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Boron-mediated aldol reactions of ethyl α-(*N*,*N*)-dibenzylamino ketones: control of enolisation geometry and aldehyde π-facial selectivity

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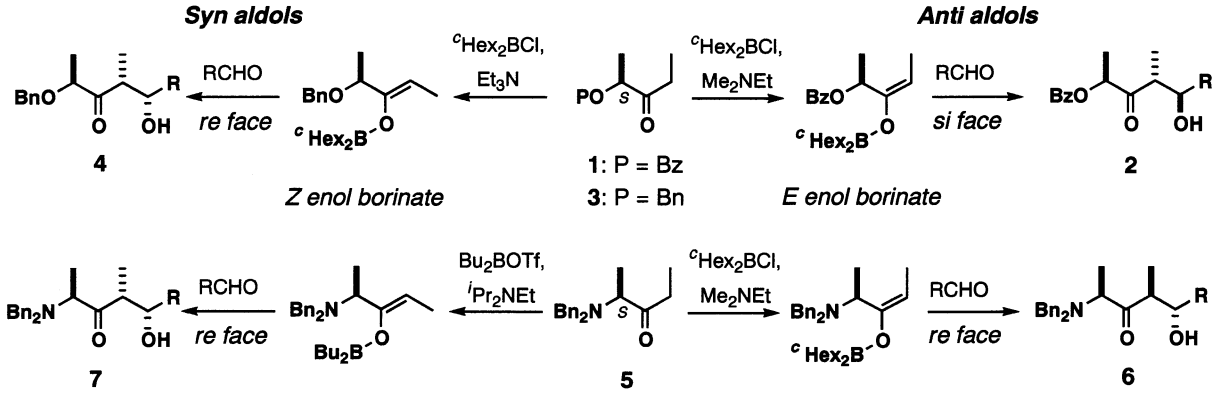
Abstract—The boron-mediated aldol reactions of a range of chiral α-(*N*,*N*)-dibenzylamino ketones with aldehydes can be controlled to provide stereodefined adducts. Complementary induction can be achieved with $^{c}Hex_2BCl/Me_2NEt$ leading to preferential formation of the 1,2-*anti*-2,4-*syn* adducts, while $Bu_2BOTf/^{i}Pr_2NEt$ provides 1,2-*syn*-2,4-*anti* adducts.

The boron-mediated aldol reaction is one of the most important methods for acyclic stereocontrol, enabling the efficient synthesis of a wide variety of β-hydroxy carbonyl compounds in a highly regio-, diastereo-, and enantioselective manner.[1] The use of lactate-derived α-alkoxy ketones is one such method that has been developed in our laboratory.[2,3] Here the simple choice of oxygen protecting group determines the enolisation geometry with $^{c}Hex_2BCl/R_3N$, leading to *anti* or *syn* additions to aldehydes with high levels of π-facial selectivity, i.e. **1**→**2** and **3**→**4** (Scheme 1). As an extension to this work, we now report a study of the aldol reactions of ethyl α-(*N*,*N*)-dibenzylamino ketones,[4] as versatile chiral building blocks prepared from α-amino acids. By appropriate choice of boron reagent and amine base, control of enolisation geometry and aldehyde π-facial selectivity results in preferential access to stereodefined *anti* or *syn* adducts, as in **5**→**6** or **7**. These may be useful as precursors of novel *N*,*O*-based chiral ligands for asymmetric catalysis,[5] as well as for incorporation into peptidomimetic and other libraries of pharmaceutical interest.

For this study, the ethyl ketones **5** and **8** were prepared (Scheme 2) from the corresponding L-alanine and L-phenylalanine methyl esters, **9** and **10**, via *N*-benzylation and EtMgCl addition to the derived Weinreb amides.[6] Ketone **11** was prepared by Grignard addition to *N*,*N*-dibenzylated valinal followed by oxidation.[4]



Scheme 1. Boron-mediated aldol reactions of lactate and α-amino acid derived ketones.

Keywords: boron aldol; amino acids; amino ketones; stereoinduction; libraries.

