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Enantioselective Liquid–Liquid Extractions of Underivatized General Amino Acids with a Chiral Ketone Extractant

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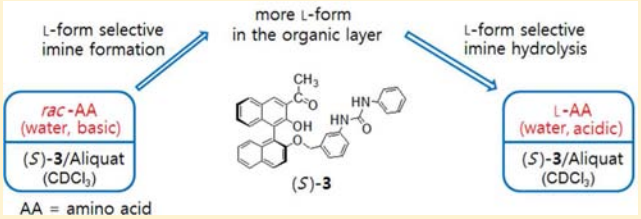
Supporting Information

ABSTRACT: The chiral ketone (*S*)-**3** shows high kinetic enantioselectivities toward the L form for general underivatized amino acids with hydrophobic side chains and a high thermodynamic enantioselectivity toward the D form for cysteine with its −SH polar side chain when used as an extractant in enantioselective liquid–liquid extractions in the presence of Aliquat 336. Consecutive extractions by imine formation and hydrolysis increase the enantiopurity of the amino acid, as both of these reactions are L-form-selective.



INTRODUCTION

Enantioselective liquid–liquid extraction (ELLE) is one of the promising extraction processes because of its low cost in energy consumption, green production, and advantages in scaling up.[1] Over the years, chiral receptors of crown ethers and metal complexes were developed as extractants for ELLE of amino acids.[2,3] Optically pure forms of amino acids are of wide interest because of the increasing demand in peptide and pharmaceutical industries.[4] Despite the long history of research on chiral extractants, the low operational enantioselectivities and the narrow range of application scope are the limitations to be overcome within the field of ELLE, especially for underivatized amino acids.[3e]

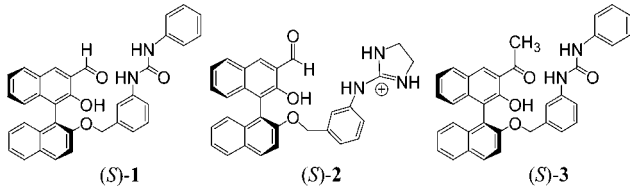
Axially chiral 1,1′-bi-2-naphthol (BINOL) derivatives have been widely studied for enantiomeric recognition of chiral compounds,[5] and it has been reported that chiral recognition of amino acids can be accomplished through reversible imine formation by chiral BINOL aldehyde (*S*)-**1** (Chart 1) and amino acids in dimethyl sulfoxide solution.[6]

Even though reversible imine bonds are well-recognized in enzyme chemistry[7] and utilized in preparing Schiff bases,[8] there is very little literature[9] reporting on the extraction of underivatized amino acids using a neutral aldehyde as an extractant. Indeed, our preliminary experiments on the extraction of amino acids were not successful when a neutral aldehyde alone was used as the extractant.

On the other hand, the cationic aldehyde (*S*)-**2** (Chart 1) was successful in extracting some underivatized hydrophobic amino acids from a basic aqueous layer to a $CDCl_3$ layer with moderate enantioselectivities of 3/1 to 4/1.[10] During the course of our extraction studies on amino acids, it was observed that the phase-transfer reagent trioctylmethylammonium chloride (Aliquat 336) can assist even neutral aldehydes to form imines in a biphasic system.[11]

The rate of imine formation from amino acids with ketones is generally much lower than that with aldehydes.[12] Therefore, it is quite surprising that the ketone in this work extracts amino acids via reversible ketimine formation under mild conditions and in a relatively short time. Herein we report the use of the chiral ketone (*S*)-**3** (Chart 1) as a promising extractant for ELLE of general underivatized amino acids with high enantioselectivities in the presence of Aliquat 336.

