Effects of Neighboring Functional Groups in the Asymmetric Reduction of ω-Substituted Alkyl Phenyl Ketones with Lithium Tri-*l*-Menthoxyaluminum Hydride[1]

Shozo YAMAGUCHI and Kuninobu KABUTO

Department of Chemistry, College of General Education, Tohoku University, Kawauchi, Sendai 980

(Received May 25, 1977)

In the enantioselective reduction of ω-substituted alkyl phenyl ketones, $PhCO(CH_2)_nY$, with lithium tri-*l*-menthoxyaluminum hydride, the effect of the functional groups, $Y(NR_2$, OMe, and SMe) on the stereoselectivity was examined in comparison with that of the alkyl group. Of the functional groups tested, the MeO group is more effective in enhancing the stereoselectivity than the NMe_2 or SMe group except in the case of $n=1$. The optical yields are also affected by the number of the methylene group (n) in the substrates. These results strongly suggest that the coordination of the Y group with the reducing reagent is one of the essential factors in the stereoselectivity. The absolute configurations of the resulting alcohols are correlated with the relative magnitudes of the lanthanide-induced shifts(LIS) of their (+)-MTPA esters.

There have been many studies[2] of the asymmetric reduction of achiral ketones with lithium aluminum hydride modified by chiral reagents. Although some systematic studies[3] have been done in exploring effective chiral ligands, attention has so far been mostly focused on the steric effects of the substituents around the chiral center on the asymmetric bias. Mosher and his co-workers have developed the LAH–chiral amino alcohol complexes,[4] which give excellent asymmetric yields of as much as 75% in the reduction of acetophenone. They explained this high stereoselectivity in terms of a rigid conformation of the chiral hidride reagent as a result of the coordination of such functional groups as NMe_2 in the chiral ligand with Li^+. A similar coordinating effect has also been reported[5] in the asymmetric reduction with LAH–*N*-(*o*-substituted benzyl)-α-methylbenzylamine complexes.

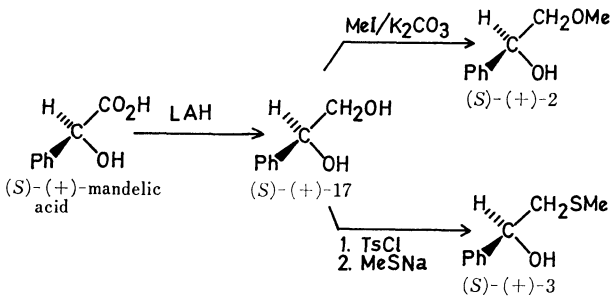
On the other hand, in order to conduct the asymmetric reduction of the substrates with functional groups effectively, it is necessary to get information on the effect of the functional group on asymmetric induction. Such investigation has, however, been limited to the diastereoselective reductions[6] of the carbonyl group, and little is known about the role of the groups[7] in substrates on enantioselective reduction.

For the purpose of clarifying the stereoselectivity enhancement by the functional group in substrates in the case of enantioselective reductions, it is desirable that a chiral ligand not have any additional group other than the one essential for complex formation with a reducing reagent, and that the asymmetric yield not be high when the functional group is absent in the substrates.[8]

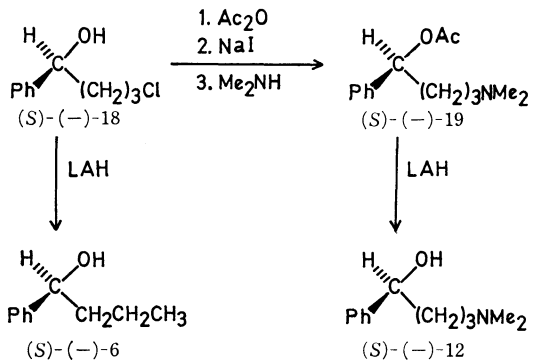
On the basis of these considerations, the asymmetric reduction of ω-substituted alkyl phenyl ketones, $PhCO(CH_2)_nY$ ($Y=NR_2$, OMe, SMe, and alkyl; $n=1-4$), with $LiAlH(O\text{-Menthyl})_3$ was carried out in order to find the most profitable group(Y) and number of the methylene group(*n*).

The reduction of ketones was conducted in ether under a nitrogen atmosphere. The synthetic yields were 80—100%, and the resulting secondary alcohols were purified by preparative GLC. The results are shown in Table 1.

Of the absolute configurations of the alcohols obtained by this reduction, those of 2-methoxy-1-phenylethanol(**2**) and 2-methylthio-1-phenylethanol(**3**) were assigned as *S*(+) by correlating them chemically to (*S*)-(+)-mandelic acid according to the procedure outlined in Scheme 1, while that of 4-dimethylamino-1-phenyl-1-butanol(**12**) was determined to be *R*(+) by correlation to 1-phenyl-1-butanol(**6**) (Scheme 2).



Scheme 1.



Scheme 2.

