Kinetic Resolution of Racemic Aldehydes by Enantioselective Alkylation

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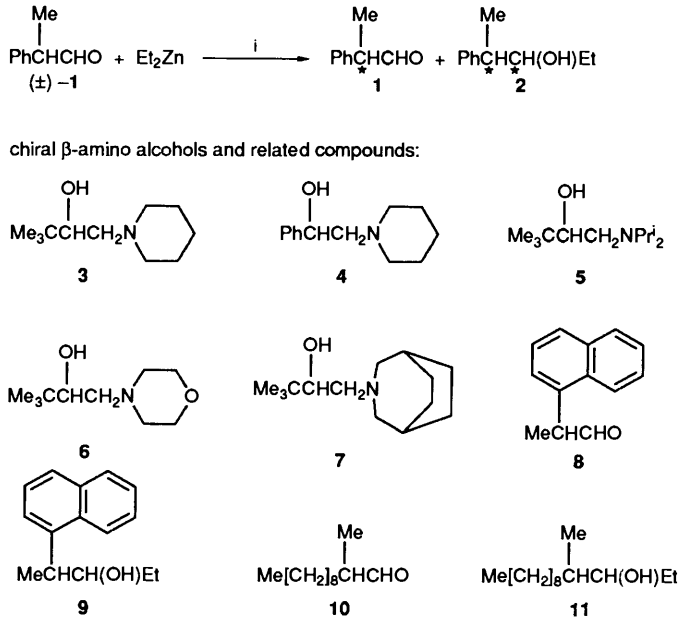
Various types of racemic aldehydes were kinetically resolved by reaction with diethylzinc in the presence of a catalytic amount of a chiral β-amino alcohol. Kinetic resolution of racemic chloro(phenyl)acetaldehyde gave an optically active form as an unchanged substrate, which could be converted into styrene oxide in high optical purity (97.5% ee).

Kinetic resolution of racemic compounds is now recognized as one of the indispensable methods for obtaining optically active compounds,[1] and recently several successful such resolutions using organometallics have been reported.[2]

On the other hand, the catalytic asymmetric alkylation of aldehydes with dialkylzincs was discovered by us and has been intensively investigated by many researchers since.[3] However, there was no report on the kinetic resolution of racemic aldehydes by catalytic asymmetric alkylation.† Here we want to describe the first successful example of kinetic resolution of racemic aldehydes based on enantioselective ethylation catalysed by a small amount of chiral β-amino alcohols.[5]

Results and Discussion

Kinetic Resolution of Racemic 2-Phenylpropanal **1**.—We first examined the reaction of racemic 2-phenylpropanal **1** with diethylzinc catalysed by chiral β-amino alcohols (Scheme 1). After screening various reaction conditions, the reaction in hexane at −20 °C was found to be most suitable to achieve efficient kinetic resolution, as can be seen from the results in entries 1–10 in Table 1, with chiral catalyst **3**.



Scheme 1 *Reagents and conditions:* i, 1–5 mol% chiral β-amino alcohol, −30 to +17 °C, 13–69 h

Under the aforementioned best reaction condition, a variety of chiral β-amino alcohols were used as catalysts, and the obtained results are summarized in Table 1. It can be seen from Table 1 that the k_f/k_s-value ($=k_{rel}$)[6] is highly dependent on the kind of chiral β-amino alcohols used, where k_f and k_s represent the fast and slow ethylation rates of the two enantiomers, respectively. Efficient kinetic resolution was realized by use of the chiral β-amino alcohols with a t-butyl group at the carbon atom bonded to the hydroxy group. The catalyst **4**, bearing a phenyl group instead of the t-butyl group in **3**, gave only a low k_f/k_s-value (1.3). The type of *N*-substitute also had an important effect in obtaining high k_f/k_s-values. For example, the reaction with 2 mol % of (*R*)-1-(diisopropylamino)-3,3-dimethylbutan-2-ol **5** gave (*S*)-2-phenylpropanal **1** of 85.7% ee as unchanged aldehyde at 69.8% conversion (k_f/k_s 5.4), whereas the reactions catalysed by chiral β-amino alcohols with morpholino or 3-azabicyclo[3.2.2]nonan-3-yl substituents (compound **6** or **7**) showed only a low level of enantiomer discrimination (k_f/k_s 1.5–1.6). The optical purity of recovered aldehyde **1** was determined by HPLC analysis of the corresponding 3,5-dinitrophenylcarbamate of 2-phenylpropanol obtainable after reduction with $LiAlH_4$. The stereochemical outcome was as follows. When we used the *R*-configurational β-amino alcohols, the faster reacting enantiomer was always *R* (*i.e.*, *S*-enriched aldehyde was recovered). The absolute configuration was determined by comparison of the rotation values with those in the literature.[7]

