Catalytic Asymmetric Synthesis of γ-Hydroxy Ketones and Aromatic Hydroxy Ketones by the Chemo- and Enantio-selective Alkylation of Keto Aldehydes with Dialkylzincs

Masami Watanabe and Kenso Soai*
Department of Applied Chemistry, Faculty of Science, Science University of Tokyo, Shinjuku, Tokyo, 162 Japan

Optically active γ-hydroxy ketones and aromatic hydroxy ketones with high (up to 96%) enantiomeric excesses have been synthesized by the chemo- and enantio-selective addition of dialkylzincs to γ-keto aldehydes and aromatic keto aldehydes, respectively, using *N,N*-dibutylnorephedrine (DBNE) **1** and (1-methylpyrrolidin-2-yl)diphenylmethanol (DPMPM) **5** as chiral catalysts. The method provides a non-homoaldol approach to optically active γ-hydroxy ketones.

Optically active hydroxy ketones are important synthetic intermediates. The asymmetric aldol reaction is commonly used for the synthesis of chiral β-hydroxy ketones.[1] However, the enantioselective syntheses of γ-(4)-hydroxy esters and their equivalents have been reported by enantioselective[2] and diastereoselective[3] homo-aldol condensations using homo-enolate anion[4] equivalents and by the enantioselective alkylation of 3-formyl esters.[5] However, to the best of our knowledge, catalytic enantioselective synthesis of γ-hydroxy ketones by a carbon–carbon bond-forming reaction is very rare.

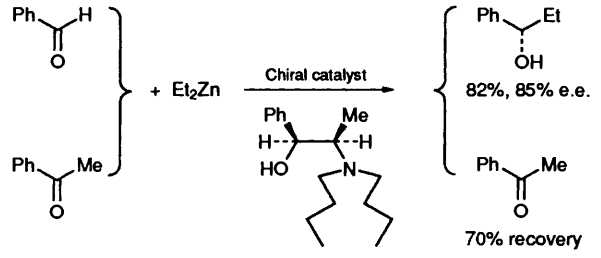
Chemo- and enantio-selective alkylation of the formyl group of prochiral keto aldehydes is considered to be a versatile and direct method for the synthesis of chiral hydroxy ketones with various structures. However, most organometallic reagents such as alkyllithium and Grignard reagents are so nucleophilic that they usually fail to react chemoselectively with aldehydes in the presence of ketones.[6] Although the chemoselective non-asymmetric alkylation of aldehydes in the presence of ketones has been the subject of considerable attention,[7] to the best of our knowledge, no catalytic asymmetric synthesis of hydroxy ketones from the enantioselective alkylation of prochiral keto aldehydes has been reported.

We previously reported the synthesis of various racemic hydroxy ketones by the chemoselective alkylation of the formyl group of keto aldehydes with dialkylzincs in the presence of an achiral catalyst such as 2-dimethylaminoethanol.[8] We have also reported the highly enantioselective alkylation of aldehydes with dialkylzincs using chiral β-amino alcohols such as (1*S*,2*R*)-(−)-, (1*R*,2*S*)-(+)-2-(*N*,*N*-dibutylamino)-1-phenylpropan-1-ol (*N*,*N*-dibutylnorephedrine) (DBNE) **1**,[9a] (*S*)-(+)-(1-methylpyrrolidin-2-yl)diphenylmethanol (DPMPM) **5**,[9b] and using chiral ammonium salts[10] and chiral piperazines.[11,12]

In this paper, we describe the first catalytic asymmetric synthesis of various hydroxy ketones by the chemo- and enantio-selective alkylation of the formyl group of keto aldehydes with dialkylzincs in the presence of DBNE **1** and DPMPM **5** as chiral catalysts.[13]

Results and Discussion

We first examined the chemo- and enantio-selective alkylation of benzaldehyde with diethylzinc in the presence of acetophenone using (1*S*,2*R*)-DBNE **1** as the chiral catalyst (Scheme 1). Treatment of an equimolar mixture of benzaldehyde and acetophenone with 4.4 mol equiv. of diethylzinc in the presence of 6 mol% of (1*S*,2*R*)-**1** as the chiral catalyst at 0 °C afforded 1-phenylpropan-1-ol with 85% e.e. in 82% yield as a result of the chemo- and enantio-selective ethylation of benzaldehyde; 70% of the acetophenone was recovered. This enantioselectivity during the alkylation of benzaldehyde in the presence of acetophenone is similar to that during the alkylation of benzaldehyde (90% e.e.) in the absence of acetophenone.[9a] Thus, benzaldehyde was enantioselectively ethylated without being affected by the presence of a ketone.



