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ENANTIO- AND DIASTEREOSELECTIVE ALDOL REACTIONS OF ACHIRAL ETHYL AND METHYL KETONES WITH ALDEHYDES: THE USE OF ENOL DIISOPINOCAMPHEYLBORINATES.¶

Ian Paterson,* Jonathan M. Goodman, M. Anne Lister, Russell C. Schumann,
Cynthia K. McClure,§ and Roger D. Norcross
University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.

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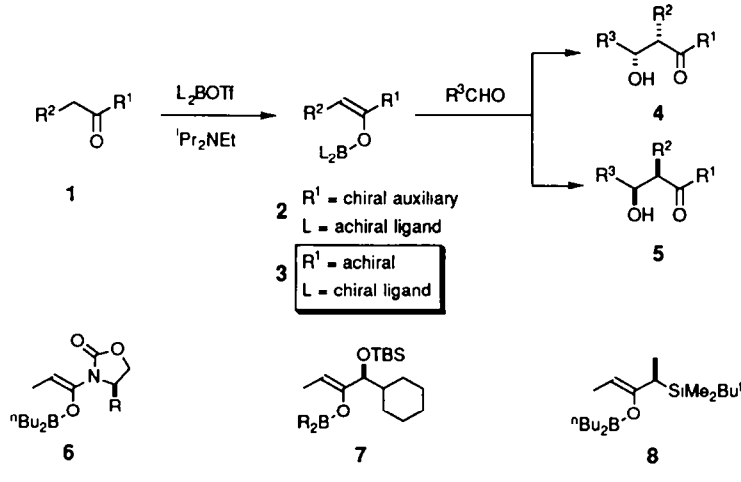
Summary: Enol diisopinocampheylborinates, derived from achiral ethyl and methyl ketones by enolisation in the presence of tertiary amine bases ($^{i}Pr_2NEt$ or Et_3N), undergo enantio- and diastereoselective aldol reactions with aldehydes. The reagents employed, (+)- and (-)-$(Ipc)_2BOTf$, are easily prepared in enantiomerically pure form in two steps from (-)- and (+)-α-pinene, respectively. The aldol reaction between ethyl ketones and aldehydes using (+)- or (-)-$(Ipc)_2BOTf/^{i}Pr_2NEt$ in dichloromethane gives, *via* the derived chiral Z-enol borinates, *syn*-α-methyl-β-hydroxy ketones in good enantiomeric excess (66-93% ee) and with high diastereoselectivity (≥95%). In contrast, the *anti*-selective aldol reaction of diethylketone *via* the isomeric *E*-enol diisopinocampheylborinate (by enolisation with (-)-$(Ipc)_2BCl$) with methacrolein proceeds with negligible enantioselectivity. Use of both the triflate and chloride reagents in the aldol reaction of methyl ketones with aldehydes gives β-hydroxy ketones in moderate enantiomeric excess (53-78% ee) with a reversal in the enantioface selectivity of the aldehyde compared to the corresponding ethyl ketone *syn* aldol. This variable selectivity is interpreted as evidence for the participation of competing chair and boat transition states. Other chiral dialkylboron triflate reagents investigated led to reduced enantioselectivities in diethylketone-aldehyde aldol reactions.

Tremendous advances have been made over the last decade in the development of new methodology for asymmetric synthesis, leading to the recognition of the importance of reagent control of stereochemistry in modern synthesis design.[1,2] The aldol reaction,[1] in particular, has now emerged as one of the most powerful tools for stereocontrolled carbon-carbon bond formation.

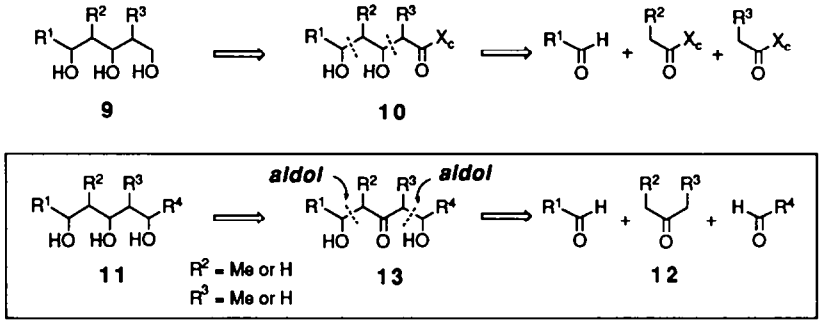
Scheme 1



¶ *Dedicated to Professor David Ollis on the occasion of his 65th birthday.*

The aldol reaction of enol borinates,[3-4] which affords high levels of diastereoselectivity *via* highly ordered chair transition states (*Z* enolate → *syn*-aldol *vs E* enolate → *anti*-aldol), is especially useful for the enantiosel-ective synthesis of β-hydroxy carbonyl compounds. For *syn* aldol reactions (see **Scheme 1**), this is usually achieved by the use of chiral auxiliaries attached to the carbonyl carbon in **1** to control the π-face selectivity in the derived *Z* enol borinate **2** to give the adducts **4** or **5**. After the aldol reaction, the auxiliary is then removed in one or more steps. The enol borinates **6**[4a] and **7**[4b] (and more recently **8**[4c]) are good examples of this approach. The use of chiral ligands on boron, as in enol borinate **3**, to directly promote enantio- and diastereoselective aldol reactions between achiral carbonyl compounds, *e.g.* **1** → **4** or **1** → **5**, is potentially a powerful alternative.[5,6]

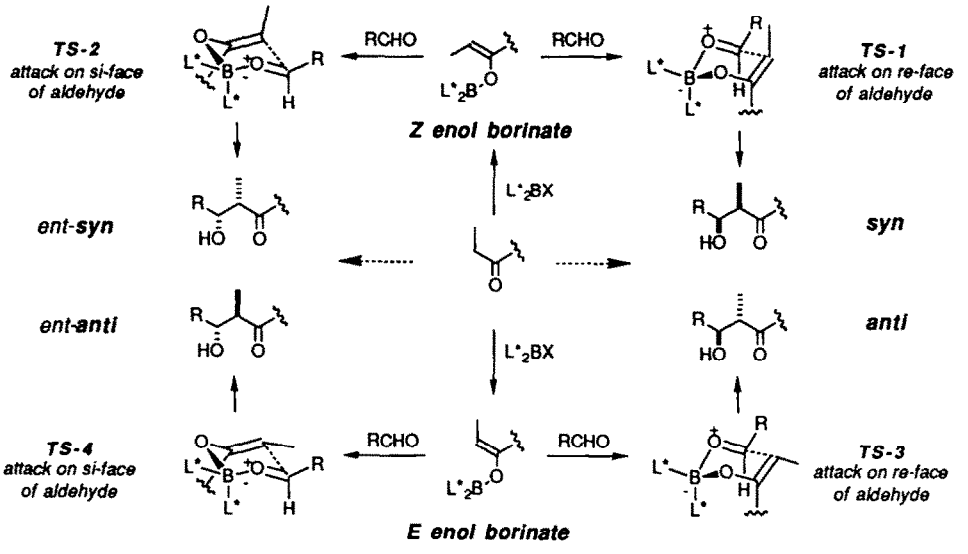
Scheme 2



Such new asymmetric aldol methodology should be particularly valuable in the total synthesis of macrolide and polyether antibiotics.[7] Successful aldol-based approaches have already been demonstrated for the stereocontrolled assembly of typical polyketide-type segments of general structure **9** (**Scheme 2**). These rely on the iterative addition of chiral propionate enolate equivalents (X_C = chiral auxiliary), *e.g.* **6** or **7**, to a growing aldehyde fragment to give **10**.[8] An alternative and more convergent approach to a comparable segment **11** is based on achieving regio-, diastereo- and enantioselective aldol reactions of ethyl and methyl ketones with achiral aldehydes, *i.e.* **12** → **13** for R^2, R^3 = Me or H.[9] Aldol reactions on both sides of the ketone carbonyl group of **12** are now employed to assemble the carbon skeleton with the required stereochemistry and oxygenation pattern. This is potentially shorter than the iterative chain-extension routes, as it eliminates the need for the introduction and removal of chiral auxiliaries, as well as the manipulation of oxidation states in readiness for the next addition (*i.e.* X_C → H). *Our main objective was then to find effective, readily accessible, chiral boron reagents for stereochemical control in the aldol reactions of ethyl and methyl ketones, both achiral and chiral, with simple aldehydes.*[5,9,10]

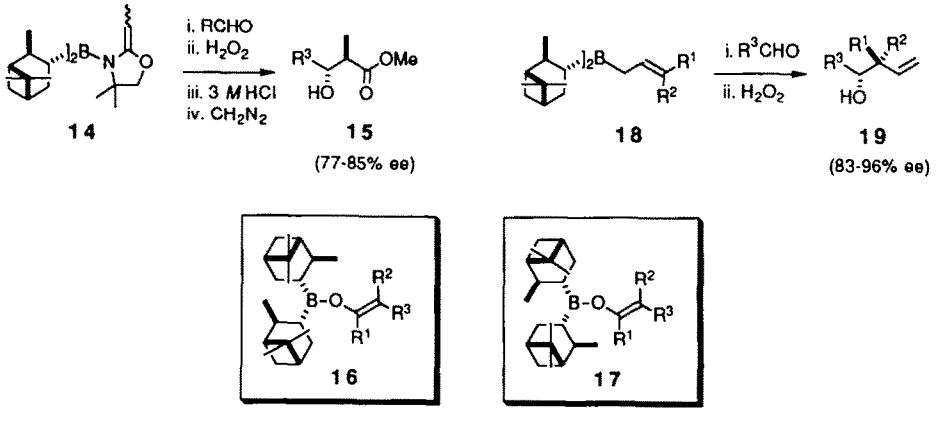
In the case of achiral ethyl ketones (**Scheme 3**), this would require suitable enolisation conditions to selectively obtain either the *Z* or *E* enol borinates, which should then each show high levels of π-face selectivity on aldol addition to aldehydes. This assumes the aldol addition step takes place only through chair-like transition states (*i.e.* ***TS-1*** *etc.*). The choice of suitable chiral ligands, L*, on boron could either be made by rational design (based on modelling of the likely aldol transition state geometries ***TS-1*** *vs* ***TS-2*** and ***TS-3*** *vs* ***TS-4*** for a single enantiomer of the reagent) or empirical reasoning (extrapolating from known results for apparently related reactions). Purely for practical reasons, we chose to begin by following the latter course.