Chart 1



RESULTS AND DISCUSSION

Synthesis of (*S*)-3. The optically pure axially chiral compound (*S*)-**3** was conveniently synthesized from (*S*)-BINOL-3-carboxylic acid through a two-step protocol, as shown in Scheme 1. The reaction of the carboxylic acid with excess methyllithium afforded BINOL-ketone (*S*)-**4** in a fairly good yield. The two −OH protons of (*S*)-**4** are apparently

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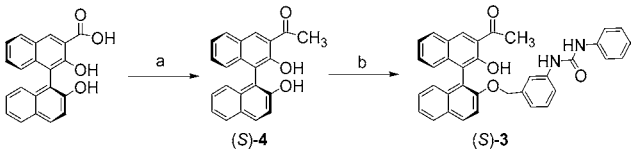
Scheme 1. Synthesis of (*S*)-3[a]



[a]Reagents and conditions: (a) Methyllithium/THF, 0 °C, 6 h, 90%. (b) 3-(Phenyluryl)benzyl bromide, NaH/DMF, 20 °C, 12 h, 41%.

distinguished in its ^{1}H NMR spectrum; the signal at 12.01 ppm, which is shifted as a result of internal hydrogen bonding with the carbonyl oxygen, is assigned to the proton of the −OH group at the 2-position, and the signal at 5.02 ppm is assigned to the proton of the −OH group at the 2′-position. The substitution reaction of (*S*)-**4** with 3-(phenyluryl)benzyl bromide led to side products, and the substitution of the −OH at C-2′ was confirmed by the disappearance of the signal at ∼5.02 ppm. The final product, (*S*)-**3**, is well soluble in $CDCl_3$ and characterized by the signals appearing at 2.83 ppm (methyl), 11.73 ppm (−OH), 8.49 ppm (C-4 proton), and 5.05 ppm (doublet of doublets, benzyl $-CH_2-$) in its ^{1}H NMR spectrum.

Enantioselective Liquid−Liquid Extraction of Phenylalanine. As a representative ELLE experiment, an aqueous solution (250 mM) of the sodium salt of racemic phenylalanine (DL-Phe-Na) was stirred with an equal volume of $CDCl_3$ solution containing (*S*)-**3** (10 mM) and the phase-transfer reagent Aliquat 336 (1.05 equiv relative to the ketone). The imine formation in the organic layer was monitored by ^{1}H NMR spectroscopy, by which the two imine diastereomers (*S*)-**3**−L-Phe and (*S*)-**3**−D-Phe were apparently discriminated, especially in the signals of the uryl −NH− and benzyl $-CH_2-$ moieties. The rate of formation and the diastereomeric ratio of the imine were thus determined by the ^{1}H NMR analysis. The same experiment was carried out at different temperatures. Figure 1 displays partial ^{1}H NMR spectra of the organic layers in the uryl and benzyl regions taken when the imine formation was nearly complete.

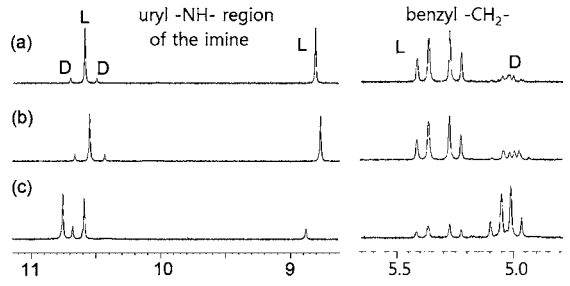


Figure 1. Partial ^{1}H NMR spectra (250 MHz, $CDCl_3$) of the organic layer after ELLE of DL-Phe with (*S*)-**3** for 12 h at (a) 0, (b) 20, and (c) 40 °C.

The imine formation reached ∼95% completion in 12 h at 0 °C, and the partial ^{1}H NMR spectra for the organic layer are shown in Figure 1a. The peaks appearing at 8.81 and 10.58 ppm are assigned to the two uryl protons of (*S*)-**3**−L-Phe and the peaks at 10.49 and 10.70 ppm to the two uryl protons of (*S*)-**3**−D-Phe. The doublet-of-doublets signal centered at 5.31 ppm is due to the benzyl $-CH_2-$ moiety of the imine of L-Phe, and the signal centered at 5.03 ppm is due to the imine of D-Phe. The benzyl signal of the free form of (*S*)- **3** appears at 5.00 ppm, partially overlapping the signal of (*S*)-**3**−D -Phe. The integration of the signals of Figure 1a shows that (*S*)-**3**−L -Phe exists in larger amount in the organic layer than (*S*)-**3**−D -Phe by the ratio of 13/1.

Figure 1b shows the partial ^{1}H NMR spectra for the organic layer when the experiment was performed at 20 °C for 12 h. They exhibit the same sense of the stereoselectivity, but with a decreased selectivity of ∼7.5/1.

