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Lithium Aluminum Hydride Partially Decomposed with (−)-*N*-Methylephedrine and 2-Alkylaminopyridine: An Improved Chiral Hydride Useful for the Practical Asymmetric Reduction of Achiral Cyclic Ketones[1)]

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The title chiral hydride was found to reduce various achiral cyclic ketones, giving the corresponding optically active cyclic (*R*)-alcohols in high optical (73—98% ee) yields. The development of the improved chiral hydride and some characteristics of the reagent are also described.

Keywords——asymmetric reduction; lithium aluminum hydride; (−)-*N*-methylephedrine; 2-alkylaminopyridine; 2-cyclohexen-1-one; achiral cyclic ketone; optically active cyclic alcohol

The asymmetric reduction of achiral ketones with chiral hydrides has been extensively studied in recent years,[2)] and high optical yields have been realized in the asymmetric reduction of achiral open-chain ketones.[3–5)] However, the number of chiral hydrides which can produce highly optically active cyclic alcohols from achiral cyclic ketones such as 2-cyclohexen-1-one and α- or β-tetralone seems to be quite limited,[4d,6,7)] despite the usefulness of these optically active compounds as starting materials in natural product synthesis.[10)]

Previously, it was reported that lithium aluminum hydride (LAH) partially decomposed with (1*R*,2*S*)-(−)-*N*-methylephedrine [(−)-*N*-methylephedrine] and *N*-ethylaniline serves as an excellent chiral hydride, affording optically active open-chain alcohols from achiral open-chain ketones.[5)] Since this reagent was less effective for achiral cyclic ketones,[5b,c)] an efficient chiral hydride was sought which could be utilized for practical asymmetric synthesis of optically active cyclic alcohols from the corresponding cyclic ketones.

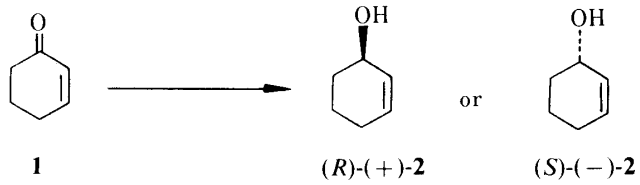
We have now found that the chiral hydride reagent prepared by modifying LAH with (−)-*N*-methylephedrine and 2-alkylaminopyridine can reduce achiral cyclic ketones to give the corresponding optically active alcohols in high optical (max. 98% ee) yields.[11)]

This report deals with the development of the improved chiral hydride, studies performed to optimize the reagent and the reduction conditions, application of the reagent to the asymmetric reduction of various types of achiral cyclic ketones, and comparison of the chiral hydride with that previously prepared by the use of *N*-ethylaniline as an additive.[5)]

Results and Discussion

The chiral hydride which can be prepared by partially decomposing LAH with (−)-*N*-methylephedrine and *N*-ethylaniline, has been reported to reduce 2-cyclohexen-1-one (**1**) to afford (*S*)-(−)-2-cyclohexen-1-ol ((*S*)-(−)-**2**) in 45% optical and 58% chemical yields.[5b,c)] Therefore, the development of a more effective chiral LAH for the asymmetric reduction of achiral cyclic ketones was examined by employing **1** and (−)-*N*-methylephedrine as a reduction substrate and a chiral source, respectively. Various *N*-ethylaniline derivatives which

had not been employed in the previous studies,[5b,c] were first chosen as achiral additives to replace two of the four hydrides of LAH. These studies were performed in the expectation that replacement of *N*-ethylaniline with *N*-ethylaniline derivatives carrying extra electron-donating or -withdrawing group(s) might change the steric and/or electronic nature of the chiral hydride. This might result in the improvement of the optical and chemical yields of optically active **2**.



1 (*R*)-(+)-**2** (*S*)-(−)-**2**

Chart 1

TABLE I. Asymmetric Reduction of 2-Cyclohexen-1-one (**1**) by Using Lithium Aluminum Hydride Partially Decomposed with (−)-*N*-Methylephedrine and Various Achiral Amine Additives[a]

Run	Achiral amine additive	Optically active 2-cyclohexen-1-ol (**2**)			
		Chemical yield (%)[b]	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)[c]	Optical yield (%)[d]	Absolute config.[d]
1	PhNHEt	31	−45.2° (4.02)	40	(*S*)
2	*p*-MeOPhNHEt	0	—	—	—
3	*p*-MePhNHEt	33	−37.5° (0.72)	33	(*S*)
4	*p*-ClPhNHEt	39	−23.4° (0.73)	21	(*S*)
5	3,5-$(MeO)_2$PhNHEt	32	+0.8° (0.81)	1	(*R*)
6	3,5-Me_2PhNHEt	33	−33.7° (0.70)	30	(*S*)
7	3,5-Cl_2PhNHEt	40	−34.7° (0.62)	31	(*S*)
8	1-EtNHC$_{10}$H$_7$[e]	34	+4.9° (0.72)	4	(*R*)
9	2-EtNHC$_{10}$H$_7$[f]	33	+1.4° (0.62)	1	(*R*)
10	$PhCH_2NHPh$	20	−3.3° (0.62)	3	(*S*)
11	$PhCH_2CH_2NHPh$	3	−3.8° (0.70)	3	(*S*)
12	3-EtNH-Py[g]	<5[h]	—	—	—
13	2-EtNH-Py[i]	45	+100° (0.60)	90	(*R*)