Scheme 3



Meyers' earlier work[11] on chiral boron azaenolate additions to aldehydes leading to the enantioselective production of *anti*-α-methyl-β-hydroxyesters, **14** → **15** in **Scheme 4**, suggested to us that enolates with isopinocampheyl (Ipc) ligands on boron, as in **16** and **17**, might also prove useful in simple ketone aldol reactions. These ligands, originally introduced by Brown for asymmetric hydroboration, are particulary attractive since they are inexpensive, readily available in enantiomerically pure form,[12] and enjoy wide use in asymmetric synthesis.[13] For example, Brown's group have used them to control allyl- and crotylborane additions to aldehydes to give homoallylalcohols with high levels of enantio- and diastereoselectivity, as in **18** → **19**.[14]

Scheme 4



We now present our results in full[5] for the enantio- and diastereoselective aldol reactions of achiral ethyl and methyl ketones with aldehydes using enol diisopinocampheylborinates. Some previously unreported examples, as well as results for aldol reactions using other chiral boron reagents, are described. The scope and limitations of this method, along with comparisons with other methods available, are also discussed.

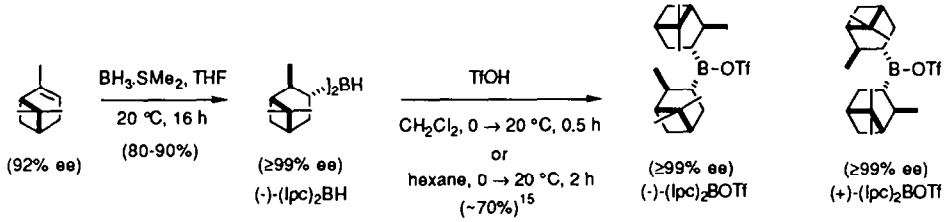
Results and Discussion

Enantioselective syn aldol reactions of ethyl ketones using (-)- and (+)-diisopinocampheylboron triflates

(-)-Diisopinocampheylborane can be easily prepared in >99% ee (80-90% yield) by hydroboration of commercial grade (+)-α-pinene using $BH_3.SMe_2$ complex in THF, following either of the two recent methods recommended by Brown and co-workers.[12] We now routinely use the more recent procedure, which carries out the reaction at room temperature (**Scheme 5**).[12b] Note that this provides enantiomerically pure dialkylborane from starting material of ~91% ee. This crystalline intermediate can be conveniently stored for several months at ≤ 0 °C under argon without loss of activity.

In our initial work,[5a] we prepared the triflate derivative by reaction of (-)-$(Ipc)_2BH$ with triflic acid *in situ* in dichloromethane and then carried out the aldol reaction in the same flask by sequential addition of the various reactants. This is referred to as general procedure A. Reagent solutions prepared in this fashion tend to be orange-red in colour and cannot be stored. Subsequently,[10a] we have preformed the triflate reagents as clear solutions in hexane[11] (0 → 20 °C, 2h), which can be separated from an immiscible coloured lower layer. In calculating the molarity of the resulting reagent solution, we assume a 60-70% conversion to the triflate.[15] The enantiomeric reagent, (+)-$(Ipc)_2BOTf$, can be prepared analogously from (+)-$(Ipc)_2BH$, which is made by hydroboration of commercial grade (-)-α-pinene (~87% ee).[12] These stock solutions of reagents in hexane can then be used in the required aldol reactions and in some cases this leads to improved yields[10a] and stereoselectivities. This newer method is referred to as general procedure B. We now routinely prepare the triflate reagents in hexane and use them within 24 h. The majority of the aldol results described here are based on this newer procedure (see aldol procedure B in the experimental section).

Scheme 5

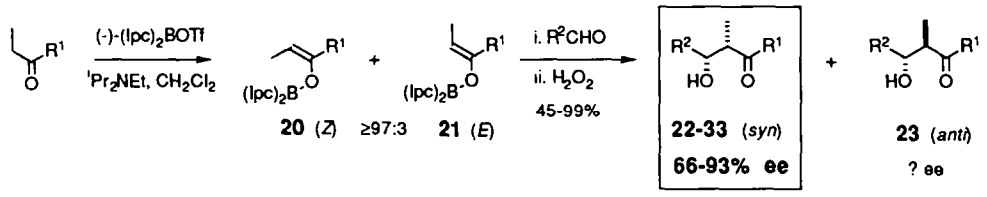


Our initial experiments concentrated on diethylketone-aldehyde aldol reactions using (-)-diisopinocampheyl-boron triflate. Previous studies[3c] had shown that for given ligands on boron, reaction temperature and solvent, *Z* enol borinate formation is optimised by maximising the kinetic selection in the deprotonation of the ketone-reagent complex by using a sterically demanding base. For example, highly stereoselective enolisation of diethylketone (*Z*:*E* >99:1) was obtained using di-*n*-butylboron triflate in the presence of diisopropylethylamine.

The direct enolisation of diethylketone using (-)-diisopinocampheylboron triflate in the presence of $^iPr_2NEt$ was examined in various solvents by 250 MHz ^1H NMR. Dichloromethane gave the best conversion

and led to ≥97% stereoselectivity for formation of the *Z* enolate **20** (R^1 = Et) at 20 °C, as shown in **Scheme 6**, as judged by the relative intensity of the quartet of triplets at δ 4.73 (*J* 6.7, 1.1 Hz) for the olefinic proton (see later). In ether and hexane, an additional quartet was present for the isomeric *E* enolate **21** (R^1 = Et). Addition of an aldehyde to the enol borinate solution led to rapid reaction (disappearance of the enol borinate signals occurred within 5 min at 20 °C).

Scheme 6



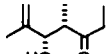
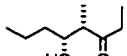
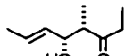
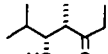
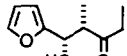
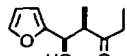
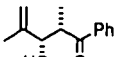
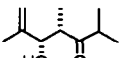
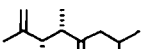
95:5 - 98:2 *syn:anti* selectivity

On a preparative scale, enolisation of diethylketone was carried out in dichloromethane using (-)-$(Ipc)_2BOTf$ (1.3 equiv.) and $^iPr_2NEt$ (2-3 equiv.), followed by addition of the aldehyde and a standard oxidative workup (30% H_2O_2, MeOH/pH7 buffer). Typical reaction times and temperatures employed were 2-3 h at -78 °C for enolisation and 12-16 h at -15 °C for the aldol step. Much shorter reaction times can also be used successfully if desired and the enolisation/addition steps can also be performed at 0 °C, as previously reported.[5a] In many cases, there does not appear to be much change in enantioselectivity at these different reaction temperatures. An oxidative workup (H_2O_2) was found to be essential to liberate the β-hydroxyketone from the initially formed boron aldolate.[16] The aldol product was usually separated from the ligand alcohol (IpcOH) by flash chromatography (separation by distillation was also found to be possible in some instances). For addition to acetaldehyde, general procedure B gave a 91% yield of the (2*R*, 3*S*)-stereoisomer **22** in 79% ee with ≥97% diastereoselectivity (R^1 = Et, R^2 = Me in **Scheme 6**). Our earlier result using general procedure A was an 80% yield of **22** in 82% ee. In our preliminary work,[5a] the configuration was determined by comparison of the specific rotation of its derived TBS ether, $[\alpha]_D^{20}$ = +25.0° (*c* 2.4, $CHCl_3$; 82%ee), with enantiomerically pure material prepared as previously described[5a] using Evans[4a] methodology: $[\alpha]_D^{20}$ = +32.3° (*c* 1.3, $CHCl_3$).

Using *in situ* generated triflate reagent following general procedure A, the enantiomeric excess and yield of the product was found to depend on the reaction solvent. Dichloromethane gave the highest ee as well as chemical yield and so was generally the solvent of choice. The corresponding diethylketone-acetaldehyde reaction in ether and hexane gave **22** in 51 and 56% ee, respectively. Since the enantioselectivity is reduced in hexane, it is best to use the minimum quantities of hexane in the preparation of the triflate reagents, such that a dichloromethane to hexane ratio of 8:1 is used in general procedure B for the aldol reaction.[17] These conditions have now become our standard procedure.

The aldol reactions of a range of ethyl ketones using (-)- or (+)-$(Ipc)_2BOTf/^iPr_2NEt$ have been carried out with several different aldehydes. The results are given in **Table I** using general aldol procedures A or B. Note that some of the results recorded here are improvements over that previously reported by us in the preliminary communication.[5a] The *syn:anti* selectivity obtained was determined by 400 MHz ^1H NMR and was generally in the range 95:5 to 98:2. Enantiomeric excesses in the range 66-91% were obtained for the major *syn* adducts with diethylketone using (-)-$(Ipc)_2BOTf$ (entries 1-6). The enantiomeric excesses were all determined by ^1H NMR chiral shift studies at 250 MHz with $Eu(hfc)_3$ (in some cases, ^1H NMR analysis of the derived

Table I. Enantioselective aldol reactions of ethyl ketones using (-)-$(Ipc)_2BOTf$ and $^iPr_2NEt$ in CH_2Cl_2.[a,b]

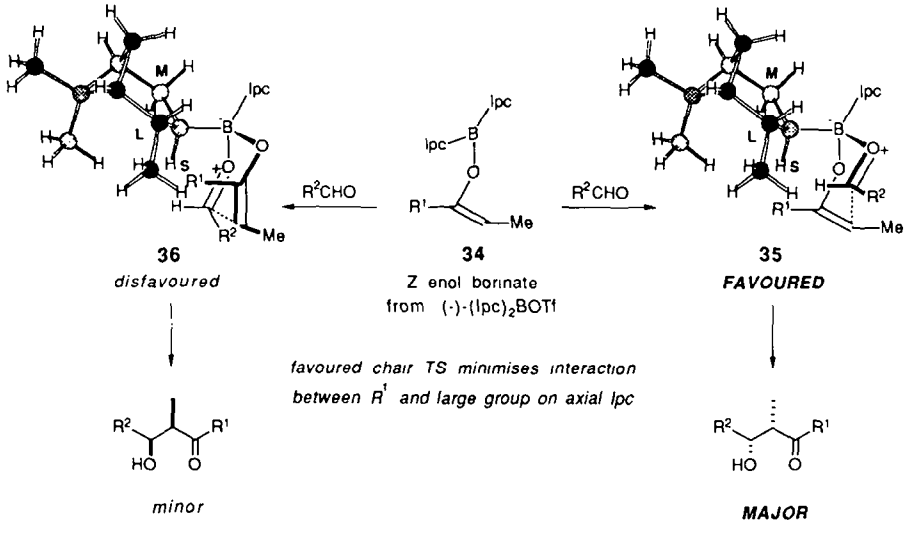
entry	ketone/aldehyde	syn:anti[c]	major isomer[d]	% ee[e]	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)	% yield[f]
1	Et_2CO/ MeCHO	97:3	 **22**[g]	79[b] (82)[a]	-32.7° (5.9)	91
2	Et_2CO/ H_2C=C(Me)CHO	98:2	 **24**	91[b]	-33.8° (3.7)	78
3	Et_2CO/ ^nPrCHO	97:3	 **25**[e]	80[a]	-7.8° (6.4)	92
4	Et_2CO/ *E*-MeCH=CHCHO	98:2	 **26**	86[b] (68)[a]	+5.6° (4.3)	75
5	Et_2CO/ ^iPrCHO	96:4	 **27**	66[a]	-23.2° (1.8)	45
6	Et_2CO/ 2-furylCHO	96:4	 **28**	80[a]	-10.8° (5.4)	84
7[i]	Et_2CO/ 2-furylCHO	96:4	 **29**[i]	80[a]	+11.0° (5.4)	86
8	PhCOEt/ H_2C=C(Me)CHO	98:2	 **30**	91[b]	+1.1° (2.5)	97
9	^iPrCOEt/ H_2C=C(Me)CHO	95:5	 **31**	88[b]	-16.7° (3.0)	99
10	$^iPrCH_2COEt$/ H_2C=C(Me)CHO	97:3	 **32**	86[b]	-34.1° (3.1)	79

[a] General procedure A: triflate prepared *in situ* for aldol reaction. [b] General procedure B: triflate prepared in hexane and used in aldol reaction. [c] Determined by 400 MHz ^1H NMR. [d] Common configurational assignments for **22**, **24-28** and **30-32** are based on same shift behaviour with $Eu(hfc)_3$. [e] Determined by 250 MHz ^1H NMR using $Eu(hfc)_3$. [f] Isolated yield after chromatography. [g] (2*R*,3*S*) configuration established as described in ref 5a. [h] 3-40 mmol scale. [i] Reaction using (+)-$(Ipc)_2BOTf$.

