Efficient Synthesis of Chiral Binaphthol Aldehyde with Phenyl Ether Linkage for Enantioselective Extraction of Amino Acids

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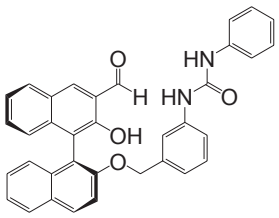
A binaphthol aldehyde with phenyl ether linkage, compound **2**, has been synthesized starting from binaphthol-3-carboxylic acid. The axially chiral binaphthol ring was racemized during the synthesis due to high temperatures required in *O*-phenylation reaction. The enantiomerically pure form of **2** was obtained from the resolution of the diastereomeric imine of **2**. Optically pure compound (*S*)-**2** was applied to the enantioselective liquid–liquid extraction of amino acid between CH_2Cl_2 and aqueous layers. The stereoselectivities, that is, D/L ratio of the amino acid extracted, ranged from 3.57 to 11.1. One carbon was absent in compound (*S*)-**2** compared to the compound (*S*)-**1** with benzyl ether linkage, which differentiated the conformations of their imines formed with amino acids.

Keywords: Enantioselective extractor, Optical resolution, Chiral imine

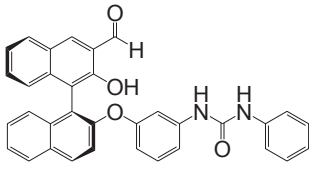
Introduction

Chirotechnologies for obtaining optically pure amino acids include dynamic kinetic resolution (DKR), which combines enzymatic and chemical processes,[1] and chemical syntheses controlled by chiral catalysts.[2–5] The enantioselective liquid–liquid extraction (ELLE) is considered to be an economical process due to low energy consumption, green production, and the advantages in scaling-up.[6] The chiral compounds of crown ethers[7] and metal complexes[8] have been tested as extractants for ELLE of amino acids. They, however, usually suffer from low operational enantioselectivities and the narrow range of application especially to underivatized amino acids.[9]

Compound **1** has been developed as a chiral conversion reagent and is also known to work as a chiral extractant in ELLE of amino acids when it is used together with Aliquat 336.[10,11] In this work, we have designed and synthesized compound **2** with a phenyl ether linkage, which has a reduced distance from the naphthol ring to the uryl group compared to that of compound **1**. This change would result in the difference of the stereoselectivities of compound **2** in the imine formation with amino acids from those of compound **1**. Here we report the synthesis, enantiomeric resolution, and the stereoselectivities of **2** as a chiral extractant for ELLE of underivatized amino acids.



Compound (*S*)-**1**



Compound (*S*)-**2**

Experimental

General. Chemicals such as sodium borohydride, boron trifluoride diethyl etherate, 2,2-dimethoxy propane, palladium 10 wt% on activated carbon, phenyl isocyanate, potassium persulfate, triphosgene, 2-aminobenzimidazole, 3-fluoronitrobenzene and 2,2,6,6-tetramethylpoperidine-1-oxyl were purchased from Aldrich, Seoul, Korea and TCI, Tokyo, Japan. The starting compound, 2,2′-binaphthol-3-carboxylic acid, was provided by company Aminologics, Seoul, Korea. All chemicals were used as received without further purifications. NMR spectra were recorded on Bruker AM 250 spectrometer, Bruker, in $CDCl_3$ and dimethylsulfoxide (DMSO)-d_6 solutions containing tetramethylsilane as an internal standard. Melting points were measured with an Electrothermal IA 9000 digital melting point apparatus, Bibby Scientific. Optical rotations were measured on a DIP 360 polarimeter, Jasco Legacy. For column chromatography, silica gel of 230–400 mesh from Aldrich was used.

3-Hydroxymethyl-2,2′-binaphthol (4). Boron trifluoride diethyl etherate (8 mL, 60 mmol) was added to sodium borohydride (2.84 g, 75 mmol) in tetrahydrofuran (THF, 30 mL), to which a solution of 2,2′-binaphthol-3-carboxylic acid (**3**) (10.0 g, 30.2 mmol) in THF was transferred in oxygen- and moisture-free condition, and the resulting mixture was stirred for 20 h at 65 °C. The progress of the reaction was monitored by TLC (Thin Layered Chromatography), and THF/HCl/H_2O (1:1:1) solution (45 mL) was added to quench the reaction. Compound **4** was isolated by column chromatography of the crude mixture, which was obtained by the evaporation of the oganic layer after the extraction of the reaction mixture with CH_2Cl_2 and water (9.0 g, yield 94 %). Melting point = 69 °C, ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.99–7.87 (m, 11H), 5.91 (s, 1H, —OH), 5.03 (s, 2H).