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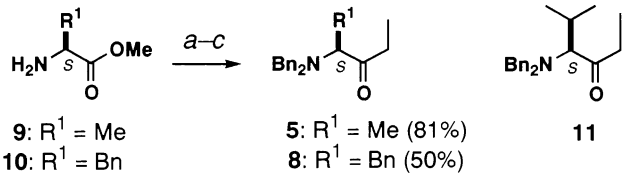
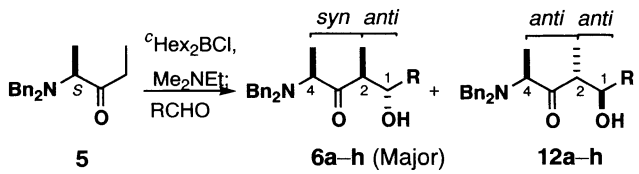


Scheme 2. (a) BnBr, $NaHCO_3$, THF/DMSO (4:1), 16 h, 85°C; (b) HNMe(OMe)·HCl, ^{i}PrMgCl, THF, −5°C, 1 h, then rt, 2 h; (c) EtMgCl, THF, 0°C→rt, 3 h.

By using $^{c}Hex_2BCl$ in the presence of tertiary amine bases, suitable conditions for achieving *anti*-selective aldol reactions with ketone **5** were developed.[7] To ensure optimum selectivity and conversion, Me_2NEt was selected as the preferred base with enolisation in Et_2O at 0°C, followed by addition of the aldehyde to the resulting solution of (*E*)-enol borinate cooled to −78°C.[8] For a range of aldehydes (Table 1), the *anti* adducts **6a–h** and **12a–h** were obtained in high yield without any detectable *syn* adducts.[9]

For simple achiral aldehydes, a typical level of diastereoselection of 85:15 was obtained in favour of the adducts **6a–f** (1,2-*anti*-2,4-*syn* as depicted), corresponding to preferred *re*-face attack on the aldehyde. In each case, the major adduct was isolated in good yield after chromatographic separation of the mixture. The use of a Felkin-matched α-chiral aldehyde led to essentially complete π-facial selectivity for **6g** (>98:2 dr), whereas the selectivity was eroded for the mismatched pair (64:36 dr). For the addition of **5** to isobutyraldehyde (entry c), the configuration of the major diastereomer **6c** was rigorously assigned by single crystal X-ray diffraction analysis (Fig. 1), while the other examples were assigned by analysis of their ^{1}H NMR spectra.[10,11]

Table 1. *Anti*-selective aldol reactions of ketone (*S*)-**5**



entry	R	yield (%)[a]	dr (**6** : **12**)[b]
a	Me	90	85:15
b	Et	88	85:15
c	^{i}Pr	95	85:15
d	(*E*)-MeCH=CH	82	84:16
e	H_2C=C(Me)	80	89:11
f	Ph	65	86:14
g	TBSO	57 (95)[c]	>98:2
h	TBSO	81	64:36

[a] isolated yields; [b] Ratio determined by 400 MHz ^{1}H NMR and HPLC analysis;

[c] Yield based on recovered starting material.

For boron-mediated aldol reactions, substantial levels of stereoinduction result from a tight cyclic transition state, which is energetically responsive to quite subtle steric and electronic influences.[1] In this case (Fig. 2), the preferred *re*-face attack of the (*E*)-enolate on the aldehyde can be rationalised by the addition proceeding via transition structure ***TS-I***, where A(1,3) strain is minimised.[12] Here the large steric demands of the α-dibenzylamino group lead to it being directed outside with the methyl group oriented inwards. Notably, this contrasts with the preferred *si*-face attack of the (*E*)-enolate of the (*S*)-lactate-derived α-benzoyloxy ketone (cf Scheme 1, **1**→**2**);[2] where the benzoyloxy group is directed inside in ***TS-II***.[2a,c]