Mosher ester was also used). The highest ee (91% ee) was obtained with diethylketone-methacrolein (1-40 mmol reaction scale produced identical results). This aldol adduct has since been obtained in ≥95% ee by kinetic resolution and was elaborated into
a C_{19}-C_{27} ansa segment of rifamycin S.[9b] Using general procedure B, the diethylketone-crotonaldehyde reaction (entry 4) gave improvements in both enantioselectivity (86% ee) and diastereoselectivity (*syn*:*anti* 98:2) over our earlier result.[5a] In most cases, good to excellent yields of aldol adducts were obtained. An exception was the aldol addition to isobutyraldehyde (entry 5), which proceeded in only a moderate yield (45%) and gave the lowest ee (66%) encountered. Several fruitless attempts were made to improve on this unsatisfactory result. *This suggests that the present aldol procedure is best suited to reactions with sterically undemanding aldehydes, i.e. α-branched saturated aldehydes should be avoided.* In these latter cases, the asymmetric aldol reaction with the corresponding α,β-unsaturated aldehyde should be employed and then the double bond can be reduced or hydroborated, *etc.*[9b] The enantiomeric reagent, (+)-$(Ipc)_2BOTf$, gave comparable results in aldol addition to furfural, but now in favour of the formation of **29** (entry 7 *vs* entry 6).

The aldol reactions of certain unsymmetrical ethyl ketones with a common aldehyde (methacrolein) were examined (entries 8-10). In entries 9 and 10, the kinetically controlled aldol proceeded with complete regioselectivity towards the less-substituted ethyl side to give only **31** and **32**. No other aldol isomers were detected. Similar regiocontrol is known for the di-*n*-butylboron triflate mediated aldol reactions of these ketones with benzaldehyde.[3c] Again high levels of diastereoselectivity (*syn*:*anti* ≥95:5) and enantioselectivity (86-91% ee) were obtained. In the case of butanone, aldol reaction with methacrolein on the ethyl side gave the *syn* adduct in 93% ee (see **Table II**, entry 9). The sense of asymmetric induction appeared to be consistant across the series of ketones and aldehydes in **Table I** for a given chirality of boron reagent. For example, the aldol products obtained using (-)-Ipc_2BOTf showed the same relative shift behaviour with $Eu(hfc)_3$.

Scheme 7



A rough working model to rationalise the enol borinate π-face selectivity is based on a Zimmerman-Traxler chair transition state. This is shown in **Scheme 7** for the (-)-$(Ipc)_2BOTf$ reaction proceeding *via* the *Z* enol borinate **34**. In the favoured chair TS **35**, the steric interactions between the two Ipc ligands themselves and the large methyl-bearing substituent (L) of the axial Ipc ligand with the enol borinate substituent R^1 are minimised. This leads to production of the major *syn* stereoisomer observed. In contrast, reaction on the

opposite π-face of the enol borinate is disfavoured as it leads to a destabilising interaction between the large group on the axial ligand and R^1 in the diastereomeric chair TS **36**.

However, this simple qualitative model is limited to *syn* aldol reactions. It fails to explain the stereochemical results obtained for methyl ketones and the *anti* aldol reactions of ethyl ketones (see later). A more refined quantitative model for this and other chiral enol borinate aldol reactions is presently under development,[18,19] which also takes boat transition states into consideration.

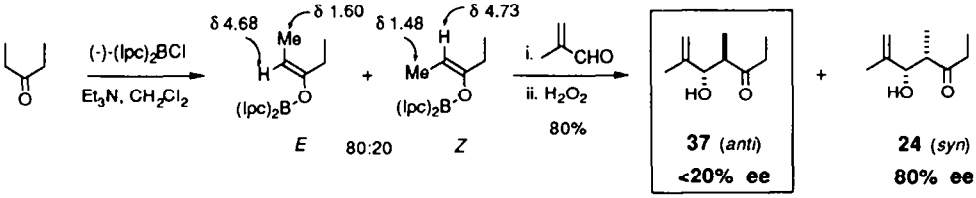
The anti-selective aldol reaction of diethylketone using (-)-diisopinocampheylboron chloride

Brown has introduced the corresponding chloride reagents, (-)- and (+)-$(Ipc)_2BCl$, for the asymmetric reduction of ketones.[20] These are solids and are commercially available (Aldrich) in both enantiomeric forms. In the presence of a suitable amine like Et_3N or $^iPr_2NEt$, the chloride reagent can be used to enolise ketones to give enol diisopinocampheylborinates. However, we have found that the stereochemical outcome of the ethyl ketone aldol reaction is different from that obtained from the triflate procedure (**Scheme 8**). Reaction of diethylketone with (-)-$(Ipc)_2BCl/Et_3N$ in dichloromethane at 0°C, followed by addition of methacrolein, now gave predominantly the *anti* aldol adduct **37** (*anti:syn* = 4:1). This is consistant with enolisation with the chloride reagent producing mainly the *E* enol borinate, which was confirmed by an NMR study of the reaction.

The direct enolisation of diethylketone using (-)-diisopinocampheylboron triflate in the presence of $^iPr_2NEt$ was examined in CD_2Cl_2 at 20°C by 250 MHz ^1H NMR. The *Z* enolate was formed in ≥97% stereoselectivity giving a quartet of triplets at δ 4.73 (*J* 6.7, 1.1 Hz) for the olefinic proton and a doublet of triplets at δ 1.48 (*J* 6.7, 1.3 Hz) for the *Z* methyl group. Using (-)-diisopinocampheylboron chloride and Et_3N with diethylketone (CD_2Cl_2, 20°C), however, the *E* enolate was formed selectively (*E*:*Z* = 80:20), giving an additional quartet at δ 4.68 (*J* 6.8 Hz) for the olefinic proton and a further doublet at δ 1.60 (*J* 6.8 Hz) for the *E* methyl group (**Scheme 8**). Similar ^1H NMR data has been reported by Köster for *Z* and *E* enol diethylborinates.[3a] Selective *E* enolisation of diethylketone by dicyclohexylboron chloride has also been described by Brown.[3e]

The surprising result, however, in this (-)-$(Ipc)_2BCl$ mediated diethylketone-methacrolein aldol reaction is that the *anti* adduct is formed in low enantiomeric excess (<20% ee), while the *syn* adduct is obtained in 80% ee (*cf.* 90% for the triflate reaction). *This indicates that enol diisopinocampheylborinates with E configuration are unlikely to be useful for asymmetric anti aldol reactions.*

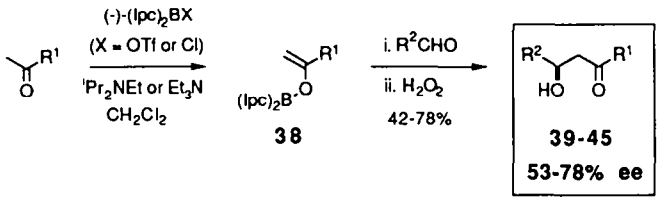
Scheme 8



Enantioselective aldol reactions of methyl ketones via enol diisopinocampheylborinates

For some chiral auxiliary based methods, aldol addition reactions which proceed with high stereoselectivity for α-substituted enolates give little or no stereoselectivity if the α-substituent is lacking.[21] This is the case, for example, with the enol borinates **6** and **7**. Therefore, it was important to examine the effectiveness of enol diisopinocampheylborinates in controlling the stereochemistry of methyl ketone aldol reactions. As shown in **Scheme 9**, we find that the aldehyde enantioface selectivity in addition of the methyl ketone derived enolate **38** is now *reversed* relative to the ethyl ketone reaction.[5c] The β-hydroxyketones **39-45** are produced with moderate levels of enantioselectivity, typically 53-78% ee. The results for a range of methyl ketones and aldehydes following general aldol procedure B are given in **Table II**.

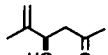
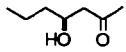
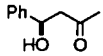
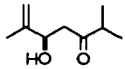
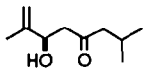
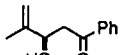
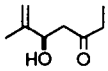
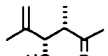
Scheme 9



A study of the effect of solvent and temperature on the aldol reaction of acetone was first made. Enolisation of acetone with (-)-$(Ipc)_2BOTf/Pr^i_2NEt$ was carried out in a range of solvents (dichloromethane, hexane and toluene) at -78 °C, followed by addition of methacrolein, then warming to 0 °C and working up the reaction in the usual way. These conditions were based on general procedure B as used for ethyl ketones. Dichloromethane gave the best result in terms of both ee (68 %) and yield (61%) of the adduct **39**, such that these conditions were again adopted as the standard; although reasonably similar ee values were obtained in the other two solvents (65% ee for hexane, 67% ee for toluene). When the reaction in dichloromethane was repeated at different reaction temperatures (-110, -78 and 20 °C), only small changes were obtained in the product enantiomeric excess. Enolisation and aldol addition at -78 °C (without warming to 0 °C) gave **39** with a slightly improved 73% ee (entry 1). A similar result was obtained when (-)-$(Ipc)_2BCl/Et_3N$ was used in the aldol reaction, which provided **39** in 62% ee (entry 2). *The commercially available chlorides, (-)- and (+)-$(Ipc)_2BCl$, can then be used as a viable alternative to the triflate reagents in enantioselective methyl ketone-aldehyde aldol reactions.* The acetone aldol using (-)-$(Ipc)_2BOTf$ with *n*-butyraldehyde gave **40** in 78% ee (entry 3), while addition to benzaldehyde gave **41** in 57% ee (entry 4). In these two cases, the absolute configuration of the adduct was assigned as shown from literature data.[22a,b,23] The sense of asymmetric induction again appeared to be consistant across the series.[23] *This means that the aldehyde enantioface selectivity is opposite for methyl ketones to that obtained in the ethyl ketone reaction.*[24]

We next looked at the regioselectivity of the aldol reaction with unsymmetrical methyl alkyl ketones. Under the standard conditions, >90% regioselectivity for reaction at the methyl position was obtained with methyl isopropyl ketone and methyl isobutyl ketone (entries 5 and 6). The major aldol adducts **42** and **43** were obtained in 65 and 53% ee, respectively. Butanone (entry 8) gave poorer regioselectivity, despite attempts to improve the kinetic discrimination in deprotonation using more hindered amine bases. The regioselectivity could be reversed to 1:4.5 (entry 9) by using thermodynamic conditions, enolising at room temperature in CH_2Cl_2 using Et_3N, to give **46** as the major aldol product in 93% ee.