The ^{1}H NMR studies right after the beginning of the reaction (not shown in Figure 1) revealed that the imine of L-Phe dominated relative to the imine of D-Phe in much greater ratios than those in Figure 1a,b. However, as the imine formation went toward completion, the ratio gradually decreased. After 12 h, the ratio decreased further, and it was even observed several weeks later that the imine of D-Phe existed in larger portions than the imine of L-Phe.

When the temperature was increased to 40 °C for 12 h, the spectra of the organic layer showed the reverse enantioselectivity, with L/D = 1/3.5 (Figure 1c); this ratio was maintained even after 72 h.

The sense of the stereoselectivities shown in Figure 1a,b was an unexpected result considering the stereoselectivity shown by the aldehyde (*S*)-**1**, which favored the formation of the imine with D-Phe.[6] The preference of (*S*)-**1** to form the imine with the D-amino acid has been explained by a comparison of the stabilities of the imine diastereomers. Density functional theory (DFT) calculations to obtain the energy-minimized structures of the imine diastereomers (*S*)-**3**−D-Phe and (*S*)-**3**−L-Phe predicted that the imine of the D form is more stable than that of the L form, as in the case of the imines obtained using (*S*)-**1**; this will be discussed further in detail in a later section.

Generally, longer times were required to reach thermodynamic equilibrium because of the lower reaction rates at low temperatures. The preference for the imine of the L-form at 0 and 20 °C is thus due to a kinetic effect. On the other hand, the sense of the selectivity shown at 40 °C (Figure 1c) is due to the effect of the thermodynamic stabilities of the imine diastereomers.

Figure 2 shows the kinetics of the imine formation, which was studied by monitoring the ^{1}H NMR spectra for the organic layers in the extractive reactions carried out separately for L-Phe and D-Phe. The values of $\ln(C_0/C_t)$ were plotted against time, where C_0 is the initial concentration of (*S*)-**3** and C_t is its

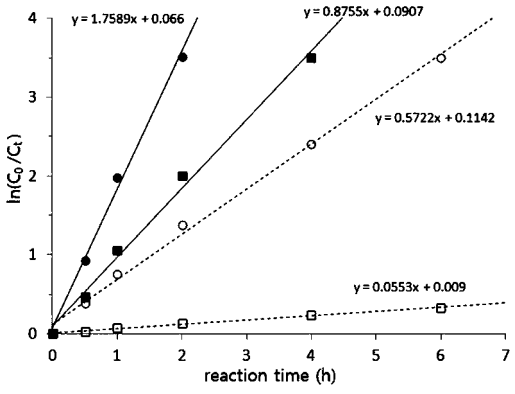


Figure 2. Linear plots of $\ln(C_0/C_t)$ vs t, where C_0 is the initial concentration of (*S*)-**3** and C_t is its concentration at time t. The dashed and solid lines are fits to the data at 0 and 20 °C, respectively. Squares and circles denote the data for D-Phe and L-Phe, respectively.

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concentration at time t. The reaction was assumed to follow a pseudo-first-order rate law because an excess amount of amino acid was used. The rate constants for imine formation, k, were obtained from the slopes of the corresponding linear fits. The k_L/k_D ratio reached 14.5/1 at 0 °C (dashed lines) and 3/1 at 20 °C (solid lines). These rate constant ratios are fairly consistent with the enantioselectivities observed in Figure 1a,b. The imine formations from both L-Phe and D-Phe at 40 °C were fast, reaching completion in less than 1 h, and the difference in their rates could not be distinguished apparently in the ^{1}H NMR studies, which can partly account for the thermodynamically controlled selectivity at 40 °C.

