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Optical Resolution of 2′-Methoxy-1,1′-binaphthyl-2-carboxylic Acid, and Application to Chiral Derivatizing Agent for HPLC Separation of Enantiomeric Alcohols and Amines

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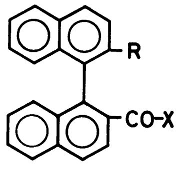
Racemic 2′-methoxy-1,1′-binaphthyl-2-carboxylic acid was separated on a multi-gram scale into its antipodes via silica-gel column chromatography followed by alkaline hydrolysis of the diastereomeric esters prepared from (*R*)-1-phenylethanol or (−)-menthol. The molecular structure of (−)-menthyl (a*S*)-2′-methoxy-1,1′-binaphthyl-2-carboxylate was determined by single-crystal X-ray analysis. The (a*S*)-acid was converted to crystalline acid chloride, which was conveniently utilized as efficient chiral derivatizing agent for differentiation of enantiomeric alcohols and amines by high-performance liquid chromatography on silica gel. The elution behavior of a pair of diastereomeric esters or amides was explained by the steric interactions between the solutes and the silica-gel stationary phase on the basis of the X-ray analysis.

During the last two decades, a number of chiral derivatizing agents have been developed for discrimination of enantiomers.1,2) Almost all of these possess C-centrochirality to exert stereo-differentiating ability, among which, Mosher's α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) has been most widely used.3)

It has been well-recognized recently that axially dissymmetric biaryls are efficient chiral auxiliaries in a variety of asymmetric reactions,4) and then, these biaryls should also be good candidates for chiral derivatizing agents. Only a few reports, however, have appeared dealing with atropisomeric biaryls as such.5,6) This seems mainly because of the difficulties accompanying the preparation of prerequisite chiral biaryl components. For example, the synthesis of optically active 2′-methyl-1,1′-binaphthyl-2-carbonyl cyanide (**1′**), the first chiral derivatizing agent with axially chiral binaphthyl unit reported in 1982 by Goto et al., required lengthy and subtle manipulations via 1,1′-binaphthyl-2,2′-dicarboxylic acid.5)



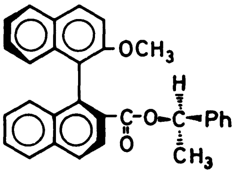
1 ; R = CH_3, X = OH
1′ ; R = CH_3, X = CN
2 ; R = OCH_3, X = OH
2′; R = OCH_3, X = Cl

We previously reported a practical method for the synthesis of 1,1′-binaphthyl-2-carboxylic acids.7) As part of a program in our laboratory directed toward the use of these acids for elaboration of efficient chiral recognizing elements,8) we wish to report herein a multi-gram scale optical resolution of 2′-methoxy-1,1′-binaphthyl-2-carboxylic acid (**2**) and its application to chiral derivatizing agent for differentiation of enantiomeric alcohols and amines by high-performance liquid chromatography (HPLC).

Results and Discussion

Optical Resolution of 2. Wilson and Cram reported the preparation of optically pure (a*S*)-**2**9) by repeated crystallization of quinidine salt of rather pure (a*S*)-**2** (81%ee) which had been obtained by a chiral version of the oxazoline-assisted nucleophilic displacement on alkoxyarenes (the Meyers reaction).10) We repeated the resolution procedure starting from racemic **2**, but realized that it was very sensitive to the experimental conditions, thus making difficult to obtain reproducible results. Furthermore, preferential precipitation of the racemate caused frequent decrease of the optical rotations of partially active samples of **2** during manipulations.10)