(1*S*,2*R*)-(−)-DBNE 1

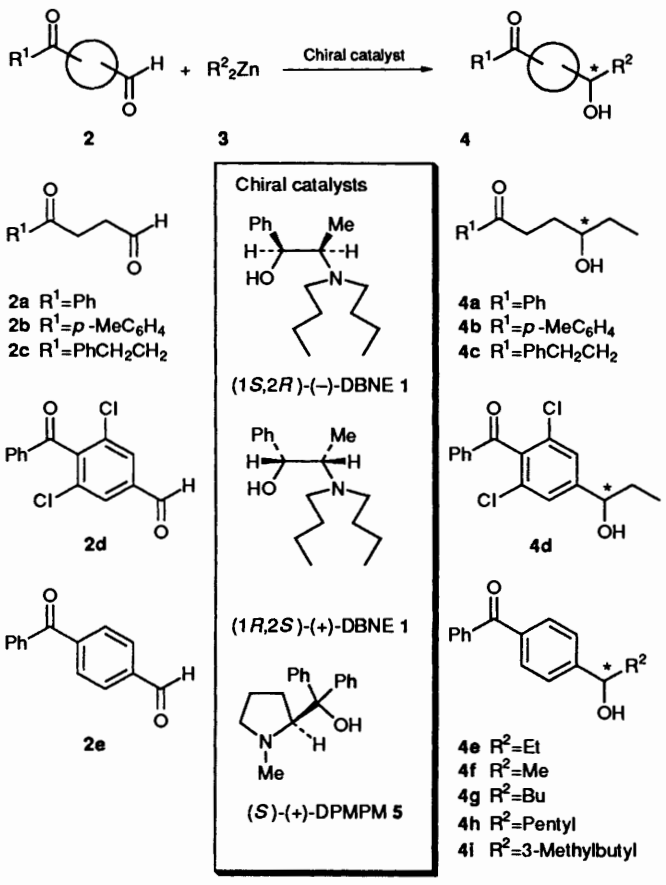
Scheme 1

The chemo- and enantio-selective alkylation of 4-oxo-4-phenylbutanal **2a**, a γ-keto aldehyde that possesses α-protons adjacent to the carbonyl groups of the ketone and aldehyde, was then examined with diethylzinc using (1*S*,2*R*)-**1** as a chiral catalyst (Scheme 2). E.e.s of the obtained 4-hydroxy-1-phenylhexan-1-one **4a**, a γ-hydroxy ketone, were determined by HPLC analyses of the corresponding (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) ester[14] of **4a** using a chiral column.

The effects of the amount of the chiral catalyst (1*S*,2*R*)-**1** added and the solvent used during the chemo- and enantio-selective ethylation of keto aldehyde **2a** are shown in Table 1. The treatment of **2a** with 2.2 equiv. of diethylzinc in the presence of 6 mol% of (1*S*,2*R*)-**1** as chiral catalyst at 0 °C afforded compound **4a** with 64% e.e. (Table 1, entry 1). When 12 mol% of catalyst **1** was used, the e.e. of **4a** increased to 87% (Table 1, entry 2). The use of 20 mol% of catalyst **1** gave **4a** with a similar e.e. (85% e.e. Table 1, entry 3).

As to the effect of solvent, the enantioselectivity during the ethylation reaction using toluene as solvent (84% e.e., Table 1, entry 4) was comparable with that using toluene–hexane (87% e.e., Table 1, entry 2). The use of 4.4 equiv. of Et_2Zn increased the yield of **4a** (66%) (Table 1, entry 5).

The effect of the chiral catalyst structure (**1** and **5**) during the chemo- and enantio-selective ethylation of **2a** was examined. The results are shown in Table 2. When (1*S*,2*R*)-**1** was used, (+)-**4a** with 87% e.e. was obtained in 52% yield (Table 2, entry 1). However, when (1*R*,2*S*)-**1** was employed, (−)-**4a** with 85% e.e. was obtained in 48% yield (Table 2, entry 2). Thus, by



Scheme 2

Table 1 Effect of the amount of chiral catalyst (1*S*,2*R*)-(−)-**1** added and the solvent used in the chemo- and enantio-selective ethylation of γ-keto aldehyde **2a**

				4a	
Entry	mol% of **1**	Solvent[a]	*t*/h	Yield (%)	%e.e.[b]
1[c]	6	T–H	116	41	64
2[c]	12	T–H	116	52	87
3[c]	20	T–H	110	30	85
4[c]	12	T	116	49	84
5[d]	12	T–H	116	66	84

[a] T = toluene, H = hexane. [b] Based on HPLC analyses of the corresponding (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) ester[14] using a chiral column (Daicel Chiralcel OD, 250 mm, 254 nm UV detector). [c] 2.2 Equiv. of diethylzinc was used. [d] 4.4 Equiv. of diethylzinc was used.

