Tetrahedron Letters,Vol.27,No.39,pp 4787-4790,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

ENANTIOSELECTIVE ALDOL CONDENSATIONS: THE USE OF KETONE BORON ENOLATES WITH CHIRAL LIGANDS ATTACHED TO BORON.†

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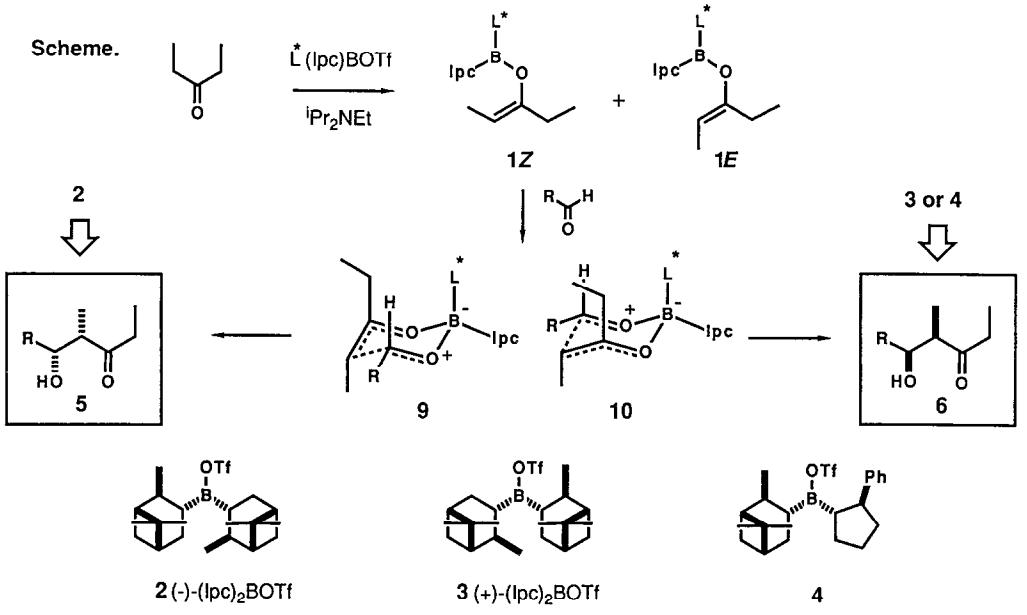
Summary Aldol condensation between diethylketone and simple aldehydes using $(Ipc)_2BOTf/^iPr_2NEt$ in CH_2Cl_2 gives *syn*-adducts in good ee (66-90%) and with high diastereoselectivity (≥90%). Other chiral dialkylboron triflate reagents examined give lower ees.

The aldol condensation reaction of boron enolates,[1a-g] which affords high levels of relative stereocontrol (*Z* enolate → *syn vs E* enolate → *anti* aldol), has recently become important in the area of absolute stereocontrol through the use of specially designed chiral auxiliaries[1b,c] attached to the carbonyl carbon. The alternative use of readily-available chiral ligands on boron, as in enolates **1*Z*** or **1*E***, to directly promote enantioselective C-C bond formation between simple carbonyl compounds and aldehydes is an attractive idea which has not been nearly so well demonstrated.[2] A particularly appealing application is to the synthesis of β-hydroxyketones[4] of high ee with predictable relative and absolute stereochemistry. We now report our initial results on the enantioselective synthesis of α-methyl-β-hydroxy ethylketones by aldol condensation of diethylketone with aldehydes using the chiral dialkylboron triflate reagents **2**, **3**, and **4** (Scheme). *Syn* aldol adducts, **5** and **6**, are obtained with high diastereoselectivity (≥90%) and, with the more selective reagents **2** and **3**, in enantiomeric excesses of 66-90%. These aldol products may then be subjected to a second stereocontrolled aldol condensation on the other side of the ketone carbonyl group to give useful chiral fragments for macrolide construction.[5]

Scheme.