Model To Explain the Thermodynamic Selectivity. The relative thermodynamic stabilities of the imines (*S*)-**3**−D-Phe and (*S*)-**3**−L-Phe can be assessed by principles similar to those proposed in previous works.[6] Figure 3 displays the energy-optimized structures of (*S*)-**3**−D-Phe and (*S*)-**3**−L-Phe obtained by DFT calculations at the B3LYP/3-21G* level[13] using the Gaussian 03 program package.[14] The resonance-assisted hydrogen bond occurring around the aromatic −OH and imine C═N bonds[15] and the hydrogen bond between the carboxylate and uryl groups restrict the freedom of the three-dimensional structure of the imine. Consequently, a large amount of steric hindrance around the C═N bond between the methyl and benzyl groups is induced in the (*S*)-**3**−L-Phe diastereomer in comparison with the steric repulsion between methyl group and the hydrogen in (*S*)-**3**−D-Phe. The calculations predict that the imine of D-Phe is more stable than the imine of L-Phe by 5.4 kcal/mol, which is a large enough difference that it may bring about almost exclusive stereoselective imine formation. Unfortunately, we did not observe stereoselectivities comparable to this large difference of thermodynamic energy, probably because of the adverse kinetic effect, and decomposition of the imine compounds made it difficult to elevate the temperature above ∼50 °C. It should be also considered that the multiple hydrogen bonds, which are important in the molecular recognition, are weakened at high temperatures, thus altering the free energy changes.

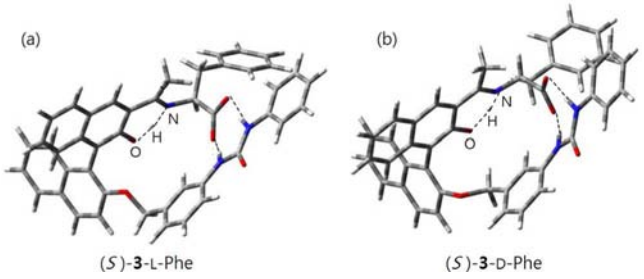
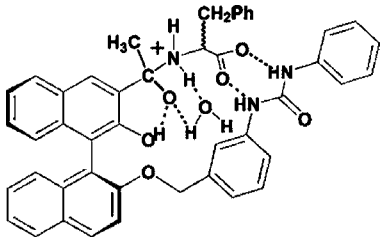


Figure 3. Energy-optimized structures of (a) (*S*)-**3**−L-Phe and (b) (*S*)-**3**−D-Phe obtained by DFT calculations. Dashed lines denote hydrogen bonds.

Model To Explain the Kinetic Selectivity. To account for the kinetic selectivities of this work, we propose (*S*)-**3**-Phe-H_2O* (Chart 2) as a possible intermediate on the basis of the generally accepted mechanism for Schiff base formation.[16] In this intermediate, the amino group attacks the electrophilic carbonyl group, while the phenol hydroxy group and one water molecule are assumed to stabilize the anionic carbonyl oxygen and the cationic amine and the uryl group is assumed to stabilize the anionic carboxylate group by hydrogen bonds.

Chart 2. The Proposed Intermediate (*S*)-3-Phe-H_2O*



The DFT-optimized structures of the diastereomeric intermediates (*S*)-**3**−L-Phe-H_2O* and (*S*)-**3**−D-Phe-H_2O* are shown in Figure 4a,b, respectively. The calculations indicate that intermediate (*S*)-**3**−D-Phe-H_2O* experiences more steric hindrance because the benzyl group is placed closer to the naphthol ring. Such steric repulsion pushes the D-phenylalanine moiety slightly away from receptor (*S*)-**3** (1.608 Å vs 1.594 Å for the C−N bond), causing the energy of (*S*)-**3**−D-Phe-H_2O* to be higher than that of (*S*)-**3**−L-Phe-H_2O* by 3.2 kcal/mol.

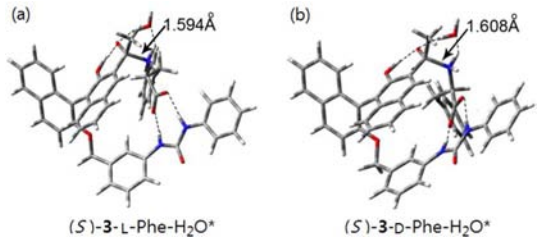


Figure 4. DFT-optimized structures of (a) (*S*)-**3**−L-Phe-H_2O* and (b) (*S*)-**3**−D-Phe-H_2O* .

Figure 5 shows an energy level diagram for the imine formation reaction of (*S*)-**3** with DL-Phe based on the results of the calculations discussed above. The kinetic selectivities are closely related to the relative energies of the reaction intermediates and the thermodynamic selectivities with the relative energies of the final products. The energy levels in Figure 5 explain quite well the experimental results of different kinetic and thermodynamic selectivities.