a) All reactions were carried out using LAH (3.1—3.3 eq) partially decomposed with (−)-*N*-methylephedrine (3.2—3.4 eq) and an achiral amine additive (6.5—6.8 eq) in ether at −78 °C for 3 h.
b) Calculated on a sample purified by preparative TLC (SiO_2, CH_2Cl_2).
c) Measured on a sample further purified by bulb-to-bulb distillation.
d) Optically pure (*S*)-(−)-**2** gives $[\alpha]_D^{20}$ −112.0° (*c*=0.60, $CHCl_3$). See ref. 10*b*.
e) *N*-Ethyl-α-naphthylamine.
f) *N*-Ethyl-β-naphthylamine.
g) 3-Ethylaminopyridine.
h) Measurement of the optical rotation was not performed.
i) 2-Ethylaminopyridine.

The results of these examinations are summarized in Table I along with that of a re-examination of *N*-ethylaniline as an achiral additive. In these experiments, the reduction product (**2**) was purified by preparative thin layer chromatography (PTLC) to remove a small amount of the remaining starting material (**1**) and some impurities (*vide infra*). Therefore, the chemical yields were lower than those when column chromatography was used for purification.[12] As shown in Table I, these attempts did not improve the optical yields of optically active **2** (Table I, runs 2—7). Similar low optical yields were obtained when *N*-ethyl-α- or β-

naphthylamine, *N*-benzylaniline, and *N*-(2-phenylethyl)aniline were employed as achiral additives (Table I, runs 8—11).

We next turned our attention to the ethylaminopyridine derivatives, which have extra ligands in their aromatic rings. While 3-ethylaminopyridine again gave an unsatisfactory result, 2-ethylaminopyridine was found to behave as a highly effective achiral additive, giving (*R*)-(+)-**2** in 90% optical and 45% chemical yields (Table I runs 12 and 13).[13]

In order to refine this chiral LAH, various N-alkyl substituents of 2-alkylaminopyridines, reaction solvents, and reaction temperatures were tested, and the results are shown in Tables II and III. Since the reduction product ((*R*)-(+)-**2**) was purified by column chromatography in these experiments, the chemical yields were higher than those in Table I. Based on these

TABLE II. Asymmetric Reduction of 2-Cyclohexen-1-one (**1**) by Using Lithium Aluminum Hydride Partially Decomposed with (−)-*N*-Methylephedrine and 2-Alkylaminopyridine[a]

Run	Alkyl group of 2-alkylaminopyridine[e]	(*R*)-(+)-Cyclohexen-1-ol ((*R*)-(+)-**2**)		
		Chemical yield (%)[b]	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)[c]	Optical yield (%)[d]
1	Me	17[f]	+69.3° (0.37)	62
2[g]	Et	81 (9)	+110° (0.60)	98
3	*n*-Pr	67 (4)	+103° (0.58)	92
4	iso-Pr	49 (7)	+34.6° (0.48)	31
5	$PhCH_2$	60 (2)	+103° (0.58)	92

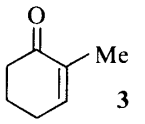
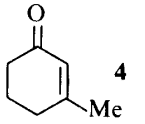
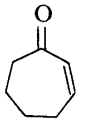
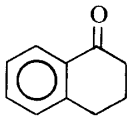
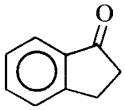
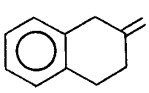
a) All reactions were carried out using LAH (3.3 eq) partially decomposed with (−)-*N*-methylephedrine (3.4 eq) and 2-alkylaminopyridine (6.8 eq) in ether at −78 °C for 3 h.
b) Calculated on a sample purified by column chromatography. Numbers in parentheses show the recovery yields of **1**.
c) Measured on a sample further purified by bulb-to-bulb distillation.
d) Optically pure (*S*)-(−)-**2** gives $[\alpha]_D^{20}$ −112.0° (*c* = 0.60, $CHCl_3$). See ref. 10*b*.
e) For preparation methods, see the experimental section.
f) Recovery of **1** was not attempted.
g) (−)-*N*-Methylephedrine (3.6 eq) and 2-ethylaminopyridine (7.2 eq) were used for decomposing LAH (3.3 eq).