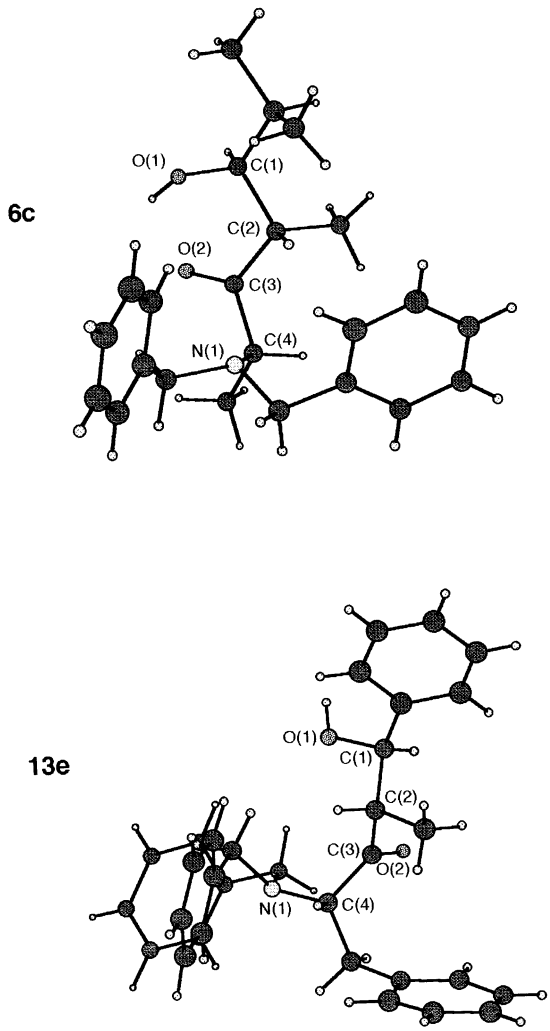


Figure 1. Crystal structure of major aldol adducts **6c** and **13e**.

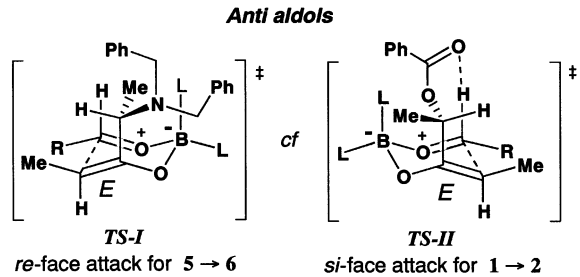
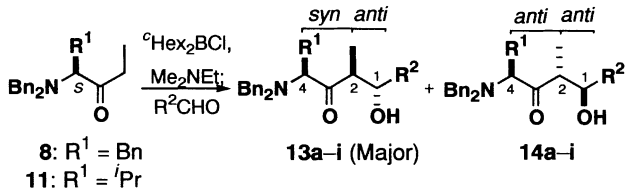


Figure 2. Preferred aldol transition structures.

Table 2. *Anti*-selective aldol reactions of ketones (*S*)-**8** and (*S*)-**11**



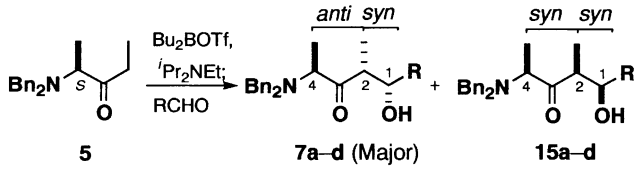
8: R^1 = Bn
11: R^1 = ^{i}Pr

13a–i (Major) **14a–i**

entry	R^1	R^2	yield (%)[a]	dr (**13** : **14**)[b]
a	Bn	Me	75	74:26
b	Bn	Et	85	78:22
c	Bn	^{i}Pr	82	85:15
d	Bn	H$_2$C=C(Me)	82	95:5
e	Bn	Ph	80	93:7
f	Bn	TBSO	80	95:5
g	^{i}Pr	Et	41 (92)[c]	72:28
h	^{i}Pr	^{i}Pr	41 (83)[c]	65:35
i	^{i}Pr	H$_2$C=C(Me)	40 (87)[c]	66:34

[a] Isolated yields; [b] Ratio determined by 400 MHz ^{1}H NMR and HPLC analysis; [c] Yield based on recovered starting material.

Table 3. *Syn*-selective aldol reactions of ketone (*S*)-**5**



5 **7a–d** (Major) **15a–d**

entry	R	yield (%)[a]	dr (**7** : **15**)[b]
a	Et	95	97:3
b	^{i}Pr	96	86:14
c	H$_2$C=C(Me)	90	87:13
d	Ph	100	93:7

[a] Isolated yields; [b] Ratio determined by 400 MHz ^{1}H NMR and HPLC analysis.

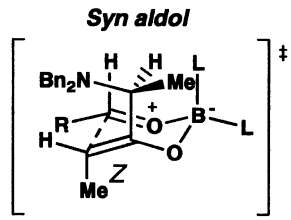


Figure 3. Preferred aldol transition structure.