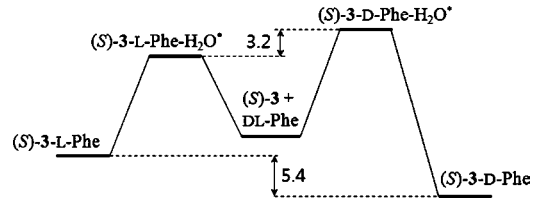


Figure 5. Relative energy levels for the imine formation reaction (energy values in kcal/mol).

Stereoselective Hydrolysis. Figure 5 shows that the hydrolysis of (*S*)-**3**−L-Phe, the reverse reaction of the imine formation, must be faster than that of (*S*)-**3**−D-Phe because the kinetic and thermodynamic stereopreferences are different. Thus, with receptor (*S*)-**3**, we can take advantage of the different stereopreferences to increase the optical purity of an amino acid through consecutive extractions by imine formation and hydrolysis.

Figure 6 illustrates the stereoselective hydrolysis of the imine. When racemic phenylalanine was extracted with (*S*)-**3** at low temperature (i.e., under kinetically controlled conditions), the

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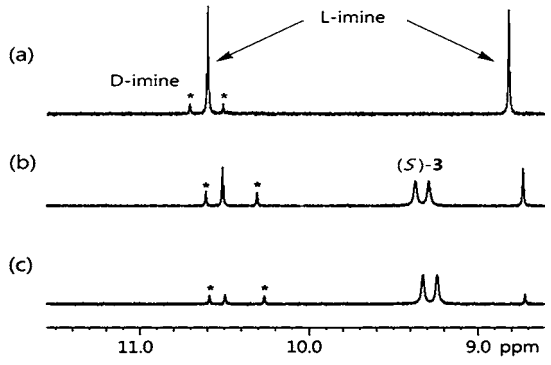

Figure 6. Partial ^{1}H NMR spectra of the uryl −NH− region for the organic layer during enantioselective hydrolysis: (a) before hydrolysis; (b) after 4 h of hydrolysis; (c) after 12 h of hydrolysis. Asterisks denote the signals of (*S*)-**3**−D-Phe.

imine in the organic layer was predominantly in the L form, as shown in Figure 6a, which is actually the same as Figure 1a. This organic layer was separated and stirred with a 2 N aqueous NH_4Cl solution, and the phenylalanine in the imine was extracted into the aqueous layer by hydrolysis. Figure 6b,c shows the partial ^{1}H NMR spectra of the organic layers after 4 and 12 h of hydrolysis. The concentration of (*S*)-**3**−L-Phe in the organic layer decreased remarkably faster than that of (*S*)-**3**−D-Phe, indicating that the extractive hydrolysis is L-form-selective. The measurement of the aqueous layer using HPLC revealed that the optical purity of L-Phe was over 98%.

ELLE of General Amino Acids. The stereoselectivities of the extractive imine formation reaction for general amino acids obtained by the same procedures as described above are summarized in Table 1. All of the amino acids with

Table 1. Enantioselectivities and Yields of Imine Formation in ELLE of Underivatized Amino Acids with (*S*)-3[a]

	kinetic control[b]		thermodynamic control[c]	
amino acid	L/D (time)	yield (%)	L/D (time)	yield (%)
Ala	10/1 (20 h)	92	1/5.5 (18 h)	90
Ile	13/1 (7 h)	93	1/5.1 (10 h)	96
Leu	6.5/1 (6 h)	92	1/4.7 (9 h)	95
Met	7.3/1 (10 h)	93	1/3.8 (9 h)	96
Phe	13/1 (12 h)	95	1/3.5 (12 h)	97
Phe[d]	1/13 (12 h)	94	3.5/1 (12 h)	96
Trp	11/1 (8 h)	91	1/3.0 (10 h)	92
Tyr[e]	12/1 (18 h)	85	1/4.8 (15 h)	83
Val	12/1 (9 h)	92	1/3.3 (10 h)	96
Thr	–	–	1/4.5 (24 h)	75
Ser	–	–	1/8.5 (24 h)	55
Cys	–	–	1/18 (24 h)	93

[a]Organic layer ($CDCl_3$): 10 mM (*S*)-**3** + 1.05 equiv of Aliquat 336. Aqueous layer: 250 mM amino acid sodium salt. [b]0 °C. [c]40 °C. [d]The experiment was performed using (*R*)-**3**. [e]The disodium salt of Tyr and 2.1 equiv of Aliquat 336 were used.

hydrophobic side chains showed high kinetic selectivities, with L/D ratios ranging from 13/1 to 6.5/1 (entries 1−8). The preferences for these amino acids were all reversed to the D form under thermodynamic conditions.