Determination of the Stereochemistry of Ethylated Product **2**.—In order to assign the stereochemistry of the isomers of 2-phenylpentan-3-ol **2** which were produced by kinetic resolution of 2-phenylpropanal **1**, we first examined the reaction of racemic 2-phenylpropanal **1** with diethylzinc using racemic 1-(diisopropylamino)-3,3-dimethylbutan-2-ol **5** as catalyst in hexane at −20 °C. After completion of the reaction, the racemic product **2** was treated with 3,5-dinitrophenyl isocyanate and pyridine to afford the corresponding 3,5-dinitrophenylcarbamate, and this carbamate was analysed by HPLC using a chiral stationary phase (column, Sumitomo Chemical Co. SUMIPAX OA 4000). Four peaks could be observed in the proportions 43:43:7:7 in order of retention time (abbreviated as peaks A, B, C and D). This selectivity could be explained by Cram's rule; that is, (2*R*,3*R*)- and (2*S*,3*S*)-isomer could be produced overwhelmingly more than were the (2*R*,3*S*)- and (2*S*,3*R*)-isomer. We then used *S*-enriched (86% ee) 2-phenylpropanal as a substrate and racemic **3** as catalyst, and the optically active alcohol **2** thus obtained was analysed in a similar manner (HPLC) as described above. The proportions of the peak intensities in this case were 75:7:17:1. Based on these results, the four peaks A, B, C and D could be assigned to the stereoisomers which correspond to (2*S*,3*S*)-, (2*R*,3*R*)-, (2*S*,3*R*)- and (2*R*,3*S*)-2-phenylpentan-3-ol, respectively. Based on this assignment, it was found that when β-amino alcohols with the *R* configuration were used (2*R*,3*R*)-2-phenylpentan-3-ol was obtained as the main product, and the proportions of the stereoisomers

† Very recently, the kinetic resolution of diene aldehydes' $Fe(CO)_3$ derivatives by asymmetric allylboration was reported (see ref. 4).

Table 1 Kinetic resolution of racemic 2-phenylpropanal **1** by enantioselective ethylation catalysed by chiral β-amino alcohols

		Conditions			Unchanged aldehyde			
Entry	Chiral catalyst (mol %)	Solvent	Temp (T/°C)	Time (t/h)	% Conversion[a]	% ee[b]	Config.[c]	k_f/k_s[d]
1	(*R*)-(−)**3** (2)	Hexane	0	13	84.5	90.6	*S*	3.5
2	(*R*)-(−)**3** (2)	Hexane	−10	20	70.6	69.5	*S*	3.5
3	(*R*)-(−)**3** (2)	Hexane	−20	16	71.0	77.3	*S*	4.1
4	(*R*)-(−)**3** (2)	Hexane	−30	68	59.3	52.2	*S*	3.4
5	(*R*)-(−)**3** (1)	Hexane	−20	24	61.2	33.3	*S*	2.1
6	(*R*)-(−)**3** (3)	Hexane	−20	19	66.8	49.5	*S*	2.5
7	(*R*)-(−)**3** (5)	Hexane	−20	17	77.9	31.2	*S*	1.5
8	(*R*)-(−)**3** (2)	Et_2O	17	20	72.3	21.0	*S*	1.4
9	(*R*)-(−)**3** (2)	Et_2O	−20	69	56.8	37.4	*S*	2.5
10	(*R*)-(−)**3** (2)	Toluene	−20	52	58.0	47.1	*S*	3.1
11	(*R*)-(+)**4** (2)	Hexane	−20	48	60.0	11.2	*S*	1.3
12	(*R*)-(−)**5** (2)	Hexane	−20	16	69.8	85.7	*S*	5.4
13	(*R*)-(−)**6** (2)	Hexane	−20	40	72.6	30.7	*S*	1.6
14	(*R*)-(−)**7** (2)	Hexane	−20	40	69.5	23.4	*S*	1.5

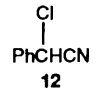
[a] Determined by GLC analysis using naphthalene as internal standard. [b] HPLC analysis. [c] Ref. 7. [d] Calculated by Kagan's equation.[6]