The absolute configurations of the other alcohols with functional groups were assigned[9] by means of the (*R*)-(+)-MTPA*/$Eu(fod)_3$ method[10] previously reported by the present authors, since it has been confirmed that this method is also applicable to 1-phenylethanols with the functional groups [$Y=NMe_2$ (**1**); OMe(**2**); SMe(**3**)] at the C-2 position.

The (*R*)-(+)-MTPA/$Eu(fod)_3$ method correlates the

* (*R*)-(+)-α-Methoxy-α-trifluoromethylphenylacetic acid (Mosher's Reagent).

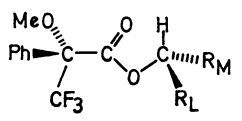
TABLE 1. ASYMMETRIC REDUCTION OF ω-SUBSTITUTED ALKYL PHENYL KETONES WITH $LiAlH(O\text{-}l\text{-Menthyl})_3$ AND THE ABSOLUTE CONFIGURATION OF THE RESULTING ALCOHOLS

$PhCO(CH_2)_nY$ (1′—16′) —$LiAlH(O\text{-Menthyl})_3$, Ether, 0 °C→ $PhCH(OH)(CH_2)_nY$ (1—16)

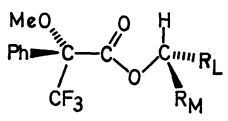
Entry	Alcohol	Functional group(Y)	LIS_{OMe} LIS_A	LIS_B	ΔLIS	Config[a]	%ee[b]
1	$n=1$	NMe_2 (**1**)	4.4	4.2	0.2	$S(-)$[c,d]	7
2		OMe (**2**)	7.1	4.9	2.2	$R(-)$[c]	4
3		SMe (**3**)	8.4	6.4	2.0	$S(+)$[c]	12
4		H (**4**)	12.6	8.6	4.0	$R(+)$[e]	3
5		Me (**5**)	9.6	7.5	2.1	$R(+)$[e]	7
6		Et (**6**)	9.8	7.8	2.0	$R(+)$	15
7	$n=2$	NMe_2 (**7**)				$R(+)$[f]	25[g]
8		OMe (**8**)	10.0	8.2	1.8	$R(+)$	35
9		SMe (**9**)	10.0	9.3	0.7	$R(+)$	17
10		Et (**10**)	9.3	8.3	1.0	$R(+)$	19
11		(**11**)				$R(+)$[f]	37[g]
12	$n=3$	NMe_2 (**12**)				$R(+)$	3[h]
13		OMe (**13**)	9.5	7.4	2.1	$R(+)$	38
14		SMe (**14**)	8.7	7.9	0.8	$R(+)$	14
15		Et (**15**)	11.5	10.0	1.5	$R(+)$	13
16	$n=4$	OMe (**16**)	11.3	9.6	1.7	$R(+)$	16

a) The optical rotations, $[\alpha]_D$, were taken in cyclopentane unless otherwise specified. b) All the data are the averages of 2—3 runs. The enentiomeric excesses were determined based on the relative peak area of the MeO signals of the (*R*)-(+)-MTPA acid moiety in the presence of $Eu(fod)_3$. c) In these three alcohols, the $-CH_2Y$ group takes nomenclatural precedence over that of the Ph group; therefore, the *S* configuration in these alcohols corresponds to the *R* of the others. d) Sign for the hydrochloride of **1** in water; H. Yoshimura, *Yakugaku Zasshi*, **84**, 305 (1963). e) Ref. 10. f) Sign for a methanol solution; Ref. 7. g) Based on the absolute rotations: **7**, $[\alpha]_D$ +27.6° (*c* 1.61, MeOH); **11**, $[\alpha]_D$ +29.3° (*c* 1.9, MeOH). Refs. 7 and 14. h) Determined on the basis of the relative peak area of carbinyl protons in the ^1H NMR spectrum of **12** in the presence of the chiral shift reagent, $Eu(hfc)_3$, since (*R*)-(+)-MTPA esters of **12** were not obtained under ordinary conditions.

relative magnitude of LIS_{OMe} (the lanthanide-induced shift by $Eu(fod)_3$ of the MeO signal of the MTPA acid moiety in (*R*)-(+)-MTPA esters of secondary alcohols) with their absolute configurations; the diastereomeric ester with the larger LIS value has Structure A, while the other ester, with the smaller LIS value, has Structure B. The results are also summarized in Table 1.



A



B

$R_L > R_M$

The most pertinent observations in the asymmetric reduction are as follows: (1) When the Y group is alkyl or H, the preferential attack of the hydride ion occurs on the *si*-face of the carbonyl group, and the presence of the functional group does not alter the sense of the asymmetric induction except in the case of 2-methoxyacetophenone(Table 1, Entry 2); (2) The stereoselectivity in the reduction dependes on the functional group. Among the functional groups examined, OMe(when $n=2$ and 3) and NR_2 (when $n=2$) functioned effectively to increase the stereoselectivity (Table 1, Entries 7, 8, 11, and 13) while the SMe group did not give any higher asymmetric induction, in comparison with the non-polar ethyl group. The ethyl group was chosen as a standard, since its steric requirement, including the extention effect,[11] was considered to be similar to those of OMe and SMe, and its steric effect would be the sole controlling factor in the stereoselectivity; (3) As can be seen from Fig. 1, the stereoselectivity also depends on the number of the methylene group(n) in the case of Y=OMe or NMe_2; even the sense of asymmetric induction was reversed when Y=OMe($n=1$). The highest selectivity was observed at $n=2$(Y=NMe_2, 25%ee) or $n=3$(Y=OMe, 38%ee). On the other hand, when Y=SMe or Et, there was no distinct dependence.

