure complete removal of water. The solid was over-layered with benzene and the suspension refluxed for 3 h with removal of water via a Dean-Stark trap. The hot suspension was filtered and the filtrate cooled to room temperature to precipitate 35.0 g (66%) of **35** (as a benzene solvate) as a white crystalline solid: mp

(45) (a) Izumiya, N. *Bull. Chem. Soc. Jpn.* **1953**, *26*, 53–56. (b) Pravda, Z.; Rudinger, J. *Collect. Czech. Chem. Commun.* **1955**, *20*, 1–12.

Table VIII

shift reagent, mg	racemic ketone 26a		opt active ketone 26a	
	CH_3	methine H	CH_3	methine H
0	2.31, s	3.96, d of d	2.30, s	3.96, d of d
1.5	2.80, s; 2.87, s (1:1 ratio)	4.78, m	2.93, s	4.92, d of d
3.0	3.73, s; 3.90, s (1:1 ratio)	6.50–6.06, m	3.78, s	6.21, d of d

92–96 °C; lit.[45a] mp 95–98 °C; IR (CH_2Cl_2) 3540–2400 (broad), 1760, 1720, 1595, 1475, 1345, 1195, 1160, 1090, 1010, 810, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.87 (s, 1 H, $-CO_2H$), 7.78 (d, J = 8 Hz, 2 H, aromatic H's), 7.35 (benzene solvate, 13.2% by integration), 7.32 (d, J = 8 Hz, 2 H, aromatic H), 4.40–4.20 (d of d, J = 4.5, 7 Hz, 1 H, >NC*H*CO_2H), 3.65–3.10 (m, 2 H, $-CH_2N<$), 2.45 (s, 3 H, CH_3), 2.22–1.53 (m, 4 H, $-CH_2CH_2CH_2N<$). The properties of this compound are identical with those reported in the literature.[45]

(*S*)-(−)-[1-(4-Toluenesulfonyl)-1-azacyclopentan-2-yl]ethanone (26a). To a solution of the benzene solvate of **35** (3.3 g of the benzene solvate, 13.2% benzene; 10.7 *m*mol of **35**) in ether (100 mL) cooled to 0 °C was added a solution of methyllithium in ether (12.2 mL, 1.80 M, 22.0 mmol) dropwise over 30 min. After the addition was complete, the white suspension was warmed to room temperature and stirred for 5 h. The reaction mixture was quenched by the slow addition of 30-mL aliquots to ice-cold 20% HCl solution. The aliquots were combined and the ether layer was washed with 20% sodium carbonate and brine solutions. The ether layer was dried (Na_2SO_4) and the solvent removed in vacuo to give 1.9 g (66%) of a colorless oil containing ketone **26a** (TLC, silica gel, 50% EtOAc–hexane, R_f 0.23). Purification by MPLC (Merck Lobar size B, 50% EtOAc–hexane) gave 1.4 g (50%) of a colorless oil which crystallized upon standing to give **26a** as a white solid: mp 59–60.5 °C; IR ($CHCl_3$) 3020, 2980, 2890, 1715, 1600, 1365, 1350, 1310, 1225, 1190, 1165, 1095, 1065, 1015, 1010, 915, 820, 665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.73 (d, J = 9 Hz, 2 H, aromatic H's), 7.31 (d, J = 9 Hz, 2 H, aromatic H's), 3.96 (d of d, J = 7 Hz, 1 H, TsNC*H*$COCH_3$), 3.68–3.07 (m, 2 H, $-CH_2CH_2$NTs), 2.40 (s, 3 H, tosyl CH_3), 2.31 (s, 3 H, $-COCH_3$), 2.03–1.40 (m, 4 H, TsN$CH_2CH_2CH_2$–); ^{13}C NMR ($CDCl_3$) δ 208.1, 143.9, 133.5, 129.7, 127.5, 67.5, 49.2, 29.6, 26.1, 24.7, 21.6; $[\alpha]_D$ −155.6° (*c* 0.0447, $CHCl_3$).

Anal. ($C_{13}H_{17}NO_3S$): C, H, N.

