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ALDOL CONDENSATIONS OF CHIRAL ETHYLKETONES: CONTROL BY CHIRAL BORON REAGENTS.

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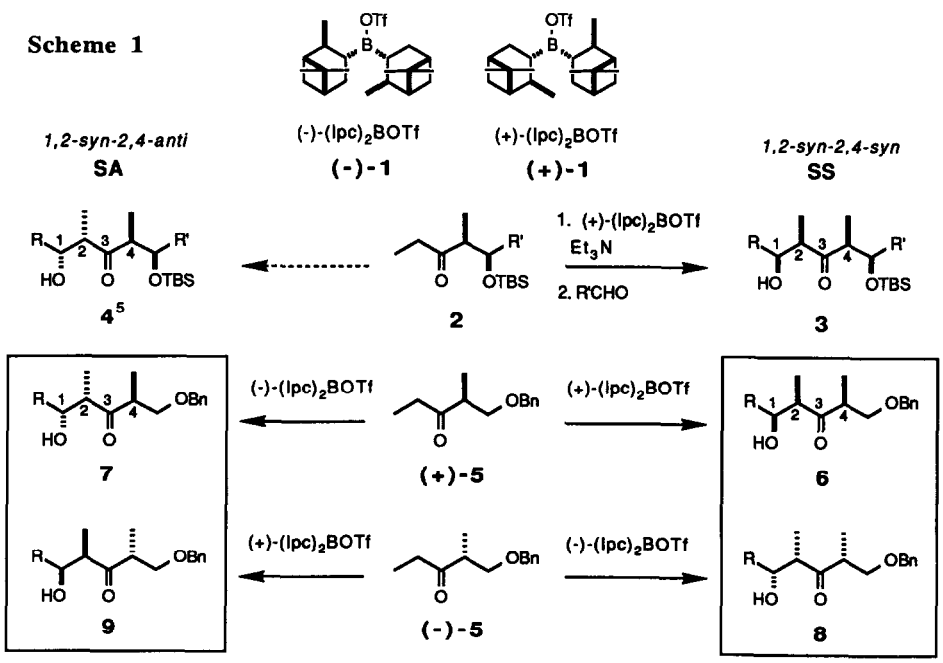
Summary: The chiral reagents (+)- and (-)-Ipc)$_2$BOTf, in the presence of Et_3N, are used to control the aldol condensation reactions of chiral ethylketone **5** with prochiral aldehydes. The *SS* isomer, **6** or **8**, or *SA* isomer, **7** or **9**, is then formed in >99% ee and with up to 93% diastereoselectivity.

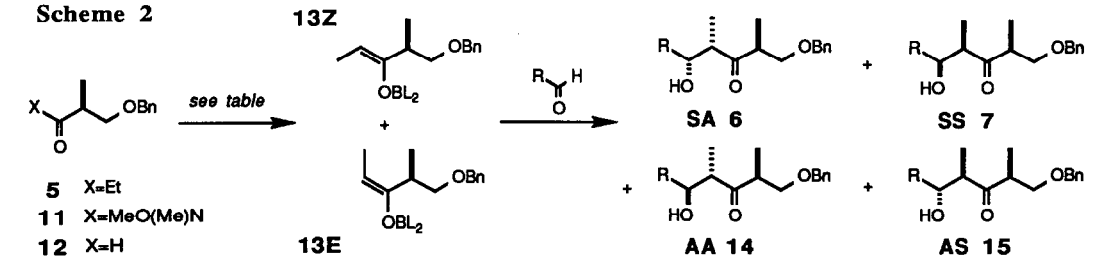
The use of chiral boron reagents,[1,2] such as (+) and (-)-**1**,[3] to control the enantio- and diastereoselective aldol condensation reactions of ketones with aldehydes is a powerful and practical alternative to chiral auxiliary methodology.[4] We recently described[1b] a concise approach to polypropionate-type fragments based on sequential ethylketone aldol condensations, where the dialkylboron enolate of **2**, obtained using $^nBu_2BOTf$ or 9-BBNOTf, gave the *SS* (*i.e.* 1,2-*syn*-2,4-*syn*) isomer **3** with good selectivity. This high substrate stereoselectivity, **2** → **3**, could be further improved by using the appropriate chiral boron triflate[1a] of matched chiral influence, *i.e.* (+)-**1**. However, in the mismatched case using the enantiomeric reagent (-)-**1**, while the stereoselectivity towards *SS* could be decreased, it could not be pushed over enough to make the *SA* (1,2-*syn*-2,4-*anti*) isomer major.[5] We now report that these chiral boron reagents can be used to control the aldol addition reactions of the readily available chiral ethylketones (+)-**5** and (-)-**5**. By proper choice of reagent chirality (see **Scheme 1**), the *SS* isomers, **6** and **8**, and *SA* isomers, **7** and **9**, can each be obtained in enantiomerically pure form with up to 93% diastereoselectivity. These aldol products may then be used in the synthesis of a wide range of propionate-derived natural products.[6]