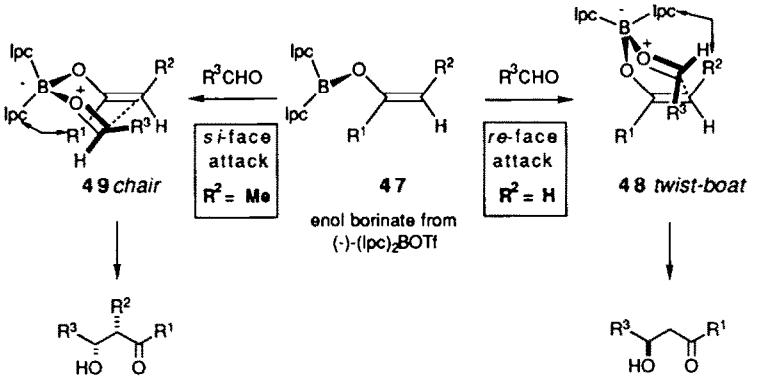
Table II. Enantioselective aldol reactions of methyl ketones using (-)-$(Ipc)_2BX$ (X = OTf[a] or Cl[b]) and $^iPr_2NEt$ in CH_2Cl_2.

entry	ketone/aldehyde	regiosel[c]	major isomer[d]	% ee[e]	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)	% yield[f]
1	Me_2CO/ H_2C=C(Me)CHO	_	 **39**	73[g] (68)[a]	+48.9° (3.8)	59[g] (61)[a]
2	Me_2CO/ H_2C=C(Me)CHO	_	**39**	62[b]	_	67
3	Me_2CO/ ^nPrCHO	_	 **40**[h]	78[a]	+39.19° (6.3)	68
4	Me_2CO/ PhCHO	_	 **41**[i]	57[a]	+40.9° (10.3)	78
5	^{i}PrCOMe/ H_2C=C(Me)CHO	12:1	 **42**	65[j]	+35.9° (3.2)	56
6	^{i}PrCH$_2$COMe/ H_2C=C(Me)CHO	>30:1	 **43**	53[a]	+39.0° (1.2)	62
7	PhCOMe/ H_2C=C(Me)CHO	_	 **44**	61[a]	+57.9° (2.3)	48
8	EtCOMe/ H_2C=C(Me)CHO	1.6:1	 **45**	62[a]	+24.6° (6.8)	71
9	EtCOMe/ H_2C=C(Me)CHO	5.4:1	 **46**	93[k]	-45.7° (4.3)	43

[a] General procedure B: triflate prepared in hexane and used in aldol reaction under standard conditions. [b] Using (-)-$(Ipc)_2BCl/Et_3N$ in general procedure B. [c] Enolisation towards underlined group; isomer ratios determined by weighing isolated components after chromatographic separation. [d] Common configurational assignments for **39-45** based on same shift behaviour with Eu(hfc)$_3$. [e] Determined by 250 MHz ^{1}H NMR using Eu(hfc)$_3$. [f] Isolated yield after chromatography. [g] Enolisation and aldol addition at -78 °C. [h] Configuration assigned from ref 22a. [i] Configuration assigned from ref 22b. [j] Reaction in toluene at -78 °C. [k] Reaction in CH_2Cl_2 at 20 °C using Et_3N.

The change in the aldehyde enantioface selectivity for methyl *vs* ethyl ketones suggests that the mechanism of this aldol reaction cannot easily be rationalised by considering a common Zimmerman-Traxler chair model as in **Scheme 7**.[24] One possibility, as shown in **Scheme 10**, is that with the methyl ketone derived enolate, R^2 = H, the twist-boat arrangement **48** is favoured[21] in the aldol reaction as it avoids steric interactions between R^1 and a bulky Ipc group in the chair structure **49**. The ethyl ketone reaction, however, favours the chair form **49** avoiding the more serious interaction between R^2 = Me and an Ipc group in the twist-boat structure **48**. This then leads to opposite enantioface selectivity in the aldehyde for attack on the same π-face (top face) of the enolate **47**, which prefers to have the $(Ipc)_2B$ group tilted up out of the plane.[18b] Recent *ab initio* calculations[19a] on simple boron enolate aldol transition structures suggest that a twist-boat is easily accessible if there is no *Z* substituent in the enolate, *i.e.* R^2 = H in **48**. However, a more extensive theoretical analysis is still needed to appreciate the subtle controlling factors in these chiral enolate aldol reactions.[18,19]

Scheme 10



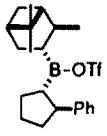
Aldol reactions using other chiral boron reagents

The Ipc ligands that have been used so far lead to useful levels of enantioselectivity in many ketone-aldehyde aldol reactions. However, there is room for improvement, particularly with methyl ketones.[6b,22,25] The main practical advantage of starting with (+)- and (-)-α-pinene is that the enantiomeric reagents can each be prepared in enantiomerically pure form without any resolution step. In this section, we give an account of some other ligand systems which we and other groups have examined.

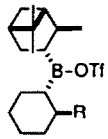
In the early stages of the ethyl ketone work, we briefly explored the effect of structural variation in one of the chiral ligands on boron keeping the other constant as Ipc.[5a] The hope was to design a less sterically demanding ligand system, which would also be effective in aldol reactions with α-branched aldehydes like isobutyraldehyde. Altogether, we prepared three triflate reagents **50**, **51** and **52**, where the common Ipc ligand was derived from (+)-α-pinene. The corresponding dialkylboranes L*(Ipc)BH were each prepared in high enantiomeric purity by the method developed in Brown's group.[26] The appropriate cycloalkene (1-phenylcyclopentene, 1-methylcyclohexene, and 1-phenylcyclohexene) was subjected to asymmetric hydroboration with (-)-$IpcBH_2$ followed by selective crystallisation to give the dialkylborane. The hydroboration product from 1-phenylcyclopentene (77% yield) was the easiest to prepare.[27]

As with the initial work with (-)-$(Ipc)_2BOTf$, the corresponding triflates were freshly prepared *in situ* by the addition of triflic acid to a cooled suspension of the borane in dichloromethane, *cf.* **Scheme 4**. These new reagents **50-52** were then used to mediate the aldol reaction between diethylketone and acetaldehyde

(**Table III**, entries 1-3). High *syn:anti* ratios (≥95:5) were obtained reflecting selective formation of the *Z* enol borinate at the enolisation step. Although the aldol reaction with acetaldehyde in all of these cases proceeded in lower ee than with the C_2-symmetric reagent, (-)-$(Ipc)_2BOTf$, the enantiomeric adduct **53** was now clearly preferred. The best result was obtained for the (1*S*,2*R*)-2-phenylcyclopentyl ligand on boron which gave **53** in 52% ee. The aldol reaction of diethylketone using this reagent was repeated with three other aldehydes. A similar trend was obtained, see **Table III**, with the enantiomeric adducts **54-56** obtained selectively relative to the (-)-$(Ipc)_2BOTf$ reaction. The enantioselectivity obtained was only modest (28-52% ee), so this approach was not pursued further.

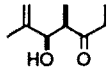
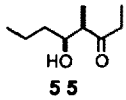
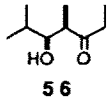


50



51 R = Me
52 R = Ph

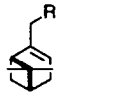
Table III. Enantioselective aldol reactions of diethylketone using L*(Ipc)BOTf[a] and $^iPr_2NEt$ in CH_2Cl_2.

entry	L*	aldehyde	major isomer[b]	% ee[c]	syn:anti[d]	% yield[e]
1		MeCHO	 **53**	52	97:3	60
2		MeCHO	**53**	33	97:3	26
3[f]		MeCHO	**53**	33	97:3	17
4		H_2C=CH(Me)CHO	 **54**	28	96:4	52
5		^{n}PrCHO	 **55**	46	97:3	65
6		^{i}PrCHO	 **56**	32	96:4	36

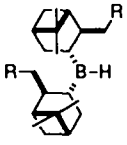
[a] General procedure A: triflate prepared *in situ* for aldol reaction. [b] Aldol products showed opposite sign of specific rotation and chiral shift reagent behaviour to those prepared using (-)-$(Ipc)_2BOTf$, see Table I. [c] Determined by 250 MHz ^1H NMR using Eu(hfc)$_3$. [d] Determined by 250 MHz ^1H NMR. [e] Isolated yield after chromatography. [f] The borane could not be satisfactorily crystallised and so the triflate used was not stereochemically pure.

The stereochemical outcome of the aldol reaction using these reagents is consistant with the less sterically demanding ligand, L*, which has opposite configuration and chiral influence relative to Ipc, occupying the controlling axial position in the diastereomeric chair transition states in **Scheme 7**. The conflicting chiral influences of the two ligands on boron may also be responsible for the lower enantioselectivity; it may not simply be a case of the new ligands displaying intrinsically inferior asymmetric induction. Clearly, the opposing chiral influences of the ligands in these L*(Ipc)B enolates is an undesirable and avoidable complication. Future efforts at refinement of the chiral directing groups on boron, therefore, should concentrate on C_2-symmetric reagents, *i.e.* L_2*BX, and boron reagents with only one chiral ligand attached, *i.e.* L*RBX.

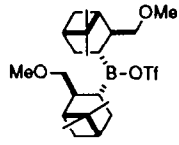
In another approach, we started with structural analogues of α-pinene to prepare the corresponding C_2-symmetric dialkylborane and hence the triflate. In our chair rationale for the sense of asymmetric induction in the $(-)$-$(Ipc)_2BOTf$ mediated aldol reaction of ethyl ketones, we assumed that steric interactions between the methyl group adjacent to boron on the axial Ipc ligand and the R^1 group on the enol borinate were the controlling feature. This suggested that structural modification of α-pinene might enhance the aldol enantioselectivity.[28] We, therefore, prepared the substituted α-pinenes **57-59**, R = OMe,[29] Ph,[30] and $SiMe_3$.[31] Unfortunately, these alkenes did not form crystalline dialkylboranes as easily as with α-pinene. In two cases, R = Ph or $SiMe_3$, oxidation showed that only the initial monoalkyl borane was formed indicating that the new substituents are now too large to allow formation of the dialkyl borane **60**.