Optical Purity of Ketone 26a. The optical purity was determined by ^1H NMR analysis employing the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III). A sample of racemic ketone **26a** was prepared from racemic proline according to the above procedures. In the proton spectrum of the racemic ketone containing 1.5 mg of the chiral shift reagent, the ketone methyl protons appeared at δ 2.80 and 2.87 ppm (s) and the methine resonances appeared at 4.78 ppm (m). With 1.5 mg of the chiral shift reagent added to the sample of the optically active ketone, the methyl protons appeared only at δ 2.93 ppm (s) and the methine proton appeared at 4.92 ppm (d of d). With additional chiral shift reagent these distinctive differences became even more pronounced (Table VIII). Considering the limits of NMR detection, the optical purity of ketone **26a** was determined to be ≥95%.

(*S*)-(−)-1-[1-(4-Toluenesulfonyl)-1-azacyclopentan-2-yl]-1-propanone (26b). To a solution of the benzene solvate of **35** (12.4 g of the benzene solvate, 13.2% benzene; 40.0 mmol of **35**) in THF (360 mL) cooled to −35 °C were added triethylamine (5.56 mL, 40.0 mmol) and trimethylacetyl chloride (5.00 mL, 40.0 mmol).[46] After 25 min the mixture was cooled to −78 °C and a solution of ethylmagnesium bromide in ether (19.9 mL, 2.01 M, 40.0 mmol) was added over 10 min. After an additional 10 min the reaction was quenched with 10% ammonium chloride solution (100 mL) and warmed to room temperature. The mixture was partitioned between ether and 10% aqueous ammonium chloride. The ether layer was washed with 5% sodium bicarbonate and brine solutions, dried (Na_2SO_4), and filtered. Removal of solvent in vacuo gave 7.61 g (68%) of a white solid containing ketone **26b** (TLC, silica gel, 50% EtOAc–hexane, R_f 0.46) accompanied by minor impurities. Purification by MPLC (Merck Lobar size C, 50% EtOAc–hexane) gave 5.9 g (53%) of ketone **26b** as a white solid: mp 73–74.5 °C; IR (CH_2Cl_2) 3060, 2980, 2940, 2880, 1715, 1600, 1460, 1350, 1305, 1205, 1185, 1170, 1160, 1095, 1010, 990, 820, 670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.71 (d, J = 9 Hz, 2 H, aromatic H's), 7.32 (d, J = 9 Hz, 2 H, aromatic H's), 4.05 (d of d, J = 7 Hz, 1 H, >C*H*$COCH_2CH_3$), 3.68–2.50 (m, 4 H, $-CH_2$NTs, $-COCH_2CH_3$), 2.43 (s, 3 H, tosyl CH_3), 2.07–1.37 (m, 4 H, TsNC$H_2CH_2CH_2$–), 1.09 (t, J = 7.5 Hz, 3 H, $-COCH_2CH_3$); ^{13}C NMR ($CDCl_3$) δ 210.8, 143.9, 134.0, 129.8, 127.6, 67.1, 49.3, 31.8, 29.8, 24.8, 21.6, 7.5; $[\alpha]_D$ −157.8° (*c* 0.0203, $CHCl_3$).

Anal. ($C_{14}H_{19}NSO_3$): C, H, N.

1-[1-(4-Toluenesulfonyl)-1-azacyclopentan-2-yl]-3-hydroxy-3-phenyl-1-propanone (Table VI, Entry D). Kinetic enolization of 1.38 g (5.62 mmol) of ketone **26a** with 0.836 g (6.47 mmol) of diisopropylethylamine and 1.69 g (6.18 mmol) of di-*n*-butylboryl triflate in 20 mL of ether at −78 °C for 60 min was followed by aldol condensation and MoOPH workup with 0.596 g (5.62 mmol) of benzaldehyde to yield 1.59 g (80%) of a yellow solid. Analysis of the unpurified aldol adduct by HPLC (μ-Porasil, 3.9 mm × 30 cm, 25% EtOAc–hexane) showed both diastereoisomers in a 3:1 ratio: k_A (major) = 8.83; k_B (minor) = 6.92. Purification on a Waters' Prep 500 (silica gel, 2 × 325 g, 2 columns, 15% EtOAc–hexane) gave 1.13 g (57%) of aldol diastereoisomer **28a** as a white solid and 0.38 g (19%) of aldol diastereoisomer **29a** as a white solid.

