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ALDOL REACTIONS IN POLYPROPIONATE SYNTHESIS: HIGH π-FACE SELECTIVITY OF ENOL BORINATES FROM α-CHIRAL METHYL AND ETHYL KETONES UNDER SUBSTRATE CONTROL.

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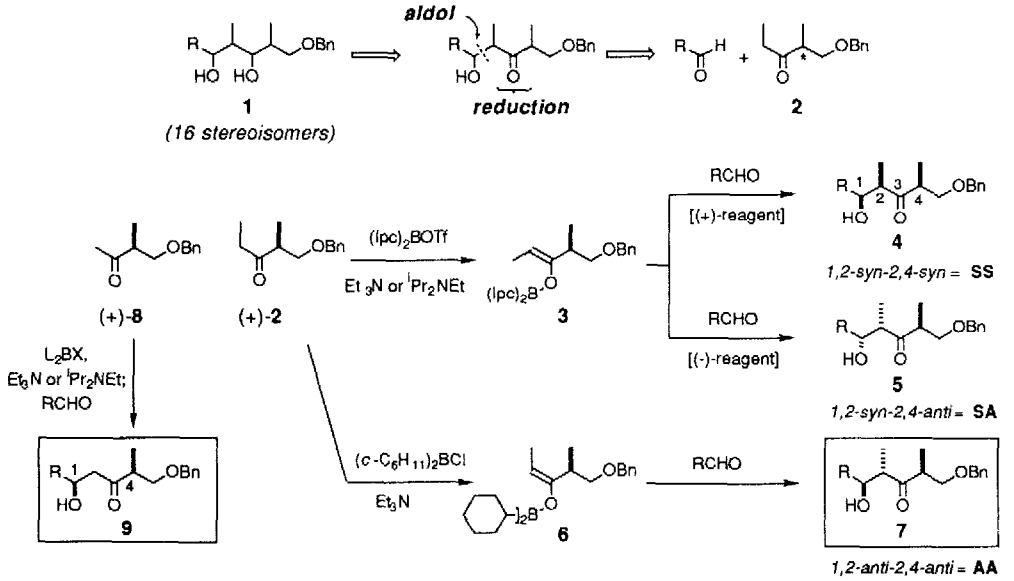
Summary: Use of $(c\text{-}C_6H_{11})_2BCl$ in the *anti*-selective aldol reaction of the α-chiral ethylketone **2** leads to high stereoselectivity (>94%) for the 1,2-*anti*-2,4-*anti* isomer **7**. The related α-chiral methylketone aldol reaction, **8** → **9**, proceeds with 84-93% diastereoselectivity for a range of boron reagents.

We recently described a useful entry into the synthesis of polypropionate-derived natural products based on the aldol reactions of α-chiral ethylketones using enol borinates.[1,2] For an aldol/reduction approach to the generalised stereotetrad **1** in **Scheme 1**, the controlled synthesis[3] of each of the sixteen possible stereoisomers from the appropriate enantiomer of the starting ketone **2** is required. In our earlier work, the use of (+)- and (-)-$(Ipc)_2BOTf$ reagents with ethylketone (+)-**2** gave, *via* the *Z* enol borinates **3**, the 1,2-*syn* adducts **4** and **5** (SS and SA) respectively with 90-93% diastereoselectivity (*i.e.* a reagent controlled aldol reaction).[1a] However, using achiral ligands on boron in **3** provided negligible π-face selectivity and gave an *ca* 1:1 mixture of **4** and **5**.

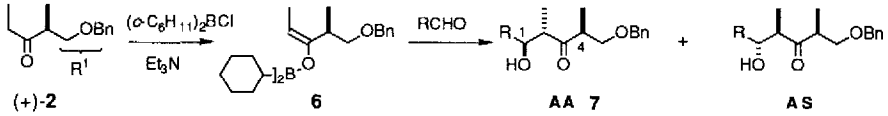
We now report the contrasting behaviour of **6**, the corresponding *E* enol borinate derivative of **2** with *achiral* ligands, which gives the 1,2-*anti*-2,4-*anti* adduct **7** (**AA**) with >94% diastereoselectivity (*i.e.* a substrate controlled aldol reaction). The aldol reaction of the α-chiral methylketone (+)-**8** also occurs with an unprecedented level of stereoselectivity (84-93%), favouring the 1,4-*syn* adduct **9** for a range of boron reagents.