Scheme 1



The commercially available (*R*)-(-)-methyl-3-hydroxy-2-propionate **10** was best converted into ethylketone (+)-**5** *via* the *N*-methoxy-*N*-methylamide derivative **11**. This route avoided any racemisation of the substrate, which was found to be a problem when **5** was prepared *via* the aldehyde **12**.[7] Benzylation of **10** using benzyl 2,2,2-trichloroacetimidate[8] (2:1 hexane/CH_2Cl_2, cat. TfOH, 20°C, 2 h) was followed by conversion into the amide **11** by the method of Weinreb[9] ($Me_2AlN(OMe)Me$, PhMe, 70°C, 1 h) and addition of ethylmagnesium bromide (THF, 0°C) to give (+)-**5**, $[\alpha]_D^{20}$=+23.0° (c 8.2, $CHCl_3$) , in 62% overall yield. This material was judged to be of at least 97% ee.[10]

Scheme 2



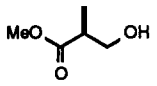


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Table 1. Aldol condensation reactions of ethylketone **5** using achiral dialkylboron triflate reagents in CH_2Cl_2.

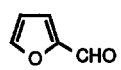
			product composition[b]					
entry	aldehyde	reagent (°C)[a]	*SA*	*SS*	*AS* + *AA*[c]	*syn*:*anti*[d]	*SA*:*SS*	% yield[e]
1		$^nBu_2BOTf$ (0)[f]	8	8	84	1:5	1:1	66
2		9-BBNOTf (0)[f]	12	13	75	1:3	1:1	66
3		$^nBu_2BOTf$ (0)[f]	<2	4	94	1:16	—	57
4		$^nBu_2BOTf$ (-78)[g]	41	48	11	8:1	1:1.2	76

[a] Enolisation temperature. [b] Isomer ratios determined by weighing isolated components after HPLC separation. [c] Ratios of 1,2-*anti* isomers in the range 4-7:1, major isomer not determined. [d] Ratio for (*SA* + *SS*)/(*AS* + *AA*). [e] Isolated yield after chromatography. [f] In the presence of 2 equiv. $^iPr_2NEt$. [g] In the presence of 2 equiv. Et_3N.

We initially examined the aldol condensation of **5** using achiral boron reagents (**Scheme 2**) to check if there was any significant enolisation stereoselectivity and/or enolate π-face diastereoselectivity resulting from the ketone chiral centre. Enolisation of **5** with either $^nBu_2BOTf/Et_3N$ or 9-BBNOTf/Et_3N (0°C, CH_2Cl_2) followed by aldol addition to furfural gave a mixture of all 4 possible diastereomeric adducts (entries 1 and 2, **Table 1**). Under these conditions, the 1,2-*anti* products, **14** and **15**, predominated (>75% of the mixture with 5:1 selectivity). Whereas the *SA* and *SS* isomers, **6** and **7**, were formed in roughly equal amounts. Similar results were obtained for methacrolein (entries 3 and 4), although the relative proportion of 1,2-*syn* products could be enhanced by enolisation with $^nBu_2BOTf/^iPr_2NEt$ at low temperature. While there was some selectivity towards one of the 1,2-*anti* products (entries 1-3), these results showed that little or no stereocontrol towards either the *SS* or *SA* adduct was possible in this reaction using achiral boron reagents (*cf.* our earlier results[1b] for **2** → **3**).