We noticed, however, that many of the pairs of diastereomeric esters prepared from (±)-**2** and chiral alcohols gave two distinct spots on silica-gel TLC. This implies the possibility of optical resolution of **2** via chromatographic separation of the diastereomeric esters followed by hydrolytic removal of the chiral alcohol residue. Our expectation was realized by the fact that a multi-gram sample of diastereomeric esters prepared from (±)-**2** and (*R*)-1-phenylethanol was readily separated into (*R*)-1-phenylethyl (a*S*)-2′-methoxy-1,1′-binaphthyl-2-carboxylate ((a*S*,*R*)-**3a**) and the (a*R*,*R*)-counterpart by a silica-gel column chromatography. Upon alkaline hydrolysis, each of the diastereomers afforded the corresponding optically pure **2** as judged by HPLC on Pirkle column as *N*-butylamide. Practically, inexpensive (−)-menthol was ad-



(aS,R)-3a

vantageously replaced for enantiomeric 1-phenylethanol; although hydrolysis of the diastereomeric esters (**3b**) required longer heating at reflux in aqueous ethanol in the presence of potassium hydroxide, no trace of racemization was observed.

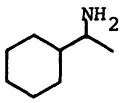
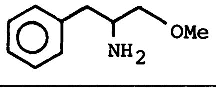
Utilization of Axially Chiral 2 as Chiral Derivatizing Agent. Treatment of (a*S*)-**2** with thionyl chloride and recrystallization from hexane gave the acid chloride (a*S*)-**2′** as pale yellow prisms. Several partially active alcohols or amines of known enantiomeric composition were acylated with a small excess of (a*S*)-**2′** in benzene–pyridine (or triethylamine) in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP) to give the corresponding diastereomeric pairs of esters or amides. These pairs were subjected to HPLC analysis, and Tables 1 and 2 list the results of separation of alcohols and amines, respectively. Although reversed-phase HPLC on a ODS column eluting with aqueous ethanol or acetonitrile gave not so good separation, normal-phase HPLC on a spherical silica-gel column

Table 1. HPLC Separation of Diastereomeric Esters Derived from (a*S*)-**2**[a)]

HO-R	k'[b)]		α[c)]	R_s[d)]
	(a*S*,*R*)	(a*S*,*S*)		
$\text{HO-}\overset{\text{Me}}{\text{C}}\text{H-Ph}$	5.85	8.39	1.43	7.40
	8.91[e)]	9.65	1.08	0.95
	9.98[f)]	9.98	1.00	0
Menthol	2.24	2.91	1.30	4.44
	14.44[e)]	14.44	1.00	0
	18.30[f)]	19.30	1.05	0.72
Borneol	3.50	4.48	1.28	4.35
$\text{HO-}\overset{\text{Me}}{\text{C}}\text{H-Et}$	4.60	5.54	1.21	3.83
$\text{HO-}\overset{\text{Me}}{\text{C}}\text{H-CHMe}_2$	3.82	5.16	1.35	6.05
$\text{HO-}\overset{\text{Me}}{\text{C}}\text{H-C}_6\text{H}_{13}$	2.74	3.99	1.46	6.41
α-Tetralol	4.58	5.61	1.22	4.10

a) Operating conditions: column, silica gel; eluent, 2.5% AcOEt/hexane, 1 ml min^{-1}. b) Capacity factor=(retention volume of diastereomer−void volume of column)/(void volume of column). c) Separation factor$=k'_{(aS,S)}/k'_{(aS,R)}$. d) Resolution factor=2× (distance between the peaks of two diastereomers)/(sum of bandwidth of the two peaks). e) ODS column; MeOH/H$_2$O (80/20), 1 ml min^{-1}. f) ODS column; MeCN/H$_2$O (80/20), 1 ml min^{-1}.