28a: mp 162–163 °C; IR ($CHCl_3$) 3580, 3020, 1710, 1600, 1495, 1455, 1405, 1380, 1350, 1310, 1215, 1165, 1095, 1055, 820, 700, 665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70 (d, J = 9 Hz, 2 H, aromatic H's), 7.50–7.20 (m, 7 H, aromatic H's), 5.18 (d of d, J = 4 Hz, 9 Hz, 1 H, >CH_2C*H*OH), 3.96 (d of d, J = 7 Hz, 1 H, TsNC*H*CO–), 3.68–2.80 (m, 5 H, $-CH_2$NTs, $-COCH_2$CHOH, OH), 2.41 (s, 3 H, tosyl CH_3), 1.98–1.16 (m, 4 H, TsN$CH_2CH_2CH_2$–); ^{13}C NMR ($CDCl_3$) δ 210.2, 144.0, 129.8, 128.4, 127.6, 127.5, 125.6, 69.7, 67.6, 49.3, 47.0, 29.3, 24.6, 21.5; $[\alpha]_D$ −90.9° (*c* 0.0444, $CHCl_3$).

Anal. ($C_{20}H_{23}NO_4S$): C, H, N.

29a: mp 117–118.5 °C; IR (CH_2Cl_2) 3580, 3060, 3000–2900, 1710, 1600, 1490, 1350, 1160, 1090, 815, 750–700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70 (d, J = 9 Hz, 2 H, aromatic H's), 7.48–7.12 (m, 7 H, aromatic H's), 5.16 (d of d, J = 4 Hz, 9 Hz, 1 H, $-CH_2$C*H*OH), 4.07 (m, 1 H, TsNC*H*CO–), 3.60–2.78 (m, 5 H, $-CH_2$NTs, $-COCH_2$CHO*H*), 2.41 (s, 3 H, tosyl CH_3), 1.97–1.32 (m, 4 H, TsN$CH_2CH_2CH_2$–); ^{13}C NMR ($CDCl_3$) δ 209.4, 144.0, 129.9, 128.4, 127.7, 125.8, 70.0, 67.2, 49.2, 47.7, 29.1, 24.6, 21.5; $[\alpha]_D$ −133° (*c* 0.0272, $CHCl_3$).

Anal. ($C_{20}H_{23}NO_4S$): C, H, N, S.

Proof of Absolute Configuration of Carbinol Stereocenters of 28a and 29a. To a solution of aldol diastereoisomer **28a** (0.125 g, 0.34 mmol) in dichloromethane cooled to 0 °C were added disodium hydrogen phosphate (0.280 g) and 13% peracetic acid in acetic acid (0.26 mL, 0.51 mmol). After 5 min the ice bath was removed and the mixture stirred for 5 h. The reaction mixture was partitioned between dichloromethane and 20% sodium carbonate solution. The carbonate solution was acidified to Congo Red test paper with dilute HCl, saturated with salt, and extracted with EtOAc (3 × 15 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give 20 mg of optically active 3-hydroxy-3-phenylpropanoic acid: IR (CH_2Cl_2) 3460, 3400–2400 (br), 3070, 1715, 1415, 1210, 1170, 1060, 1030, 1010 cm^{-1}; ^1H NMR ($CDCl_3$ + Me_2SO-d_6) δ 7.32 (m, 5 H, aromatic H's), 6.50 (broad s, 2 H, OH, CO_2H), 5.07 (d of d, J = 7 Hz, 1 H, $-CH_2$C*H*OH), 2.65 (d, 2 H, $-OCCH_2$); $[\alpha]_D$ +21.0° (c 0.0148, EtOH). The literature value for (*R*)-(+)-3-hydroxy-3-phenylpropanoic acid is +21.1° (1.9% solution, EtOH).[35] This confirmed the absolute configuration at the carbinol stereocenter in **28a** as R. In a similar manner the carbinol stereocenter in **29a** was confirmed as *S*.