It is apparent that these results could not be elucidated by an exclusive consideration of the steric effects of the functional group Y, because the similar steric requirements of the group (OMe, SMe, and Et) re-

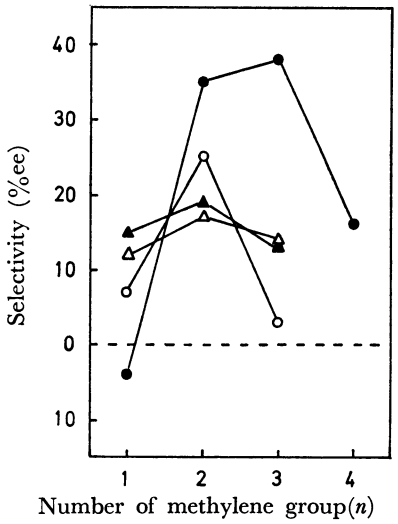
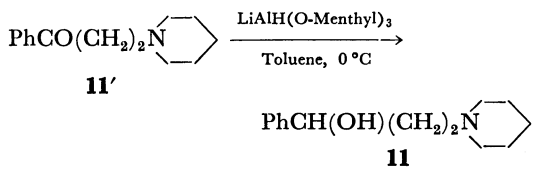


Fig. 1. Selectivity dependence on the number of methylene groups.
●: Y=OMe, ○: Y=NMe_2, ▲: Y=Et, △: Y=SMe.

Table 2. Asymmetric reduction of **11′** in the presence of TMEDA



11′ **11**

TMEDA/LAH (mol/mol)	0	1.0	2.0	4.0
Optical yield[a] (%)	23	13	12	12

a) Based on the reported absolute rotation; $[\alpha]_D$ +29.3° (*c* 1.9, MeOH). Ref. 7.

sulted in two different patterns of stereoselectivity dependence (Fig. 1, Y=OMe; SMe and Et). These observations strongly suggest that the coordination of the Y group (OMe or NR_2) with the reducing reagent also plays an important role in the stereoselectivity.

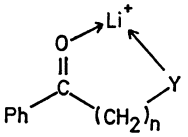
The coordination of the Y group with the reducing reagent can be substantiated by the asymmetric reduction of 3-piperidinopropiophenone (**11**) in the presence of the additive, *N,N,N′,N′*-tetramethylethylenediamine(TMEDA), which can strongly coordinate with Li^+. The reduction was conducted in toluene in order to eliminate the effect of ether oxygen, which may act as a coordinating functionality. The results are shown in Table 2. Although the change in the stereoselectivity was not very remarkable because of the rather low asymmetric induction in the absence of the additive, it can be seen that the stereoselectivity was immediately decreased by the addition of TMEDA in a 1 molar ratio and did not change upon the further addition of TMEDA. This can be interpreted as a result of the interference of the coordination of piperidino nitrogen with the reducing reagent caused by TMEDA.

The oxygen and nitrogen atoms in the functional group Y are hard bases, and they can strongly coordinate with Li^+ or Al^{3+} of hard acids, while the sulfur atom is a soft base which can hardly coordinate at all with the light metal cations. Therefore, the SMe group can be considered to act as a functionality with a poor coordinating capability in the present case. The observations that the effects of the SMe group on the stereoselectivity are almost the same as those of the non-polar Et group (see Fig. 1) is consistent with this expectation.

Experimental support for the coordination of OMe being stronger than that of SMe with Li^+ has been found in the asymmetric reduction[5] of propiophenone with LAH modified by (*S*)-(—)-*N*-(*o*-dimethylaminobenzyl)-α-methylbenzylamine, where the addition of 1,2-dimethoxyethane to the reaction mixture caused a dramatic decrease in the stereoselectivity, while that of 1,2-bis(methylthio)ethane did not.

The stereoselectivity was greatly affected by the position of the carbonyl group relative to the functional group Y (OMe, NR_2) in the present case, indicating that the reduction proceeded *via* a cyclic transition state. Concerning the mechanism of the metal hydride reduction of the carbonyl group, Pierre and Handel demonstrated that the alkali metal cation is indispensable[12] and that it also plays very important role in the stereoselectivity.[6b]

They examined the diastereomeric reduction of N-substituted 2-aziridinyl ketones and proposed a cyclic model where the alkali metal cation (not the metal hydride anion) is incorporated in the chelate ring. On the basis of this model, it can be considered that a similar coordination (C) of the carbonyl and the Y group with Li^+ occurs in the present asymmetric reduction:



C

The number of the methylene group(*n*) determines the size of the chelate ring and thus affects the rigidity of the transition state, being responsible for the stereoselectivity. As can be seen from the low stereoselectivity in the reduction of 2-methoxyacetophenone (Table 1, Entry 2), however, the ease of the chelate-ring formation, predicted from both the ring size[13] and the nature of the heteroatoms, does not always afford a high asymmetric induction.

