Reagent Control in the Aldol Addition Reaction of Chiral Boron Enolates with Chiral α-Amino Aldehydes. Total Synthesis of (3S,4S)-Statine

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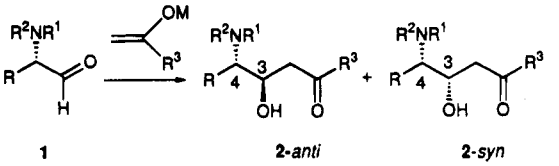
Over the past 10 years chiral α-amino aldehydes have become very popular as synthetic precursors of biologically active molecules.[1] In this paper, we report on the stereoselective aldol reactions involving chiral *N,N*-diprotected α-amino aldehydes and chiral boron enolates.[2] The aldol reaction between an acetate-derived enolate and a chiral aldehyde creates a new stereogenic center and two possible diastereoisomers (Scheme 1).

In recent years two distinct ways of stereochemical control have been used: substrate control, in which the intrinsic stereochemical preference of the α-amino aldehyde **1** determines the stereochemical outcome of the reaction, and reagent control, in which it is the chiral enolate's stereochemical preference that governs the reaction stereochemistry.[2,3] When achiral lithium enolates or achiral enolsilanes were used, selectivities ranged from modest to good in favor of either the "Felkin–Anh" products (**2**-*anti*) or the "chelation" products (**2**-*syn*), depending on the nitrogen protecting groups (R^1, R^2) and on the Lewis acid promoters.[1b,4–10] Only two types of chiral enolates were reported to control the stereochemistry of the addition to α-amino aldehydes **1** ($R^1 = R^2 =$ Bn), with selectivities ranging from fair (de = 60–92%)[11] to good (de = 86.6–93%).[4a,12,13]

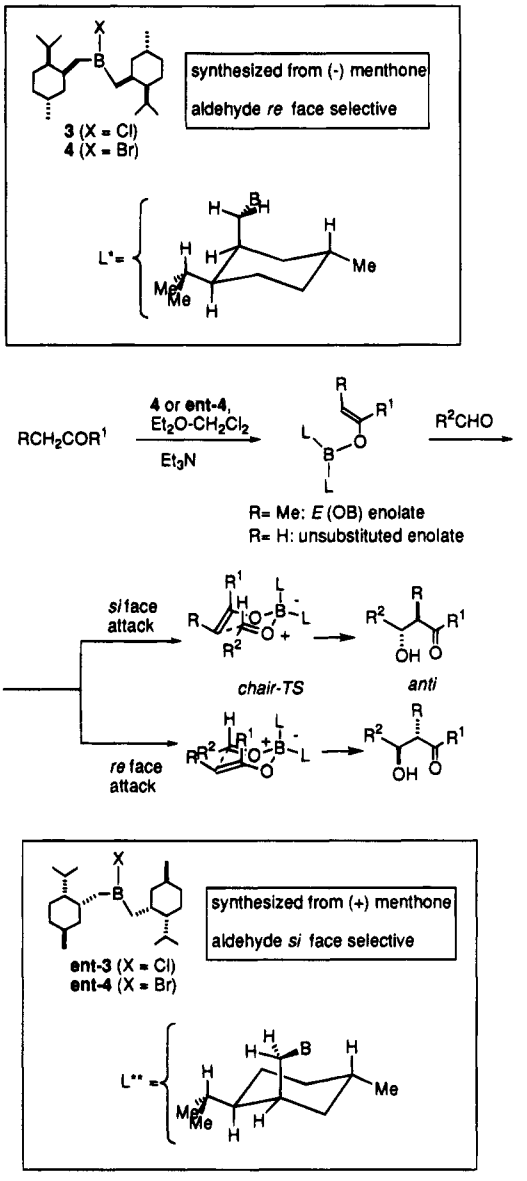
We have exploited transition state computer modeling to develop two new boron reagents (**3**, X = Cl; **4**, X = Br; Scheme 2) which allow the enantioselective synthesis of ketone-derived *anti* (74–88% ee; R = Me; R^1 = alkyl, aryl) and unsubstituted aldols (55–76% ee; R = H; R^1 = alkyl, aryl)[14a] and thioester-derived *anti* (≥98% ee; R = Me, R^1 = SBu^t) and unsubstituted aldols (87–97% ee; R = H, R^1 = SBu^t).[14b] We have also recently reported that boron enolates derived from **4** or *ent*-**4** (X = Br) show a high degree of reagent control in reactions with chiral aldehydes.[14c]

Here we report the high efficiency of this reaction involving α-amino aldehydes and its application to the

Scheme 1



Scheme 2



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Scheme 3

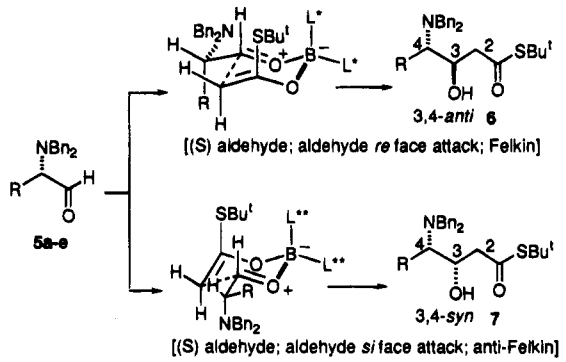


Table 1. Aldol Addition Reactions of Chiral Boron Enolates with Chiral α-Amino Aldehydes