Table 2. HPLC Separation of Diastereomeric Amides Derived from (a*S*)-**2**[a)]

H$_2$N-R	k'		α	R_s
	(a*S*,*R*)	(a*S*,*S*)		
$\text{H}_2\text{N-}\overset{\text{Me}}{\text{C}}\text{H-Ph}$	6.17	10.24	1.66	7.56
$\text{H}_2\text{N-}\overset{\text{Me}}{\text{C}}\text{H-(1-Naphthyl)}$	4.09	6.76	1.65	4.30
$\text{H}_2\text{N-}\overset{\text{Me}}{\text{C}}\text{H-(2-Naphthyl)}$	8.05	13.97	1.74	9.02
$\text{H}_2\text{N-}\overset{\text{Me}}{\text{C}}\text{H-Et}$	10.84	13.53	1.25	3.40
$\text{H}_2\text{N-}\overset{\text{Me}}{\text{C}}\text{H-C}_5\text{H}_{11}$	8.94	14.68	1.64	8.73
$\text{H}_2\text{N-}\overset{\text{Me}}{\text{C}}\text{H-C}_6\text{H}_{13}$	4.63	7.58	1.64	5.30
Bornylamine	8.77	12.53	1.45	6.30
Isobornylamine	10.18	14.38	1.41	5.48
	13.06	19.53	1.50	6.97
	18.61	36.61	1.97	12.27

a) Operating conditions: column, silica gel; eluent, 1% *i*-PrOH/hexane, 2 ml min^{-1}.

cleanly differentiated two diastereomeric esters with base-line separation (Table 1). It should be noted that among a given diastereomeric pair of esters or amides of α-chiral alcohols or amines, the (a*S*,*R*)-isomer eluted faster than the (a*S*,*S*)-counterpart (vide infra).

Kinetic resolution is a potential problem in using a chiral derivatizing agent, but it was shown that acylation of racemic 1-phenylethanol or 1-phenylethylamine by (a*S*)-**2′** under standard conditions gave essentially 1:1 mixture of (a*S*,*R*)- and (a*S*,*S*)-isomer within the limits of ^{1}H NMR detection at 60 MHz.[11] Furthermore, it was also shown that the diastereomeric composition of a mixture of diastereomeric esters prepared from a sample of partially active 1-phenylethanol was identical to the enantiomeric composition of the starting alcohol as determined by HPLC analysis (see Experimental). These facts indicate that axially chiral **2** is useful as a chiral derivatizing agent for HPLC determination of absolute configuration and enantiomeric purity of α-chiral alcohols and amines.

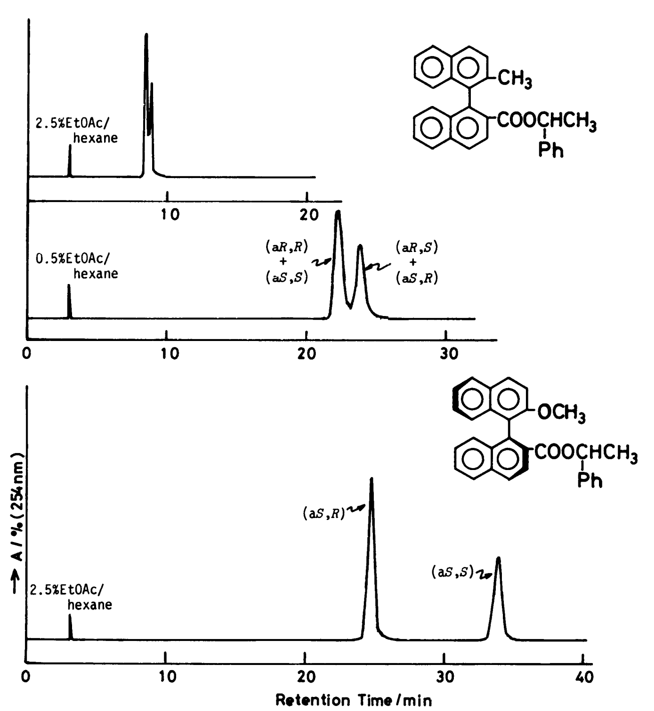
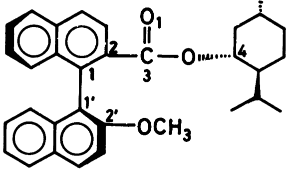


Fig. 1. HPLC resolution of diastereomeric 1-phenylethanol esters of **1** and **2**.