Experimental

Instruments. The NMR spectra were taken on a Hitachi R-22 (90 MHz) spectrometer, with TMS as the internal standard. The gas-liquid chromatographic (GLC) determination was performed on a Shimadzu GC-5A apparatus, using a PEG 20 M or PDEG succinate column (3 mm×1.5 m). The preparative GLC was carried out on a Varian Aerograph 700 using the same stationary phases (1/4″×1.5 m). The optical rotations were tekan on a Perkin Elmer 241 polarimeter, using a 1-dm thermostated microcell.

Reagents. The ether was distilled over sodium hydride and stored over Linde molecular sieves 3A. The toluene was dried over the same molecular sieves. A stock $LiAlH_4$

solution in ether was passed through a glass filter under nitrogen and stored in a flask closed with a rubber septem. It was analysed by iodometry just before use. Aliquots were taken up by syringe as needed. A commercially available *l*-menthol [Tokyo Kasei, $[\alpha]_D^{20}$ −50° (*c* 10, EtOH)] was used without further purification.

Materials. 2-Dimethylaminoacetophenone(**1'**),[15] 2-methoxyacetophenone(**2'**),[16] 3-dimethylaminopropiophenone (**7'**),[7] 3-methoxypropiophenone(**8'**),[17] 3-(methylthio)propiophenone(**9'**),[18] and 3-piperidinopropiophenone(**11'**)[7] were prepared according to the reported procedures.

*2-(Methylthio)acetophenone(**3'**)*: A solution of phenacyl bromide (30 g, 0.15 mol) in ethanol (120 ml) was cooled with ice, and then a 20% aq solution of sodium methyl sulfide (36 ml) was added over a period of 10 min under stirring. The reaction mixture gradually turned red, and stirring was continued for 1 h. The reaction mixture was then poured into 600 ml of ice water. After being salted out, it was extracted with ether and the extract was washed with water, dried(Na_2SO_4), concentrated, and distilled, giving 17.5 g (70%) of **3'** as a pale yellow oil: bp 118—119 °C/3 Torr; NMR(CCl_4) δ=2.02 (3H, s, SCH_3), 3.60 (2H, s, $-CH_2S$); Found: C, 65.06; H, 6.05%. Calcd for $C_9H_{10}OS$: C, 65.02; H, 6.06%.

*4-Dimethylaminobutyrophenone(**12'**)*: To a 100 ml portion of a cold ether solution of dimethylamine (25 g, 0.056 mol), was added, little by little, crude 4-iodobutyrophenone (7.35 g, 0.027 mol, prepared from 4-chlorobutyrophenone and sodium iodide, and heated at 90 °C for 18 h in ethyl methyl ketone). After standing for a day at room temperature, the reaction mixture was warmed at 30—40 °C for 1 h. The precipitates were filtered off, and then the filtrate was concentrated to yield a pale yellow oil, which was subsequently dissolved in ether. The ether solution was extracted with 2M HCl.

After the acid layer had been made alkaline with dilute sodium hydroxide solution, it was extracted with ether. The extract was washed with water, dried (Na_2SO_4), concentrated, and distilled *in vacuo*, yielding 2.6 g (50%) of **12'** as a colorless oil: bp 122—124 °C/0.5 Torr; NMR (CCl_4) δ= 1.80 (2H, quintet, $-CH_2\underline{CH_2}CH_2-N$), 2.13 (6H, s, $-N(CH_3)_2$), 2.27 (2H, t, $-CH_2-N$), 2.93 (2H, t, $-CO-CH_2-$); Found: N, 7.43%. Calcd for $C_{12}H_{17}ON$: N, 7.32%.

*4-Methoxybutyrophenone(**13'**)*: To a solution of sodium methoxide, prepared from 1.38 g (0.06 mol) of sodium and 60 ml of methanol, was added, by portions, 4-chlorobutyrophenone ethylene acetal (11.4 g, 0.05 mol; mp 55—57 °C; Found: C, 63.60; H, 6.83%. Calcd for $C_{12}H_{15}ClO_2$: C, 63.58; H, 6.67%, prepared from 4-chlorobutyrophenone, ethylene glycol, and a catalytic amount of *p*-toluenesulfonic acid, refluxed in benzene for 48 h with a Dean-Stark water separator; yield, 69%). The reaction mixture was subsequently stirred for 45 min at 50 °C and then cooled to room temperature. After the addition of a saturated sodium chloride solution, the reaction mixture was extracted with benzene and the extract was washed with water, dried (Na_2SO_4), and concentrated, yielding 10.2 g of a pale yellow oil. It was dissolved in 50 ml of methanol, and, after the addition of 10 ml of concd HCl, the methanol solution was stirred for 1 h at room temperature. The solvent was then removed, and the residue was extracted with ether. The extract was washed with a sodium hydrogencarbonate solution and brine successively, dried (Na_2SO_4), concentrated, and distilled, yielding 5.0 g (56%) of **13'** as a colorless oil: bp 93 °C/0.5 Torr; NMR (CCl_4) δ=1.96 (2H, quintet, $-CH_2\underline{CH_2}CH_2-O$), 3.01 (2H, t, $-CO-CH_2-$), 3.41 (2H, t, $-CH_2OMe$), 3.29 (3H, s, OMe); Found: C, 74.23; H, 8.01%. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92%.