Table 2 Effect of the structure of the chiral catalyst in the chemo- and enantio-selective ethylation of γ-keto aldehyde **2a**

			4a	
Entry[a]	Chiral catalyst	*t*/h	Yield (%)	%e.e.[b]
1	(1*S*,2*R*)-(−)-**1**	116	52	87
2	(1*R*,2*S*)-(+)-**1**	116	48	85
3	(*S*)-(+)-**5**	116	44	72

[a] Mol ratio **2a**:chiral catalyst:Et_2Zn = 1:0.12:4.4. [b] See footnote *b* in Table 1.

choosing the appropriate enantiomer of the chiral catalyst, either enantiomer of the desired product with the same

Table 3 Chemo- and enantio-selective ethylation of γ-keto aldehydes **2** with diethylzinc using (1*S*,2*R*)-DBNE **1** as chiral catalyst to give hydroxy ketones **4**

Entry[a]	**2**	*t*/h	**4**	Yield (%)	%e.e.[b]
1	**a**	116	**a**	52	87
2	**b**	123	**b**	30	85
3	**c**	116	**c**	47	81

[a] Mol ratio, keto aldehyde **2**:Et_2Zn:catalyst **1** = 1:2.2:0.12. [b] See footnote *b* in Table 1.

Table 4 Effect of the amount of chiral catalyst (*S*)-**5** used in the chemo- and enantio-selective ethylation of aromatic keto aldehyde **2d**

			4d	
Entry	mol% of catalyst	*t*/h	Yield (%)	%e.e.[a]
1	4	41	89	57
2	8	28	100	88
3	12	45	95	84

[a] Based on HPLC analyses of **4d** using a chiral column (Daicel Chiralcel OD, 250 mm; 254 nm UV detector).

enantiomeric purity and synthetic yield, within experimental error could be obtained. On the other hand, using (*S*)-**5** as the chiral catalyst, the e.e. of **4a** was decreased to 72% (entry 3). We previously reported that DBNE **1** is a highly enantioselective chiral catalyst for the alkylation of aliphatic aldehydes as well as aromatic aldehydes.[4a] The higher e.e. obtained with DBNE than that obtained with DPMPM in the present enantioselective ethylation of **2a** is consistent with our previous results on the enantioselective alkylation of simple aliphatic aldehydes.

Furthermore, the enantioselective ethylations of **2b** and **2c** were performed using 12 mol% of (1*S*,2*R*)-**1**. These results are shown in Table 3. The enantioselective ethylation of **2b** gave **4b** with 85% e.e. (Table 3, entry 2). Enantioselective ethylation of **2c** having no aromatic substituents at the α,α′ positions of the ketone carbonyl group afforded 6-hydroxy-1-phenyloctan-3-one **4c** with 81% e.e. It should be noted that the present method provides a unique non-homoaldol approach to the optically active γ-hydroxy ketones **4a–c**.

The chemo- and enantio-selective ethylation of 4-benzoyl-3,5-dichlorobenzaldehyde **2d**, an aromatic keto aldehyde, was then examined using (*S*)-DPMPM **5** as chiral catalyst. The results are shown in Table 4. During the enantioselective ethylation of **2d**, the e.e.s of 2,6-dichloro-4-(1- hydroxypropyl)phenyl-(phenyl)methanone **4d** obtained by using 8–12 mol% of (*S*)-**5** were higher (84–88% e.e., Table 4, entries 2 and 3) than that obtained using 4 mol% of **5** (Table 4, entry 1).