57 R = OMe
58 R = Ph
59 R = $SiMe_3$

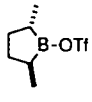


60

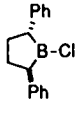


61

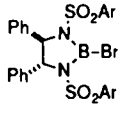
The methoxy derivative could be prepared and this was reacted with triflic acid to give the triflate reagent **61**. The aldol reaction of diethylketone with methacrolein mediated by this new triflate proceeded similarly to the enol diisopinocampheylborinate reaction. The *syn* adduct **24** was isolated with 90% ee in 45% yield. These experiments showed that increasing the size of the 10-methyl group on α-pinene is not a useful way of improving the enantioselectivity of the aldol reaction. The new substituent must be smaller than phenyl or trimethylsilyl, as these do not allow formation of a dialkylborane. A methoxy substituent, however, is too small to improve the selectivity of the aldol reaction.



62



63



64

In related work, the groups of Masamune,[6b,c] Reetz,[6d] and Corey[6a] have independently developed C_2-symmetric chiral boron reagents for asymmetric aldol reactions. The required reagents **62**, **63**, and **64** are prepared in several steps including a resolution. Hence, more effort is needed to prepare these reagents than with

the present α-pinene derived reagents. These other reagents have been shown to be particularly good at asymmetric thioester-aldehyde aldol reactions.[6a,c] Corey has also shown[6a] that the chiral reagent **64** gives high levels of enantioselectivity (≥95% ee) in diethylketone-aldehyde aldol reactions. The corresponding methyl ketone aldol reactions using these reagents, where tested,[6b,d] usually give comparable or lower levels of enantioselectivity than those in **Table II**. This again can be explained by competition between the boat and chair pathways.

Conclusions

The chiral dialkyboron triflates (-)- and (+)-$(Ipc)_2BOTf$ are found to be useful reagents for the experimentally straightforward asymmetric synthesis of β-hydroxy ketones from methyl ketones[22,25] and *syn*-α-methyl-β-hydroxyketones from ethyl ketones.[32,33] Furthermore, these chiral reagents have since been shown to be useful in influencing the stereochemistry of aldol reactions between chiral ketones and aldehydes.[9,10] This new aldol methodology has also been successfully applied to macrolide antibiotic synthesis (rifamycin S,[9b] oleandomycin[34]). However, an effective boron-mediated aldol reaction for the asymmetric synthesis of *anti*-α-methyl-β-hydroxy ketones from ethyl ketones is still needed. Further improvements in reagents are also needed with the methyl ketone aldol reaction to attain enantioselectivities of ≥80% ee. This will require the rational design of chiral ligands on boron and consideration of competing chair and boat pathways in the aldol reaction.[18]

Experimental

NMR spectra were recorded on the following instruments: 400 (^1H) and 100.6 (^{13}C) MHz, Bruker AM400; 250 (^1H) and 62.9 (^{13}C) MHz, Bruker WM250. IR spectra were recorded on a Perkin-Elmer 297 grating spectrometer. High resolution mass spectra were recorded on an AEI MS90 or MS30 spectrometer at Cambridge (EI), or by the SERC service at Swansea (CI). Optical rotations were measured on a Perkin-Elmer 241 polarimeter at the sodium D line (589 nm) and are reported as follows: $[\alpha]_D^{20}$, concentration (*c* in g/100 ml) and solvent. High performance liquid chromatography (HPLC) was carried out using a Dynamax Macro-HPLC silica column (internal diameter 21.4 mm, flow rate 10 ml/min) connected to a Gilson refractive index detector (Model 131). Starting materials and reagents were used as supplied (Aldrich), unless otherwise stated. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium metal/benzophenone ketyl and stored under argon. Dichloromethane, hexane, diisopropylethylamine, triethylamine, boron trifluoride etherate and tetramethylethylenediamine were all distilled from calcium hydride. Methacrolein, crotonaldehyde, and acetaldehyde were distilled from magnesium sulphate or calcium chloride immediately before use. All other aldehydes were distilled and stored at 0 °C. All operations were carried out under an argon atmosphere with oven-dried glassware.

Diisopinocampheylboranes: (-)-Ipc_2BH This procedure is based on that of Brown and Joshi.[12b] To a stirred solution of (+)-α-pinene (40 ml, 250 mmol, 92% ee, dried over calcium hydride before use) in dry THF (30 ml) under argon, borane-methyl sulphide complex (10 ml, 100 mmol, 10 M in DMS) was added dropwise over 30 min. Throughout the addition, the reaction flask was maintained at 20-25 °C.by external cooling (water bath). In cases where the (-)-$(Ipc)_2BH$ started to precipitate before the addition was complete, the reaction mixture was warmed (50-55 °C) to redissolve the solid. Stirring was ceased and the clear solution allowed to stand at room temperature for >16 h, during which time crystallisation occurred. The reaction mixture was then cooled to 0 °C for 2 h and the supernatant liquid removed *via* cannula. The white crystalline mass of (-)-$(Ipc)_2BH$ was broken up with a needle, washed with dry ice-cold ether (3 x 20 ml), and dried under a stream of argon to give a 80-90% yield. The borane could be stored under argon at -15 °C in the refrigerator for several months without significant loss of activity.

(+)-$(Ipc)_2BH$ This was prepared as above, or by the earlier Brown method,[12a] using (-)-α-pinene of 89% ee.

Monoisopinocampheylborane: (-)-IpcBH$_2$ This was prepared according to the literature method[26,35] from (+)-α-pinene of 92% ee and used for the preparation of the boranes **50-52** following the method Brown and Singaram.[26]

Isopinocampheyl-(1*S*,2*R*)-(2-phenylcyclopentyl)borane (50) An ether solution of (-)-IpcBH$_2$ (5.3 mmol, 1 M) was cooled to -35 °C with stirring under argon. 1-Phenylcyclopentene (776 mg, 5.39 mmol) was cooled to -35 °C under argon in a tared flask fitted with a stirrer and rubber septum. The (-)-IpcBH$_2$ solution was transferred *via* cannula into the flask containing the alkene. The reaction mixture was stored overnight at -25 °C. Crystallisation of the dialkylborane product commenced after 2 h. The product was isolated by decantation of the supernatant liquid *via* a cannula, washed with cold ether (-20 °C, 2 x 0.5 ml) and dried (1 mmHg) to give 1.16 g of borane **50** (77%).[27]

Isopinocampheyl-(1*S*,2*S*)-(2-methylcyclohexyl)borane (51)[26] An ether solution of (-)-IpcBH$_2$ (7.5 ml, 10 mmol, 1.3 M) was cooled to -35 °C with stirring under argon, and 1-methylcyclohexene (1.42 ml, 12 mmol) added *via* syringe. The reaction mixture was left standing overnight at -20 °C, after which time the dialkylborane product had crystallised. The crystals were isolated by decantation of the supernatant liquid *via* a cannula, washed with ether (2 x 2 ml) and dried under vacuum (1 mmHg) to give 2.64 g (89% based on alkene). The crystals obtained were aged in THF (10.7 ml, 1 M slurry) overnight, isolated, washed with cold ether (-20 °C, 2 x 2 ml) and dried to give 1.6 g of borane **51** (54%).

Isopinocampheyl-(1*S*,2*R*)-(2-phenylcyclohexyl)borane (52) An ether solution of (-)-IpcBH$_2$ (10 ml, 1.5 M) was cooled to -35 °C with stirring under argon in a tared flask. 1-Phenylcyclohexene (2.6 ml, 16.28 mmol) was added *via* syringe, and the reaction mixture left overnight at -35 °C. There was no sign of any crystallisation of the product at this stage, so the mixture was cooled to -78 °C giving a mass of crystals. The supernatant liquid was removed by cannula and the crystals washed with cold ether (-20 °C, 2 x 2 ml) and dried to give 2.83 g of borane **52** (62%). On warming, the dialkylborane melted below 0 °C. No attempt was made to upgrade the stereochemical purity.

GENERAL PROCEDURE A

Representative aldol reaction using in situ generated boron triflate reagent Dry dichloromethane (30 ml) was added to the appropriate chiral dialkylborane (6.5 mmol) cooled to 0 °C under argon, followed by dropwise addition of trifluoromethanesulfonic acid (0.62 ml, 7 mmol) to the stirred suspension. After 0.5 h at 0 °C, the resulting red-orange solution was warmed to room temp. for 5 min to ensure complete reaction and then recooled to 0 °C. To this solution was added diisopropylamine (2.2 ml, 13 mmol), followed by the ketone (5 mmol) in dichloromethane (2 ml). After 5 h of enolisation at 0 °C, freshly distilled aldehyde (7.5-10 mmol; 15 mmol for acetaldehyde) in dichloromethane (2 ml) was added dropwise. After a further 2-12 h at 0 °C, the reaction mixture was partitioned between ether (60 ml) and pH 7 buffer solution (40 ml). The ether extracts were concentrated *in vacuo*, and the residue dissolved in methanol (25 ml) and pH 7 buffer (5 ml). The solution was cooled to 0 °C, 30% hydrogen peroxide (6.5 ml) was added, and stirring continued at room temp. for 1-2 h. The mixture was then poured into water (50 ml) and extracted with dichloromethane (3 x 50 ml). The combined extracts were washed in turn with $NaHCO_3$ solution and brine, then dried ($MgSO_4$) and concentrated *in vacuo* to yield a yellow-orange oil. Separation of the aldol product from the ligand byproduct(s) was performed by flash chromatography (or occasionally by HPLC). *Syn/anti* ratios were determined by 400 MHz ^{1}H NMR. Chiral chift ^{1}H NMR studies were performed at 250 MHz using tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]-europium(III), Eu(hfc)$_3$, to determine the % ee.

GENERAL PROCEDURE B

Aldol reactions using preformed solutions of diisopinocampheylboron triflates: **(-)-(Ipc)$_2$BOTf** Trifluoromethanesulfonic acid (1.55 ml, 17.6 mmol) was added to a suspension of (-)-(Ipc)$_2$BH (5.03 g, 17.6 mmol) in dry hexane (4 ml) at 0 °C. The two-phase mixture (a colourless solution and an immiscible coloured lower layer) was stirred gently at 20 °C until the reaction was complete, and then the upper colourless hexane solution cannulated into a fresh flask. This stock solution of boron triflate (5.55 ml of 1.9 M solution, assuming a 60% conversion)[15] was used in the aldol reactions within 24 h. ^{13}C NMR δ(62.9 MHz, CD_2Cl_2) 118.9 (q, J = 318 Hz), 48.3, 41.5, 39.3, 37.3, 33.9, 28.6, 28.3, 23.4, 22.7.

(+)-(Ipc)$_2$BOTf This was prepared by the same procedure from (+)-(Ipc)$_2$BH.