Compound 5. Compound **5** was prepared by the procedure that was reported by Tang *et al.*[12]

Compound 6. Potassium carbonate (5.82 g, 42 mmol) was added to a solution of compound **5** (10 g, 28 mmol) in anhydrous dimethylformamide (DMF), and the solution was stirred at 80 °C. After 1 h, 3-fluoronitrobenzene (5 mL, 42 mmol) was added, and stirring was continued at 130 °C for 70 h. The mixture was cooled to room temperature, quenched by 1 M HCl, and extracted with EtOAc and brine. The organic layer was dried over anhydrous $MgSO_4$. The crude product was chromatographed on silica gel column with EtOAc/$\mathbf{CH_2Cl_2}$/hexane (1:1:10) to obtain compound **6** (8.4 g, yield = 62%). Melting point = 97.7 °C, ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.96–7.0 (m, 15H), 5.10–4.97 (dd, J = 15, 25.5 Hz, 2H), 1.35 (s, 3H), 1.23 (s, 6H).

Compound 7. Palladium 10 wt% on activated carbon (0.9 g) was added to a solution of compound **6** (9.20 g, 19 mmol) in THF, and stirred for 20 h at room temperature while H_2 gas in a balloon was injected. The mixture was filtered, and the evaporation of the filtrate gave compound **7** (8.46 g, yield 98%). Mp = 212.2 °C, ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.91–6.95 (m, 13H), 6.28–6.18 (m, 3H), 5.10–5.09 (d, J = 1.2 Hz, 2H), 1.36 (s, 3H), 1.28 (s, 3H).

Compound 8. Phenyl isocyanate (2.70 mL, 24 mmol) was added to a solution of compound **7** (8.56 g, 19 mmol) in $\mathbf{CH_2Cl_2}$ and stirred at ambient temperature. After 5 h, the solution was evaporated by a rotary evaporator, and the residue was chromatographed on silica gel column with EtOAc/hexane (1:3) to give compound **8** (9.40 g, yield 86%). Melting point = 229.7 °C, ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.78–6.40 (m, 22H), 5.03–4.89 (dd, J = 15.6, 26.4 Hz, 2H), 1.29 (s, 3H), 1.20 (s, 3H).

Compound 9. HCl (35%, 4.2 mL, 48 mmol) was added to a solution of compound **8** (9.40 g, 16 mmol) in THF/MeOH (1:1), and the mixture was heated to 50 °C for 2 h. The reaction mixture was extracted with EtOAc and water, and the organic layer was dried over anhydrous $MgSO_4$. The crude product was purified by silica column chromatography with EtOAc/hexane (1:2) to obtain compound **9** (8.41 g, yield 96 %). Melting point = 208.2 °C, ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.84–6.20 (m, 23H), 4.76–4.61 (dd, J = 12.9, 59.4 Hz, 2H), 3.70 (s, 1H).

Compound 2. 2,2,6,6-Tetramethylpiperidine-1-oxyl (TEMPO, 66 mg, 2 wt%) was added to a slurry of compound **9** (3.33 g, 6.32 mmol) in acetonitrile and heated to 50 °C. Methyltriphenylphosphonium peroxydisulfate (MTPPP, 7.10 g, 9.50 mmol) was added to the mixture and refluxed at 60 °C. The reaction was monitored by TLC. After 5 h, the reaction mixture was extracted with $\mathbf{CH_2Cl_2}$ and water, and a yellow solid precipitated from the organic solution, which was the pure compound **2** in racemic form (2.96 g, yield 90%). Melting point = 197 °C, ^{1}H NMR (DMSO, 300 MHz): δ 10.36 (s, 1H, —OH), 10.26 (s, 1H, —CHO), 8.69–8.59 (m, 3H), 8.11–8.01 (m, 3H), 7.49–6.48 (m, 17H); ^{13}C NMR (DMSO, 75 MHz): δ 197.51 (—CHO), 157.97, 153.49, 152.83, 152.74, 141.52, 139.95, 137.68, 137.23, 133.87, 130.79, 130.70, 130.63, 130.20, 129.23, 128.79, 127.57, 127.44, 125.41, 125.29, 124.91, 124.69, 122.98, 122.37, 121.42, 120.18, 118.69, 117.07, 113.12, 112.13, 108.63.

