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Studies in Polypropionate Synthesis: High π–Face Selectivity in *Syn* and *Anti* Aldol Reactions of Chiral Boron Enolates of Lactate-Derived Ketones.

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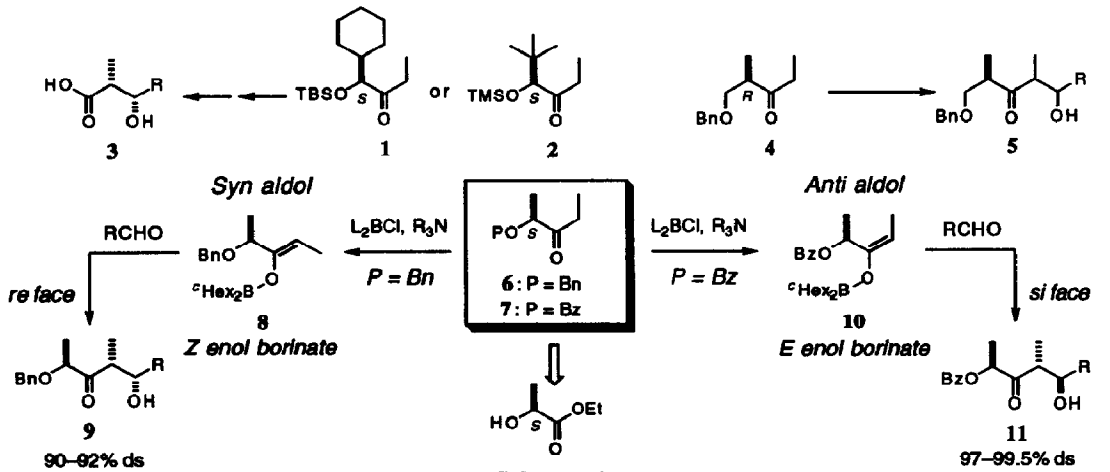
Abstract: Use of $^{c}Hex_2BCl$ / Me_2NEt in the aldol reactions of the α'-benzoyloxy ketone **7** with aldehydes leads to high stereoselectivity (97–99.5% ds) for the crystalline *anti* adducts **11**. Under similar conditions, the corresponding benzyl ether **6** favours formation of the *syn* adducts **9**.

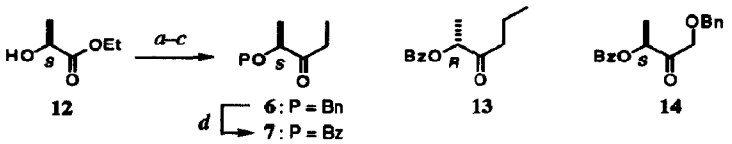
Asymmetric aldol reactions are one of the most important means of controlling acyclic stereochemistry in synthesis.[1] Typically, a stereodefined chiral enolate is employed to direct π-face selectivity in addition to an aldehyde. For example, the *Z* enol borinates of the α'-siloxy ketones **1** and **2** (**Scheme 1**),[2] as introduced by Masamune[2a] and Heathcock,[2b] enable the asymmetric synthesis of *syn* α-methyl-β-hydroxy acids **3**, where the auxiliary group is removed by oxidative cleavage. As an alternative "auxiliary-free" strategy,[3,4] we have introduced the use of β'-alkoxy ketones such as **4** for expedient polypropionate synthesis. By appropriate choice of the metal enolate derivative, high levels of π-face selectivity can be achieved in *syn* and *anti* aldol reactions to give three out of the four possible diastereomeric adducts **5**,[4a-c] where the inducing stereocentre is now retained.



Scheme 1

As an extension of this work, we now report that the *Z* and *E* enol dicyclohexylborinates of the related lactate-derived[5] ketones **6** and **7** add to aldehydes to give *syn* and *anti* aldol adducts with useful levels of π-face selectivity, as in **8** → **9** and **10** → **11**. The latter addition is especially noteworthy, where up to 200 : 1 ds can be achieved, making (*R*)- and (*S*)-**7** valuable new reagents for the asymmetric synthesis of *anti* aldols.[6] As demonstrated in this and the accompanying paper,[7] these new chiral boron enolates have several advantages over existing reagents. Their aldol adducts can be manipulated to provide a wide range of enantiomerically-pure β-hydroxy carbonyl compounds and derivatives. Notably, the α'-methyl group plays a novel "optional auxiliary" role and may be retained (*cf.* **5**).