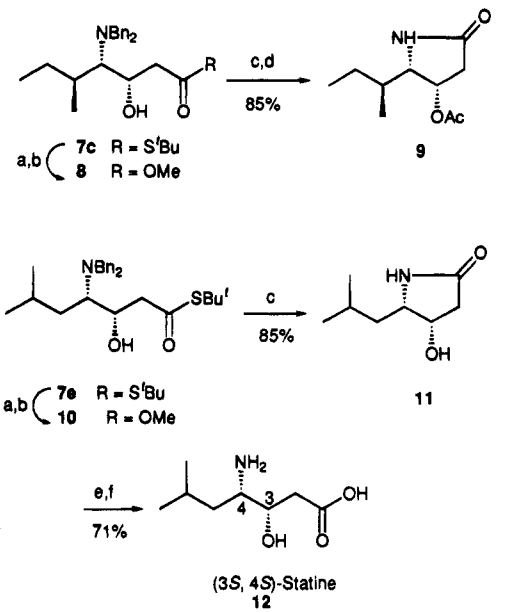
Entry	R	L	Substrates	3,4-*anti*	3,4-*syn*	Products	Yield %
1	Bn	L*	**5a**	**98.6**	1.4	**6a**	75
2	Bn	L**	**5a**	3.2	**96.8**	**7a**	70
3	Me	L*	**5b**	**98.5**	1.5	**6b**	80
4	Me	L**	**5b**	3.7	**96.3**	**7b**	75
5	*s*-Bu	L*	**5c**	**98.2**	1.8	**6c**	75
6	*s*-Bu	L**	**5c**	4.6	**95.4**	**7c**	71
7	*i*-Pr	L*	**5d**	**>100**	<1[a]	**6d**	80
8	*i*-Pr	L**	**5d**	3.5	**96.5**	**7d**	72
9	*i*-Bu	L*	**5e**	**>100**	<1[a]	**6e**	78
10	*i*-Bu	L**	**5e**	2.5	**97.5**	**7e**	71

[a] Not detected in the crude reaction mixture.

total synthesis of (3*S*,4*S*)-statine **12**,[5a,10,11a,15] the main component of pepstatine, which is a specific inhibitor of aspartic proteases.[15c,d] *N*,*N*-Dibenzylamino aldehydes **5** were prepared from the corresponding natural α-amino acids according to the procedure described by Reetz.[4b] With the chiral boron enolates of *tert*-butyl thioacetate derived from *ent*-**4** we are able to overcome the inherent substrate preference for the Felkin-type product (3,4-*anti*) observed with achiral enolates. It is worth noting that in the "matched" cases the 3,4-*anti*:3,4-*syn* diastereomeric ratios are ≥98.2:1.8, while in the "mismatched" cases the 3,4-*syn*:3,4-*anti* ratios are ≥95.4:4.6. These results prove that it is possible to obtain either the 3,4-*anti* (**6**) or the 3,4-*syn* (**7**) adduct with very high diastereoselectivity just by changing the chiral boron ligand configuration [L* derived from (−)-menthone, L** derived from (+)-menthone] (Scheme 3, Table 1).

Although the aldol products are contaminated by small amounts of the unwanted diastereomer (0−4.6%), they can be easily purified by flash chromatography. The ratios of the mixtures **6**/**7** were determined by ^{13}C-NMR analysis of the crude reaction mixtures after having previously fully characterized each diastereomer. We have determined the relative and absolute configuration of the aldol products by chemical correlation in a couple of cases (see below). We have also determined by these chemical correlations that both **6**- and **7**-type compounds are enantiomerically pure and, therefore, that in the aldol

Scheme 4[a]



[a] Key: (a) 1 N NaOH in THF; (b) CH_2N_2 in MeOH; (c) HCO_2NH_4, Pd−C, MeOH, reflux; (d) Ac_2O/Py; (e) concd HCl, 80 °C, 3 h; (f) DOWEX 50X8-100 (acid form).

reaction the substrates do not suffer any erosion of configurational integrity. The 3,4-*syn* aldol adducts **7c** and **7e** have been correlated with the known lactams **9**[16] and **11**,[15a] respectively, the latter leading in two steps to the natural β-hydroxy γ-amino acid statine **12**. Aldol adducts **7c** and **7e** were saponified and esterified with diazomethane to give methyl esters **8** and **10** in good yield (75% and 80%, respectively). Debenzylation of the −NBn_2 group was achieved using a procedure originally introduced for the deprotection of monobenzylamines (HCO_2NH_4, Pd−C, MeOH, reflux).[17] Under these reaction conditions the hydroxy amino ester intermediate undergoes cyclization, generating the γ-lactam, which is acetylated to give **9** (in the isoleucine series). Compound **9** is obtained in 85% overall yield from **8**. The $[\alpha]_D$ values of lactams **9** and **11** are in good agreement with those reported in the literature.[15a,16] Although the ring opening of **11** under acidic conditions[15e] has been reported to fail,[15b] we have found that when concentrated hydrochloric acid at 80 °C is used lactam **11** is converted into statine hydrochloride in good yield. The salt was dissolved in water and loaded onto an ion exchange column to deliver the free amino acid statine **12** as a white solid (Scheme 4).

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Supporting Information Available: Experimental procedures for all reaction products and complete spectral and analytical data for compounds **6a**−**e**, **7a**−**e**, and **8**−**12** (8 pages).

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