The effect of the structure of the dialkylzinc used on the nature of the reaction is shown by the chemo- and enantio-selective alkylation of 4-benzoylbenzaldehyde **2e**, an aromatic keto aldehyde, with various dialkylzincs using (*S*)-**5** and (1*S*,2*R*)-**1** as chiral catalysts. The results are summarized in Table 5. When **2e** was treated with 2.2 equiv. of diethylzinc using 8 mol% of (*S*)-DPMPM **5** as chiral catalyst, 4-(1-hydroxypropyl)phenyl(phenyl)methanone **4e** with 93% e.e. was obtained in quantitative yield (Table 5, entry 1). When the lithium alkoxide of (*S*)-DPMPM **5** was employed as the chiral catalyst, the e.e. of **4e** reached 96% e.e. (Table 5, entry 2). When (1*S*,2*R*)-(−)-DBNE **1** was used as the chiral catalyst, **2e** was again ethylated affording **4e** with 91% e.e. (Table 5, entry 3). Enantioselective alkylation of **2e** with dimethylzinc, dibutylzinc, dipentylzinc and bis(3-methylbutyl)zinc afforded the corresponding optically active hydroxy ketones **4f–i** with high e.e.s

Table 5 Chemo- and enantio-selective alkylation of keto aldehyde **2e** with various dialkylzincs using (1*S*,2*R*)-DBNE **1** and (*S*)-DPMPM **5** as chiral catalysts

				4	
Entry[a]	R^2	Chiral catalyst	*t*/h	Yield (%)	%e.e.[b]
1	Et	(*S*)-**5**	18	100	93
2	Et	(*S*)-**5**–Li[c]	24	82	96
3	Et[d]	(1*S*,2*R*)-**1**	20	82	91
4	Me[e]	(*S*)-**5**	72	82	87
5	Me[e]	(*S*)-**5**–Li[c]	72	83	87
6	Bu	(*S*)-**5**	19	64	92
7	Bu	(*S*)-**5**–Li[c]	27	48	91
8	Pentyl	(*S*)-**5**	78	94	94
9	3-Methylbutyl	(*S*)-**5**	20	100	95

[a] Unless otherwise noted, mol ratio was **2e**: chiral catalyst (**5**): R^2_2Zn = 1:0.08:2.2. [b] See footnote *a* in Table 4. [c] Lithium alkoxide of (*S*)-DPMPM **5** prepared *in situ* from the treatment of **5** with butyllithium. [d] Mol ratio was **2e**:**1**:Et_2Zn = 1:0.12:2.2. [e] Mol ratio **2e**:**5**:R^2_2Zn = 1:0.08:4.4.

(87–95%) in moderate to high chemical yields (64–100%) (Table 5, entries, 4, 6, 8 and 9).

In conclusion, optically active γ-hydroxy ketones and aromatic hydroxy ketones of high e.e.s were obtained by the chemo- and enantio-selective addition of dialkylzincs to γ-keto aldehydes and aromatic aldehydes, respectively, using DBNE **1** and DPMPM **5** as chiral catalysts. Either hydroxy ketone enantiomer could be synthesized by using the appropriate enantiomer of the chiral catalyst.

Experimental

General.—IR spectra, ^1H NMR spectra and optical rotations were recorded with a Hitachi 260-10 spectrophotometer, JEOL JNM-PMX-60 spectrometer and JASCO DIP-181 polarimeter, respectively. $[\alpha]_D$ Values are given in units of 10^{-1} deg cm^2 g^{-1}. Bulb-to-bulb distillation was carried out with a Shibata Glass Tube Oven GTO-250. Toluene and tetrahydrofuran (THF) were distilled over lithium aluminium hydride. All of the reactions were carried out under an argon atmosphere. E.e.s of hydroxy ketones obtained were determined on the basis of HPLC analyses of the hydroxy ketone (for **4d**) or the corresponding (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) ester[14] (for **4a–c**, **e–i**) using a chiral column (Daicel Chiralcel OD, 4.6 × 250 mm, 254 nm UV detector).

Materials.—Hexane solutions of diethylzinc and dimethylzinc were purchased from Kanto Chemical Co. and Tri Chemical Inc., respectively. Other dialkylzinc reagents were prepared according to the literature procedure.[15] Keto aldehyde **2d** was commercially available. Keto aldehydes **2a–c**,[16] **2e**,[17] chiral catalysts (1*S*,2*R*)-(−)- and (1*R*,2*S*)-(+)-DBNE **1**[9a] and (*S*)-(+)-DPMPM **5**[9b] were prepared according to the literature procedures.