As shown in **Scheme 2**, the ethyl ketones (*S*)-**6**, $[\alpha]_D^{20} = -64.0°$ (*c* 1.9, $CHCl_3$), and (*S*)-**7**, $[\alpha]_D^{20} = +20.7°$ (*c* 1.7, $CHCl_3$), were prepared from (*S*)-ethyl lactate (**12**) *via* hydroxyl protection and addition of ethyl magnesium bromide to the derived Weinreb amide.[8,9] The enantiomeric ketones were similarly obtained from (*R*)-isobutyl lactate. Related ketones such as **13** and **14** can also be prepared by suitable variation of the Grignard reagent and the configuration of the lactate-derived amide.



Scheme 2 (a) MeN(OMe)H.HCl, Me_3Al, CH_2Cl_2, 20 °C, 16 h (96–100%), (b) $BnOC(=NH)CCl_3$, TfOH (0.1 eq.), hexane, 20 °C, 16 h; (c) EtMgBr, THF, 0 °C, 2 h (77% over 2 steps); (d) H_2, 10% Pd/C, THF, 20 °C, 15 h; filter; $(PhCO)_2O$, $^iPr_2NEt$, DMAP (0.1 eq.), 20 °C, 15 h (85%).

By employing sterically-demanding ligands on boron, high levels of stereocontrol can be obtained for the *syn* and *anti* aldol reactions of ketones **1** and **4**, *via* their respective *Z*[2a] and *E*[4a] enol borinates. The latter *anti* aldol reactions[4a] make use of $^cHex_2BCl$ / Et_3N, introduced by Brown *et al.*[10a-c] for the *E*-selective enolisation of ethyl ketones. Using this reagent system[10] with the benzyl ether **6**, however, gave *syn* aldol adducts, apparently *via* the *Z* enol borinate **8** (**Scheme 1**).[11] In sharp contrast, the corresponding β'-benzyloxy ketone **4** gives only the *E* enol borinate under these same conditions.[4a] With the benzoate derivative **7**, however, the *E* enol borinate **10** was now cleanly formed,[11] leading to *anti* aldol adducts. A simple choice of the protecting group in **6** and **7**, thus allows control of *Z*/*E* enolisation and *syn*/*anti* aldol selectivity.

Table 1 *Syn* and *anti* aldol reactions of (*S*)-**6**[a] and (*S*)-**7**[b] with RCHO using $^cHex_2BCl$ / R_3N.

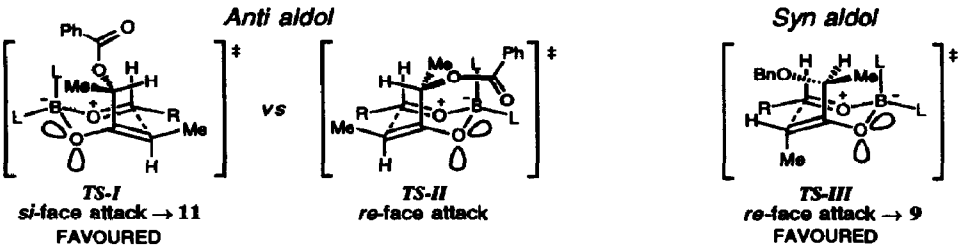
entry	ketone	R	product[c]	stereoselectivity[d]	% yield[e]
1[a]	**6**	^{n}Pr	**9a**	90 : 10	89
2[a]	**6**	^{i}Pr	**9b**[f]	92 : 8	81
3[a]	**6**	CH_2=C(Me)-	**9c**	90 : 10	87
4[b]	**7**	^{i}Pr	**11b**[f]	97 : 3	95
5[b]	**7**	CH_2=C(Me)-	**11c**	98 : 2	97
6[b]	**7**	Et	**11d**	99.5 : 0.5	93
7[b]	**7**	Ph	**11e**[f]	99.5 : 0.5	85