TABLE III. Effects of Reaction Solvents (A) and Temperature (B) on the Asymmetric Reduction of 2-Cyclohexen-1-one (**1**)[a]

A				B			
Reaction solvent	(*R*)-(+)-2-Cyclohexen-1-ol			Reaction temp. (°C)	(*R*)-(+)-2-Cyclohexen-1-ol		
	Chemical yield (%)[b]	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)[c]	Optical yield (%)[d]		Chemical yield (%)[b]	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)[c]	Optical yield (%)[d]
Et_2O	81 (9)	+110° (0.60)	98	−78	81 (9)	+110° (0.60)	98
THF	56 (14)	+84.7° (0.69)	76	−45	77 (9)	+104° (0.58)	93
PhMe	7 (23)	—[e]	—[e]	0	75[f]	+93.1° (0.72)	83
				35	75 (10)	+81.8° (0.80)	73

a) All reactions were carried out using LAH (3.3 eq) partially decomposed with (−)-*N*-methylephedrine (3.6 eq) and 2-ethylaminopyridine (7.2 eq) in the indicated solvent (for A) or in ether (for B) at −78 °C (for A) or at the indicated temperature (for B) for 3 h.
b—*d*) See Table II footnotes *b*—*d*).
e) Measurement of the optical rotation was not performed.
f) See Table II footnote *f*).

TABLE IV. Asymmetric Reduction of Various Cyclic Ketones by Using Lithium Aluminum Hydride Partially Decomposed with (−)-*N*-Methylephedrine and 2-Ethylaminopyridine[a]

Run	Cyclic ketone	Optically active cyclic alcohol			
		Chemical yield (%)[b]	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)[c]	Optical yield (%)	Absolute confign.
1[d]	 **3**	82[e]	+130° (1.39)	96[f,g]	(*R*)[h]
2[d]	 **4**	57 (24)	+87.0° (0.46)	90[i]	(*R*)[i]
3	 **5**	74 (18)	+21.3° (2.43)	73[f]	(*R*)[j]
4	 **6**	93 (7)	−31.4° (2.64)	96[i]	(*R*)[i]
5	 **7**	86 (12)	−28.0° (2.02)	81[i]	(*R*)[i]
6	 **8**	84 (15)	+68.0° (1.61)[k]	93[g]	(*R*)[h,i]

a) All reactions were carried out using LAH (3.3 eq) partially decomposed with (−)-*N*-methylephedrine (3.6 eq) and 2-ethylaminopyridine (7.2 eq) in ether at −78 °C for 3 h.
b, *c*) See Table II footnotes *b*, *c*).
d) The reaction mixture was worked up under the basic conditions (see the text).
e) Recovery of the starting ketone was not observed.
f) Determined by measuring the NMR spectrum of the corresponding acetate in the presence of $Eu(hfc)_3$ (see the experimental section).
g) Determined by measuring the NMR spectrum of the diastereomeric (*R*)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) ester in the presence of $Eu(fod)_3$ (see the experimental section).
h) Tentatively assigned based on the NMR spectrum of diastereomeric (*R*)-MTPA esters measured in the presence of $Eu(fod)_3$ (see the experimental section).[14]
i) The optical yield and absolute configuration of this sample were determined by directly comparing the observed optical rotation with that reported (see the experimental section).
j) Tentatively assigned by considering the result for the asymmetric reduction of **1**.
k) Measured at 19 °C in ethanol.

experiments, it was finally found that when **1** is treated with the chiral hydride prepared by successive decomposition of LAH (3.3 eq) with (−)-*N*-methylephedrine (3.6 eq) and 2-ethylaminopyridine (7.2 eq) in ether at −78 °C for 3 h, (*R*)-(+)-**2** can be obtained in 98% optical and 81% chemical yields (Table II run 2). In all the experiments, a small amount of **1** was always recovered. This might be due to enolization of the C_4- or C_6-position of **1** brought about by the basicity of the reducing agent.

Considering that, unlike the reported hydride,[3,4] a suspension of LAH in ether is usable for preparing our chiral hydride, and that reductions even at −45 and 0 °C can afford 93 and 83% optical yields of (*R*)-(+)-**2**, respectively (Table IIIB), this asymmetric reduction may

TABLE V. Comparisons of Chiral Lithium Aluminum Hydride Partially Decomposed with (−)-*N*-Methylephedrine–*N*-Ethylaniline (A) and with (−)-*N*-Methylephedrine–2-Ethylaminopyridine (B)[a]

Run	Open-chain ketone	Chiral lithium aluminum hydride (A)[b]			Chiral lithium aluminum hydride (B)[c]		
		Chemical yield (%)	Optical yield (%)	Absolute confign.	Chemical yield (%)[d]	Optical yield (%)[e,f]	Absolute confign.[f]
1	PhCOMe	94	84	(*S*)	97	54	(*R*)
2	PhCOEt	96	90	(*S*)	93	46	(*S*)
3	PhCO–*n*-Pr	100	80	(*S*)	96	18	(*S*)

a) All reactions were carried out in ether at −78 C for 3 h.
b) Transferred from ref. 5*c*, Tables III and IV.
c) The asymmetric reduction was performed under the same conditions as shown in Table II run 2.
d) Calculated on a sample purified by column chromatography (see the experimental section).
e) Calculated based on the optical rotation measured on a sample further purified by bulb-to-bulb distillation.
f) The optical yield and absolute configuration of optically active alcohol were determined based on the reported optical rotation (see the experimental section).

have wide practical value.