Enantiomeric Resolution of 2. (*S*)-(+)-2-Phenylglycinol (0.784 g, 5.71 mmol) was added to a solution of **2** (3.0 g, 5.71 mmol) and TPPC (2.1 g, 5.60 mmol) in $\mathbf{CH_2Cl_2}$. The mixture was stirred at room temperature for 12 h. On confirming the formation of the imine by investigating the TLC, the solvent was removed with a rotary evaporator. The two diastereomers were separated by silica column chromatography with the eluent EtOAc/$\mathbf{CH_2Cl_2}$ (1:20). The purity of the diastereomer was determined by ^{1}H NMR. The pure form of the diastereomer was hydrolyzed at room temperature for 12 h in $\mathbf{CH_2Cl_2}$ and 1 M HCl aqueous solutions. The crude product in the organic solution was column-chromatographed with EtOAc/$\mathbf{CH_2Cl_2}$ (1:15) to give pure (*S*)-**2**. (0.62 g, yield 41%). Melting point = 171 °C, $[\alpha]_D = -111.85$(*c* 0.005, Acetone); HRMS (FAB) calcd for $C_{34}H_{25}N_2O_4$ 525.1809; found: 525.1809.

Enantioselective Liquid–Liquid Extraction. An aqueous solution of the sodium salt of racemic amino acids (20 equiv relative to (*S*)-**2**) was stirred with an equal volume of $CDCl_3$ solution containing (*S*)-**2** and the phase-transfer reagent tetraphenylphosphonium chloride (TPPC) or Aliquat 336 (1.3 equiv relative to (*S*)-**2**) at room temperature. The imine formation in the organic layer was investigated by ^{1}H-NMR spectroscopy.

Results and Discussion

Optically pure compound (*S*)-**2** was synthesized starting from 2,2**n**-binaphthol-3-carboxylic acid (**3**) following the processes shown in Scheme 1. The compound **5** was prepared by the procedure reported by Tang *et al.*[12] Phenylation of **5** with 3-fluoronitrobenzene in DMF solution produced compound **6**. However, this reaction required a high temperature, 130 °C, and a long reaction time, 70 h, and unfortunately resulted in the racemization of the axially chiral binaphthol rings even though the starting compound **3** was optically pure. Thus, a special resolution method was to be developed to obtain optically pure target product, (*S*)-**2**. The reduction of the nitro group to amine to obtain compound **7** was successful by using H_2 gas in the presence of Pd/C catalyst. The reaction of compound **7** with phenyl isocyanate followed by the deprotection and the oxidation of the alcohol yielded the racemic product **2**. In the oxidation step, the product was obtained as a pure form in yellow crystalline solids by precipitation from the extracted methylene chloride solution.

The enantiomeric separation of the racemic compound **2** was successful by the formation of diastereomeric imines of **2** with (*S*)-(+)-2-phenylglycinol followed by the chromatographic separation of the diastereomers with an eluent of EtOAc/$\mathbf{CH_2Cl_2}$ (1:20) and normal silica column. Finally, an optically pure (*S*)-**2** was obtained by the hydrolysis of the single diastereomeric imine in an acidic condition.