*4-(Methylthio)butyrophenone(**14'**)*: To a solution of a 20% aq solution of sodium methyl sulfide (16 ml) was added, drop by drop, 4-chlorobutyrophenone ethylene acetal (9.08 g, 40 mmol) in 120 ml of ethanol, after which the reaction mixture was warmed at 60 °C for 1 h. After concentration *in vacuo*, the mixture was poured into water and extracted with ether. The extract was washed with a saturated sodium chloride solution. After the removal of the ether, the pale yellow residue was dissolved in 50 ml of methanol and stirred for 1 h with 10 ml of concd HCl at room temperature. The methanol was then removed under reduced pressure, and the residue was dissolved in ether, washed with saturated sodium hydrogencarbonate and brine successively, dried (Na_2SO_4), concentrated, and distilled, giving a pale yellow oil, which was subsequently distilled *in vacuo* to yield 5.6 g (72%) of **14'**: bp 118 °C/1 Torr; NMR (CCl_4) δ=1.8—2.1 (2H. m, $-CH_2\underline{CH_2}CH_2-S$), 2.07 (s, SMe), 2.56 (2H, t, $-CH_2-S$), 3.07 (2H, t, $-CO-CH_2-$); Found: C, 68.07; H, 7.40%. Calcd for $C_{11}H_{14}OS$: C, 68.00; H, 7.26%.

*5-Methoxyvalerophenone(**16'**)*: To a Grignard reagent prepared from 1-chloro-4-methoxybutane (12.3 g, 0.1 mol), magnesium turnings (2.6 g, 0.11 mol), and ether (35 ml) was added, drop by drop, benzonitrile (10.3 g, 0.1 mol) in toluene (50 ml). After the moderately exothermic reaction had subsided, about 50 ml of the solvent was distilled off. Reflux was continued for 4 h, and then the mixture was stood overnight at room temperature. It was subsequently poured into water containing concd HCl, extracted with ether, washed with dil NaOH and water successively, dried ($MgSO_4$), concentrated and distilled *in vacuo* to yield 16.3 g (85%) of **16'** as a colorless oil: bp 119—120 °C/0.2 Torr; NMR (CCl_4) δ=1.7 (4H, m, $-CO-CH_2\underline{CH_2}\underline{CH_2}CH_2$), 2.96 (2H, t, $-CO-CH_2-$), 3.29 (s, $-OCH_3$), 3.38 (t, $-CH_2-O$); Found: C, 74.96; H, 8.56%. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39 %.

*ω-Substituted 1-Phenyl-1-alkanols (**9**, **12**, **13**, **14**, and **16**)*: These new carbinols were obtained as a colorless oil by the $LiAlH_4$ reduction of the corresponding ketones in ether. (±)-**9**: NMR (CCl_4) δ=1.75—2.1 (m, $-CH(OH)-\underline{CH_2}$), 2.01 (s, SMe), 2.47 (2H, t, $-CH_2-S$), 4.67 (1H, dd, $-\underline{CH}-(OH)-$); Found: C, 65.85; H, 7.77%. Calcd for $C_{10}H_{14}OS$: C, 65.89; H, 7.74%. (±)-**12**: NMR (CCl_4) δ=1.65 (4H, m, $-CH(OH)-\underline{CH_2}\underline{CH_2}-$), 2.17—2.2 (8H, NMe_2 and $-CH_2-N$), 4.47 (1H, dd, $-\underline{CH}(OH)-CH_2-$); Found: C, 74.53; H, 9.95; N, 7.00%. Calcd for $C_{12}H_{19}ON$: C, 74.57; H, 9.91; N, 7.25%. (±)-**13**: NMR (CCl_4) δ=1.6 (4H, m, $-CH(OH)-\underline{CH_2}\underline{CH_2}-$), 3.21—3.28 (5H, OMe and $-CH_2-O$), 4.49 (1H, t, $-\underline{CH}(OH)-$); Found: C, 73.36; H, 9.04%. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95%. (±)-**14**: NMR (CCl_4) δ=1.6 (4H, m, $-CH(OH)-\underline{CH_2}\underline{CH_2}-$), 1.96 (3H, s, SMe), 2.36 (2H, t, $-CH_2-S$), 4.49 (1H, t, $-CH(OH)-$); Found: C, 67.25; H, 8.26%. Calcd for $C_{11}H_{16}OS$: C, 67.25; H, 8.28%. (±)-**16**: NMR (CCl_4) δ=1.6 (6H, m, $-CH(OH)-\underline{CH_2}\underline{CH_2}\underline{CH_2}-$), 3.20—3.26 (5H, OMe and $-CH_2-O$), 4.51 (1H, t, $-CH(OH)-$); Found: C, 74.18; H, 9.44%. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34%.