The developed chiral reagent was next applied to the asymmetric reduction of various structural types of achiral cyclic ketones (**3**—**8**). The results (Table IV) show that the reduction of **3**—**8** proceeds highly enantioselectively in the same manner as observed for **2**, affording optically active cyclic (*R*)-alcohols in high optical yields. Since optically active (*R*)-(+)-2- and 3-methyl-2-cyclohexen-1-ol were found to be readily racemizable under the acidic work-up conditions employed for (*R*)-(+)-**2**, the reaction mixture was carefully treated under basic conditions (see the experimental section). To our knowledge, the optical yields recorded in Table IV are the best values so far reported for the asymmetric reduction of these cyclic ketones with modified chiral hydrides.

Finally, in order to evaluate the explored chiral hydride, the asymmetric reductions of some aromatic ketones were examined. These results are shown in Table V along with those achieved with the chiral hydride prepared by using *N*-ethylaniline as an additive for comparison.[5a,c] Similarly to the case of the asymmetric reduction of **1** (see Table I runs 1 and 13), treatment of acetophenone under the same conditions as for **1** was found to give (*R*)-(+)-1-phenylethanol in 54% optical and 97% chemical yields (Table V run 1). However, the asymmetric reductions of propiophenone and butyrophenone afforded confusing results. Thus, while these ketones provided the corresponding (*S*)-(−)-alcohols in high optical and chemical yields when reduced with the previously exploited hydride,[5a,c] the chiral hydride produced by using 2-ethylaminopyridine gave the same (*S*)-(−)-alcohols in rather low optical yields (Table V runs 2 and 3).

Although the transition state for asymmetric reduction, including the stereo-structure of the developed chiral hydride, remains to be explored, this reagent should be quite useful for practical asymmetric synthesis of optically active cyclic alcohols due to its high optical yields, operational simplicity, and the use of a readily available chiral source and additive.

Experimental[15]

(1*R*,2*S*)-(−)-*N*-Methylephedrine——Prepared from (−)-ephedrine hydrochloride according to the reported method.[5c,16,17] mp 85—86 C, $[\alpha]_D^{20}$ −30.2 (*c*=4.48, MeOH) (lit.,[5c] mp 85—86 C, $[\alpha]_D^{20}$ −29.8 (*c*=4.50, MeOH)).

Preparation of Achiral Amine Additives——a) *N*-Alkylaniline Derivatives: *N*-Ethylaniline and *N*-Benzylaniline: Commerical samples were used after distillation *in vacuo*. *N*-Ethyl-α-naphtylamine and *N*-Ethyl-β-naphthylamine: Commercial hydrochlorides were converted to the corresponding free bases in the usual manner. The oily free bases were used for the reduction after being distilled *in vacuo*. Other *N*-alkylaniline derivatives were synthesized from the