Scheme 1



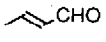
Our earlier findings[1a] for the boron mediated aldol reactions of ethylketone **2** suggested that with $^{n}Bu_2BOTf/Et_3N$ at 0 °C some selectivity (70-84%) for one of the two 1,2-*anti* isomers (**AA** or **AS**) was possible. Since the π-face selectivity of chiral enol borinates varies with the size of the ligands on boron,[2g] we chose to explore the use of more sterically demanding boron reagents to give the required *E* isomer. Brown's dicyclohexylchloroborane reagent, which gives highly selective *E* enolisation with simple ethylketones,[2b] was applied to the *anti*-selective aldol reaction of α-chiral ketone (+)-**2**, $[\alpha]_D^{20}$ = +23.0 ° (*c* 8.2, $CHCl_3$; >97% ee), as shown in **Scheme 2**. The results for various aldehydes are given in **Table 1**.

Scheme 2



(+)-**2** **6** **AA 7** **AS**

Table 1. Aldol reactions of ethylketone (+)-**2** using $(c\text{-}C_6H_{11})_2BCl/Et_3N$ in Et_2O.[a]

entry	aldehyde	temp (°C)	product composition (%)[b] AA	AS	SS + SA	AA:AS	% yield[c]
1		0[d]	92.0	5.0	<3.0	18:1	72
2		-78	>94.3	2.2	<3.5	43:1	74
3		-78	96.3	0.8	2.9	120:1	85
4	^{n}PrCHO	-78	95	5[e]		≥30:1	72
5	^{i}PrCHO	-78	>94	<6[f]		≥30:1	89

[a] Enolisation (0 °C, 2 h), condensation (-78 °C, 3 h), and oxidative workup (H_2O_2, pH7 buffer/MeOH) conditions are standard unless otherwise stated. For typical experimental conditions, see below and ref 2b. [b] Isomer ratios determined by weighing isolated components after HPLC separation. [c] Isolated yield after chromatography. [d] Aldehyde addition at 0 °C for 2 h. [e] Total of minor isomers (0.6%, 1.4%, 3%), where stereochemistry was not assigned. [f] Total of minor isomers, where stereochemistry was not assigned.

Optimisation of the reaction conditions (base, solvent, and temperature) was initially performed using methacrolein. Use of $(c\text{-}C_6H_{11})_2BCl$ (1.5 equiv.) and Et_3N (1.6 equiv.) in Et_2O, with enolisation of (+)-**2** at 0 °C for 2 h and aldol addition (2 equiv. of aldehyde) at -78 °C for 3 h, led to highest selectivity (>94.3%) for one of the 1,2-*anti* isomers (entry 2). The π-face selectivity of the intermediate *E* enol borinate **6** was 43:1 based on the ratio of 1,2-*anti* isomers obtained (**AA** and **AS**), with <3.5% of 1,2-*syn* isomers (**SS** and **SA**) detected (HPLC). Higher temperatures for aldol addition (entry 1) led to reduced enol borinate face selectivity. Highly stereoselective aldol reactions were also carried out with crotonaldehyde, butanal, and *iso*butyraldehyde (entries 3-5). In the case of the crotonaldehyde addition, the stereochemistry of the major adduct was determined as 1,2-*anti*-2,4-*anti* (**AA**),[4] *i.e.* **7** for R = *E*-MeCH=CH, and this assignment is assumed to also hold for the major adducts obtained with the other aldehydes. This high enol borinate π-face selectivity (≥30-120:1), achieved *under substrate control*, is in marked contrast to the lack of π-face bias in the *Z* isomer.[1a] Such different behaviour in the *E* and *Z* enol borinates of an α-chiral ketone is unprecedented. It was, therefore, of interest to study the behaviour of the corresponding unsubstituted enol borinate (**Scheme 3**).