[a] Reaction conditions: $^cHex_2BCl$, Et_3N, Et_2O, –78 °C, 2 h; RCHO, –78 → –20 °C, 16 h. See note 12. [b] Reaction conditions: $^cHex_2BCl$, Me_2NEt, Et_2O, 0 °C, 2 h; RCHO, –78 → –20 °C, 16 h. See note 12. [c] Enantiomeric purity (>97% ee) and hydroxyl configuration determined by ^1H NMR analysis of (*R*)- and (*S*)-MTPA esters. [d] Ratio of major isomer to sum of minor isomers by HPLC. [e] Isolated yield of aldol adducts after chromatography. [f] See ref 7.

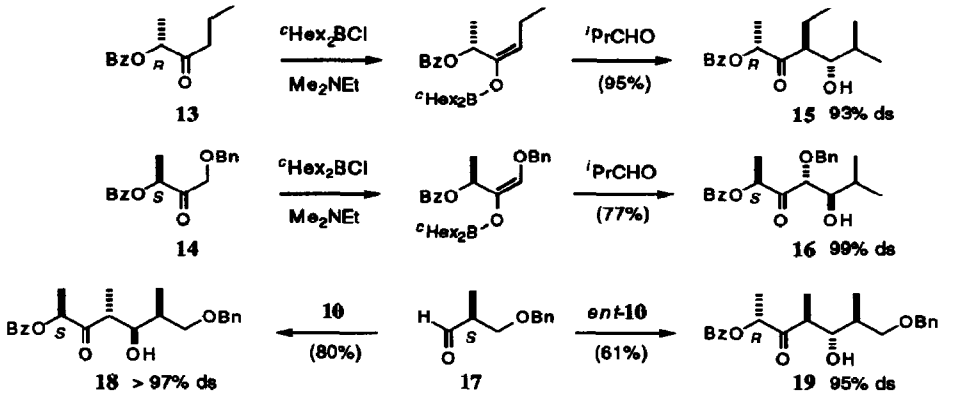
As summarised in **Scheme 1** and **Table 1**, these new stereodefined *Z* and *E* boron enolates add to aldehydes with high levels of π-face selectivity, *ca* 10 : 1, *re* : *si*, for **8** and 30–200 : 1, *si* : *re*, for **10**.[9] The optimum aldol conditions[12] for **6** used $^cHex_2BCl$ / Et_3N in Et_2O, which gave the *syn* adducts **9a-c** in 81–89% yield with 90–92% ds (entries 1–3). The *anti* aldol reactions of benzoate **7** proved even better (entries 4–7). Using $^cHex_2BCl$ / Me_2NEt in Et_2O,[12] the crystalline *anti* adducts **11b-e** were now isolated in 85–97% yield with excellent diastereoselectivity (≥ 97% ds). Here a single recrystallisation sufficed to give stereochemically homogeneous aldol adduct.

The origin of the high π-face selectivity can be traced to the relative steric and electronic contributions of the substituents at the enolate stereocentre in the aldol chair transition state. For *E* enol borinate **10**, aldol

transition state modelling[13a] suggested that ***TS-I*** is preferred. It minimises A(1,3) allylic strain with the *E*-enol methyl group, with the benzoate directed inwards and the other methyl outwards. The preference for ***TS-I*** (*si*-face attack on aldehyde) over ***TS-II*** (*re*-face attack) is believed to have an electronic origin, with the latter destabilised through lone-pair repulsion between the benzoate and enolate oxygens. We have proposed a similar rationalisation for the analogous *anti* aldol reactions of the *E* enol borinate from **4**.[4e,13a] The selectivity obtained for *Z* enol borinate **8** is essentially as expected[2] with ***TS-III*** preferred,[13b] where the ether and enolate oxygens are directed away from each other and the methyl group is outside. Note that with the analogous *syn* aldol reactions of Masamune[2a] and Heathcock,[2b] using the *Z* enol borinates from **1** and **2**, a higher level of π-face selectivity arises from use of the more sterically-demanding cyclohexyl or *tert*-butyl group.