Effects of the Presence of 2′-Methoxyl Group. Figure 1 shows HPLC chromatograms of diastereomeric 1-phenylethanol esters of **1** and **2**. It should be noted that replacement of 2′-methoxyl for 2′-methyl functionality significantly increases both of the retention volumes and the separation factor α.

X-Ray Structure of (−)-Menthyl Ester of (a*S*)-2. Wilson and Cram assigned the absolute configuration of (−)-**2** to a*S* by correlating it to (a*S*)-(−)-1,1′-bi-2-naphthol.[10] Their assignment is now unambiguously confirmed here on the basis of the fact that the configuration of the (−)-menthyl carbon, C_4 in **3b** is *R*: Recrystallization of (−)-menthyl ester of (a*S*)-**2** ((a*S*,*R*)-**3b**) from hexane gave cubic crystals proper for X-ray diffraction. The ORTEP drawings in Fig. 2 show the complete connectivity established by the crystal structure analysis. It was shown that there are two independent molecules in the unit cell (**3b-1** and **3b-2**).



(a*S*,*R*)-**3b**

These two molecules have no significant differences in the bond lengths and angles, but take slightly different conformations around the single bond linking the two naphthalene rings as shown in the ORTEP drawings; the dihedral angle (θ, C_2–C_1–$C_{1'}$–$C_{2'}$) is 89.0° in **3b-1** (see Fig. 3), while that is 97.8° in **3b-2**. At the same time, the torsion angles of the carbonyl groups are also slightly different; the dihedral angles (ϕ, C_1–C_2–C_3–O_1) are 1.1° and 10.5° for **3b-1** and **3b-2**, respectively.

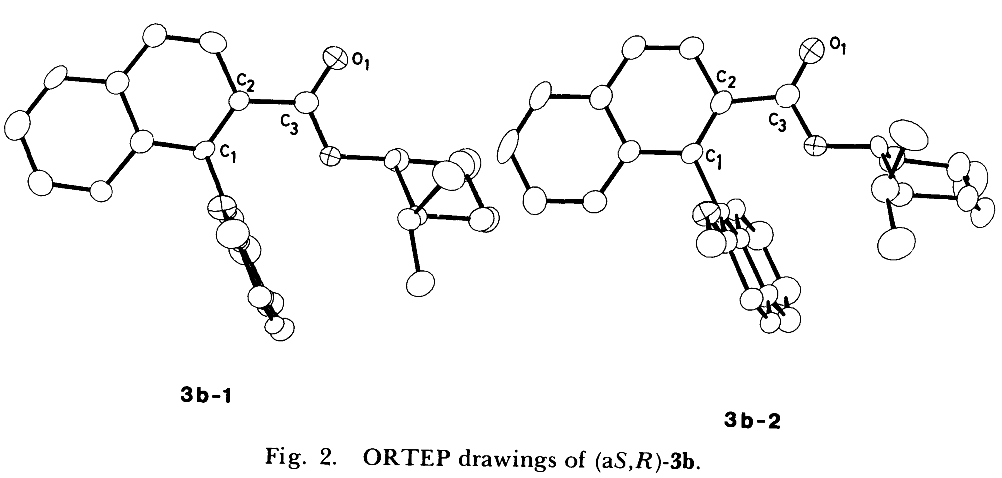


Fig. 2. ORTEP drawings of (a*S*,*R*)-**3b**.

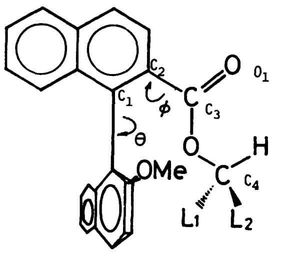


Fig. 3. Schematic view of crystal structure of alcohol (CL_1L_2H-OH) ester of (a*S*)-**2**.