We next turned our attention to the use of the chiral reagents (+)-**1** (prepared from (-)-α-pinene) and (-)-**1** (from (+)-α-pinene) in the presence of Et_3N (2 equiv.) as base. For optimum results, we found that it was best to prepare the triflates beforehand by reaction of triflic acid with the appropriate enantiomeric form of $(Ipc)_2BH$ in hexane solution and to use these stock solutions for enolate formation. This improved procedure[11] gave better conversions than reactions using the *in situ*[1a] generated triflate in dichloromethane. The results for aldol condensations of (+)-**5** and (-)-**5** mediated by these reagents with several aldehydes are given in **Table 2**. The highest yields of aldol products (up to 82% isolated) were obtained with freshly prepared reagent.[11]

Table 2. Aldol condensation reactions of chiral ethylketones (+)- and (-)-**5** using chiral boron triflates with Et_3N in CH_2Cl_2. Enolisation (0°C, 2 h), condensation (0°C, 12 h), and oxidative workup (H_2O_2, pH7 buffer/MeOH) conditions are standard.

				product composition[b]			
entry	ketone (% ee)[a]	aldehyde	reagent	*SA* (% ee)[a]	*SS* (% ee)[a]	*SA*:*SS*	% yield[c]
1	(+)-**5** (97)		(+)-**1**	7 (64)	93 (>99)	1:13	74
2	(+)-**5** (54)[d]		(+)-**1**	28 (72)	72 (>95)	1:2.6	51
3	(+)-**5** (97)		(-)-**1**	93 (>99)	7 (64)	13:1	62
4	(-)-**5** (84)[e]		(-)-**1**	13 (9)	87 (99)	1:6.7	82
5	(+)-**5** (97)		(-)-**1**	92	8	11:1	51
6	(+)-**5** (97)	MeCHO	(-)-**1**	92	8	11:1	65
7	(+)-**5** (97)		(+)-**1**	10	90	1:9	64
8	(+)-**5** (97)		(-)-**1**	92	8	11:1	60
9	(-)-**5** (84)[e]		(+)-**1**	89	11	8:1	53
10	(-)-**5** (84)[e]		(-)-**1**	14	86	1:6	81

[a] See footnote 10. [b] Isomer ratios determined by weighing isolated components after HPLC separation; 1,2-*anti* isomers were <2% of the product mixture. [c] Isolated yield after chromatography. [d] Prepared via aldehyde **12**, see footnote 7. [e] Prepared *via* aldehyde *enant*-**12**, see footnote 7.

In the aldol addition to methacrolein, the combination of (+)-**1** with (+)-**5** of 97% ee gave rise to a 1:13 ratio of *SA* and *SS* adducts in 74% yield (entry 1). Careful HPLC analysis of the product mixture showed <2% of 1,2-*anti* isomers. Moreover, determination of the enantiomeric purity[10] of the *SA* and *SS* isomers showed that the major *SS* isomer had >99% ee, while the minor *SA* isomer had 64% ee (based on **7** as the major enantiomer). *The chiral reagent, therefore, as well as controlling enolisation Z-stereoselectivity and enolate π-face selectivity, is also functioning as a resolving agent and upgrading the enantiomeric purity of the major diastereomer.* This resolution effect was more dramatic when the reaction was repeated on (+)-**5** of 54% ee (entry 2). This led to a reduced *SA*:*SS* ratio of 1:2.6 with ee values now of >95% for the major *SS* and 72% for the *SA* (*NB* now based on **9** as the major enantiomer). The corresponding methacrolein addition reaction (entry 3) using the enantiomeric reagent, *i.e.* (-)-**1**, with (+)-**5** (97% ee) gave a complete reversal in stereoselectivity leading now to a 13:1 ratio of *SA* (>99% ee) and *SS* (64% ee). Again there was <2% of 1,2-*anti* isomers formed.

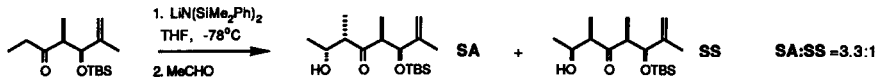
The generality of these stereochemical trends was confirmed by carrying out similar aldol condensations of (+)-**5** (97% ee) with crotonaldehyde (entry 5), acetaldehyde (entry 6), and furfural (entries 7 and 8). The *SS* isomer was formed preferentially with (+)-**1**, while the *SA* isomer was preferred with (-)-**1**. In each case, ≥90% diastereoselectivity was obtained (1,2-*anti*-isomers comprised <2% of the product). In the case of furfural, the enantiomeric ethylketone (-)-**5** (prepared[7] in 84% ee from the (*S*)-isomer of **10**) led to selective formation of the *SA* isomer from reagent (+)-**1** and the *SS* isomer from (-)-**1** (entries 9 and 10; see also entry 4 for methacrolein). These products correspond to structures **9** and **8**, R=2-furyl, in **Scheme 1.**

In summary, use of the chiral ethylketone **5** with the chiral boron triflate reagent **1** in the appropriate chirality combination permits the stereoselective synthesis of each of the aldol isomers **6, 7, 8,** and **9** in optically pure form. These products should be of value in the synthesis of macrolide and polyether antibiotics. Application of these same principles to the aldol condensation reactions of other chiral ketones should also be possible.