Reasonable explanations for the preference of the (*S*) form of **1** toward the formation of the imine with D-amino acids over L-amino acids were provided in a previous paper.[10] Figure 1 shows the energy-minimized structures calculated by using Spartan program for the imines formed between D-alanine and (*S*)-**1** and (*S*)-**2**.[13]

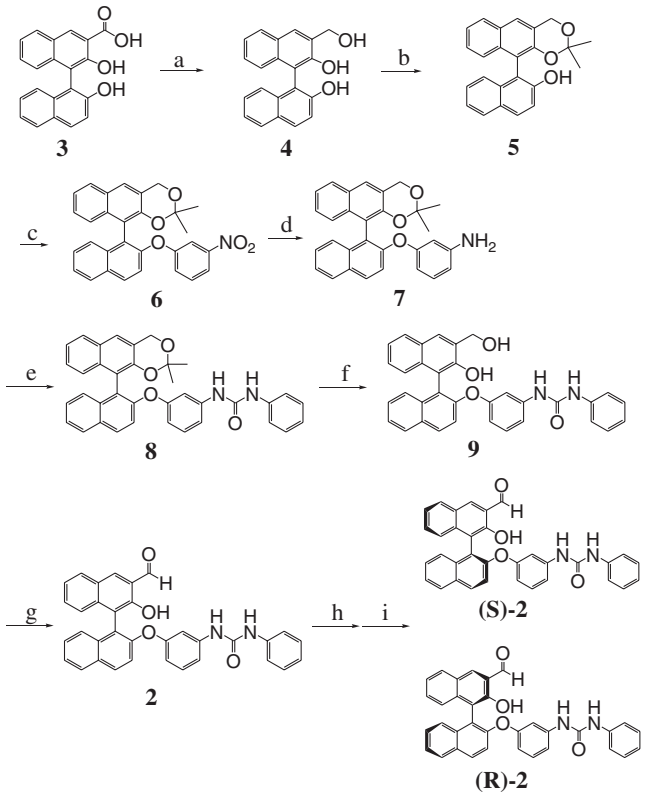
The uryl plane of the imine of (*S*)-**2** is more tilted toward the one naphthalene ring and is pulled more toward to the other naphthalene ring. It appears that the imine of **2** has a more compact structure. This difference would bring out the difference in the stereoselectivity of **2** from **1**. However, it was meaningless to predict by calculations whether **1**or **2** had a higher selectivity because the calculations could not correctly reflect on factors such as pH and solvent effects.

The aldehyde (*S*)-**2** is freely soluble in **CH_2Cl_2** when mixed with tetraphenylphosphonium chloride (TPPC) or trioctylmethylammonium chloride (Aliquat 336). Aliquat 336 is widely used as a phase-transfer catalyst,[14] which is considered to assist in bringing an anionic amino acid from the aqueous layer into the organic layer. In this study, TPPC and Aliquat 336 were used in more than a stoichiometric amount relative to (*S*)-**2** because they play an additional role as a counter-cation of the imine. The imine formed between (*S*)-**2** and an anionic amino acid has a negative charge.

The stirring of the MC solution containing (*S*)-**2** and TPPC together with the aqueous layer containing excess amount of the sodium salt of a racemic phenylalanine led to the ELLE of the amino acid from the aqueous layer to the organic layer by a stereoselective imine formation. Figure 2(a) shows the partial ^{1}H NMR spectra for the free form of (*S*)-**2** in the presence of TPPC. The singlet at 8.20 ppm was assigned to the proton of C-3 carbon of the naphthol ring. Figure 2(b) and (c) shows partial ^{1}H NMR spectra of the imines formed by the reactions of (*S*)-**2** with optically pure L- and D-phenylalanine, respectively. Multiplets appearing at 4.0–4.5 ppm are due to the α-proton of the amino acid of the imines. Figure 2(d) is the spectrum of the imine formed by (*S*)-**2** and excess DL-phenylalanine under ELLE condition. The comparison of the spectra apparently shows that the imine of D-Phe exists in larger amounts than that of L-Phe, *i.e.*, the ELLE is successful. The stereoselectivity could be determined by integration of the signals.

The stereoselectivities for several representative amino acids of the ELLE, which were measured by the same way, are listed as the D/L ratios in Table 1. The table also includes the data of the ELLE experiments carried out using both Aliquat 336 and TPPC.