While superior *syn*-selective chiral enolates are already available,[1] the *anti* aldol results obtained with the α'-benzoyloxy enol borinate **10** are noteworthy. Further examples of *anti*-selective aldol additions using such chiral *E* enol dicyclohexylborinates are shown in **Scheme 3**. Addition of ketone **13** to isobutyraldehyde, mediated by $^{c}Hex_2BCl$, gave **15** with comparable selectivity to that obtained for **7**. The aldol reactions of the benzyloxymethyl ketone **14** also proceeded with excellent stereocontrol to give **16** (99% ds), demonstrating a potential approach to the synthesis of contiguous polyols[7] and other carbohydrate-type systems.



Scheme 3

These *E* enol borinates also allow reagent-control[14] in aldol additions to chiral aldehydes. Using the standard conditions,[12] reaction of aldehyde **17** with the α'-benzoyloxy enol borinates **10** and ***ent*-10** gave **18** and **19** with > 97% and 95% ds, respectively. In these double stereodifferentiation experiments, the π-face selectivity from the *E* enolate completely overrides any Felkin-Anh type influence from the aldehyde. Notably, the stereocontrol realised with this particular aldehyde is superior to that reported for some other chiral *E* enol borinates.[15] This demonstrates that efficient aldol coupling between the ethyl ketones (*R*)- and (*S*)-**7** and α-chiral aldehydes can be carried out by the present procedure, where stereocontrol from the former dominates.

In summary, the boron-mediated aldol chemistry of ketones **6** and **7** (and their enantiomers) enables the

asymmetric synthesis of a wide range of *syn* and *anti* α-methyl-β-hydroxy carbonyl compounds in enantiopure form. In particular, (*R*)- and (*S*)-**7** are demonstrated to be valuable new reagents for the asymmetric synthesis of *anti* aldols. Key features are: (*i*) the use of a sterically-undemanding auxiliary from readily available, (*R*)- or (*S*)-lactate; (*ii*) the ability to introduce other α-substituents (*cf.* **13** and **14**). In addition, as shown in the accompanying paper,[7] the aldol products may be manipulated in various ways and the α'-methyl group may be retained.

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11. This is presumably due to chelation of the boron reagent by the adjacent ether oxygen in **6** (with concomitant displacement of chloride from the boron) and *trans* deprotonation by the amine base, giving the *Z* enol borinate. Similar results were obtained using $^{n}Bu_2BOTf/R_3N$. With the benzoate **7**, chelation is expected to be precluded and normal *cis* deprotonation giving the *E* enol borinate now occurs. For a relevant discussion of enolisation stereocontrol, see: Goodman, J. M.; Paterson, I. *Tetrahedron Lett.* **1992**, *33*, 7223.
12. **Representative experimental procedure** To a stirred solution of dicyclohexylboron chloride (1.5 equiv.) and Me_2NEt (1.8 equiv.) in dry Et_2O (3 ml/mmol of boron reagent) at -78 °C was added a solution of the ketone **7** in Et_2O. After 10 min, the reaction mixture was warmed to 0 °C for 2 h, then re-cooled to -78 °C. A solution of the aldehyde (3-5 equiv. for simple aldehydes, 0.5 equiv. for **17**) in Et_2O was added. After 30 min, the reaction mixture was kept at -20 °C for 14 h (freezer), then pH7 buffer and MeOH were added at 0 °C followed by aqueous H_2O_2 (30%, 3 ml/mmol). After stirring for 1 h, the mixture was extracted with CH_2Cl_2. The crude product was purified by recrystallisation (Et_2O/hexane) and/or flash chromatography to give the major *anti* aldol adduct **11**. A similar procedure was used for the *syn* aldol reactions of ketone **6**, except Et_3N was used in place of Me_2NEt and enolisation was performed only at -78 °C. In each case, the reaction diastereoselectivity was determined by analytical HPLC on the crude reaction mixture.
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