1-[1-(4-Toluenesulfonyl)-1-azacyclopentan-2-yl]-3-hydroxy-4-methyl-1-pentanone (Table VI, Entry G). Kinetic enolization of 0.980 g (3.67 mmol) of ketone **26a** with 0.57 g (4.4 mmol) of diisopropylethylamine and 1.10 g (4.0 mmol) of di-*n*-butylboryl triflate in 6 mL ether at −78 °C for 60 min was followed by aldol condensation and MoOPH workup with 0.32 g (4.4 mmol) of isobutyraldehyde to yield 1.28 g (100%) of a yellow oil. Analysis of the unpurified aldol adduct by HPLC (μ-Porasil, 3.9 mm × 30 cm, 25% EtOAc–hexane) showed both diastereoisomers in a 3:1 ratio: k_A (major) = 7.65; k_B (minor) = 5.80. Purification on a Waters' Prep 500 (silica gel, 2 × 325 g, 2 columns, 30% EtOAc–hexane) gave 0.700 g (56%) of aldol diastereoisomer **28b** as a colorless oil and 0.260 g (21%) of aldol diastereoisomer **29b** as a colorless oil.

28b: IR (film) 3530, 2960, 2880, 1715, 1600, 1345, 1150, 1095, 1000, 820, 670 cm^{-1}; ^1H NMR ($CDCl_3$–CCl_4) δ 7.68 (d, J = 9 Hz, 2 H, aromatic H's), 7.30 (d, J = 9 Hz, 2 H, aromatic H's), 4.10–3.63 (m, 2 H, $-CH_2$C*H*OH, TsNC*H*CO–), 3.63–2.96 (m, 2 H, $-CH_2$NTs), 2.96–2.57 (m, 3 H, $-OCCH_2$–, OH), 2.43 (s, 3 H, tosyl CH_3), 2.10–1.32 (m, 5 H, CH_3C*H*CH_3, $-CH_2CH_2CH_2$NTs), 0.96 (d, J = 6 Hz, 6 H, CH_3CHCH_3); $[\alpha]_D$ −115.3° (*c* 0.0075, $CHCl_3$).

Anal. ($C_{17}H_{25}NO_4S$): C, H.

29b: IR (film) 3540, 2960, 2880, 1715, 1600, 1340, 1160, 1095, 1000, 820, 670 cm^{-1}; ^1H NMR ($CDCl_3$–CCl_4) δ 7.70 (d, J = 9 Hz, 2 H, aromatic H's), 7.23 (d, J = 9 Hz, 2 H, aromatic H's), 4.23–3.96 (m, 1 H, TsNC*H*CO–), 3.96–3.56 (m, 1 H, $-CH_2$C*H*OH), 3.50–3.00 (m, 2 H, $-CH_2$NTs), 2.93–2.57 (m, 3 H, $-OCCH_2$–, OH), 2.42 (s, 3 H, tosyl

(46) Araki, M.; Mukaiyama, T. *Chem. Lett.* **1974**, 663–666.

Table IX

	^{13}C NMR (CH_2Cl_2), δ		
	carbinol C	CH_3 C α to ketone	HPLC[a] *k*
31E	76.5	9.5	16.7
32E	76.2	9.0	14.4

[a] Waters' Radial Pak, 8 mm × 10 cm, silica gel, 15% EtOAc–hexane, flow rate = 8.0 mL/min.

CH_3), 2.07–1.36 (m, 5 H, CH_3CHCH_3, $TsNCH_2CH_2CH_2$–), 0.94 (d, *J* = 6 Hz, 6 H, CH_3CHCH_3).

Anal. ($C_{17}H_{25}NO_4S$): C, H.