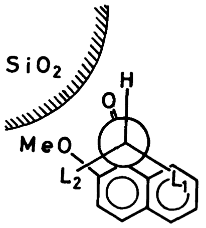


Fig. 4. Schematic view of the interaction of alcohol (CL_1L_2H-OH) ester of (a*S*)-**2** with silica-gel stationary phase.

Thus, the molecule **3b-1** has an almost orthogonal conformation concerning the naphthalene rings with almost coplanar carboxyl group with one of the naphthalene rings, while the molecule **3b-2** has a slightly deviated conformation from that of **3b-1**. These deviations seem to be due to subtle differences in the packing effect into the crystalline state.

Mechanistic Aspects of the Differentiation of Enantiomeric Alcohols and Amines by Axially Chiral 2. The most characteristic features of (a*S*,*R*)-**3b** based on the X-ray analysis are approximated as follows; 1) the dihedral angle confined by the two naphthalene rings is almost orthogonal, 2) CO-O-C_4-H atoms are nearly on the same plane that contains the naphthalene ring connecting the carboxyl function at the C_2-position, and 3), thus the plane roughly bisects the two other ligands (L_1 and L_2) attached at the C_4-carbon. These stereochemical features can be simplified as schematically shown in Fig. 3.

It is said that adsorptions of the solutes to the stationary phase mainly control the chromatographic behavior of the solutes on a normal-phase silica-gel HPLC. In this context, interactions of the diastereomeric esters or amides of **2** with the silica-gel surface by virtue of the carbonyl oxygen and/or methoxyl oxygen may play critical role.

On the assumption that prevailing conformations of these diastereomers in HPLC conditions are deducible from those of the X-ray structure of the (a*S*,*R*)-**3b**,[12] Fig. 4 shows a schematic model for the interaction of the solute with silica-gel surface based on the structure depicted in Fig. 3. It may be said that, among a given diastereomeric pair, the (a*S*,*S*)-isomer should be adsorbed more strongly than the (a*S*,*R*)-counterpart, because in the former the ligand L_2, which is arrayed toward the adsorbent, is smaller than L_1, while in the latter, the relationship of the steric bulk of the two ligands is reversed.

As mentioned above, the idea of utilizing axially chiral biaryl derivatives as chiral derivatizing agent for enantiomeric compounds was first reported by Goto et al.[5] Their 2′-methyl-1,1′-binaphthyl-2-carbonyl moiety was highly efficient for HPLC differenciation of several alcohols which contained oxycarbonyl function. At our hand, however, the moiety did not show so much discrimination, as compared with **2**, for simple alcohols such as 1-phenylethanol (Fig. 1). This is another support for the above reasoning that HPLC behavior of the diastereomeric esters and amides of **2** is largely determined by the coordination to silica-gel surface by the carbonyl oxygen as well as the methoxyl oxygen.

In conclusion, we have shown here that axially chiral **2**, which is readily obtainable in a multi-gram scale,[13] serves as an efficient chiral derivatizing agent for differentiation of enantiomeric alcohols and amines by HPLC.

Experimental

Instruments. HPLC measurements were carried out on a JASCO TRIROTAR-III and/or a Shimadzu LC-5A, with UV detection at 254 nm. Stainless-steel columns (0.46 cm i.d. ×25 cm) were packed with Hitachi Gel 3056 for the silica-gel column and JASCO FINPAK C_{18} for the ODS column, respectively, using conventional slurry techniques. IR and UV spectra were measured on a Shimadzu IR-430 grating spectrophotometer and a Shimadzu UV 160 spectrophotometer, respectively. ^{1}H NMR spectra were recorded on a JEOL JNM-FX60 instrument in benzene-d_6 using tetramethylsilane as an internal standard. Optical rotations were recorded on a Union PM-101 automatic digital polarimeter in a 1-cm cell at 23—25 °C. Melting points were measured on a Yamato MP-21 and uncorrected.