Determination of Absolute Configurations by Chemical Correlation. (S)-(+)-*2-Methoxy-1-phenylethanol(**2**)*: A mixture of (*S*)-(+)-1-phenyl-1,2-ethanediol(**17**) [1.38 g, 10 mmol, $[\alpha]_D^{20}$ +39.2° (*c* 2.62, EtOH)],[19] potassium carbonate (2.38 g), and methyl iodide (0.75 ml, 12 mmol) in acetone (15 ml) was refluxed for 15 h. The reaction mixture was then filtered, and the filtrate was concentrated, after which the residue was dissolved in ether. The ether solution was washed with water, dried (Na_2SO_4), and concentrated to give 1.24 g of a pale yellow oil containing about 50% of **2**. The monomethyl ether was concentrated by silica gel column chromatography,

using benzene-ether (10 : 1) as the eluent, purified by preparative GLC(PDEGS 1/4″×1.5 m, 170 °C, He 60 ml/min), and distilled *in vacuo* [115 °C (bath)/1 Torr]. 197 mg; NMR (CCl_4) δ=3.1—3.6 (AB part of ABX, $-CH_2-O$), 3.36 (3H, s, OMe), 4.73 (1H, dd, -CH(OH)-); $[\alpha]_D^{20}$+44.6° (*c* 4.54, cyclopentane).

(S)-(+)-*2-Methylthio-1-phenylethanol (**3**)*: Tosyl chloride (3.14 g, 16 mmol) was added, portion by portion ,to a solution of (*S*)-(+)-**17** (2.07 g, 15 mmol, $[\alpha]_D^{20}$ +39.2° in EtOH) in pyridine (20 ml) at 0 °C. After the addition was completed, the reaction mixture was allowed to stand overnight in a refrigerator, poured into water (200 ml), and extracted with benzene. The extract was washed with 2M HCl and saturated sodium hydrogencarbonate successively, dried (Na_2SO_4), and concentrated to yield crude (*S*)-(+)-1-phenyl-1,2-ethanediol 2-tosylate (4.1 g), which was then recrystallized from benzene-hexane to give fine needles (2.6 g, 59%); mp 72—73 °C; $[\alpha]_D^{20}$ +30.3° (*c* 3.35, MeOH); Found: C, 61.75; H, 5.52%. Calcd for $C_{15}H_{16}O_4S$: C, 61.63; H, 5.52%. To a stirred solution of the tosylate (584 mg, 2 mmol) in ethanol (10 ml) was added, drop by drop 20% aq sodium methyl sulfide (0.8 ml, *ca.* 3 mmol) at room temperature. Stirring was continued for 2 h. After water had been added to the mixture, it was extracted with ether. The subsequent evaporation of the solvent afforded a pale yellow oil (290 mg), which was chromatographed on silica gel using benzene–ether (20 : 1) as the eluent and distilled [120 °C(bath)/1 Torr] to yield 150 mg (45%) of **3** as a pale yellow oil: NMR (CCl_4) δ=2.02 (3H, s, SMe), 2.4—2.9 (AB part of ABX, $-CH_2-S$), 4.6 (1H, dd, -CH(OH)-); $[\alpha]_D^{20}$ +63.8° (*c* 5.63, cyclopentane).

(S)-(−)-*4-Chloro-1-phenyl-1-butanol (**18**)*: This alcohol was prepared by the asymmetric reduction of 4-chlorobutyrophenone by $LiAlH_4$ modified by (−)-(2*R*, 3*S*)-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol (LAH : R*OH=1 : 2.3) according to the reported procedure.[4b] The absolute configuration was determined to be *S*(−) by (*R*)-(+)-MTPA/$Eu(fod)_3$ method;[10] LIS_A 8.64, LIS_B 8.08, ΔLIS 0.56; 54 %ee, $[\alpha]_D^{20}$ −27.3° (*c* 2.83, cyclopentane); NMR (CCl_4) δ= 1.73 (4H, m, $-CH(OH)-CH_2CH_2-$), 3.42 (2H, bt, $-CH_2Cl$), 4.50 (1H, bt, -CH(OH)-). Acetate of **18**; $[\alpha]_D^{20}$ −49.3° (*c* 5.88, cyclopentane). The absolute configuration of **18** was confirmed by hydrogenolysis to (*S*)-(−)-1-phenyl-1-butanol (**6**) (see Table 1, Entry 6) as follows. A THF solution (8 ml) of $LiAlH_4$ (160 mg, 4 mmol) and **18** (277 mg, 1.5 mmol, $[\alpha]_D^{20}$ −27.3°) was refluxed at 95 °C for 3 h. The reaction mixture was then worked-up in a usual way, and the resulting colorless oil (198 mg) was submitted to preparative TLC (silica gel, 20% ethyl acetate in hexane) to yield 48 mg of (*S*)-(−)-**6** as colorless crystals; $[\alpha]_D^{20}$−31.0° (*c* 3.08, cyclopentane).