Proof of Absolute Configurations of Carbinol Stereocenters of 28b and 29b. Aldol diastereoisomer **28b** (0.200 g, 0.59 mmol) was oxidized with peracetic acid as outlined above to give 57 mg of a colorless oil. This oil was purified by bulb-to-bulb distillation to give optically active 3-hydroxy-4-methylpentanoic acid: IR ($CHCl_3$) 3600–2400 (broad), 1705, 1410, 1225, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.48 (broad s, 2 H, CO_2H, OH), 3.80 (m, 1 H, $-CH_2CHOH$), 2.48 (m, 2 H, $HOOCCH_2$–), 1.70 (m, 1 H, CH_3CHCH_3), 0.93 (two d, *J* = 6 Hz, 6 H, CH_3CHCH_3); $[\alpha]_D$ +40.5° (c 0.0063, $CHCl_3$). The literature value is +26.4° (c 0.021, $CHCl_3$).[36] Independent synthesis of (*S*)-(−)-3-hydroxy-4-methylpentanoic acid in our laboratories gave $[\alpha]_D$ −40.0° (c 0.0464, $CHCl_3$).[36] Nevertheless, the rotation confirmed the absolute configuration of the carbinol stereocenter of **28b** as *R*. In a similar manner the carbinol stereocenter in **29b** was confirmed as *S*.

***erythro*-1-[1-(4-Toluenesulfonyl)-1-azacyclopentan-2-yl]-2,4-dimethyl-3-hydroxy-1-pentanone (Table VII, Entry B).** Enolization of 0.500 g (1.78 mmol) of ketone **26b** with 0.275 g (2.12 mmol) of diisopropylethylamine and 0.535 g (1.96 mmol) of di-*n*-butylboryl triflate in refluxing dichloromethane for 2 h was followed by aldol condensation and MoOPH workup with 0.159 g (2.21 mmol) of isobutyraldehyde to yield 705 mg (>100%) of an oily, light yellow solid. The enolization conditions are *not* known to fully equilibrate the two possible enolates. Analysis of the unpurified aldol adduct by ^{13}C NMR and analytical HPLC (Waters' Radial Pak, 8 mm × 10 cm, silica gel, 15% EtOAc–hexane) indicated only one erythro diastereoisomer accompanied by approximately 10% of the two threo diastereoisomers. The mixture was purified by recrystallization from EtOAc–hexane to afford **31E** (57%) as fine white needles, mp 155.5–156.5 °C: IR (CH_2Cl_2) 3520, 3060, 2960, 2935, 2880, 1710, 1595, 1450, 1340, 1200, 1160, 1095, 985, 815, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70 (d, *J* = 9 Hz, 2 H, aromatic H's), 7.29 (d, *J* = 9 Hz, 2 H, aromatic H's), 4.57 (m, 1 H, $TsNCHCO$–), 3.70–3.03 (m, 4 H, $-CH_2NTs$, $-CH_2CHOH$, $-OCCHCH_3$, 2.77 (d, *J* = 3 Hz, 1 H, OH), 2.41 (s, 3 H, tosyl CH_3), 2.00–1.37 (m, 5 H, $TsNCH_2CH_2CH_2$–, CH_3CHCH_3), 1.13 (d, *J* = 7 Hz, 3 H, $-OCCHCH_3$), 1.00 (d, *J* = 7 Hz, 3 H, CH_3CHCH_3), 0.88 (d, *J* = 7 Hz, 3 H, CH_3CHCH_3); ^{13}C NMR (CH_2Cl_2) δ 213.9, 144.2, 135.0, 130.0, 127.6, 76.5, 66.0, 49.2, 44.6, 30.9, 29.7, 24.8, 21.4, 19.0, 9.5; $[\alpha]_D$ −92.5° (*c* 0.0294, $CHCl_3$).

Anal. ($C_{18}H_{27}NO_4S$): C, H, N.

***erythro*-1-[1-(4-Toluenesulfonyl)-1-azacyclopentan-2-yl]-2,4-dimethyl-3-hydroxy-1-pentanone (Table VII, Entry C).** Kinetic enolization of 0.562 g (2.00 mmol) of ketone **26b** with 0.31 g (2.4 mmol) of diisopropylethylamine and 0.60 g (2.2 mmol) of dicyclopentylboryl triflate in 3 mL of ether–2 mL of dichloromethane (dichloromethane was used to add ketone **26b**) at room temperature for 45 min was followed by aldol condensation and MoOPH workup with 0.17 g (2.4 mmol) of isobutyraldehyde to afford 540 mg (77%) of an off-white solid. Again, as above, analysis of the unpurified aldol adduct by ^{13}C NMR and analytical HPLC indicated mainly erythro diastereoisomer **31E**. A portion of the mixture was purified by analytical HPLC (Altex Li Chromosorb Si 60 5μ, 10 mm × 25 cm, 25% EtOAc–hexane) to give diastereoisomer **31E** as a white crystalline solid. Additionally, the mixture could be purified by recrystallization to give pure **31E**; vide supra.