Inspired by Meyers' earlier work[2] on chiral boron azaenolate addition to aldehydes and the recent results of Brown's group for chiral allylboranes,[3] the direct enolization of diethylketone using (-)-diisopinocampheylboron triflate (**2**), prepared *in situ* from $(-)-(Ipc)_2BH$ [6] and triflic acid, in the presence of $^iPr_2NEt$ was first studied. Using acetaldehyde as a representative aldehyde (Table 1), the aldol addition selectively gave the (2*R*, 3*S*)-stereoisomer **5** (R=Me)[7] with varying ee[8]

†*Dedicated to Professor R.A. Raphael on the occasion of his 65th birthday*

and yield depending on the reaction solvent (entries 1-3). Of the solvents tried, dichloromethane was found to give the best enolisation stereoselectivity[9] and, in the aldol step, the highest ee (82%) as well as chemical yield. The favoured (*R*)-configuration[7] at the hydroxyl bearing chiral centre of the adduct obtained using **2** is in agreement with that found for Meyers' and Brown's reactions.[2,3] A similar mechanism for asymmetric induction by the Ipc ligands is probably operating in all of these cases. We next briefly explored the effect of structural variation in one of the chiral ligands on boron keeping the other constant as Ipc. The unsymmetrical dialkylboranes L*(Ipc)BH were prepared[10] in each case from the appropriate cycloalkene (1-phenylcyclopentene[11], 1-methylcyclohexene, and 1-phenylcyclohexene) by asymmetric hydroboration, followed by

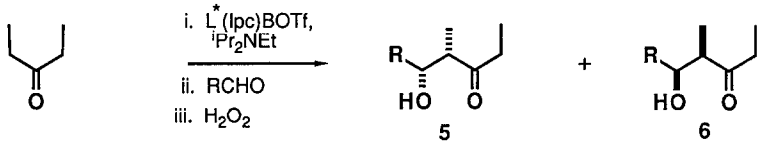


Table 1.
Enantioselective aldol condensation between diethylketone and acetaldehyde (R=Me): effect of solvent and ligands. Enolisation (-78°C - 0°C, 5h) and condensation (-78°C - 0°C, 2h) conditions are standard.

entry	L*	solvent	major syn	ee(%)[8]	entry	L*	solvent	major syn	ee(%)[8]
1		Et_2O	**5**	51					
2		hexane	**5**	56	5[b]		CH_2Cl_2	**6**	33
3	(2)	CH_2Cl_2	**5**	82		(7)			
4[a]		CH_2Cl_2	**6**	52	6[c]		CH_2Cl_2	**6**	33
	(4)					(8)			

[a]The borane was made in and crystallised from Et_2O at -30°C. [b] The borane was made in Et_2O at -30°C and aged in THF at 0°C. [c]The borane could not be satisfactorily crystallised and so the triflate was not stereochemically pure.

selective crystallisation, using $IpcBH_2$ (prepared from (+)-α-pinene). As with $(Ipc)_2BOTf$, the corresponding triflates **4**[11], **7**, and **8**, respectively, were freshly prepared *in situ* by the addition of trifluoromethanesulphonic acid to a suspension of the borane in dichloromethane. Although the aldol condensation with acetaldehyde in all of these cases (entries 4-6) proceeded in lower ee than with the C_2-symmetric reagent **2**[12], the enantiomeric adduct **6** (R=Me) was now clearly preferred. These smaller ligands (L*), **which have opposite configuration[10] and chiral influence relative to Ipc,** presumably selectively take up a controlling axial position in the diastereomeric aldol transition states **9** and **10** derived from **1*Z***, which now lead to the favoured formation of **6**.

Using the optimum conditions[13,14] already determined, we next looked at the enantioselective aldol condensation of diethylketone with several different simple aldehydes using reagents **2**, **3**, and **4** (Table 2)[15]. The *syn:anti* selectivity obtained with these chiral reagents (≥10:1) was generally at least as high as that found for the corresponding reaction with $^nBu_2BOTf/^iPr_2NEt$[1f]. Enantiomeric excesses in the range 66-90% towards **5**[16] were obtained using triflate **2** (entries 1, 3, 5, 7, 8, and 9). The highest ee of 90% was observed with methacrolein (entry 3), which was also reproducible on a larger scale (40 mmol). A slightly lower ee value of 80% was obtained for butanal (entry 5) and furfural (entry 9). In most cases good yields of aldol adducts were obtained using **2**. An exception was condensation with isobutyraldehyde (entry 8), which proceeded in only a moderate yield and gave the lowest ee (66%) encountered. This suggests that the present procedure works best for sterically undemanding aldehydes. The enantiomeric reagent **3** (prepared from (-)-α-pinene of 82% ee[6a]) gave roughly comparable results to **2** in aldol addition to furfural, but now in favour of the formation of **6** (R=2-furyl; entry 10 *vs* entry 9). In comparison, the other chiral triflate **4** proved to be less useful. It also favoured **6** (entries 2, 4, and 6), but with consistently lower ee (28-52%).