Preparation of 4-*Oxo*-4-*phenylbutanal* **2a**,[16] 4-*Oxo*-4-(p-*tolyl*)*butanal* **2b** *and* 4-*Oxo*-6-*phenylhexanal* **2c**.—To a cold solution of benzoyl chloride (4.25 g, 30.2 mmol) in THF (20 cm^3) was added 2-(1,3-dioxolan-2-yl)ethylmagnesium bromide (0.69 mol dm^{-3} in THF; 23.5 mmol) at −78 °C. The reaction was quenched with saturated aqueous sodium hydrogen carbonate. The THF was removed under reduced pressure and then the residue was extracted with diethyl ether. The ethereal layer was dried over anhydrous sodium sulfate and then evaporated under reduced pressure. The residue, mostly 2-(3-oxo-3-phenylpropyl)-1,3-dioxolane, was mixed with saturated aqueous oxalic acid and then refluxed for 4 h. The mixture was extracted with diethyl ether and the ethereal layer was washed with saturated sodium hydrogen carbonate, dried (sodium sulfate) and then evaporated under reduced pressure. The residue was purified by bulb-to-bulb distillation, bath temperature 150 °C/2 mmHg; $\delta_H(CDCl_3)$ 2.77–3.50 (4 H, m), 7.23–8.10 (5 H, m) and 9.83 (1 H, s); $\nu_{max}(CCl_4)/cm^{-1}$ 3050, 1725 and 1690.

4-Oxo-4-(*p*-tolyl)butanal **2b** and 4-oxo-6-phenylhexanal **2c** were prepared in the same manner as **2a** from 4-methylbenzoyl chloride and 3-phenylpropanoyl chloride, respectively.

Typical Procedure for the Chemo- and Enantio-selective Alkylation of the Keto Aldehydes.—(+)-4-(1-*Hydroxypropyl*)-*phenyl*(*phenyl*)*methanone* **4e** (*Table* 5, *entry* 1). To a cold solution of (*S*)-**5** (0.08 mmol, 8 mol%) in toluene (1 cm^3), was added a toluene solution (1 cm^3) of keto-aldehyde **2e** (0.210 g, 1.0 mmol) at 0 °C. After being stirred for 20 min, Et_2Zn (1 mol dm^{-3} in hexane; 2.2 cm^3, 2.2 mmol) was added. The reaction mixture was stirred at 0 °C for 18 h and then quenched with HCl (1 mol dm^{-3}; 3 cm^3). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 × 20 cm^3). The combined organic extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by silica gel TLC [$CHCl_3$–MeOH (50:1 v/v) as eluent]. Optically active (+)-4-(1-hydroxypropyl)phenyl(phenyl)methanone **4e** with 93% e.e. was obtained in 100% yield; $\delta_H(CDCl_3)$ 0.73–1.16 (3 H, t), 1.50–2.05 (2 H, m), 2.96 (1 H, s), 3.46–4.74 (3 H, t) and 7.12–7.91 (9 H, m); ν_{max}(neat)/cm^{-1} 3430, 3060, 2970, 1740, 1660 and 1610 (Found: *m*/*z* 240.1148. Calc. for $C_{16}H_{16}O_2$: *M*, 240.1151); $[\alpha]_D^{23}$ +14.5 (*c* 2.03 in $CHCl_3$) for 93% e.e. The e.e. was determined by HPLC analysis of the corresponding (*S*)-MTPA ester[14] using a chiral column (Daicel Chiralcel OD, 4.6 × 250 mm, 254 nm UV detector). Eluent 3% propan-2-ol in hexane; flow rate 0.5 cm^3 min^{-1}, retention time (t_R/min), 23.3 for minor peak, 25.6 for major peak.

(+)-4-*Hydroxy*-1-*phenylhexan*-1-*one* **4a**. γ-Hydroxy ketone **4a** with 87% e.e. was synthesized by the reaction of keto aldehyde **2a** and Et_2Zn using (1*S*,2*R*)-DBNE **1** (12 mol%) as chiral catalyst (Table 1, entry 2 and Table 2, entry 1) in 52% yield; $\delta_H(CDCl_3)$ 0.8–1.17 (3 H, m), 1.30–2.13 (2 H, t), 3.00–3.33 (2 H, t), 3.33–3.77 (1 H, m) and 7.20–8.13 (5 H, m); ν_{max}(neat)/cm^{-1} 3450, 3080 and 1700 (Found: *m*/*z* 192.1143. Calc. for $C_{12}H_{16}O_2$: *M*, 192.1151); $[\alpha]_D^{29}$ +23.1 (*c* 2.17 in $CHCl_3$) for 87% e.e. The e.e. was determined by HPLC analysis of the corresponding (*S*)-MTPA ester using a chiral column (Daicel Chiralcel OD, 4.6 × 250 mm, 254 nm UV detector). Eluent 5% propan-2-ol in hexane; flow rate 1.0 cm^3 min^{-1}, retention time (t_R/min), 15.8 for minor peak, 19.0 for major peak.