corresponding aniline derivatives as described below. *N*-Ethyl-*p*-anisidine: This was prepared from *p*-anisidine by successive acetylation (Ac_2O–Py) and reduction (LAH in THF). Pale yellow oil, bp 127 °C (15 mmHg) (lit.,[18] bp 130 °C (12 mmHg)). *N*-Ethyl-*p*-toluidine: Prepared from *p*-toluidine by the same method as used for *N*-ethyl-*p*-anisidine. Colorless oil, bp 75—82 °C (5 mmHg) (lit.,[19] bp 217 °C (760 mmHg)). *N*-Ethyl-*p*-chloroaniline: Preparation of this compound was performed by simultaneous condensation with triethyl orthoformate, acid-catalyzed rearrangement, and acidic hydrolysis according to the reported method.[20] Colorless oil, bp 93—95 °C (4 mmHg) (lit.,[20] bp 105 °C (2.9 mmHg)). *N*-Ethyl-3,5-dimethoxyaniline: This was prepared from 3,5-dimethoxyaniline by the same method as used for *N*-ethyl-*p*-anisidine. Pale yellow oil, bp 153—158 °C (5 mmHg) (lit.,[21] bp 115—116 °C (3 mmHg)). *N*-Ethyl-3,5-dichloroaniline: Prepared from 3,5-dichloroaniline by the same procedure as described for *N*-ethyl-*p*-chloroaniline.[20] Colorless oil, bp 126—130 °C (4 mmHg). IR ν_{max}^{film} cm^{-1}: 3420 (NH). NMR ($CDCl_3$) δ: 1.20 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 3.00 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 3.60 (1H, s, N$\underline{H}$), 6.40 (2H, s, aromatic protons), 6.60 (1H, s, aromatic proton). MS *m/e*: 189 (M^+), 174. MS Calcd for $C_8H_9Cl_2N$ (M^+; *m/e*): 189.0111. Found: 189.0082. *N*-Ethyl-3,5-dimethylaniline: Preparation of this compound was carried out according to the method used for *N*-ethyl-*p*-chloroaniline.[20] Colorless oil, bp 101—102 °C (5 mmHg). IR ν_{max}^{film} cm^{-1}: 3400 (NH). NMR ($CDCl_3$) δ: 1.10 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 2.15 (6H, s, $C\underline{H}_3 \times 2$), 3.00 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 3.25 (1H, s, N$\underline{H}$), 6.10 (2H, s, aromatic protons), 6.30 (1H, s, aromatic proton). MS *m/e*: 149 (M^+), 134, 105. MS. Calcd for $C_{10}H_{15}N$ (M^+; *m/e*): 149.1203. Found: 149.1200. *N*-(2-Phenylethyl)aniline: Condensation of aniline with phenylacetic acid in the presence of diethyl phosphorocyanidate[22] followed by reduction with LAH, gave the product as a colorless oil, bp 150—160 °C (5 mmHg) (bath temp.) (lit.,[23] bp 155—160 °C (0.4 mmHg)).

b) 2- and 3-Alkylaminopyridine Derivatives: 2-Methylaminopyridine: Formylation of 2-aminopyridine with HCOOH[24] gave 2-formamidopyridine as colorless pillars, mp 70—71 °C (lit.,[24] mp 71 °C). Methylation of 2-formamidopyridine with sodium hydride–methyl iodide in DMF followed by hydrolysis with aq. HCl, gave the product as a pale yellow oil in 63% yield, bp 130 °C (10 mmHg) (bath temp.) (lit.,[25] bp 100—102 °C (18 mmHg)). 2-Ethylaminopyridine: Alkylation of 2-formamidopyridine with sodium hydride–ethyl bromide in DMF followed by hydrolysis with aq. HCl gave the product as a pale yellow oil in 77% yield, bp 76 °C (4 mmHg) (lit.,[26] bp 79—82 °C (4 mmHg)). 2-Ethylaminopyridine was also produced in 39% yield by direct alkylation of 2-aminopyridine with sodium hydride–ethyl bromide in THF. Separation of the product from 2-diethylaminopyridine and the starting material was achieved by column chromatography (EtOAc–C_6H_{14} (1 : 1)→EtOAc). 2-Propylaminopyridine: Direct alkylation of 2-aminopyridine with sodium hydride–propyl iodide in THF followed by separation by column chromatography (EtOAc–C_6H_{14} (1 : 3)→EtOAc–C_6H_{14} (1 : 1)), gave the product in 48% yield as a pale yellow oil, bp 130 °C (2 mmHg) (bath temp.) (lit.,[27] bp 145—160 °C (21 mmHg)). 2-Isopropylaminopyridine: Preparation from 2-aminopyridine and isopropyl iodide in 75% yield according to the same procedure as used for 2-propylaminopyridine. Pale brown oil, bp 125 °C (3 mmHg) (bath temp.) (lit.,[28] bp 105 °C (16 mmHg)). 2-Benzylaminopyridine: Refluxing of a mixture of 2-aminopyridine and benzaldehyde in 99% HCOOH for 6 h gave the product in 50% yield after extractive isolation and recrystallization from EtOH, mp 92—93 °C (lit.,[24] mp 94 °C; lit.,[29] 98 °C). 3-Ethylaminopyridine: This was prepared from 3-aminopyridine and ethyl iodide in 48% yield according to the method described for 2-propylaminopyridine, bp 110 °C (5 mmHg) (lit.,[30] bp 83 °C (0.6 mmHg)).

Asymmetric Reduction of 2-Cyclohexen-1-one (1)——A typical experimental procedure is given for Table II run 2. Other asymmetric reductions shown in Tables I, II, and III were all performed in a similar manner. An ethereal solution (14 ml) of (−)-*N*-methylephedrine (mp 85—86 °C, $[\alpha]_D^{20}$ −30.2° (*c*=4.48, MeOH)) (1.94 g, 10.8 mmol) was added to a suspension of LAH (376 mg, 9.9 mmol) in ether (8.5 ml), and the mixture was heated at reflux for 1 h with stirring. An ethereal solution (8.5 ml) of 2-ethylaminopyridine (2.64 g, 21.6 mmol) was added to the ethereal suspension prepared above, and the mixture was further heated at reflux for 1 h with stirring to give a yellowish-green suspension of the reducing agent.