(S)-(−)-*4-Dimethylamino-1-phenyl-1-butanol (**12**)*: The acetate (412 mg, $[\alpha]_D^{20}$−49.3° in cyclopentane) of **18** was refluxed for 6 h with sodium iodide (600 mg) in ethyl methyl ketone and then transformed to 493 mg of crude 4-iodo-1-phenyl-1-butanol as a colorless oil: $[\alpha]_D^{20}$ −33.6° (*c* 3.21, cyclopentane). This was used without further purification. To a solution of dimethylamine (5 g) in ether (10 ml) was added crude 4-iodo-1-phenyl-1-butanol (480 mg) in dry ether (5 ml), and the mixture was stood overnight at room temperature. The precipitates were filtered off, and the filtrate was concentrated *in vacuo*. The residue was dissolved in ether and extracted with 2M HCl. After having been washed with ether, the acid layer was made alkaline and extracted with ether, washed with water, dried (Na_2SO_4), concentrated, and distilled [120 °C (bath)/0.4 Torr], yielding 225 mg of **19**: NMR (CCl_4) δ=1.2—1.9 (4H, m, $-CH(OAc)-CH_2CH_2-$), 2.0 (3H, s, OAc), 2.09 (6H, s, NMe_2), 2.22 (2H, t, $-CH_2-N$), 5.67 (1H, t, -CH(OAc)-); $[\alpha]_D^{20}$ −42.5° (*c* 3.30, cyclopentane). The reduction of **19** (200 mg) with $LiAlH_4$ (150 mg) in ether (4 ml) at room temperature for 4 h afforded **12** (125 mg) as a colorless oil, which was distilled *in vacuo* [90 °C (bath)/0.2 Torr]; $[\alpha]_D^{20}$ −28.6° (*c* 3.40, cyclopentane).

Asymmetric Reduction of ω-Substituted Alkyl Phenyl Ketones with Lithium Tri-l-menthoxyaluminum Hydride. Under a nitrogen atmosphere, to a stirred solution of $LiAlH_4$ (1.2 mmol) in ether (2.5 ml) was added *l*-menthol (562 mg, 3.6 mmol) in 2 ml of the same solvent at 0 °C. The container of *l*-menthol was washed with 1 ml of ether, and the washing was added to the $LiAlH_4$ solution. Three minutes after the initial addition of menthol, ketone (1 mmol) in 0.5 ml of ether was added, drop by drop, to the LAH–menthol complex and the container of ketone was also washed with 0.5 ml of ether. The reaction mixture was stirred for 3 h at 0 °C to give a transparent solution. The excess hydride was decomposed with a small amount of water. After the addition of excess dil HCl, the mixture was extracted with ether. The extract was washed with saturated sodium hydrogencarbonate and water successively and dried (Na_2SO_4). The product was purified by preparative GLC and finally distilled *in vacuo*. In the case of the reduction of amino ketones, the products were extracted with dil HCl from the reaction mixture. After the extract had then been made alkaline, the amino alcohol liberated was extracted with ether and purified by preparative GLC and distilled *in vacuo*.

The enantiomeric purities of the resulting alcohols were determined according to a method previously reported.[10]

Optical rotations, $[\alpha]_D^{20}$ in cyclopentane, of the new optically active alcohols are as follows. (*S*)-**2**, +44.6° (*c* 4.54) optically pure; (*S*)-**3**, +63.8° (*c* 5.63) optically pure; (*R*)-**8**, +11.1° (*c* 3.78) 34%ee; (*R*)-**9**, +3.63° (*c* 3.94) 18%ee; (*R*)-**12**, +1.65° (*c* 4.67) 3%ee; (*R*)-**13**, +15.2° (*c* 4.72) 38 %ee; (*R*)-**14**, +1.43° (*c* 4.44) 12%ee; (*R*)-**15**, +2.86° (*c* 5.71) 13%ee; (*R*)-**16**, +0.322° (*c* 8.73) 16%ee.