Representative aldol reaction The diisopinocampheylboron triflate solution (2.05 ml, 3.9 mmol, ~1.9 M in hexane) was diluted with dichloromethane (16 ml) and cooled to -78 °C under argon. To the stirred solution was added dropwise diisopropylethylamine (1.04 ml, 6 mmol), followed by the ketone (3 mmol). If the boron triflate solution was faintly yellow, it usually became colourless with addition of the amine. After 2-3 h of enolisation at -78 °C, freshly distilled aldehyde ((4-6 mmol; 8 mmol for acetaldehyde) was added dropwise and the reaction mixture was stirred at -78 °C for a further 1 h, before being left in the refrigerator (-15 °C) for 12-16 h. The reaction mixture was then partitioned between ether (3 x 20 ml) and pH 7 buffer (20 ml). The combined ether extracts were concentrated *in vacuo*, and the residue dissolved in methanol (15 ml) and pH 7 buffer (3 ml). The solution was cooled to 0 °C, 30% hydrogen peroxide (4 ml) was added, and stirring was continued at room temp. for 1-2 h. The mixture was then poured into water (30 ml) and extracted with dichloromethane (3 x 30 ml). The combined extracts were washed in turn with $NaHCO_3$ solution and brine, then dried ($MgSO_4$) and concentrated *in vacuo* to yield a yellow-orange oil. Separation of the aldol product from the ligand byproduct, IpcOH, was usually performed by flash chromatography. *Syn/anti* ratios were determined by 400 MHz ^{1}H NMR. Chiral chift ^{1}H NMR studies were performed at 250 MHz using tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium-(III), Eu(hfc)$_3$, to determine the % ee.

ALDOL REACTIONS OF ETHYL KETONES

(4*S*,5*R*)-5-hydroxy-4-methyl-3-hexanone (22) (Table I, entry 1). Using *aldol procedure A* with (-)-(Ipc)$_2$BOTf, diisopropylethylamine, 6.6 mmol of diethylketone, and acetaldehyde (condensation time of 2 h), **22** was obtained in 80% yield as an oil after flash chromatography (40% ethyl acetate/hexane, R_f = 0.25). The *syn/anti* ratio was determined by ^{1}H NMR to be 97:3; a chiral shift experiment and Mosher ester analysis indicated 82% ee. The aldol configuration was determined via its TBS ether derivative as described earlier.[5a] Using *aldol procedure B* with (-)-(Ipc)$_2$BOTf, diisopropylethylamine, 1.0 mmol of diethylketone, and acetaldehyde (condensation time of 16 h), **22** was obtained in 91% yield as an oil after flash chromatography (40% ethyl acetate/hexane, R_f = 0.25). The *syn/anti* ratio was determined by ^{1}H NMR to be 97:3; a chiral shift experiment indicated 79% ee. $[\alpha]_D^{20}$ = -32.7° (*c* 5.9, $CHCl_3$); υ_{max}(liquid film) 3450, 1710 cm^{-1}; ^{1}H NMR δ(400 MHz, $CDCl_3$) 4.08 (1H, qd, *J* = 6.4, 3.5 Hz), 2.71 (1H, br), 2.55 (1H, dq, *J* = 18.1, 7.3 Hz), 2.54 (1H, qd, *J* = 7.3, 3.5 Hz), 2.46 (1H, dq, *J* = 18.1, 7.3 Hz), 1.12 (3H, d, *J* = 6.4 Hz), 1.12 (3H, d, *J* = 7.3 Hz), 1.03 (3H, t, *J* = 7.3 Hz); ^{13}C NMR δ(100.6 MHz, $CDCl_3$) 216.7, 67.2, 50.9, 35.3, 19.9, 10.2, 7.5; HRMS (CI, NH_3) $[M+H]^+$ 131.1072, $C_7H_{15}O_2$ requires 131.1072.

(4*R*,5*S*)-5-hydroxy-4-methyl-3-hexanone (53) (Table III, entries 1-3). Using *aldol procedure A* with boron triflate **50**, diisopropylethylamine, 0.93 mmol of diethylketone, and acetaldehyde (condensation time of 2 h), **53** was obtained as an oil in 60% yield after flash chromatography. The *syn/anti* ratio was determined by ^{1}H NMR spectroscopy to be 97:3; a chiral shift experiment and Mosher ester analysis indicated 52% ee. $[\alpha]_D^{20}$ = +15.4° (*c* 6.5, $CHCl_3$); spectroscopic data as for **22**. Using boron triflates **51** and **52**, the aldol product **53** was obtained in 26% (33% ee) and 17% yield (33% ee), respectively.

(4*S*,5*S*)-5-hydroxy-4,6-dimethyl-6-hepten-3-one (24) (Table I, entry 2). Using *aldol procedure B* with (-)-(Ipc)$_2$BOTf, diisopropylethylamine, 3 mmol of diethylketone, and methacrolein (condensation time of 12 h), **24** was obtained as an oil in 78% yield after flash chromatography (10% ether/dichloromethane; R_f = 0.30). The *syn/anti* ratio was determined by ^{1}H NMR spectroscopy to be 98:2; a chiral shift experiment indicated 91% ee. $[\alpha]_D^{20}$ = -33.8° (*c* 3.7, $CHCl_3$); υ_{max}(liquid film) 3460, 1700, 1650 cm^{-1}; ^{1}H NMR δ(400 MHz, $CDCl_3$) 5.04 (1H, m), 4.92 (1H, m), 4.37 (1H, br d, *J* = 3.6 Hz), 2.72 (1H, qd, *J* = 7.2, 3.6 Hz), 2.57 (1H, dq, *J* = 18.1, 7.3 Hz), 2.49 (1H, dq, *J* = 18.1, 7.3 Hz), 1.68 (3H, s), 1.06 (3H, d, *J* = 7.2 Hz), 1.04 (3H, t, *J* = 7.3 Hz); ^{13}C NMR δ(100.6 MHz, $CDCl_3$) 215.8, 143.9, 111.7, 74.0, 47.7, 34.8, 19.2, 9.8, 7.5; this spectroscopic data is in agreement with that reported in the literature for the racemate.[3c]

(4*R*,5*R*)-5-hydroxy-4,6-dimethyl-6-hepten-3-one (54) (Table III, entry 4). Using *aldol procedure A* with boron triflate **50**, diisopropylethylamine, 0.75 mmol of diethylketone, and methacrolein (condensation time of 12 h), **54** was obtained as an oil in 52% yield after HPLC purification (10% ether/dichloromethane; R_t = 17 min). The *syn/anti* ratio was determined by ^{1}H NMR spectroscopy to be 96:4; a chiral shift experiment indicated 28% ee. $[\alpha]_D^{20}$ = +9.2° (c 4.2, $CHCl_3$); spectroscopic data as for **24**.

(4*S*,5*S*)-5-hydroxy-4-methyl-3-octanone (25) (**Table I**, entry 3). Using *aldol procedure A* with (-)-$(Ipc)_2BOTf$, diisopropylethylamine, 0.84 mmol of diethylketone, and *n*-butyraldehyde (condensation time of 12 h), **25** was obtained as an oil in 92% yield after flash chromatography (15% ether/dichloromethane; R_f = 0.38). The *syn/anti* ratio was determined by ^1H NMR spectroscopy to be 97:3; a chiral shift experiment indicated 80% ee. $[\alpha]_D^{20}$ = -7.8° (c 6.4, $CHCl_3$); υ_{max}(liquid film) 3450, 1700 cm^{-1}; ^1H NMR δ(250 MHz, $CDCl_3$) 3.90 (1H, ddd, *J* = 8.5, 4.4, 3.3 Hz), 2.56 (1H, qd, *J* = 7.0, 3.3 Hz), 2.54 (1H, dq, *J* = 18.1, 7.3 Hz), 2.46 (1H, dq, *J* = 18.1, 7.3 Hz), 1.55-1.20 (4H, m), 1.11 (3H, d, *J* = 7.0 Hz), 1.04 (3H, t, *J* = 7.3 Hz), 0.91 (3H, t, *J* = 6.9 Hz); ^{13}C NMR δ(62.9 MHz, $CDCl_3$) 216.5, 70.9, 49.9, 36.2, 35.1, 19.2, 13.9, 10.0, 7.6; this spectroscopic data is in agreement with that reported in the literature for the racemate.[3c]

(4*R*,5*R*)-5-hydroxy-4-methyl-3-octanone (55) (**Table III**, entry 5). Using *aldol procedure A* with boron triflate **50**, diisopropylethylamine, 1.24 mmol of diethylketone, and *n*-butyraldehyde (condensation time of 12 h), **55** was obtained as an oil in 65% yield after HPLC purification. The *syn/anti* ratio was determined by ^1H NMR spectroscopy to be 97:3; a chiral shift experiment and Mosher ester analysis indicated 46% ee; spectroscopic data as for **25**.

(4*S*,5*S*,6*E*)-5-hydroxy-4-methyl-6-octen-3-one (26) (**Table I**, entry 4). Using *aldol procedure A* with (-)-$(Ipc)_2BOTf$, diisopropylethylamine, 0.91 mmol of diethylketone, and crotonaldehyde (condensation time of 12 h), **26** was obtained as an oil in 75% yield after HPLC purification (15% ether/dichloromethane; R_t = 20 min); R_f = 0.38 (20% ethyl acetate/hexane). The *syn/anti* ratio was determined by ^1H NMR spectroscopy to be 90:10; a chiral shift experiment indicated 68% ee.

Using *aldol procedure B* with (-)-$(Ipc)_2BOTf$, diisopropylethylamine, 2.0 mmol of diethylketone, and crotonaldehyde (condensation time of 12 h), **26** was obtained as an oil in 75% yield after flash chromatography (12% ether/dichloromethane; R_f = 0.35). The *syn/anti* ratio was determined by ^1H NMR spectroscopy to be 98:2; a chiral shift experiment indicated 86% ee. $[\alpha]_D^{20}$ = +5.6° (*c* 4.3, $CHCl_3$); υ_{max}(liquid film) 3440, 1705 cm^{-1}; ^1H NMR δ(400 MHz, $CDCl_3$) 5.69 (1H, dqd, *J* = 15.3, 6.5, 1.1 Hz), 5.44 (1H, ddq, *J* = 15.3, 6.7, 1.6 Hz), 4.31 (1H, ddqn, *J* = 6.7, 4.2, 1.1 Hz), 2.65 (1H, qd, *J* = 7.2, 4.2 Hz), 2.53 (1H, dq, *J* = 18.1, 7.3 Hz), 2.47 (1H, dq, *J* = 18.1, 7.3 Hz), 1.68 (3H, ddd, *J* = 6.5, 1.6, 1.1 Hz), 1.11 (3H, d, *J* = 7.2 Hz), 1.03 (3H, t, *J* = 7.3 Hz); ^{13}C NMR δ(100.6 MHz, $CDCl_3$) 215.8, 130.6, 127.9, 72.8, 50.6, 35.5, 17.7, 11.0, 7.4; HRMS (EI) M+ 156.1153, $C_9H_{16}O_2$ requires 156.1151.