A solution of **1** (288 mg, 3.0 mmol) in ether (3 ml) was gradually added to the ethereal suspension of the reducing agent cooled at −78 °C, and the mixture was stirred at the same temperature for 3 h. MeOH (0.5 ml) was added to quench the reduction, and the reaction mixture was stirred at −78 °C for 5 min. The mixture was further diluted with 3 N HCl (35 ml), then extracted with Et_2O. The combined ethereal extracts were washed successively with 1% HCl, satd. $NaHCO_3$, and satd. NaCl. Filtration and concentration of the filtrate *in vacuo* gave an oily residue (340 mg), which was purified by column chromatography ($CHCl_3$–Et_2O, 19 : 1) to afford **1** (25 mg, 9%) and (*R*)-(+)-**2** (239 mg, 81%). (*R*)-(+)-**2** was further purified by bulb-to-bulb distillation, giving pure (*R*)-(+)-**2** as a colorless oil (224 mg, 76%), bp 150 °C (100 mmHg) (bath temp.), $[\alpha]_D^{20}$ +110° (*c*=0.60, $CHCl_3$). Since optically pure (*S*)-(−)-**2** had been reported to show $[\alpha]_D^{20}$ −112.0° (*c*=0.60, $CHCl_3$),[10b] the optical yield of this sample could be calculated as 98% ee. The spectral (infrared (IR) and nuclear magnetic resonance (NMR)) properties of this sample were identical with those reported.[5c]

(*R*)-(+)-2-Methyl-2-cyclohexen-1-ol (Table IV Run 1)——The asymmetric reduction of **3** (330 mg, 3.0 mmol) was carried out in the same manner as described for **1** (Table II run 2). Since (+)-2-methyl-2-cyclohexen-1-ol was found to be readily racemizable under the acidic work-up conditions employed for **1**, the reduction was quenched by successive additions of MeOH, H_2O, 15% NaOH, and H_2O. An oily mixture obtained by filtration and concentration *in vacuo* was directly separated by column chromatography (C_6H_6→C_6H_6–EtOAc (8 : 1)) to give (+)-2-methyl-2-

cyclohexen-1-ol as an oil (275 mg, 82%). The optical rotation was measured on a sample further purified by bulb-to-bulb distillation (255 mg, 76%), bp 100—110 °C (15 mmHg) (bath temp.), $[\alpha]_D^{20}$ +130° (c=1.39, $CHCl_3$).

The spectral (IR and NMR) properties of this sample were identical with those reported.[5c] In order to determine its optical purity and absolute configuration, (+)-2-methyl-2-cyclohexen-1-ol was converted to its acetate and (*R*)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) ester by treatment with Ac_2O–Py and (*R*)-MTPA chloride–Py, respectively. (+)-2-Methyl-2-cyclohexen-1-yl acetate: bp 130 °C (30 mmHg) (bath temp.), $[\alpha]_D^{20}$ +130° (c=1.09, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1740 (ester). NMR ($CDCl_3$) δ: 1.4—2.3 (12H, m, CH_3CO, $(CH_2)_3CH=$, and $CH_3C=$), 5.1—5.3 (1H, m, CHO), 5.5—5.7 (1H, m, $CH=$). MS *m/e*: 154 (M^+), 94, 79. MS Calcd for $C_9H_{14}O_2$ (M^+; *m/e*): 154.0992. Found: 154.0973. 2-Methyl-2-cyclohexen-1-ol (*R*)-MTPA ester: IR ν_{max}^{film} cm^{-1}: 1745 (ester). NMR ($CDCl_3$) δ: 1.2—2.1 (9H, m, $(CH_2)_3CH=$ and $CH_3C=$), 3.4—3.6 (3H, m, OCH_3), 5.2—5.5 (1H, m, CHO), 5.5—5.8 (1H, m, $CH=$), 7.2—7.7 (5H, m, aromatic protons). MS *m/e*: 189, 95. The NMR spectrum of (+)-2-methyl-2-cyclohexen-1-yl acetate measured in the presence of $Eu(hfc)_3$ (the acetate : $Eu(hfc)_3$, 1 : 1) showed the acetyl group signal as two singlets at 7.33 and 7.24 ppm in an integration ratio of 2.3 : 97.7. On the other hand, the NMR spectrum of 2-methyl-2-cyclohexen-1-ol MTPA ester recorded in the presence of $Eu(fod)_3$ (the ester : $Eu(fod)_3$, 10 : 1) exhibited the methoxy group signal as two singlets at 6.34 and 6.00 ppm in an integration ratio of 98 : 2. Therefore, the optical purity of (+)-2-methyl-2-cyclohexen-1-ol was calculated as 96% ee. According to the latter spectral feature, in which the larger intensity was observed for the lower singlet (6.34 ppm), (+)-2-methyl-2-cyclohexen-1-ol was assumed to have the (*R*)-configuration.[14]