The aldehyde (*S*)-**2** showed D/L ratios in the range 3.57–11.1, which are similar but slightly lower than those



Scheme 1. Reagents and conditions: (a) $NaBH_4/BF_3$/THF, 65 °C, 20 h, 94%; (b) 2,2-Dimethoxypropane/acetone, H^+, rt, 20 h, 86%; (c) (i) K_2CO_3/DMF, 80 °C, 1 h; (ii) 3-Fluoronitrobenzene/DMF, 130 °C, 70 h, 62%; (d) Pd/C, H_2(g)/THF, rt, 20 h, 98%; (e) Phenylisocyanate/**CH_2Cl_2**, rt, 5 h, 86%; (f) HCl/THF, MeOH, 50 °C, 2 h, 96% (g) MTPPP, TEMPO/CH_3CN, 60 °C, 5 h, 90%; (h) (*S*)-(+)-2-phenylglycinol/**CH_2Cl_2**, rt, 12 h; (i) HCl (1 M)/**CH_2Cl_2**, rt, 12 h, 41%.

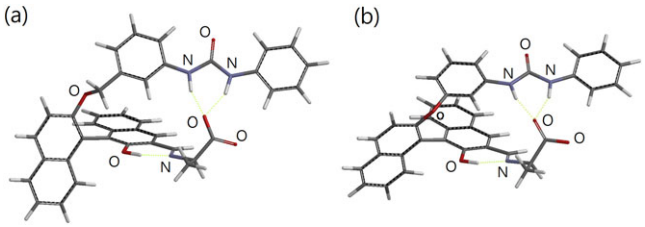


Figure 1. Model structures of the imines of (*S*)-**1** (a) and (*S*)-**2** (b) formed with D-alanine, which were calculated by the Spartan program.[13]

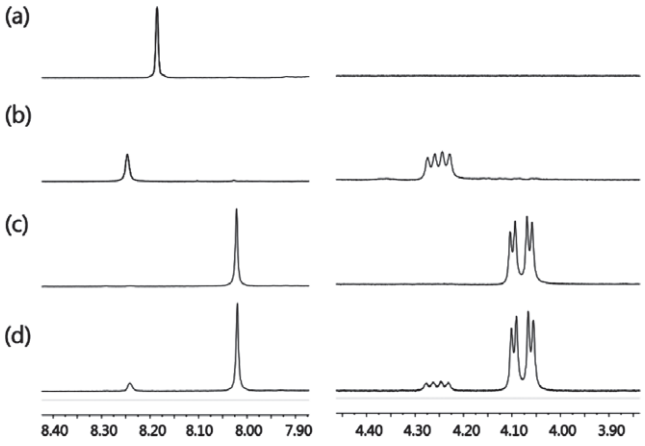


Figure 2. (a) Free form of (*S*)-**2**. (b) Imine formed between (*S*)-**2** and L-Phe. (c) Imine of D-Phe. (d) Imine formed with excess amount of DL-Phe.

Table 1. Diastereomeric ratio (D-amino acid imine)/(L-amino acid imine) and enatiomeric excess (ee) values (in parentheses) at the organic layer after ELLE with (*S*)-**2**, which were determined by ^{1}H-NMR studies.

	Diastereomeric ratio (ee%)	
Amino acids	TPPC	Aliquat 336
Phenylalanine	7.60 (76.8)	7.14 (75.4)
Serine	3.76 (58.0)	3.84 (58.8)
Valine	11.1 (83.4)	11.1 (83.4)
Leucine	7.69 (77.0)	8.33 (78.6)
Alanine	3.57 (56.2)	4.00 (60.0)

of **1**. The selectivities of (*S*)-**2** were not significantly affected by change of Aliquat 336 to TPPC.

In these ELLE experiments, the imine formation was completed in several hours of stirring, and the imine in the organic layer could be hydrolyzed by stirring with an acidic aqueous solution. The hydrolysis reproduced the organic layer completely as in its initial state and transferred the hydrolyzed amino acid to the aqueous layer. The organic layer could be recycled again and again without isolation processes such as evaporation and precipitation. This ensured the economical management of the ELLE, as reported in the previous paper.[11]

Conclusion

In summary, a new type of chiral binol-aldehyde with phenyl ether linkage, (*S*)-**2**, has been synthesized. During the synthesis, the axially chiral binaphthol ring was racemized as a result of high reaction temperatures. The enantiomerically pure product was obtained through the resolution of diastereomeric imine of **2** formed with an aminoalcohol by normal column chromatography. The stereoselectivities of (*S*)-**2** toward the imine formation with amino acids in the ELLE condition were measured by ^{1}H NMR spectroscopic studies.

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