Table 2 Kinetic resolution of racemic aldehydes by enantioselective ethylation catalysed by chiral β-amino alcohols[a]

					Unchanged aldehyde		
Entry	Aldehyde	Chiral catalyst	Solvent	Time (t/h)	% Conversion[b]	% ee[c]	k_f/k_s[d]
1	(±)-**8**	(*R*)-(−)-**3**	Hexane	48	52.8	47.2	3.8
2	(±)-**8**	(*R*)-(−)-**5**	Hexane	48	63.9	74.7	5.2
3	(±)-**10**	(*R*)-(−)-**3**	Hexane	16	87.7	48.2[e]	1.6
4	(±)-**10**	(*R*)-(−)-**5**	Hexane	16	78.1	70.8[e]	2.8
5	(±)-**13**	(*R*)-(−)-**3**	Toluene	30	61[f]	82.2	7.8
6	(±)-**13**	(*R*)-(−)-**3**	Toluene	60	75[f]	98.2	7.7
7	(±)-**13**	(*R*)-(−)-**5**	Toluene	30	58[f]	18.2	1.5
8	(±)-**13**	(*R*)-(−)-**3**	Et_2O	60	62[f]	56.7	3.5

[a] All reactions were carried out at −20 °C using diethylzinc (1.1 mol equiv.) and 2 mol% (*R*)-(−)-β-amino alcohol (>99% ee) per mol of aldehyde under argon. [b] GLC analysis unless otherwise noted. [c] HPLC analysis unless otherwise noted. [d] Calculated by Kagan's equation.[6] [e] ^1H NMR analysis of its MPTA ester after reduction. [f] Determined by isolated yield after silica gel column chromatography. Isolated yield (%) of unchanged aldehyde **13**, ethylated product **14**, reductive product **15** was 39, 28, 29 (entry 5); 25, 36, 37 (entry 6); 42, 34, 21 (entry 7) and 38, 28, 28 (entry 8), respectively.

(2*S*,3*S*):(2*R*,3*R*):(2*S*,3*R*):(2*R*,3*S*) were 6:69:25:0 at 70% conversion.



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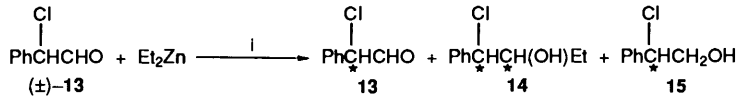
Kinetic Resolution of Racemic 2-(α-*Naphthyl*)*propanal* **8**, 2-*Methylundecanal* **10**, *and Chloro*(*phenyl*)*acetaldehyde* **13**.—The above kinetic resolution method could be also applied to other aldehydes such as 2-(α-naphthyl)propanal **8**, 2-methylundecanal **10** and chloro(phenyl)acetaldehyde **13**. For the kinetic resolution of racemic aldehydes **8** and **10**, chiral β-amino alcohol **5** with the diisopropylamino group served as an effective catalyst, in which reaction k_f/k_s-values were 5.2 and 2.8, respectively (entries 2 and 4 in Table 2). In the kinetic resolution of racemic chloro(phenyl)acetaldehyde **13**, toluene or diethyl ether was used as solvent because compound **13** was insoluble in hexane, and also the reaction with diethylzinc did not take place in hexane. In the reaction performed with 1.1 mol equiv. of diethylzinc at −20 °C for 30 h, 39% of starting aldehyde **13** could be recovered in 88.2% ee, and for 60 h, 25% of the aldehyde in 98.2% ee. From these results, enantioselection was calculated to be k_f/k_s 7.8 for the reaction of racemic aldehyde **13** (see entries 5 and 6 in Table 2). It should be noted that in the reaction of aldehyde **13** with diethylzinc, not only the ethylated product **14** but also the reduction product **15** was obtained (Scheme 2). The reduction of aldehyde **13** with diethylzinc may occur *via* β-hydride transfer in the ethyl group (Fig. 1). The ratios of ethylated product to reduction product were almost equal for both toluene and diethyl ether as solvent, though k_f/k_s in diethyl ether (3.5) was lower than that in toluene (entry 8 in Table 2). Unchanged optically active chloro(phenyl)-acetaldehyde **13** was converted into optically active styrene oxide according to the route shown in Scheme 3. Resolved aldehyde **13** (98.2% ee at 75% conversion) was treated with borane–dimethyl sulphide complex to afford the chlorohydrin, followed by treatment with sodium hydride to give styrene oxide **16** (97.5% ee) in 78% yield from the resolved substrate **13**. The ee was calculated based upon the reported optical rotation values.[8] The styrene oxide obtained possessed the *R* configuration; therefore, the absolute configuration of the recovered aldehyde was determined as *S*.