Table 2.
Enantioselective aldol condensations of diethylketone with aldehydes.[13,14]

entry	aldehyde	reagent	syn:anti[a]	major syn[16]	ee(%)[8,15]	yield(%)[b]
1		**2**	97:3	**5**	82	80
2		**4**	97:3	**6**	52	60
3		**2**	95:5	**5**	90	75, 75[d]
4		**4**	96:4	**6**	28	52
5		**2**	97:3	**5**	80	92
6		**4**	97:3	**6**	46	65
7		**2**	90:10	**5**	68	75
8		**2**	96:4	**5**	66	45
9		**2**	96:4	**5**	80	84[c]
10		**3**	96:4	**6**	80	86[c]

[a] Determined by ^{1}H-NMR. [b] Except where otherwise stated, isolated yields after chromatography (flash column or HPLC) are based on ketone (2-7 mmol scale) using 2-3 equiv. of aldehyde. [c] Isolated yield based on aldehyde using 1.5 equiv. of ketone. [d] Reaction carried out on a 40 mmol scale using 1.5 equiv. aldehyde.

In summary, reagent **2**, which is readily made in optically pure form from inexpensive (+)-α-pinene (*ca* 92%ee), and its enantiomer **3**, prepared from (-)-α-pinene (*ca* 82%ee), are useful reagents for the simple stereocontrolled synthesis of *syn*-α-methyl-β-hydroxyketones like **5** and **6**. Furthermore, these chiral dialkylboron triflates are potentially useful in influencing the stereochemistry of aldol condensations between simple ketones and chiral aldehydes, as well as that between chiral ketones and aldehydes.[5] We are now looking at their use with other ketones as well as the stereocontrolled preparation of $(Ipc)_2B$ enolates by other means.[17]

Acknowledgements We thank the SERC for support and Roussel Laboratories Ltd. for a Research Fellowship (to C.K.M.). We also thank Drs. R. Westwood and P. D. Kennewell at Roussel for their interest in this work.

References and Notes

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(2) For the ***anti***-selective synthesis of α-methyl-β-hydroxyesters in 77-85% ee using chiral boron azaenolates, see: A. I. Meyers and Y. Yamamoto, *J. Am. Chem. Soc.*, **103**, 4278 (1981); A. I. Meyers and Y. Yamamoto, *Tetrahedron* **40**, 2309 (1984).

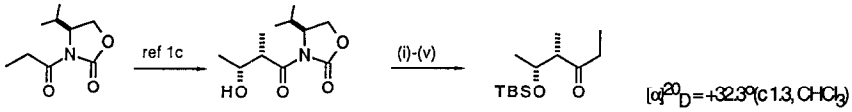
(3) P. K. Jadhav, K. S. Bhat, P. T. Perumal, and H. C. Brown, *J. Org. Chem.* **51**, 432 (1986) and references cited therein.

(4) For existing methods for enantioselective and diastereoselective directed aldol reaction between aliphatic ethylketones and aldehydes, see: (a) *syn*-selective aldols: N. Iwasawa and T. Mukaiyama, *Chem. Lett.* 1441 (1982); (b) *anti*-selective aldols: K. Narasaka and T. Miwa, *Chem. Lett.* 1217 (1985).

(5) C. K. M^{c}Clure and I. Paterson, unpublished results.

(6) (a) H. C. Brown and B. Singaram, *J. Org. Chem.* **49**, 945 (1984); (b) H. C. Brown, M. C. Desai, and P. K. Jadhav, *J. Org. Chem.* **47**, 5065 (1982).

(7) The (2*R*, 3*S*)-configuration of the acetaldehyde adduct was determined by comparison of the optical rotation of its derived TBS ether, $[\alpha]^{20}_D$ = +25.0°(c 2.4, $CHCl_3$; 82%ee), with enantiomerically-pure material prepared using Evans methodology:



(i) NaOMe, MeOH; (ii) TBSOTf, lutidine, CH_2Cl_2; (iii) DIBAL, CH_2Cl_2; (iv) $(COCl)_2$, DMSO, CH_2Cl_2; Et_3N; (v) EtMgBr, Et_2O; (v) repeat (iv) then purify by HPLC (R_f=0.30 in 5%EtOAc/hexane).

(8) Enantiomeric excesses of aldol products were determined by ^{1}H-NMR chiral shift studies (Eu(hfc)$_3$) and confirmed by ^{1}H-NMR and/or capillary gc analysis of the derived (-)-MTPA ester: J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.* **34**, 2543 (1969).

(9) The enolisation of diethylketone by (-)-(Ipc)$_2$BOTf/^{i}Pr$_2$NEt at 0°C was also examined by 250 MHz ^{1}H-NMR in Et_20, hexane, and CD_2Cl_2. Dichloromethane showed the best conversion and led to ≥95% stereoselectivity for formation of the ***Z*** enolate as judged by the relative intensity of the quartet of triplets at δ 4.68 (*J* 6.8, 1.1 Hz). In Et_20 and hexane the ***E*** enolate was also present appearing as a qt at δ 4.75.