(4*S*,5*R*)-5-hydroxy-4,6-dimethyl-3-heptanone (27) (**Table I**, entry 5). Using *aldol procedure* A with (-)-$(Ipc)_2BOTf$, diisopropylethylamine, 0.78 mmol of diethylketone, and isobutyraldehyde (condensation time of 12 h), **27** was obtained as an oil in 45% yield after HPLC purification (15% ether/dichloromethane; R_t = 19.5 min; R_f = 0.41). The *syn/anti* ratio was determined by ^1H NMR spectroscopy to be 98:2; a chiral shift experiment indicated 66% ee. $[\alpha]_D^{20}$ = -23.2° (*c* 1.8, $CHCl_3$); υ_{max}(liquid film) 3450, 1700 cm^{-1}; ^1H NMR δ(400 MHz, $CDCl_3$) 3.51 (1H, dd, *J* = 8.4, 3.0 Hz), 2.73 (1H, qd, *J* = 7.2, 3.0 Hz), 2.57 (1H, dq, *J* = 18.0, 7.3, Hz), 2.48 (1H, dq, *J* = 18.0, 7.3 Hz), 1.65 (1H, dqq, *J* = 8.4, 6.7, 6.6 Hz), 1.11 (3H, d, *J* = 7.2 Hz), 1.05 (3H, t, *J* = 7.3 Hz), 1.00 (3H, d, *J* = 6.6 Hz), 0.84 (3H, d, *J* = 6.7 Hz); ^{13}C NMR δ(100.6 MHz, $CDCl_3$) 216.9, 76.3, 47.1, 34.8, 30.5, 19.0, 18.9, 9.5, 7.6; this spectroscopic data is in agreement with that reported in the literature for the racemate.[3c]

(4*S*,5*S*)-5-(2-furanyl)-5-hydroxy-4-methyl-3-pentanone (28) (**Table I**, entry 6). Using *aldol procedure A* with (-)-$(Ipc)_2BOTf$, diisopropylethylamine, 1.72 mmol of diethylketone, and furfural (1.15 mmol, condensation time of 12 h), **28** was obtained as an oil in 84% yield after HPLC purification (15% ether/dichloromethane; R_t = 18 min; R_f = 0.34 in 10% ether/dichloromethane). The *syn/anti* ratio was determined by ^1H NMR spectroscopy to be 96:4; a chiral shift experiment indicated 80% ee. $[\alpha]_D$ = -10.8° (*c* 5.4, $CHCl_3$); υ_{max}(liquid film) 3440, 1700.cm^{-1}; ^1H NMR δ(250 MHz, $CDCl_3$) 7.34 (1H, m), 6.33-6.24 (2H, m), 5.01 (1H, d, *J* =4.7 Hz), 3.03 (1H, dq, *J* = 7.3, 4.7 Hz), 2.53 (1H, dq, *J* = 18.0, 7.3 Hz), 2.39 (1H, dq, *J* = 18.0, 7.3Hz), 1.16 (3H, d, *J* =7.3 Hz), 1.01 (3H, t, *J* =7.3 Hz); ^{13}C NMR δ(62.9 MHz, $CDCl_3$) 214.7, 154.7, 141.7, 110.3, 106.7, 68.7, 49.9, 35.0, 11.5, 7.5; HRMS (EI) M^+ 182.0953, $C_{10}H_{14}O_3$ requires 182.0943.

(4*R*,5*R*)-5-(2-furanyl)-5-hydroxy-4-methyl-3-pentanone (29) (**Table I**, entry 7). Using *aldol procedure A* with (+)-$(Ipc)_2BOTf$, diisopropylethylamine, 1.55 mmol of diethylketone, and furfural (1.03 mmol, condensation time of 12 h), **29** was obtained as an oil in 86% yield after HPLC purification (15%

ether/dichloromethane; R_t =18 min; R_f = 0.34 in 10% ether/dichloromethane). The *syn/anti* ratio was determined by ^{1}H NMR spectroscopy to be 96:4; a chiral shift experiment indicated 80% ee; spectroscopic data as for **28**.

(2*S*,3*S*)-3-hydroxy-2,4-dimethyl-1-phenyl-4-penten-1-one (30) (Table I, entry 8). Using *aldol procedure* B with (-)-(Ipc)$_2$BOTf, diisopropylethylamine, 3.0 mmol of propiophenone, and methacrolein (condensation time of 12 h), **30** was obtained as an oil in 97% yield after flash chromatography (10% ether/dichloromethane; R_f = 0.41). The *syn/anti* ratio was determined by ^{1}H NMR spectroscopy to be 98:2; a chiral shift experiment indicated 91% ee. $[\alpha]_D^{20}$ = +1.1° (*c* 2.5, $CHCl_3$); υ_{max}(liquid film) 3500, 1660, 1600, 1580 cm^{-1}; ^{1}H NMR δ(400 MHz, $CDCl_3$) 7.96 (2H, dd, *J* = 7.4, 1.2 Hz), 7.60 (1H, tt, *J* = 7.4, 1.2 Hz), 7.50 (2H, dd, *J* = 7.4, 7.4 Hz), 5.16 (1H, s), 4.98 (1H, q, *J* = 1.5 Hz), 4.51 (1H, br d, *J* = 3.1 Hz), 3.65 (1H, qd, *J* = 7.2, 3.1 Hz), 3.34 (1H, br), 1.77 (3H, d, *J* = 1.5 Hz), 1.21 (3H, d, *J* = 7.2 Hz); ^{13}C NMR δ(100.6 MHz, $CDCl_3$) 205.3, 143.6, 135.8, 133.5, 128.8, 128.4, 112.1, 74.0, 42.5, 19.6, 10.9; HRMS (CI, NH_3) $[M+H]^+$ 205.1229, $C_7H_{15}O_2$ requires 205.1229.

(4*S*,5*S*)-5-hydroxy-2,4,6-trimethyl-6-hepten-3-one (31) (Table I, entry 9). Using *aldol procedure B* with (-)-(Ipc)$_2$BOTf, diisopropylethylamine, 3.0 mmol of 2-methylpentan-3-one, and methacrolein (condensation time of 12 h), **31** was obtained as an oil in 99% yield after flash chromatography (10% ether/dichloromethane; R_f = 0.43). The *syn/anti* ratio was determined by ^{1}H NMR spectroscopy to be 95:5; a chiral shift experiment indicated 88% ee. $[\alpha]_D^{20}$ = -16.7° (*c* 3.0, $CHCl_3$); υ_{max}(liquid film) 3470, 1695, 1645 cm^{-1}; ^{1}H NMR δ(400 MHz, $CDCl_3$) 5.07 (1H, s), 4.93 (1H, br d, *J* = 1.3 Hz), 4.32 (1H, br d, *J* = 3.4 Hz), 3.10 (1H, br), 2.90 (1H, qd, *J* = 7.2, 3.4 Hz), 2.78 (1H, septet, *J* = 6.9 Hz), 1.69 (3H, s), 1.11 (3H, d, *J* = 6.9 Hz), 1.10 (3H, d, *J* = 6.9 Hz), 1.05 (3H, d, *J* = 7.2 Hz); ^{13}C NMR δ(100.6 MHz, $CDCl_3$) 219.6, 143.5, 111.8, 73.9, 45.7, 40.0, 19.3, 18.4, 18.0, 9.9; HRMS (CI, NH_3) $[M+H]^+$ 171.1385, $C_{10}H_{19}O_2$ requires 171.1385.

(5*S*,6*S*)-6-hydroxy-2,5,7-trimethyl-7-octen-4-one (32) (Table I, entry 10). Using *aldol procedure B* with (-)-(Ipc)$_2$BOTf, diisopropylethylamine, 3.0 mmol of 5-methylhexan-3-one, and methacrolein (condensation time of 12 h), **32** was obtained as an oil in 79% yield after flash chromatography (10% ether/dichloromethane; R_f = 0.46). The *syn/anti* ratio was determined by ^{1}H NMR spectroscopy to be 97:3; a chiral shift experiment indicated 86% ee. $[\alpha]_D^{20}$ = -34.1° (*c* 3.1, $CHCl_3$); υ_{max}(liquid film) 3460, 1700, 1645 cm^{-1}; ^{1}H NMR δ(400 MHz, $CDCl_3$) 5.06 (1H, s), 4.93 (1H, m), 4.37 (1H, br d, *J* = 3.4 Hz), 2.97 (1H, br), 2.68 (1H, qd, *J* = 7.2, 3.4 Hz), 2.39 (1H, d, *J* = 0.7 Hz), 2.38 (1H, s), 2.15 (1H, septet, *J* = 6.7 Hz), 1.68 (3H, s), 1.04 (3H, d, *J* = 7.2 Hz), 0.92 (3H, d, *J* = 6.7 Hz), 0.90 (3H, d, *J* = 6.7 Hz); ^{13}C NMR δ(100.6 MHz, $CDCl_3$) 215.2, 143.6, 111.7, 73.6, 50.7, 47.9, 24.1, 22.5, 22.4, 19.2, 9.4; HRMS (CI, NH_3) $[M+H]^+$ 185.1541, $C_{11}H_{21}O_2$ requires 185.1542.

(4*R,5*S**)-6-hydroxy-4,6-dimethyl-6-hepten-3-one (37)** Using *aldol procedure B* with (-)-(Ipc)$_2$BCl in place of the triflate, triethylamine, 1.8 mmol of diethylketone, and methacrolein (reaction at 0 °C; condensation time of 2 h), the *anti* aldol isomer **37** was obtained as an oil in 64% yield after HPLC (10% ether/dichloromethane, R_t = 23 min; R_f = 0.43 in 40% ethyl acetate/hexane), together with the *syn* product **24** (16% yield). The *syn/anti* ratio was 1:4; chiral shift experiments indicated that **37** was obtained in <20% ee, while **24** had 80% ee. *Anti* isomer **37** had $[\alpha]_D^{20}$ = 0° (*c* 12.8, $CHCl_3$); ^{1}H NMR δ(250 MHz, $CDCl_3$) 4.85 (2H, m), 4.11 (1H, d, *J* = 8.6 Hz), 2.73 (1H, dq, *J* = 8.6, 7.0 Hz), 2.60 (1H, br s), 2.49 (2H, q, *J* = 7.0 Hz), 1.67 (3H, s), 0.99 (3H, t, *J* = 7.0 Hz), 0.92 (3H, d, *J* = 7.0 Hz); ^{13}C NMR δ(100 MHz, $CDCl_3$) 215.9, 144.6, 113.6, 78.3, 48.3, 36.4, 16.7, 14.1, 7.3; HRMS (CI, NH_3) $[M+H]^+$ 157.1228, $C_9H_{16}O_2$ requires 157.1228.