Stereochemistry and Reaction Mechanism.—When we used *R*-β-amino alcohols in the kinetic resolution of racemic aldehyde **1**, the *R*-enantiomer reacted faster than the *S* one, so that the *S*-enriched aldehyde was recovered. The newly produced asymmetric centre, formed by addition of the ethyl group, also had the *R* configuration. These stereochemical properties can be explained by considering the reaction intermediates described in Fig. 2. Enantioselective ethylation will proceed *via* a dinuclear zinc complex, and the chirality of the 5/4-fused bicyclic intermediates will determine the chirality of the alcoholic products. Thus, dinuclear intermediates possessing an



Scheme 2 *Reagents and conditions:* i, 2 mol% chiral β-amino alcohol, −20 °C, 16–60 h

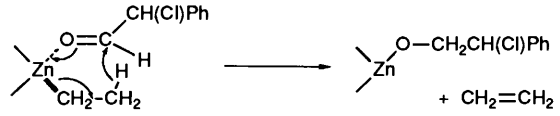
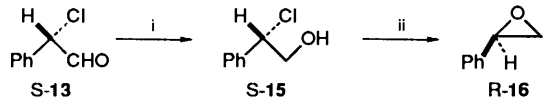


Fig. 1



Scheme 3 *Reagents and conditions:* i, BH_3·SMe_2 (1.2 mol equiv.), Et_2O, 18 °C, 2 h; ii, NaH (1.3 mol equiv.), DMF, 18 °C, 3 h

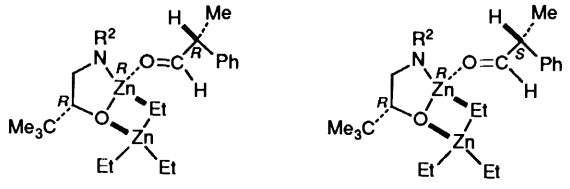


Fig. 2

R configurational Zn atom would lead to the *R* products.* It would be reasonable to assume that the intermediate **17** is more preferable in comparison with stereoisomer **18**, because an ethyl group in structure **17** can attack from the less hindered side of the carbonyl group, a situation which does not pertain in **18**. This is the origin of the enantiomeric discrimination in the kinetic resolution of racemic aldehydes.

In conclusion, kinetic resolution of racemic aldehydes proceeded by enantioselective ethylation catalysed by a small amount of a chiral β-amino alcohol, thus providing a novel method for the preparation of optically active aldehydes.

Experimental

General.—^{1}H NMR spectra were measured on a Hitachi R-250 Fourier Transfer NMR spectrometer (250 MHz) with [^{2}H]chloroform as solvent and recorded in ppm relative to internal tetramethylsilane standard. *J*-Values are given in Hz. Optical rotations were measured on a JASCO DIP-4 digital polarimeter for solutions in a 5 dm cell. Preparative column chromatography was carried out on a Wacogel-200 column. HPLC analyses were carried out on a JASCO 880-PU liquid chromatograph with a JASCO UVIDEC 100 UV detector. GLC was performed on a Hitachi 263-30 instrument using a PEG 6000 column.

Materials.—Toluene, hexane and diethyl ether for kinetic resolution were distilled from sodium benzophenone ketyl under argon and degassed before use. Diethylzinc was kindly donated by Tosoh Akzo Co. Racemic 2-phenylpropanal **1** and 2-methylundecanal **10** were purchased from Aldrich and distilled before use. Racemic 2-(α-naphthylpropanal **8** was prepared according to the reported method.[9] (*R*)-1-(Dialkylamino)-3,3-dimethylbutan-2-ols (compounds **3**, **5**, **6** and **7**) were prepared by the reaction of (*R*)-t-butylethylene oxide with a bromomagnesium dialkylamide,[3c,10] and (*S*)-2-phenyl-1-piperidinobutan-2-ol **4** was prepared by the reported method.[11]