The *anti* aldol reactions of the protected α-amino ketones **8** and **11** with a range of aldehydes were also explored under similar reaction conditions (Table 2). For the addition of **8** to benzaldehyde, the configuration of the major adduct **13e** (entry e) was established by X-ray diffraction analysis to be analogous to that obtained in the alanine series (Fig. 1).[10] On reaction with aliphatic aldehydes, selectivities for **13a**, **b**, **g** and **h** were lower compared to the corresponding reactions of **5**. This appears to be in line with the anticipated destabilising effect of locating a bulkier alkyl group (^{i}Pr or Bn in place of Me) in the inside position in ***TS-I***. However, reaction of **8** with methacrolein and benzaldehyde gave improved stereoselectivity for **13d** and **e**, respectively, comparable to the Felkin-matched reaction giving **13f**, suggesting the contribution of other factors. Reactions of the more highly substituted ketone **11** proved sluggish, leading to incomplete conversion. Here the same sense of stereoinduction towards **13g–i** was assigned in analogy to the results for the other two ketones.

To achieve stereochemical flexibility in the aldol reactions of protected α-amino ketones, we next developed a complementary *syn*-selective process through the (*Z*)-enol borinate (Table 3).[13] Using both sodium and lithium enolates and invoking an open transition state, Liotta and co-workers have shown that these ethyl ketones undergo diastereoselective aldol reactions with aldehydes to provide the *syn* adducts **7**.[4] For the boron-mediated reaction, enolisation of ketone **5** with Bu$_2$BOTf, in the presence of ^{i}Pr$_2$NEt, in CH$_2$Cl$_2$ at −78°C generated the (*Z*)-enol borinate cleanly, which added to aldehydes with a pronounced π-facial bias towards the *syn* adducts **7a–d** (1,2-*syn*-2,4-*anti* as depicted) over **15a–d** and in high yield.[8] Once again, the enolisation step was found to be completely selective as determined by the lack of any detectable *anti* adducts. Flash chromatography allowed ready isolation of the major diastereomers **7a–d** (>80% yield), which were stereochemically identical to those obtained using Liotta's protocol. Here the observed *re*-face selectivity concurs with that found for the (*S*)-lactate-derived α-benzyloxy ketone (cf Scheme 1, **3**→**4**). Taking account of steric and electronic factors, this can be rationalised in a similar manner by invoking ***TS-III*** (*re*-face attack) as the preferred transition structure (Fig. 3), where the enolate C–O and C–N dipoles are opposed and the methyl group on the α-stereocentre is directed outwards.

In conclusion, complementary diastereoselectivities can be obtained in the boron-mediated aldol reactions of ethyl α-(*N*,*N*)-dibenzylamino ketones depending on the choice of reagent. It should be possible to manipulate the resulting stereodefined β-hydroxy ketones along the lines already demonstrated for the lactate-derived series.[2,14] By using the wide variety of α-amino acids available,[15] extensive stereochemical and structural diversification should enable the parallel synthesis of novel libraries.[16]

Acknowledgements

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8. Representative experimental procedure: To a stirred solution of $^{c}Hex_2BCl$ (1.3 equiv.) and Me_2NEt (1.5 equiv.) in dry Et_2O (1 mL/mmol of ketone) at 0°C was added a solution of the ketone (*S*)-**5** in Et_2O. After 2 h, the reaction mixture was cooled to −78°C. A solution of the aldehyde (2 equiv.) in Et_2O was added. After 3 h, the reaction mixture was kept at −26°C for 14 h (freezer), then pH 7 buffer and MeOH (1:1, 2 mL/mmol) were added at 0°C followed by aqueous H_2O_2 (30%, 1 mL/mmol). After stirring for 1 h, the mixture was extracted with CH_2Cl_2. Purification by flash chromatography gave the major *anti* aldol adduct **6**. In each case, the reaction diastereoselectivity was determined by analytical HPLC on the crude reaction mixture. A similar procedure was used for the *syn* aldol reactions of ketone (*S*)-**5**, except Bu_2BOTf and $^{i}Pr_2NEt$ were used for the enolisation at −78°C in CH_2Cl_2.
9. All new compounds gave spectroscopic data in agreement with the assigned structures. For adducts in Tables 1 and 2, the measured vicinal coupling constants ($^3J_{1,2}=6.6$–7.5 Hz) were consistent with the *anti* stereochemistry throughout. The corresponding *syn* isomers in Table 3 had $^3J_{1,2}=1.8$–4.4 Hz.
10. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC165296 and CCDC165297. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
11. ^1H NMR analysis of coupling constants and (*R*)- and (*S*)-MTPA ester derivatives supported this same preference in other cases. In addition, enantiomeric purity of >96% ee was established by Mosher ester analysis. Ohtani, I.; Kusumi, T.; Kasman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.
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