ALDOL REACTIONS OF METHYL KETONES

(*R*)-4-hydroxy-5-methyl-5-hexen-2-one (39) (Table II, entries 1-2). Using *aldol procedure B* with (-)-(Ipc)$_2$BOTf, diisopropylethylamine, 1.0 mmol of acetone, and methacrolein (condensation at -78 °C for 5 h), **39** was obtained as an oil in 59% yield after HPLC (25% ether/dichloromethane); a chiral shift experiment indicated 73% ee; $[\alpha]_D^{20}$=+48.9° (c 3.8, $CHCl_3$); υ_{max}(liquid film) 3350-3500, 1700, 1640 cm^{-1}; ^{1}H NMR δ(250 MHz, $CDCl_3$) 4.99 (1H, m), 4.84 (1H, m), 4.48 (1H, t, *J* = 6.0 Hz), 2.65 (2H, d, *J* = 6.0 Hz), 2.18 (3H, s), 1.72 (3H, s); ^{13}C NMR δ(100 MHz, $CDCl_3$) 209.2, 145.6, 111.1, 71.0, 48.4, 30.8, 16.3; HRMS (CI) M^+ 129.0918, $C_7H_{12}O_2$ requires 129.0915. This reaction was also carried out in hexane (→ 65% ee) and

toluene (→ 68% ee) with condensation at 0 °C, as well as at different temperatures in dichloromethane (-110 °C → 66% ee, 20 °C → 62% ee).

Using *aldol procedure B* with (-)-$(Ipc)_2BCl$ in place of the triflate, triethylamine, 1.0 mmol of acetone, and methacrolein (condensation at 0 °C for 2 h), **39** was obtained as an oil in 67% yield after flash chromatography (10% ether/dichloromethane, $R_f = 0.27$); a chiral shift experiment indicated 62% ee.

(*S*)-4-hydroxy-2-heptanone (40) (**Table II**, entry 3). Using *aldol procedure B* with (-)-$(Ipc)_2BOTf$, diisopropylethylamine, 0.94 mmol of acetone, and *n*-butyraldehyde (condensation time 2 h), **40** was obtained as an oil in 68% yield after flash chromatography (25% ether/dichloromethane, $R_f = 0.26$); a chiral shift experiment indicated 78% ee. $[\alpha]_D^{20} = +39.1°$ (*c* 6.3, $CHCl_3$), *cf* lit.[22a] $[\alpha]_D^{25} = +35.1°$ (*c* 2.1, $CHCl_3$; 58% ee); υ_{max} (liquid film) 3500-3600, 1710 cm^{-1}; ^1H NMR δ(250 MHz, $CDCl_3$) 4.02 (1H, m), 2.96 (1H, br s), 2.62 (1H, dd, *J* = 17.7, 3.2 Hz), 2.51 (1H, dd, *J* = 17.7, 8.7 Hz), 2.16 (3H, s), 1.23-1.52 (4H, m), 0.91 (3H, t, *J* = 7.0 Hz); HRMS (EI) M^+ 129.0922, $C_7H_{13}O_2$ requires 129.0915.

(*R*)-4-hydroxy-4-phenyl-2-butanone (41) (**Table II**, entry 4). Using *aldol procedure B* with (-)-$(Ipc)_2BOTf$, diisopropylethylamine, 0.94 mmol of acetone, and benzaldehyde (condensation time 2 h), **41** was obtained in 78% yield after HPLC (30% ethyl acetate/hexane); a chiral shift experiment indicated 57% ee. $[\alpha]_D^{20} = +40.9°$ (*c* 1.03, $CHCl_3$), *cf* lit.[22b] $[\alpha]_D^{23} = -48.8°$ (*c* 1.0, $CHCl_3$; 65% ee) for its enantiomer; υ_{max}(liquid film) 3500-3600, 1700 cm^{-1}; ^1H NMR δ(250 MHz, $CDCl_3$) 7.25-7.35 (5H, m), 5.16 (1H, dd, *J* = 4.0, 8.6 Hz), 2.89 (1H, dd, *J* = 17.7, 8.6 Hz), 2.79 (1H, dd, *J* = 17.7, 4.0 Hz), 2.18 (3H, s); ^{13}C NMR δ(100 MHz, $CDCl_3$) 209.0, 142.6, 128.5, 127.6, 125.6, 69.8, 52.0, 30.7; HRMS (EI) M^+ 164.0834, $C_{10}H_{12}O_2$ requires 164.0837.

(*R*)-5-hydroxy-2,6-dimethyl-6-hepten-3-one (42) (**Table II**, entry 5). Using *aldol procedure B* (except that the reaction solvent was toluene) with (-)-$(Ipc)_2BOTf$, diisopropylethylamine, 0.75 mmol of 3-methyl-2-butanone, and methacrolein (condensation time 2 h), **42** was obtained as the major aldol product as an oil in 51% yield (56% combined yield of aldol isomers) after HPLC (10% ether/dichloromethane, R_t = 13.4 min; $R_f = 0.5$ in 25% ether/dichloromethane). The ratio of regioisomers was 12:1; a chiral shift experiment on **42** indicated 65% ee. $[\alpha]_D^{20} = +35.9°$ (3.2, $CHCl_3$); υ_{max}(liquid film) 3500, 1700, 1650 cm^{-1}; ^1H NMR δ(250 MHz, $CDCl_3$) 5.00 (1H, m), 4.85 (1H, m), 4.48 (1H, t, *J* = 6.0 Hz), 3.12 (1H, br s), 2.68 (1H, d, *J* = 6.0 Hz), 2.67 (1H, d, *J* = 7.0 Hz), 2.61 (1H, septet, *J* = 6.9 Hz), 1.74 (3H, s), 1.11 (6H, d, *J* = 6.9 Hz); ^{13}C NMR δ(100 MHz, $CDCl_3$) 215.5, 145.7, 111.0, 71.1, 45.2, 41.5, 18.3, 17.9; HRMS (EI) M^+ 156.1161, $C_9H_{16}O_2$ requires 156.1150.

(*R*)-6-hydroxy-2,7-dimethyl-7-octen-4-one (43) (**Table II**, entry 6). Using *aldol procedure B* with (-)-$(Ipc)_2BOTf$, diisopropylethylamine, 0.75 mmol of 4-methyl-2-pentanone, and methacrolein (condensation time 2 h), **43** was obtained in 62% yield after HPLC (10% ether/dichloromethane, R_t = 19 min; $R_f = 0.40$ in 10% ether/dichloromethane). The ratio of regioisomers was >30:1; a chiral shift experiment indicated 53% ee. $[\alpha]_D^{20} = +39.0°$ (*c* 1.2, $CHCl_3$); υ_{max}(liquid film) 3500, 1700 cm^{-1}; ^1H NMR δ($CDCl_3$, 250 MHz) 5.00 (1H, m), 4.85 (1H, m), 4.49 (1H, t, *J* = 6.0 Hz), 2.61 (2H, d, *J* = 6.0 Hz), 2.32 (2H, d, *J* = 7.0 Hz), 2.16 (1H, m), 1.73 (3H, s), 0.91 (6H, d, *J* = 6.6 Hz); ^{13}C NMR δ($CDCl_3$, 100 MHz) 211.4, 145.7, 111.0, 71.0, 52.6, 48.0, 24.4, 22.5, 16.3; HRMS (CI, NH_3) $[M+NH_4]^+$ 188.1654, $C_8H_{14}O_2.NH_4$ requires 188.1650.

(*R*)-3-hydroxy-4-methyl-1-phenyl-4-penten-1-one (44) (**Table II**, entry 7). Using *aldol procedure B* with (-)-$(Ipc)_2BOTf$, diisopropylethylamine, 0.75 mmol of acetophenone, and methacrolein (condensation time 2 h), **44** was obtained in 48% yield after HPLC (25% ether/dichloromethane, R_t = 14 min; $R_f = 0.36$ in dichloromethane); a chiral shift experiment indicated 61% ee. $[\alpha]_D^{20} = +57.9°$ (*c* 2.3, $CHCl_3$); υ_{max}(liquid film) 3500-3600, 1675, 1580, 1600 cm^{-1} ; ^1H NMR δ($CDCl_3$, 250 MHz) 7.96 (2H, d, *J* = 7.0 Hz), 7.59 (1H, t, *J* = 7.0 Hz), 7.47 (2H, t, *J* = 7.0 Hz), 5.08 (1H, m), 4.91 (1H, m), 4.68 (1H, dd, *J* = 7.6, 4.4 Hz), 3.21 (1H, d, *J* = 4.4 Hz), 3.20 (1H, d, *J* = 7.6 Hz), 1.81 (3H, s); ^{13}C NMR δ($CDCl_3$, 100 MHz) 200.4, 145.7, 136.7, 133.5, 128.6, 128.1, 111.3, 71.2, 43.7, 18.5; HRMS (EI) $[M-H_2O]^+$ 172.0891, $C_{12}H_{12}O$ requires 172.0888

(*R*)-5-hydroxy-6-methyl-6-hepten-3-one (45) (**Table II**, entry 8). Using *aldol procedure B* with (-)-$(Ipc)_2BH$, diisopropyl-ethylamine, 0.92 mmol of butanone, and methacrolein (condensation time of 2 h), **45** was obtained in 44% yield after HPLC (25% ether/dichloromethane, R_t = 16.4 min; $R_f = 0.37$ in 10%

ether/dichloromethane) together with a 27% yield of **46** (R_f = 18 min); a chiral shift experiment on **45** indicated 62% ee. $[\alpha]_D^{20}$=+24.6° (*c* 6.8, $CHCl_3$); υ_{max}(liquid film) 3500, 1700 cm^{-1}; ^1H NMR δ(250 MHz, $CDCl_3$) 4.99 (1H, m), 4.85 (1H, m), 4.49 (1H, t, *J* = 6.1 Hz), 3.00 (1H, br s), 2.64 (2H, d, *J* = 6.1 Hz), 2.47 (2H, q, *J* = 7.3 Hz), 1.73 (3H, s), 1.06 (3H, t, J = 7.3 Hz); ^{13}C NMR δ(100 MHz, $CDCl_3$) 212.0, 145.7, 111.0, 71.1, 47.2, 36.8, 18.2, 7.4; HRMS (CI, NH_3) $[M+NH_4]^+$ 160.1335, $C_8H_{14}O_2.NH_4$ requires 160.1337.

(3*S*,4*S*)-4-hydroxy-3,5-dimethyl-5-hexen-2-one (46) (**Table II**, entry 9). Using *aldol procedure B* with (-)-$(Ipc)_2BOTf$, triethylamine, 0.73 mmol butanone, and methacrolein (enolisation at 20 °C and condensation at 20 °C for 1 h), **46** was obtained in 36% yield after HPLC (as above) together with a 6.6% yield of **45**; a chiral shift experiment on **46** indicated 93% ee. $[\alpha]_D^{20}$=-45.7° (*c* 4.3, $CHCl_3$); ^1H NMR δ(250 MHz, $CDCl_3$) 5.04 (1H, m), 4.93 (1H, m), 4.40 (1H, d, *J* = 3.5 Hz), 2.69 (1H, dq, *J* = 3.5, 7.3 Hz), 2.20 (3H, s), 1.67 (3H, s), 1.06 (3H, d, *J* = 7.3 Hz); HRMS (EI) M^+ 142.0991, $C_8H_{14}O_2$ requires 142.0994.

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§ Roussel-Emmanuel Research Fellow 1985-87. Present address: Department of Chemistry, University of Delaware, Newark, DE 19716, USA.

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