31E: mp 155–156 °C; IR (CH_2Cl_2) 3520, 3060, 2960, 2935, 2880, 1710, 1595, 1450, 1340, 1200, 1160, 1095, 985, 815, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70 (d, *J* = 9 Hz, 2 H, aromatic H's), 7.29 (d, *J* = 9 Hz, 2 H, aromatic H's), 4.57 (m, 1 H, $TsNCHCO$–), 3.70–3.03 (m, 4 H, $-CH_2NTs$, $-CH_2CHOH$, $OCCHCH_3$), 2.77 (d, *J* = 3 Hz, 1 H, OH), 2.41 (s, 3 H, tosyl CH_3), 2.00–1.37 (m, 5 H, $TsNCH_2CH_2CH_2$–, CH_3CHCH_3), 1.13 (d, *J* = 7 Hz, 3 H, $-OCCHCH_3$), 1.00 (d, *J* = 7 Hz, 3 H, CH_3CHCH_3), 0.88 (d, *J* = 7 Hz, 3 H, CH_3CHCH_3); ^{13}C NMR (CH_2Cl_2) δ 213.8, 144.1, 134.9, 129.9, 127.6, 76.4, 65.9, 49.2, 44.6, 30.9, 29.6, 24.8, 21.4, 19.0, 9.5. These spectra are identical with the spectra reported for entry B in Table VII.

The aldol condensation of the lithium enolate of **26b** (LDA, −78 °C, 60 min) and isobutyraldehyde was performed under "kinetic" conditions according to the published procedure.[6] The unpurified aldol adduct was then analyzed by ^{13}C NMR and HPLC as outlined above. All four possible diastereoisomers were detected and this served as an authentic mixture. The differences in the two possible erythro diastereoisomers which allowed their distinction are outlined in Table IX.

(2*R*,3*S*)-2,4-Dimethyl-3-hydroxypentanoic Acid (33) via Boron Aldol. To a solution of aldol diastereoisomer **31E** (0.900 g, 2.55 mmol) in dichloromethane (25 mL) cooled to 0 °C were added disodium hydrogen phosphate (4.0 g) and 13% peracetic acid in acetic acid (2.60 mL, 5.1 mmol). After 5 min the ice bath was removed and the mixture heated to the reflux temperature of dichloromethane. Additional peracid (1.30 mL, 2.55 mmol) was added 48 h later. After 72 h the reaction mixture was partitioned between dichloromethane and 5% sodium bicarbonate solution (caution, CO_2 evolved vigorously). The carbonate solution was adjusted to pH 4 with concentrated hydrochloric acid, saturated with salt, and extracted with EtOAc (3 × 50 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give 200 mg of a colorless oil. The oil was purified by bulb-to-bulb distillation to afford 130 mg (35%) of acid **33** as a colorless oil: IR (film) 3440, 3700–2200 (broad), 2980, 1715, 1470, 1460, 1390, 1220, 1000, 980, 950, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.11 (broad s, 2 H, OH, CO_2H), 3.62 (d of d, *J* = 4, 8 Hz, 1 H, >CHOH), 2.68 (d of q, *J* = 4 Hz, 7 Hz, 1 H, $-CH(CH_3)CHOH$), 1.67 (m, 1 H, CH_3CHCH_3), 1.20 (d, *J* = 7 Hz, 3 H, $-COCHCH_3$), 1.00 (d, *J* = 6 Hz, 3 H, $>CHCH_3$), 0.89 (d, *J* = 6 Hz, 3 H, $>CHCH_3$), $[\alpha]_D$ +10.5° (*c* 0.0921, $CHCl_3$).

Anal. ($C_7H_{14}O_3$): C, H.

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