(*R*)-(+)-3-Methyl-2-cyclohexen-1-ol (Table IV Run 2)——The asymmetric reduction of **4** (330 mg, 3.0 mmol) was performed in the same manner as described for **1** (Table II run 2). Since (*R*)-(+)-3-methyl-2-cyclohexen-1-ol was also found to be readily racemizable under the acidic conditions, the reaction mixture was worked up in the same manner as used for (*R*)-(+)-2-methyl-2-cyclohexen-1-ol, giving **4** (80 mg, 24%) and (*R*)-(+)-3-methyl-2-cyclohexen-1-ol (191 mg, 57%) after separation by column chromatography (C_6H_6–EtOAc, 5 : 1, then C_6H_6–Me_2CO, 6 : 1). Measurement of the optical rotation was carried out on a sample further purified by bulb-to-bulb distillation, bp 100—110 °C (15 mmHg) (bath temp.), $[\alpha]_D^{20}$ +87.0° (c=0.46, $CHCl_3$).

The spectral (IR and NMR) properties of this sample were identical with those reported.[5c] Since optically pure (*S*)-(−)-3-methyl-2-cyclohexen-1-ol had been reported to have $[\alpha]_D^{20}$ −96.3±0.3° (c=0.458, $CHCl_3$),[31] the optical yield and absolute configuration of (+)-3-methyl-2-cyclohexen-1-ol were determined as 90% ee and (*R*)-series, respectively.

(*R*)-(+)-2-Cyclohepten-1-ol (Table IV Run 3)——The ketone (**5**) (331 mg, 3.0 mmol) was treated in the same manner as described for **1** (Table II run 2) to give **5** (59 mg, 18%) and (+)-2-cyclohepten-1-ol (248 mg, 74%) after extractive isolation and separation by column chromatography (Et_2O–$CHCl_3$ (1 : 4)→Et_2O–$CHCl_3$ (1 : 1)). Measurement of the optical rotation was carried out using a sample further purified by bulb-to-bulb distillation (219 mg, 65%), bp 125 °C (15 mmHg) (bath temp.), $[\alpha]_D^{20}$ +21.3° (c=2.43, $CHCl_3$).[11] IR ν_{max}^{film} cm^{-1}: 3280, 1030 (OH). NMR ($CDCl_3$) δ: 1.1—2.4 (8H, m, $(CH_2)_4CH=$), 2.60 (1H, br s, OH), 4.15—4.55 (1H, m, CHO), 5.5—5.9 (2H, m, $CH=CH$). The absolute configuration of (+)-2-cyclohepten-1-ol was tentatively assigned as (*R*)-series by taking account of the result of asymmetric reduction of **1**. In order to determine the optical yield, this sample was converted to its acetate by treatment with Ac_2O–Py. (+)-2-Cyclohepten-1-yl acetate showed bp 130 °C (30 mmHg) (bath temp.) and $[\alpha]_D^{20}$ +29.4° (c=1.24, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1740 (ester). NMR ($CDCl_3$) δ: 1.2—2.3 (11H, m, $(CH_2)_4CH=$ and CH_3CO), 5.2—6.0 (3H, m, $CH=CHCHO$). MS *m/e*: 154 (M^+), 94, 79. MS Calcd for $C_9H_{14}O_2$ (M^+; *m/e*): 154.0992. Found: 154.0972. The NMR spectrum of this sample measured in the presence of $Eu(hfc)_3$ (the acetate : $Eu(hfc)_3$, 9 : 5) showed the acetyl group signal as two singlets at 5.16 and 5.02 ppm in an integration ratio of 13.4 : 86.6. Therefore, the optical purity of (*R*)-(+)-2-cyclohepten-1-ol was calculated as 73% ee.

(*R*)-(−)-1,2,3,4-Tetrahydro-1-naphthol (Table IV Run 4)——The same treatments of **6** (439 mg, 3.0 mmol) as described for **1** (Table II run 2) gave **6** (29 mg, 7%) and (−)-1,2,3,4-tetrahydro-1-naphthol (414 mg, 93%) after extractive isolation and separation by column chromatography (EtOAc–C_6H_{14} (1 : 4)→EtOAc–C_6H_{14} (1 : 2)). The optical rotation was measured on a sample further purified by bulb-to-bulb distillation (346 mg, 78%), bp 130 °C (3 mmHg) (bath temp.), $[\alpha]_D^{20}$ −31.4° (c=2.64, $CHCl_3$). The spectral (IR and NMR) properties of this sample were identical with those reported.[5c] Since optically pure (*S*)-(+)-1,2,3,4-tetrahydro-1-naphthol had been reported to have $[\alpha]_D^{17}$ +32.65° (c=2.5, $CHCl_3$),[32,33] the optical yield and absolute configuration of (−)-1,2,3,4-tetrahydro-1-naphthol were determined as 96% ee and (*R*)-series, respectively.