Acknowledgement We thank the SERC for support (Studentship to M.A.L.)

References and Notes

1. (a) Paterson, I., Lister, M. A., McClure, C. K. *Tetrahedron Lett.*, **1986**, *27*, 4787; (b) Paterson, I., McClure, C. K. *Tetrahedron Lett.*, **1987**, *28*, 1229.
2. For related aldol studies using C_2-symmetric dialkylborolane reagents, see: Masamune, S., Sato, T., Kim, B. M., Wollmann, T. A. *J. Am. Chem. Soc.*, **1986**, *108*, 8279; Reetz, M. T., Kunisch, F., Heitmann, P. *Tetrahedron Lett.*, **1986**, *27*, 4721.
3. For the use of the $(Ipc)_2B$ group in the asymmetric synthesis of homoallylalcohols, see: Jadhav, P. K., Bhat, K.S., Perumal, P. T., Brown, H. C. *J. Org. Chem.*, **1986**, *51*, 432.
4. Reviews: Masamune, S., Choy, W., Petersen, J. S., Sita, L. R., *Angew. Chem. Int. Ed.*, **1985**, *24*, 1; Heathcock, C. H. in *Asymmetric Synthesis*, Morrison, J. D., ed., Academic Press, New York, Vol. 3, 1984.
5. The *SA* isomer in this series can, however, be formed with moderate overall stereoselectivity (*ca* 70%) by use of the corresponding Li enolate (McClure, C. K., *unpublished results*), *e.g.*:



See also: McCarthy, P. A., Kageyama, M., *J. Org. Chem.*, **1987**, *52*, 4681.

6. Hoffmann, R. W., *Angew Chem. Int. Ed.*, **1987**, *26*, 489; Paterson, I., Mansuri, M. M. *Tetrahedron*, **1985**, *41*, 3569; Masamune, S., McCarthy, P. A. in *Macrolide Antibiotics. Chemistry, Biology, and Practice*, Omura, S., Ed., Ch. 4, Academic Press, New York, 1984.
7. All new compounds gave spectroscopic data in agreement with the assigned structures. Preparation of (+)-**5** from **10** by the 4-step sequence: (i) $Cl_3CC(=NH)OBn$, 2:1 hexane/CH_2Cl_2, cat. TfOH, 20°C; (ii) DIBAL, CH_2Cl_2, -98°C; (iii) EtMgBr, THF, -78°C; (iv) $(COCl)_2$, DMSO, CH_2Cl_2; Et_3N; gave material of <90% ee probably due to partial racemisation of the aldehyde **12.** In the enantiomeric series, a similar route gave (-)-**5** of 84% ee, $[\alpha]_D^{20}$=-18.5° (c 9.0, $CHCl_3$), which was used in **Table 2** entries 4, 9 and 10.
8. Iverson, T., Bundle, D. R., *J. Chem. Soc. Chem. Comm.*, **1981**, 1240; Widmer, U., *Synthesis*, **1987**, 568.
9. Levin, J. I., Turos, E., Weinreb, S. M., *Synth. Comm.*, **1982**, *12*, 989; Nahm, S., Weinreb, S. M., *Tetrahedron Lett.*, **1981**, *22*, 3815.
10. Enantiomeric compositions of aldol products were all determined by ^{1}H-NMR chiral shift reagent experiments using $Eu(hfc)_3$. The ee values of the starting ketones were determined from the $^nBu_2BOTf$-mediated aldol products with methacrolein (or by Mosher ester formation after reduction of **5**).
11. *Improved procedure*: the (-)-$(Ipc)_2BOTf$ reagent was prepared by addition of triflic acid (1.44 ml, 16.3 mmol) to a stirred suspension of (-)-$(Ipc)_2BH$ (4.66 g, 16.3 mmol) in dry hexane (6 ml) at 0°C under Ar. After 15 min, the mixture was warmed to 20°C ($H_2\uparrow$) and after completion of reaction the colourless solution of reagent was removed from the orange residue by cannula transfer into a fresh flask. After dilution with hexane (6 ml) the resulting reagent solution (*ca* 1 *M*) was used for the aldol condensation reaction in CH_2Cl_2, using Et_3N as base, as in ref. 1a.

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