Kinetic Resolution of Racemic 2-Phenylpropanal **1** (*Entry* 12 *in Table* 1).—In a flame-dried Schlenk tube were placed (*R*)-1-(diisopropylamino)-3,3-dimethylbutan-2-ol **5** (30 mg, 0.15 mmol), naphthalene (100 mg), and dry hexane (15 cm^3). The mixture was degassed and converted with argon. To this solution at 0 °C was added diethylzinc (0.84 cm^3, 8.2 mmol), and the resulting solution was stirred at 17 °C for 30 min. After the mixture had been cooled to −20 °C, 2-phenylpropanal **1** (1.0 g, 7.45 mmol) was added, and the mixture was stirred at this temperature and monitored by GLC. After 16 h, the solution was quenched by 10% aq. HCl (20 cm^3). Conversion was determined as 69.8% by GLC analysis. Retention times t_R: naphthalene, 4 min; 2-phenylpropanal **1**, 5 min; 2-phenylpentan-3-ol **2**, 7.3 min. The usual extraction with diethyl ether (50 cm^3 × 3), followed by separation by silica gel column chromatography [eluent hexane–ethyl acetate (12:1)], gave unchanged aldehyde **1** (285 mg, 28.5% recovery) and ethylated product **2** (831 mg, 68%). Unchanged aldehyde was further purified by distillation (b.p. 85–88 °C/10 mmHg) (240 mg, 24%); $[\alpha]_D^{24}$ +197.4° (*c* 1.5, $CHCl_3$).

Determination of Optical Purity of Unchanged 2-Phenylpropanal **1**.—Kinetically resolved aldehyde **1** (100 mg, 0.75 mmol) was reduced with $LiAlH_4$ (28 mg, 0.74 mmol) in diethyl ether (5 cm^3) to give 2-phenylpropanol (100 mg, 99%). The ee of the unchanged aldehyde was determined as 85.7% by HPLC analysis of the corresponding 3,5-dinitrophenylcarbamate, using a column of SUMIPAX OA 4000 (Sumitomo Chemical Co.). The procedure for the preparation of the carbamate was as follows: 3,5-dinitrophenyl isocyanate (20 mg) and pyridine (5 mm^3) were added to a toluene solution (0.5 cm^3) of 2-phenylpropanol (10 mg). After being vigorously stirred for 30 min at 20 °C, an aliquot (2 mm^3) of the reaction mixture containing the 3,5-dinitrophenylcarbamate was analysed by HPLC; t_R of *R*-carbamate, 28 min; t_R of *S*-carbamate, 26 min [eluent hexane–ethanol (97:3), 1.0 cm^3 min^{-1}].

Kinetic Resolution of Racemic 2-(α-Naphthyl)propanal **8** (*Entry* 2 *in Table* 2).—Kinetic resolution as described for aldehyde **1** was performed, in this case, in hexane (10 cm^3) with compound **5** (22 mg, 0.108 mmol), naphthalene (100 mg), diethylzinc (0.61 cm^3, 5.97 mmol) and 2-(α-naphthyl)propanal **8** (1.0 g, 5.43 mmol) at −20 °C for 48 h (63.9% conversion by GLC analysis). After work-up, evaporation of volatiles provided an oil, which was subjected to silica gel column chromatography [eluent hexane–ethyl acetate (12:1)] to give unchanged aldehyde **8** (340 mg, 34% recovery) and ethylated product **9** (721 mg, 62%). The ee of the recovered aldehyde was determined as 74.7% by HPLC analysis using a column of CHIRAL-CEL OD [eluent hexane–propan-2-ol (10:1), 1.0 cm^3 min^{-1}] after reduction with $LiAlH_4$; t_R 14 min (major isomer), 17 min (minor isomer). Absolute configuration was not determined.

Kinetic Resolution of 2-Methylundecanal **10** (*Entry* 4 *in Table* 2).—Kinetic resolution as described for aldehyde **1** was performed, in this case, in hexane (10 cm^3) with compound **5** (33 mg, 0.163 mmol), naphthalene (150 mg), diethylzinc (1 cm^3,

* The mechanism of asymmetric induction was discussed by Noyori *et al.* See refs. 3*b*, 3*c*.