Materials. Racemic binaphthylcarboxylic acids **1** and **2** were prepared as described in previous paper.[7] Samples of partially active alcohols and amines (20—70%ee) were prepared by adding commercial enantiomers to the corresponding racemates unless otherwise noted. (*S*)-(+)-2-Octanamine was the sample obtained in this laboratory.[14] Solvents were purified as usual. Wako Gel C-200 was dried by heating at 120 °C for several hours before use for silica-gel column chromatography. Analytical, and preparative TLC were performed using Merck Kieselgel 60 F_{254}, and Merck Kieselgel 60 G, respectively. Water-sensitive reactions were routinely carried out in a nitrogen atmosphere.

Optical Resolution of 2 via (*R*)-1-Phenylethanol Ester. Racemic **2** (5.0 g, 15.2 mmol) was boiled in 30 ml of freshly distilled thionyl chloride for 5 h. After volatiles were evaporated in vacuo, residual thionyl chloride was removed by addition and evaporation of small portions of benzene (×3) to give (±)-**2′** as a brown solid. The acid chloride was dissolved in 70 ml of benzene. This was added dropwise to a solution of (*R*)-1-phenylethanol (2.3 g, 18.9 mmol) and 4-dimethylaminopyridine (1 g) in benzene (80 ml) and pyridine (5 ml). The mixture was stirred overnight at ambient temperature, and then heated at ca. 70 °C for 3 h. The cool mixture was diluted with benzene, washed (2 M[††] HCl, 1 M Na_2CO_3, and water), and dried over $MgSO_4$ in the presence of activated charcoal. After filtration and evaporation of volatiles in vacuo, the organic residue was subjected to chromatography using a 7 cm i.d. ×30 cm silica-gel column with benzene as the eluent. Fractions containing two components were combined together and chromatographed again, finally affording the following diastereomerically pure samples beside 0.65 g of a mixture of **3a**:

(a*S*,*R*)-**3a**: 2.75 g (42% based on (±)-**2**); IR (KBr) 3060, 1705, 1272, and 765 cm^{-1}; UV (MeOH) 232.4 (λ_{max}) (ε 10.3×10^4) and ε 1.05×10^4 at 254 nm; ^1H NMR δ=0.68 (3H, d, *J*=6.45 Hz, C-CH_3), 3.15 (3H, s, O-CH_3), 5.79 (1H, q, *J*=6.45 Hz, -CH-), and 6.7—8.5 (17H, m, Ar-H). The sense of axial chirality was confirmed by the optical rotaion of **2** obtained by hydrolysis (vide infra).

(a*R*,*R*)-**3a**: 2.40 g (36%); IR (KBr) 3060, 1710, 1272, and 763 cm^{-1}; UV (MeOH) 232.4 (λ_{max}) (ε 9.35×10^4) and ε 1.02×10^4 at 254 nm; ^1H NMR δ=0.86 (3H, d, *J*=6.45 Hz, C-CH_3), 3.20 (3H, s, O-CH_3), 5.85 (1H, q, *J*=6.45 Hz, -CH-), and 6.4—8.5 (17H, m, Ar-H).

A sample of (a*S*,*R*)-**3a** (2.0 g, 4.62 mmol) was boiled in a solution of KOH (10 g) in ethanol (100 ml) and water (5 ml) for 3 h. Solvents were evaporated in vacuo, and the residue was dissolved in water. After extracted with ether, the aqueous layer was made acidic with concd HCl, and extracted with ether. Combined ether extracts were treated as usual to give (a*S*)-**2**, 1.50 g (99% yield); IR (KBr) 1690 cm^{-1}; $[\alpha]_D$ −25.5° (*c* 2.60, THF) (lit,[10] $[\alpha]_D$ −25.98° (*c* 1.22, THF)). A sample of (a*S*)-**2** (ca. 20 mg) was treated with excess butylamine in the presence of dicyclohexylcarbodiimide to give the *N*-butylamide,[8] which was confirmed to be more than 99.5%ee by HPLC on a Pirkle column.