The methylketone (+)-**8**, $[\alpha]_D^{20}$ = +16.6 ° (*c* 8.7, $CHCl_3$; >97% ee), was prepared[5] by an analogous three step sequence to that used in the synthesis of (+)-**2**. The enol borinate was generated with a range of reagents and reacted with methacrolein (entries 1-3, **Table 2**). Using achiral reagents, the reaction diastereoselectivity was 5:1 (^{13}C NMR on the mixture and capillary gc analysis after silylation), which did not vary significantly with the size of the ligands on boron (entries 1 *vs* 2). In contrast, the corresponding Li enolate reaction of **8** (LDA, THF, -78 °C) with methacrolein was non-

selective (57:43).[6] The diastereoselectivity could be improved to 13:1 by use of the chiral reagent (-)-$(Ipc)_2BOTf$ (entry 3).[7] Similar levels of stereoselectivity (5-11:1) were obtained with benzaldehyde (entry 4) and butanal (entries 5 and 6). In these two cases, the major aldol adduct was determined to be 1,4-*syn* (**9** for R = Ph, ^nPr).[8] These results contrast with the low aldol stereoselectivities shown by most other α-chiral methylketones investigated.[9]

Scheme 3

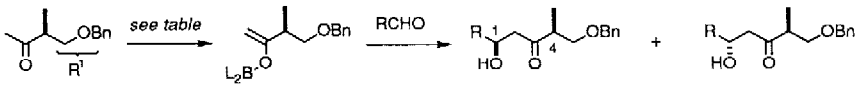


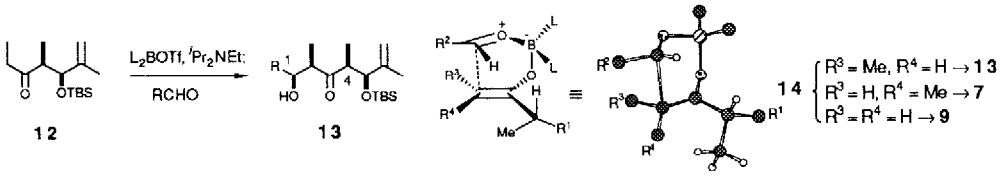
Table 2. Aldol reactions of methylketone (+)-**8** *via* enol borinate **10**.[a]

entry	aldehyde	boron reagent	amine	isomer ratio[b]	% yield[c]
1		$^nBu_2BOTf$[d]	$^iPr_2NEt$	84:16	45
2		$(c\text{-}C_6H_{11})_2BOTf$[d]	$^iPr_2NEt$	86:14	40
3		$(-)\text{-}(Ipc)_2BOTf$[d]	$^iPr_2NEt$	93:7	84
4	PhCHO	$(-)\text{-}(Ipc)_2BOTf$[d]	$^iPr_2NEt$	84:16	77
5		$(c\text{-}C_6H_{11})_2BCl$[e]	Et_3N	88:12	84
6	^{n}PrCHO	$(-)\text{-}(Ipc)_2BOTf$[d]	$^iPr_2NEt$	92:8	74

[a] Enolisation (0 °C, 2 h), condensation (-78 °C, 3 h), and oxidative workup (H_2O_2, pH7 buffer/MeOH) conditions are standard unless otherwise stated. For typical experimental conditions, see ref 2f. [b] The isomers were inseparable by HPLC. Isomer ratios were determined by both ^{13}C NMR on the mixture and capillary gc after trimethylsilylation (Me_3SiCl, Et_3N, CH_2Cl_2, 20 °C). [c] Isolated yield of **9** and **11** after chromatography. [d] Reaction in CH_2Cl_2. [e] Reaction in Et_2O.