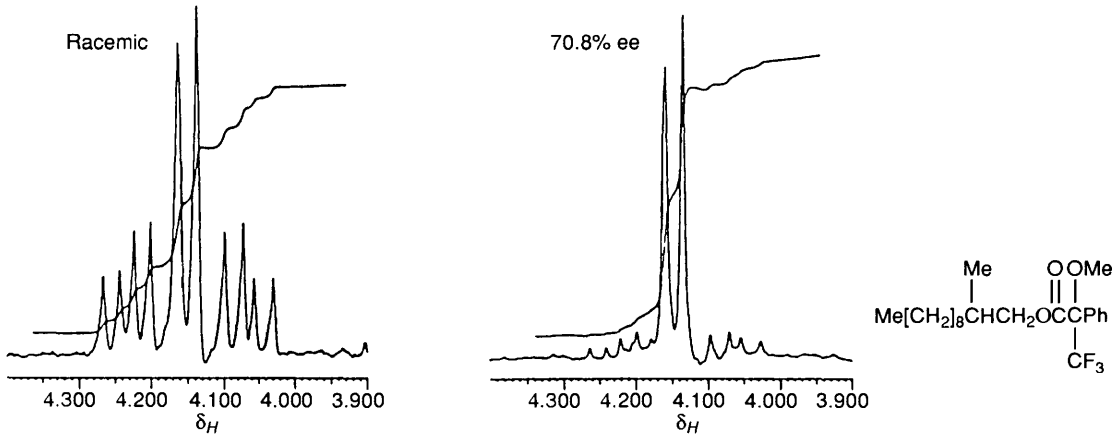


Fig. 3 ^{1}H NMR spectra of MTPA esters of 2-methylundecanol; racemic (left) and 70.8% ee (right)

9.77 mmol) and 2-methylundecanal **10** (1.50 g, 8.14 mmol) at −20 °C for 16 h. After work-up, evaporation of volatiles provided an oil, which was subjected to silica gel column chromatography [eluent hexane–ethyl acetate (5:1)] to give the unchanged aldehyde **10** (0.29 g, 19.3% recovery) {$[\alpha]_D^{25}$ +11.6° (*c* 1.0, $CHCl_3$)} and ethylated product **11** (1.34 g, 77%). The ee of recovered aldehyde **10** was determined as follows. To a mixture of $LiAlH_4$ (10 mg) and diethyl ether (5 cm^3) was added resolved **10** (20 mg) and the mixture was stirred at 18 °C for 1 h. Then water (3 cm^3) and 10% aq. HCl (5 cm^3) were added to the mixture at 0 °C. After extraction with diethyl ether (20 cm^3 × 2), the combined extract was concentrated to give 2-methylundecanol (18 mg), $\delta_H(CDCl_3)$ 0.9–1.0 (9 H, m), 1.27 (16 H, br s), 1.4–1.5 (3 H, m), 1.6 (1 H, br s) and 3.3–3.5 (1 H, m). Without further purification this alcohol was esterified by (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPACl). To a mixture of 2-methylundecanol (10 mg) and CH_2Cl_2 (1 cm^3) were added MTPACl (15 mg), pyridine (10 mg) and 4-dimethylaminopyridine (10 mg). The mixture was stored for 5 h at room temperature, treated with saturated aq. NaCl (5 cm^3) and extracted with diethyl ether (20 cm^3 × 2). Silica gel column chromatography [eluent hexane–ethyl acetate (15:1)] gave the corresponding MTPA ester. The ee of the product was determined as 70.8% by integration of methylene proton signals in the ^{1}H NMR spectrum of the MTPA ester (Fig. 3).

Chloro(phenyl)acetonitrile **12**.[12] To a solution of benzaldehyde (2.0 g, 18.8 mmol) in dichloromethane (30 cm^3) at 0 °C was added titanium(IV) chloride (2.5 cm^3, 22.6 mmol) *via* syringe and the mixture was stirred for 30 min. Then trimethylsilyl cyanide (1.9 g, 18.8 mmol) was added to the mixture at 0 °C. After being stirred for 24 h at room temperature, the resulting mixture was poured into ice–water (100 cm^3) and the organic layer was extracted with diethyl ether (80 cm^3 × 3). The combined extract was washed successively with saturated aq. $NaHCO_3$ (20 cm^3 × 2) and brine (20 cm^3 × 2), and dried (Na_2SO_4). After removal of the solvent, the crude product was purified by distillation (2.8 g, 98%), b.p. 115–118 °C/1 mmHg; $\delta_H(CDCl_3)$ 5.59 (3 H, s) and 7.5–8.0 (5 H, m).