(+)-4-*Hydroxy*-1-(p-*tolyl*)*hexan*-1-*one* **4b**. γ-Hydroxy ketone **4b** with 85% e.e. was synthesized by the reaction of keto aldehyde **2b** and Et_2Zn using (1*S*,2*R*)-DBNE **1** (12 mol%) as chiral catalyst (Table 3, entry 2) in 30% yield; $\delta_H(CDCl_3)$ 0.83–1.17 (3 H, m), 1.17–2.13 (5 H, m), 2.30–2.50 (3 H, m), 2.93–3.30 (2 H, m) and 7.07–8.00 (4 H, m); $\nu_{max}(CCl_4)/cm^{-1}$ 3450, 1720, 1680 and 1610 (Found: *m*/*z* 206.1310. Calc. for $C_{13}H_{18}O_2$: *M*, 206.1307); $[\alpha]_D^{24}$ +22.9 (*c* 2.53 in $CHCl_3$) for 85% e.e. The e.e. was determined by HPLC analysis of the corresponding (*S*)-MTPA ester using a chiral column (Daicel Chiralcel OD, 4.6 × 250 mm, 254 nm UV detector). Eluent 1% propan-2-ol in hexane; flow rate 0.5 cm^3 min^{-1}; retention time (t_R/min), 26.6 for minor peak, 32.7 for major peak.

(+)-6-*Hydroxy*-1-*phenyloctan*-3-*one* **4c**. γ-Hydroxy ketone **4c** with 81% e.e. was synthesized by the reaction of keto aldehyde **2c** and Et_2Zn using (1*S*,2*R*)-DBNE **1** (12 mol%) as chiral catalyst (Table 3, entry 3) in 47% yield; $\delta_H(CDCl_3)$

0.73–1.13 (3 H, m), 1.13–2.20 (7 H, m), 2.40–3.50 (5 H, m) and 6.97–7.37 (5 H, m); $\nu_{max}(CCl_4)$ 3450, 3030 and 1720 (Found: *m/z* 220.1464. Calc. for $C_{14}H_{20}O_2$: *M*, 220.1464); $[\alpha]_D^{30}$ +16.0 (*c* 1.63 in $CHCl_3$) for 81% e.e. The e.e. was determined by HPLC analysis of the corresponding (*S*)-MTPA ester using a chiral column (Daicel Chiralcel OD, 4.6 × 250 mm, 254 nm UV detector). Eluent 5% propan-2-ol in hexane; flow rate 1.0 cm^3 min^{-1}, retention time (t_R/min), 9.1 for minor peak, 11.3 for major peak.

(−)-2,6-*Dichloro*-4-(1-*hydroxypropyl*)*phenyl*(*phenyl*)*methanone* **4d** (*Table* 4, *entry* 2). Hydroxy ketone **4d** with 88% e.e. was synthesized by the reaction of keto aldehyde **2d** and Et_2Zn using (*S*)-DPMPM **5** (8 mol%) as chiral catalyst (Table 4, entry 2) in 100% yield; $\delta_H(CDCl_3)$ 0.83–1.20 (3 H, t), 1.47–2.23 (3 H, m), 4.87–5.33 (1 H, m) and 7.24–8.93 (7 H, m); ν_{max}(neat)/cm^{-1} 3370, 3020, 2920 and 1660 (Found: *m/z* 308.0378. Calc. for $C_{16}H_{14}Cl_2O_2$; *M*, 308.0372); $[\alpha]_D^{21}$ −34.9 (*c* 2.02 in $CHCl_3$) for 88% e.e. The e.e. was determined by HPLC analysis using a chiral column (Daicel Chiralcel OD, 4.6 × 250 mm, 254 nm UV detector). Eluent 5% propan-2-ol in hexane; flow rate 1.0 cm^3 min^{-1}; retention time (t_R/min), 11.7 for minor peak, 15.8 for major peak.