Similar treatment of 2.30 g of (a*R*,*R*)-**3b** gave 1.71 g of (a*R*)-**2** which was confirmed enantiomerically pure by HPLC as above; $[\alpha]_D$ +25.4° (*c* 2.66, THF).

Synthesis and Separation of (−)-Menthyl Ester Diastereomers of (±)-2. (−)-Menthol (12.8 g, 82.1 mmol) was treated with (±)-**2′** (prepared from 9.15 g (27.8 mmol) of **2**) in the presence of DMAP (1 g) in benzene (100 ml) and pyridine (5 ml) as above. After as much menthol as possible was removed by sublimation under vacuum, remaining organic material was chromatographed twice on silica-gel column eluting with toluene to give 3.79 g of diastereomerically pure (a*S*,*R*)-**3b** (29% yield based on (±)-**2**)), 4.10 g of (a*R*,*R*)-**3b** (32%), and 2.64 g of a mixture of the diastereomers.

(a*S*,*R*)-**3b**: mp 145—146 °C (hexane); ^1H NMR δ=3.28 (3H, s, OCH_3); $[\alpha]_D$ −142° (*c* 2.11, $CHCl_3$).

(a*R*,*R*)-**3b**: mp 126—129 °C (hexane); ^1H NMR δ=3.24 (3H, s, OCH_3); $[\alpha]_D$ −55.4 °C (*c* 2.75, $CHCl_3$).

Both diastereomers of **3b** were heated at reflux with KOH in aqueous ethanol for 8—10 h to give optically pure acids as judged by HPLC as above.

Preparation of (aS)-2′. In a typical run, (a*S*)-**2** (1.09 g, 3.32 mmol) was treated with thionyl chloride as above, dissolved in hot hexane, filtered hot from activated charcoal, and allowed to stand to give (a*S*)-**2′** as prisms, 0.98 g (85% yield), mp 139—142 °C, IR (KBr) 1770 cm^{-1}.

Preparation of Diastereomeric Esters and Amides of (aS)-2. General procedure for the preparation of HPLC samples of diastereomers is as follows: To a stirred mixture of partially active alcohol or amine (0.3—0.4 mmol) and DMAP (0.1 g) in benzene (5 ml) and pyridine (1 ml) was added dropwise a solution of 1.2—1.5 equiv of (a*S*)-**2′** in benzene (10 ml). The mixture was stirred overnight, and then heated at 60—70 °C (amines) or at gentle reflux (alcohols) for 2—3 h. To the cool mixture was added 0.1 ml of 3-(dimethylamino)propylamine. It was diluted with ether, washed successively with 2 M HCl, 1 M Na_2CO_3, and water, and dried over $MgSO_4$. After volatiles were evaporated in vacuo, the mixture of diastereomeric esters or amides were recovered by TLC, care being taken not to cause fractionation of either of the diastereomers.

In case of (−)-borneol (*endo*-(1*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol), (−)-menthol ((1*R*, 2*S*, 5*R*)-2-isopropyl-5-methylcyclohexanol), (+)-bornylamine (*endo*-(1*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine), and (+)-isobornylamine (*exo*-(1*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine), excess of optically pure enantiomers was allowed to react with partially active (−)-**2′** of known enantiomeric composition (ca. 50%ee). For the sake of simplicity, diastereomers of these alcohols and amines were also presented in Tables 1 and 2 as if they were those prepared from (a*S*)-**2′** and partially active enantiomers.