Chloro(phenyl)acetaldehyde **13**.†—To a solution of chloro(phenyl)acetonitrile **12** (7.0 g, 46.2 mmol) in hexane (100 cm^3) at −45 °C was added diisobutylaluminium hydride (DIBAL-H) (8.23 cm^3, 46.2 mmol) dropwise *via* syringe during 10 min. After being stirred for 3 h at −45 °C, the mixture was warmed up to 0 °C and stirred for 3 h. The reaction mixture was then poured into a mixture of saturated aq. NH_4Cl (100 cm^3) and diethyl ether (50 cm^3). Then 5% aq. H_2SO_4 (100 cm^3) was added and the mixture was stirred for 20 min. The organic layer was extracted with diethyl ether (150 cm^3 × 2), and the combined extract was washed with brine (50 cm^3 × 2). After removal of the solvent, the crude product was distilled to give chloro(phenyl)acetaldehyde **13** (5.1 g, 71%, b.p. 65–67 °C/2 mmHg; $\delta_H(CDCl_3)$ 5.21 (1 H, d, *J* 2.7), 7.3–7.4 (5 H, m) and 9.52 (1 H, d, *J* 2.7).

Kinetic Resolution of Racemic Chloro(phenyl)acetaldehyde **13** (*Entry* 5 *in Table* 2).—Kinetic resolution as described for aldehyde **1** was performed, in this case, with toluene (12 cm^3), compound **3** (24 mg, 0.129 mmol), diethylzinc (0.73 cm^3, 7.12 mmol) and chloro(phenyl)acetaldehyde **13** (1.0 g, 6.47 mmol) at −20 °C for 30 h. After work-up, evaporation of volatiles provided an oil, which was subjected to silica gel column chromatography [eluent hexane–diethyl ether (2:1)] to afford unchanged aldehyde **13** (390 mg, 39% recovery; 82.2% ee), ethylated product **14** (334 mg, 28%), and reductive product **15** (294 mg, 29%). Optical purity of recovered **13** was determined by HPLC analysis of the corresponding 3,5-dinitrophenylcarbamate after reduction with borane–dimethyl sulphide complex; t_R of *R*-carbamate, 39 min; t_R of *S*-carbamate, 33 min [column Sumipax OA 4000, Sumitomo Chemical Co.; eluent hexane–ethanol (97:3), 1.0 cm^3 min^{-1}].

(*R*)-*Styrene Oxide* **16**.—To a solution of resolved aldehyde **13** (400 mg, 2.59 mmol) in diethyl ether (3 cm^3) at 0 °C was added borane–dimethyl sulphide complex (0.29 cm^3, 3.10 mmol). After being stirred for 2 h at 18 °C the mixture was treated with water (3 cm^3) and stirred for another 30 min. Then 3 mol dm^{-3} aq. sodium hydroxide (5 cm^3) was added, the mixture was extracted with diethyl ether (10 cm^3 × 3), and the extract was dried (Na_2SO_4). Evaporation of the solvent gave crude 2-chloro-2-phenylethanol **15** (380 mg). The alcohol **15** was used in the next step without further purification.

To sodium hydride (38 mg, 1.60 mmol) were added dimethylformamide (2 cm^3) and the alcohol **15** (200 mg, 1.28 mmol) dropwise. After the mixture had been stirred for 3 h, saturated aq. NaCl was added. After extraction of the product with diethyl ether (20 cm^3 × 3) and evaporation of the extract, isolation was carried out by molecular distillation (88–92 °C/23 mmHg) to afford *R*-styrene oxide **16** [218 mg, 72% from resolved chloro(phenyl)acetaldehyde **13**], $[\alpha]_D^{25}$ −21.9° (*c* 0.5, $CHCl_3$) {lit.,[8] $[\alpha]_D$ −22.5° ($CHCl_3$)}; $\delta_H(CDCl_3)$ 2.81 (1 H, dd, *J*

† Chloro(phenyl)acetaldehyde **13** was reported to be prepared by reaction of phenylacetaldehyde and sulphuryl dichloride in dichloromethane in 60% yield,[13] but in our experience the reduction of compound **12** with DIBAL-H gave better results with regard to chemical yield.

5.5 and 2.4), 3.15 (1 H, dd, *J* 5.5 and 3.7), 3.87 (1 H, dd, *J* 2.4 and 3.9) and 7.3–7.4 (5 H, m).

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Paper 0/04215C
Received 17*th September* 1990
Accepted 27*th November* 1990