(−)-4-(1-*Hydroxyethyl*)*phenyl*(*phenyl*)*methanone* **4f** (*Table* 5, *entry* 4). Hydroxy ketone **4f** was synthesized using Me_2Zn in a similar manner (but using 4.4 mol equiv. of Me_2Zn) as for hydroxy ketone **4e** (Table 5, entry 1) in 82% yield, 87% e.e.; $\delta_H(CDCl_3)$ 1.40–1.67 (3 H, d), 2.76–3.17 (1 H, br s), 4.67–5.10 (1 H, m) and 7.17–7.90 (9 H, m); ν_{max}(neat)/cm^{-1} 3420, 3050, 2975, 1660 and 1610 (Found: *m/z* 226.0994. Calc. for $C_{15}H_{14}O_2$: *M*, 226.0994); $[\alpha]_D^{29}$ −23.5 (*c* 2.2 in $CHCl_3$) for 87% e.e. The e.e. was determined by HPLC analysis of the corresponding (*S*)-MTPA ester using a chiral column (Daicel Chiralcel OD, 4.6 × 250 mm, 254 nm UV detector). Eluent 3% propan-2-ol in hexane; flow rate 0.5 cm^3 min^{-1}, retention time (t_R/min), 28.5 for minor peak, 32.1 for major peak.

(−)-4-(1-*Hydroxypentyl*)*phenyl*(*phenyl*)*methanone* **4g** (*Table* 5, *entry* 6). Hydroxy ketone **4g** was synthesized using Bu_2Zn in a similar manner as for compound **4e** (Table 5, entry 1) in 64% yield, 92% e.e.; $\delta_H(CDCl_3)$ 0.78–1.07 (3 H, m), 2.30–2.57 (1 H, br s), 4.50–4.87 (1 H, m) and 7.17–7.87 (9 H, m); ν_{max}(neat)/cm^{-1} 3420, 3050, 2975, 1650 and 1600 (Found: *m/z* 268.1462. Calc. for $C_{18}H_{20}O_2$: *M*, 268.1764); $[\alpha]_D^{21}$ −8.28 (*c* 2.21 in $CHCl_3$) for 92% e.e. The e.e. was determined by HPLC analysis of the corresponding (*S*)-MTPA ester using a chiral column. Eluent 3% propan-2-ol in hexane; flow rate 1.0 cm^3 min^{-1}, retention time (t_R/min), 17.2 for minor peak, 19.3 for major peak.

(−)-4-(1-*Hydroxyhexyl*)*phenyl*(*phenyl*)*methanone* **4h** (*Table* 5, *entry* 8). Hydroxy ketone **4h** was synthesized using dipentylzinc in a similar manner as for compound **4e** (Table 5, entry 1) in 94% yield, 94% e.e.; $\delta_H(CDCl_3)$ 0.63–1.07 (3 H, m), 1.07–2.07 (8 H, m) 2.12–3.00 (1 H, br s), 4.58–4.98 (1 H, m) and 7.20–7.86 (9 H, m); ν_{max}(neat)/cm^{-1} 3420, 3050, 2930, 1660 and 1610 (Found: *m/z* 282.1613. Calc. for $C_{19}H_{22}O_2$: *M*, 282.1621); $[\alpha]_D^{23}$ −6.06 (*c* 2.2 in $CHCl_3$) for 94% e.e. The e.e. was determined by HPLC analysis of the corresponding (*S*)-MTPA ester using a chiral column (Daicel Chiralcel OD, 4.6 × 250 mm, 254 nm UV detector). Eluent 5% propan-2-ol in hexane; flow rate 0.5 cm^3 min^{-1}, retention time (t_R/min), 18.8 for minor peak, 21.0 for major peak.

(−)-4-(1-*Hydroxy*-4-*methylpentyl*)*phenyl*(*phenyl*)*methanone* **4i** (*Table* 5, *entry* 9). Hydroxy ketone **4i** was synthesized using bis(3-methylbutyl)zinc in a similar manner as for compound **4e** (Table 5, entry 1) in 100% yield, 95% e.e.; $\delta_H(CDCl_3)$ 0.68–1.07 (6 H, m), 1.07–2.05 (5 H, m), 2.43–2.70 (1 H, br s), 4.50–4.87 (1 H, m) and 7.13–7.88 (9 H, m); ν_{max}(neat)/cm^{-1} 3420, 3050, 2950, 1710, 1650 and 1605 (Found: *m/z* 282.1619. Calc. for $C_{19}H_{22}O_2$: *M*, 282.1621); $[\alpha]_D^{23}$ −6.14 (*c* 2.2 in $CHCl_3$) for 95% e.e. The e.e. was determined by HPLC analysis of the corresponding (*S*)-MTPA ester using a chiral column (Daicel Chiralcel OD, 4.6 × 250 mm, 254 nm UV detector). Eluent 1% propan-2-ol in hexane; flow rate 0.5 cm^3 min^{-1}, retention time (t_R/min), 29.7 for minor peak, 36.5 for major peak.