*Asymmetric Reduction of 3-Piperidinopropiophenone (**11′**) in the Presence of TMEDA.* To a solution of $LiAlH_4$ (2.0 mmol) in 5 ml of ether was added *l*-menthol (938 mg, 6 mmol) in 4 ml of ether at 0 °C. The ether was subsequently removed *in vacuo*, and the residue was dissolved in 9 ml of dry toluene. *N,N,N′,N′*-Tetramethylethylenediamine (TMEDA) [Run 1, 0.3 ml (2 mmol); 2, 0.6 ml (4 mmol); 3, 1.2 ml (8 mmol); 4, none] was added to the solution, and the resulting solution was cooled to 0 °C. After 3 min, **11′** (217 mg, 1 mmol) in 1 ml of toluene was added. The reaction mixture was kept overnight at 0 °C. After the cautious addition of water, the reaction mixture was extracted with dil HCl. The acid layer was made alkaline with dil NaOH and extracted with ether. The solvent and TMEDA were removed *in vacuo*, and the product was purified by distillation [120 °C(bath)/0.5 Torr]. No starting ketone was detected on GLC. The results are shown in Table 2.

The authors wish to express their deep gratitude to Professor Harry S. Mosher, Stanford University, for his helpful suggestions throughout this work. The authors also wish to thank Mrs. Fujiko Yasuhara for the measurement of the NMR spectra.

References

1) A part of this work was presented at 31st Annual Meeting of the Chemical Society of Japan, Sendai, October 1974.

2) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Englewood Cliffs, New Jersey

(1971), p. 202.

3) (a) O. Cěrvinka and O. Belovsky, *Coll. Czech. Chem. Commun.*, **32**, 3897 (1967); (b) O. Cěrvinka, *ibid.*, **30**, 1684 (1965); (c) O. Cěrvinka and O. Belovsky, *ibid.*, **30**, 2487 (1965).

4) (a) S. Yamaguchi, H. S. Mosher, and A. Pohland, *J. Am. Chem., Soc.* **94**, 9254 (1972); (b) S. Yamaguchi and H. S. Mosher, *J. Org. Chem.*, **38**, 1870 (1973); (c) C. J. Reich, Ph. D. Thesis, Stanford University, 1976.

5) S. Yamaguchi, F. Yasuhara, and K. Kabuto, *J. Org. Chem.*, **42**, 1578 (1977).

6) S. Yamada and K. Koga, *Chem. Pharm. Bull.*, **20**, 526 (1972) and the references therein; (b) H. Handel and J. L. Pierre, *Tetrahedron*, **31**, 997 (1975).

7) R. Andrisano, A. S. Angeloni, and S. Marzocchi, *Tetrahedron*, **29**, 913 (1973).

8) (a) A. Horeau, H. B. Kagan, and J. P. Vigneron, *Bull. Soc. Chim. Fr.*, **1968**, 3795; (b) R. J. Evans, S. R. Landor and J. P. Regan, *J. Chem. Soc., Pekin Trans. 1*, **1974**, 552.

9) The same results were obtained by means of Mosher's method based on the chemical-shift difference of the MeO signals of the (*R*)-(+)-MTPA acid moiety, except in the case of Y=OMe (**2**, **8**, **13**, and **16**), where a partial overlapping between the MeO(MTPA) and the methylene(–CH_2–OMe) signals made the configurational determination difficult. The chemical-shift differences of the OMe, SMe, and NMe_2 of the carbinyl moiety can also be utilized for the configurational determination; J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, **95**, 512 (1973).

10) S. Yamaguchi, F. Yasuhara, and K. Kabuto, *Tetrahedron*, **32**, 1363 (1976).

11) (a) G. R. Sullivan, J. A. Dale, and H. S. Mosher, *J. Org. Chem.*, **38**, 2143 (1973); (b) S. Yamaguchi, J. A. Dale, and H. S. Mosher, *ibid.*, **37**, 3174 (1972).

12) J. L. Pierre and H. Handel, *Tetrahedron Lett.*, **1974**, 2317.

13) R. W. Parry in "Chemistry of the Coordination Compounds," ed by J. C. Bailar, Reinhold Publishing Cooporation, New York (1956), p. 220.

14) While this study was in progress, higher optical yields (**7**, 77%ee; **11**, 66%ee) were reported by Andrisano *et al.*[7] under similar reaction conditions. In spite of the repeated reinvestigation of the various reaction conditions which are considered to be important factors in regulating the optical yields (the aging factor of the reagent;[4a,20] the concentration and composition of the reagent; the purities of the substrates, ligand, and LAH), the results reported in the literature were not duplicated.

15) N. B. Chapman, *J. Chem. Soc.*, **1963**, 1387.

16) R. B. Moffett and R. L. Schriner, *Org. Synth.* **21**, 79 (1941).

17) R. E. Lesile and H. R. Henze, *J. Am. Chem. Soc.*, **71**, 3480 (1949).

18) M. J. Weiss and M. D. O'Donoghue, *J. Am. Chem. Soc.*, **79**, 4774 (1957).

19) V. Prelog, M. Wilhelm, and D. B. Bright, *Helv. Chim. Acta*, **37**, 221 (1954).

20) (a) L. J. Altman and Y. Li, *Tetrahedron Lett.*, **1976**, 2493; (b) D. J. Sandman, K. Mislow, W. P. Giddings, J. Dirlam, and G. C. Hanson, *J. Am. Chem. Soc.*, **90**, 4877 (1968).