(*R*)-(−)-Indan-1-ol (Table IV Run 5)——The ketone (**7**) (396 mg, 3.0 mmol) was treated in the same manner as described for **1** (Table II run 2) to give **7** (48 mg, 12%) and (−)-indan-1-ol (345 mg, 86%) after extractive isolation and separation by column chromatography (EtOAc–C_6H_6 (1 : 8)→EtOAc–C_6H_6 (1 : 3)). Measurement of the optical rotation was carried out using a sample further purified by bulb-to-bulb distillation, bp 130 °C (3 mmHg) (bath temp.), $[\alpha]_D^{20}$ −28.0° (c=2.02, $CHCl_3$). The spectral (IR and NMR) properties of this sample were identical with those reported.[5c] Since optically pure (*S*)-(+)-indan-1-ol had been reported to show $[\alpha]_D^{20}$ +34.4° (c=1.97, $CHCl_3$),[33,34] the optical yield and absolute configuration of (−)-indan-1-ol obtained by the asymmetric reduction were determined as 81% ee and (*R*)-series, respectively.

(*R*)-(+)-1,2,3,4-Tetrahydro-2-naphthol (Table IV Run 6)——The same treatments of **8** (439 mg, 3.0 mmol) as

described for **1** (Table II run 2) gave **8** (66 mg, 15%) and (+)-1,2,3,4-tetrahydro-2-naphthol (365 mg, 82%) after extractive isolation and separation by column chromatography (EtOAc–C_6H_{14} (1 : 4)→EtOAc–C_6H_{14} (1 : 2)). The optical rotation was recorded on a sample further purified by bulb-to-bulb distillation, bp 140 °C (3 mmHg) (bath temp.), $[\alpha]_D^{19}$ +68.0° (c = 1.61, EtOH). Since (*S*)-(−)-1,2,3,4-tetrahydro-2-naphthol had been reported to give $[\alpha]_D^{19}$ −72.2° (c = 1.61, EtOH),[35] the absolute configuration of the (+)-isomer was established as (*R*)-series. In order to determine its optical yield, (+)-1,2,3,4-tetrahydro-2-naphthol was converted to the corresponding (*R*)-MTPA ester as described for (*R*)-(+)-2-methyl-2-cyclohexen-1-ol. IR ν_{max}^{film} cm^{-1}: 1745 (ester). NMR ($CDCl_3$) δ: 1.9—2.2 (2H, m, $CH_2\underline{CH}_2CHO$), 2.7—3.2 (4H, m, $ArC\underline{H}_2 \times 2$), 3.4—3.6 (3H, m, $OC\underline{H}_3$), 5.3—5.6 (1H, m, $C\underline{H}O$), 7.0—7.7 (9H, m, aromatic protons). The NMR spectrum of this sample measured in the presence of Eu(fod)$_3$ (the ester : Eu(fod)$_3$, 10 : 1) showed the methoxy signal as two singlets at 5.45 and 5.15 ppm in an integration ratio of 96.5 : 3.5. Therefore, the optical yield of (*R*)-(+)-1,2,3,4-tetrahydro-2-naphthol was calculated as 93% ee.

Asymmetric Reduction of Aromatic Ketones (Table V Runs 1—3)——When acetophenone, propiophenone, and butyrophenone were reduced in the same manner as described for **1** (Table II run 2), (*R*)-(+)-1-phenylethanol, (*S*)-(−)-1-phenylpropanol, and (*S*)-(−)-1-phenylbutanol were obtained in 97, 93, and 96% yields, respectively, after extractive isolation and purification by column chromatography. These optically active alcohols, which were further purified by bulb-to-bulb distillation, showed the following optical rotations. (*R*)-(+)-1-Phenylethanol: bp 120 °C (5 mmHg) (bath temp.), $[\alpha]_D^{23}$ +28.2° (c = 2.23, CH_2Cl_2), 54% ee (lit.,[36] $[\alpha]_D^{22}$ −52.5° (c = 2.27, CH_2Cl_2) for the optically pure (*S*)-(−)-alcohol). (*S*)-(−)-1-Phenylpropanol: bp 130 °C (5 mmHg) (bath temp.), $[\alpha]_D^{20}$ −20.9° (c = 5.36, $CHCl_3$), 46% ee (lit.,[37] $[\alpha]_D$ −45.45° (c = 5.15, $CHCl_3$) for the optically pure (*S*)-(−)-alcohol). (*S*)-(−)-1-Phenylbutanol: bp 135 °C (5 mmHg) (bath temp.), $[\alpha]_D^{22}$ −8.4° (c = 6.23, C_6H_6), 18% ee (lit.,[38] $[\alpha]_D^{22}$ −45.93° (c = 6.1, C_6H_6) for the optically pure (*S*)-(−)-alcohol).

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