References

1 Reviews: R. W. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 489; D. A. Evans, J. V. Nelson and T. R. Taber, *Top. Stereochem.*, 1982, **13**, 1; C. H. Heathcock, in *Asymmetric Synthesis*, ed. J. D. Morrion, Academic Press, New York, 1984, vol. 3, p. 111; S. Masamune, W. Choy, J. S. Petersen and L. R. Sita, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 1; R. O. Duthaler and A. Hafner, *Chem. Rev.*, 1992, **92**, 807 and references cited therein.

2 D. Hoppe and O. Zschage, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 69.

3 H. Roder, G. Helmchen, E.-M. Peters, K. Peters and H.-G. von Schnering, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 898; V. J. Jephcote, A. J. Pratt and E. J. Thomas, *J. Chem. Soc., Chem. Commun.*, 1984, 800.

4 Review: I. Kuwajima and E. Nakamura, in *Comprehensive Organic Chemistry*, eds. B. M. Trost, I. Fleming and C. H. Heathcock, Pergamon Press, Oxford, 1991, vol. 2, ch. 1.14.

5 K. Soai, S. Yokoyama, T. Hayasaka and K. Ebihara, *Chem. Lett.*, 1988, 843.

6 Reviews: K. Nützel, *Methoden Org. Chem.* (*Houben-Weyl*), 1973, **13/2a**, 47; U. Schöllkopf, *Methoden Org. Chem.* (*Houben-Weyl*), 1970, **13/1**, 87.

7 Y. Okude, S. Hirano and H. Nozaki, *J. Am. Chem. Soc.*, 1977, **99**, 3179; Y. Yamamoto and J. Yamada, *J. Am. Chem. Soc.*, 1987, **109**, 4395; T. Kauffmann, C. Pahde and D. Wingbemuhle, *Tetrahedron Lett.*, 1982, **23**, 2301; 1985, **26**, 4059; M. Wada, M. Ohki and K. Akiba, *Tetrahedron Lett.*, 1986, **27**, 4771; K. Maruoka, Y. Araki and H. Yamamoto, *Tetrahedron Lett.*, 1988, **29**, 3101; M. T. Reetz, J. Westermann, R. Steinbach, B. Weneroth, R. Peter, R. Ostarek and S. Maus, *Chem. Ber.*, 1985, **118**, 1421.

8 K. Soai, M. Watanabe and M. Koyano, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 2124.

9 (*a*) K. Soai, S. Yokoyama, K. Ebihara and T. Hayasaka, *J. Chem. Soc., Chem. Commun.*, 1987, 1980; K. Soai, S. Yokoyama, T. Hayasaka and K. Ebihara, *J. Org. Chem.*, 1988, **53**, 4148; (*b*) K. Soai, A. Ookawa, K. Ogawa and T. Kaba, *J. Chem. Soc., Chem. Commun.*, 1987, 467; K. Soai, A. Ookawa, T. Kaba and K. Ogawa, *J. Am. Chem. Soc.*, 1987, **109**, 7111.

10 K. Soai and M. Watanabe, *J. Chem. Soc., Chem. Commun.*, 1990, 43.

11 K. Soai, S. Niwa, Y. Yamada and H. Inoue, *Tetrahedron Lett.*, 1987, **28**, 4841; S. Niwa and K. Soai, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2717.

12 Reviews: D. A. Evans, *Science*, 1988, **240**, 420; R. Noyori and M. Kitamura, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 49; K. Soai and S. Niwa, *Chem. Rev.*, 1992, **92**, 833 and references cited therein.

13 Preliminary communication: K. Soai, M. Watanabe and M. Koyano, *J. Chem. Soc., Chem. Commun.*, 1989, 534.

14 J. A. Dale, D. L. Dull and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543.

15 L. R. Noller, *Org. Synth.*, 1966, Coll. Vol. II, 184.

16 T. Sato, T. Kawara and T. Fujisawa, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 505.

17 S. V. Lieberman and R. Connor, *Org. Synth.*, 1966, Coll. Vol. 2, 441.

Paper 4/03731F
Received 20*th June* 1994
Accepted 5*th July* 1994