In the aldol reactions of both enol borinates **6** and **10**, the sense of aldehyde π-face selectivity is the same, with the former showing a greater level of selectivity. Furthermore, the finding that for achiral ligands, the unsubstituted enolate **10** shows much higher selectivity than the Z-methyl substituted system is the reverse to other cases.[2g,9] Overall, the 1,4-*syn* stereoselectivity of the present aldol reactions are in accord with that previously observed[1b,c] for **12** → **13** (**Scheme 4**). While the preferred chair-like transition state **14**[1b,2c] (R^1 is the large group attached to the α-position) can be extended to explain some of these new results, it should only be considered as a rough working model as other transition states must also be important (especially for the Z isomer of **6**[1a]).

Scheme 4



In summary, the stereoselective aldol reactions **2** → **7** and **8** → **9** should both prove valuable in polyketide synthesis. Moreover, since reliable reduction methods already exist for β-hydroxyketones to give selectively 1,3-*syn*[10] or 1,3-*anti*-[11] diols (*e.g.* see footnote 4), twelve of the sixteen stereoisomers of the stereotetrad **1** should now be readily accessible *via* the ketones **4**, **5**, or **7** in **Scheme 1**, or their corresponding enantiomers.

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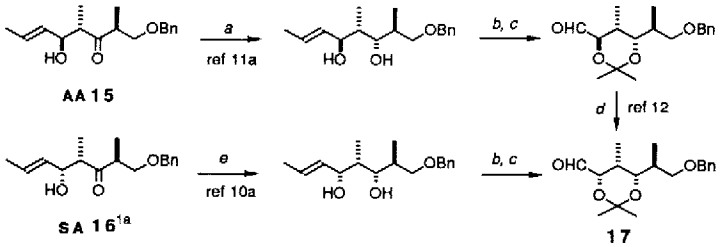
3. For a review on stereotriad synthesis, see: Hoffmann, R. W. *Angew. Chem., Int. Ed.* **1987**, *26*, 489.
4. The stereochemistry of the major aldol adduct for crotonaldehyde **15** was determined as 1,2-*anti*-2,4-*anti* by chemical correlation with **17**, independently prepared from the 1,2-*syn*-2,4-*anti* isomer **16**, by the following sequence:



(a) $Me_4N.HB(OAc)_3$, AcOH/MeCN, -20 °C, 16 h (>95:5, 99%); (b) $(MeO)_2CMe_2$, PPTS, CH_2Cl_2, 20 °C, 16 h (67 and 88%); (c) O_3, CH_2Cl_2/Et_2O, -78 °C, 5 min; $Me_2S \rightarrow$ 20 °C (75 and 59%); (d) K_2CO_3, MeOH, 20 °C, 60 h (90%); (e) Bu_2BOMe, MeOH-THF (1:5), -78 °C, 15 min; $LiBH_4$, 1 h; H_2O_2 (≥97:3, 89%).

5. All new compounds gave spectroscopic data in agreement with the assigned structures. Preparation of (+)-**8** from (*S*)-(-)-methyl-3-hydroxy-2-propionate (72% overall): (i) $Cl_3CC(=NH)OBn$, 2:1 hexane/CH_2Cl_2, cat. TfOH, 20 °C, 2 h; (ii) MeON(Me)H.HCl, Me_3Al, PhMe, 70 °C, 2 h; (iii) MeMgCl, THF, 0 °C, 1 h. See also: White, J.D.; Reddy, G. N.; Spessard, G. O. *J. Am. Chem. Soc.* **1988**, *110*, 1624.
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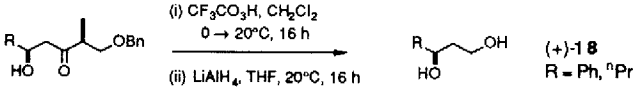
8. The stereochemistry of the major aldol adducts for benzaldehyde and butanal was determined as 1,4-*syn* by conversion into diols (+)-**18**, R = Ph and ^nPr:[2e]



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