(10) H. C. Brown and B. Singaram, *J. Am. Chem. Soc.* **106**, 1797 (1984).

(11) The configurational purity of the 2-phenylcyclopentyl ligand in **4** was found to be ≥95% by analysis of the enantiomeric purity of the derived alcohol (L*OH) isolated after the aldol reaction.

(12) ^{13}C-NMR of (-)-(Ipc)$_2$BOTf: δ (CD_2Cl_2; 62.5 MHz) 118.9, 48.3, 41.4, 39.2, 37.3, 33.8, 28.6, 28.2, 23.4, 22.6.

(13) Representative procedure for enantioselective aldol reaction using *in situ* generated triflate **2**[14]: dry dichloromethane (25 ml) was added to (-)-diisopinocampheylborane[6] (2.45 g, 8.6 mmol) at 0°C under Ar, followed by the dropwise addition of trifluoromethanesulphonic acid (0.83 ml, 9.4 mmol) to the stirred suspension over 5 min. After 0.5 h at 0°C, the resulting red-orange solution was cooled to -78°C and diisopropylethylamine (2.3 ml, 13.3 mmol) followed by diethylketone (0.70 ml, 6.6 mmol) were added and the reaction mixture was allowed to warm to 0°C. After a further 5 h, a solution of freshly distilled acetaldehyde (1.11 ml, 19.9 mmol) in dichloromethane (3 ml) was added to the enolate solution at -78°C, followed by warming to 0°C. After 2h, the reaction mixture was poured into pH7 buffer solution and extracted with ether. The ether extracts were concentrated *in vacuo* , and hydrogen peroxide (30%, 6.6 ml) was added to a stirred solution of the residue in MeOH-pH7 buffer (5:1, 25 ml) at 0°C. After 1 h at room temperature, extractive workup using dichloromethane and water gave a mixture of the aldol product and ligand byproducts, which on flash chromatography (40% EtOAc/hexane) on SiO_2 gave 680 mg (80%) of (2*R*, 3*S*)-2-hydroxy-3-methyl-4-hexanone; R_f=0.3, $[\alpha]^{20}_D$=-23.4 (c 5.3, $CHCl_3$). ^{1}H-NMR analysis showed a *syn:anti* ratio of 97:3, while ^{1}H-NMR chiral shift studies (Eu(hfc)$_3$) and (-)-MTPA ester analysis both indicated an 82% ee for the *syn*-isomer. The experimental procedure for the aldol reactions performed in other solvents as well as using other triflate reagents were essentially identical to the above. The chiral boranes corresponding to **4**, **7**, and **8** were prepared as described by Brown and Singaram.[10]

(14) In some experiments the triflate **2** was first distilled (oven 130°C, 0.05 mm Hg), after preparation in hexane[2] or dichloromethane, and used as a stock solution in dichloromethane. No significant difference in ee or yield in the aldol reaction was found compared to use of the *in situ* generated reagent. The most convenient procedure experimentally was to prepare[6a] the precursor dialkylborane in the same flask that was to be used for the aldol reaction (the (+)-α-pinene and $H_3B.SMe_2$ were mixed in THF under Ar at 0°C and after 16h the solution was removed from the precipitated (-)-(Ipc)$_2$BH, which was then dried *in vacuo* in the reaction flask).

(15) Optimum specific rotations ($CHCl_3$) for aldol products obtained using reagent **2** in Table 2 (uncorrected for small traces of *anti*-isomers): $[\alpha]^{20}_D$ =-23.4 (c 5.3) for acetaldehyde (entry 1); -30.9 (c 7.6) for methacrolein (entry 3); -7.8 (c 6.4) for butanal (entry 5); -6.8 (c 4.4) for crotonaldehyde (entry 7); -23.2 (c 1.8) for isobutyraldehyde (entry 8); -10.8 (c 5.4) for furfural (entry 9).

(16) The common configurational assignment of the major aldol stereoisomers in Table 2 produced using (-)-(Ipc)$_2$BOTf (**2**) follows from them all showing the same behaviour as entry 1[7] with the Eu(hfc)$_3$ chiral shift reagent.

(17) M. Wada, *Chem. Lett.* 153 (1981); I. Kuwajima, M. Kato, and A. Mori, *Tetrahedron Lett.* **21**, 4291 (1980).

(Received in UK 22 July 1986)