^{1}H NMR Study of the Diastereomeric Ester or Amide Mixture of (±)-1-Phenylethanol or (±)-1-Phenylethylamine. (±)-1-Phenylethanol (50 mg, 0.41 mmol) was acylated with (a*S*)-**2′** (0.21 g, 0.61 mmol) as above. The diastereomeric ester mixture **3a**, which was obtained in 81% yield (0.144 g) after preparative TLC, was subjected to ^1H NMR measurement. The methoxyl protons of (a*S*,*R*)-**3a** which appeared at δ 3.15 shifted to δ 4.84 on addition of 1 equiv amount of lanthanoide shift reagent $Eu(fod)_3$ to the diastereomeric **3a**, while those of (a*S*,*S*)-**3a** which appeared at δ 3.19 shifted to δ 4.42. The ratio of peak areas of those lanthanoide-shifted methoxyl signals was 50.3 : 49.7, which should be regarded to indicate that the diastereomeric composition was practically 1 : 1 whithin the error limits of the integration of NMR peak areas at 60 MHz (vide infra).

Similar treatment of (±)-1-phenylethylamine with (a*S*)-**2′** gave the amide mixture in 93% yield. Addition of 1 equiv amount of $Eu(fod)_3$ caused shift of the methoxyl protons of (a*S*,*R*)-amide from δ 3.04 to δ 5.47, while those of (a*S*,*S*)-isomer from δ 3.12 to δ 5.19, with base-line separation of the two peaks. The ratio of areas of those two peaks measured to be 49.8 : 50.2.

HPLC Estimation of the Diastereomeric Composition of Partially Active 1-Phenylethanol Esters of (aS)-2. A sample of partially active 1-phenylethanol enriched in (*R*)-isomer was prepared to be 50%ee by addition of the racemate to the (*R*)-enantiomer. Aliquot of the sample was converted to the 3,5-dinitrophenylcarbamates. HPLC analysis of the carbamates on a chiral column developed in our laboratory[15] demonstrated that the mixture should be 49.9%ee.

The remainder of the partially active alcohol was converted to the diastereomeric esters by treatment with (a*S*)-**2′**. HPLC analysis of the mixture on silica-gel column showed the peaks of (a*S*,*R*)- and (a*S*,*S*)-**3a** in the ratio of

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[††] 1 M=1 mol dm^{-3}.

3.07:1 in the order of increasing retention time. The peak ratio was corrected for molar response indicating that the diastereomeric composition of the sample should be 49.7% de (diastereomeric excess), on the basis that the ratio of the peak areas of the aforementioned diastereomeric (a*S*,*R*)- and (a*S*,*S*)-**3a** from racemic 1-phenylethanol was 1.03:1 (see footnote a in Table 1 for the HPLC operating conditions).

Crystal Structure Determination of (a*S*,*R*)-3b. A prism-like crystal of (a*S*,*R*)-**3b** with the dimensions of 0.2×0.2×0.3 mm was used for the data collection on a Rigaku-Denki automated four-circle diffractometer (Rigaku AFC-5R), equipped with a rotating anode (40 kV, 200 mA) using Mo $K\alpha$ radiation (λ=0.71029 Å). Crystal data are as follows: M.F.=$C_{32}H_{34}O_3$, M.W.=466.59, orthorhombic space group $P2_12_12_1$, a=16.852(3), b=22.307(4), c=14.047(2) Å, V=5280.5(9) $Å^3$, Z=8, D_{calcd}=1.17 g cm^{-3}, μ(Mo $K\alpha$)=0.688 cm^{-1}. A total of 6027 reflections within 2θ=52° were measured using $2\theta-\theta$ scan mode and 3567 reflections with $|F_o|>3\sigma|F_o|$ were used for the structure determination. The structure was solved by the direct method and refined by the block-diagonal least-squares method to give an R factor of 0.09 including all hydrogen atoms which were calculated and verified by the difference Fourier synthesis.

Tables of atomic coordinates, temperature factors, bond lengths, bond angles, and the F_o-F_c list are kept at the Chemical Society of Japan (Document No. 8867).

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