Interestingly, the amino acids with polar side chains, such as serine, threonine, and cysteine, did not show kinetic selectivities. It is likely that the transition states for imine formation from these amino acids are different from those for the amino acids with hydrophobic side chains because of the hydrogen-bonding influence of the −OH or −SH side groups. Instead, cysteine exhibited high thermodynamic selectivity, with an L/D ratio of 1/18.

The yields of imine formation for amino acids with hydrophobic side chains were generally more than 90%, except for tyrosine. The phenolic −OH group of tyrosine is acidic, and thus, and additional 1 equiv of Aliquat 336 was required for the ELLE. The high yields of imine formation mean that ketone (*S*)-**3** is very efficient as an extractant. The yields of imine formation for threonine (75%) and serine (55%) were significantly lower than those for the other amino acids. The amino acids with charged side chains such as aspartate, glutamate, histidine, and lysine experienced much lower yields of imine formation, and thus, ELLEs for those were not effective.

The opposite enantiomer, (*R*)-**3**, was prepared following the same procedures as for (*S*)-**3** but starting from (*R*)-BINOL-3-carboxylic acid, and it was tested for the ELLE of racemic phenylalanine as a representative example. The ^{1}H NMR spectrum of the imine (*R*)-**3**−D-Phe was totally same as that of (*S*)-**3**−L-Phe, and (*R*)-**3** selectively extracted D-Phe under kinetic conditions and L-Phe under thermodynamic conditions.

It is likely that all of the stereopreferences of the other amino acids in Table 1 would be reversed if (*R*)-**3** were used instead of (*S*)-**3**, and similar results would be obtained for other analogous amino acids. Thus, the proper choice of the chirality of **3** should enable the selective extraction of any enantiomer of a natural or non-natural amino acid having branches analogous to those in Table 1.

The Role of Aliquat 336. Aliquat 336 is widely used as a phase-transfer catalyst,[17] which is considered to assist in bringing the amino acid from the aqueous layer into the organic layer. However, Aliquat 336 had been used in more than a stoichiometric amount relative to (*S*)-**3** in this work because it plays an additional role as a countercation of the imine. The imine formed between (*S*)-**3** and the anionic amino acid has a negative charge. Once the quaternary ammonium ion of Aliquat 336 becomes the countercation of the imine, it is likely that it loses the role of phase-transfer agent. It is noteworthy that the imine is insoluble in the aqueous layer and freely soluble in the organic layer despite its ionic character.

■ CONCLUSIONS

The chiral ketone (*S*)-**3** is an efficient extractant for enantioselective liquid−liquid extraction of general underivatized amino acids with hydrophobic side chains by kinetic control and of amino acids with polar side chains by thermodynamic control. High selectivities and a wide application scope toward underivatized amino acids are great advantages of (*S*)-**3** compared with other chiral extractants developed to date.

We believe that this work may open the way for the use of neutral chiral ketones/aldehydes as promising extractants for ELLE of general underivatized amino acids with the assistance of a phase-transfer reagent. In addition, this work shows that different stereochemical preferences under thermodynamic and kinetic conditions may be exploited to increase the optical purities of the amino acids by consecutive extractive imine formation and hydrolysis reactions.

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EXPERIMENTAL SECTION

General Procedures, Reagents, and Equipment. (*S*)-BINOL-3-carboxylic acid and its opposite enantiomer were provided by Aminologics. NaH (60%), methyllithium (3.0 M in diethoxymethane), and other conventional reagents were used as received without further purification. 3-(Phenyluryl)benzyl bromide was prepared according to the previously described method.[6] ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ with chemical shifts reported in parts per million using tetramethylsilane as an internal standard. High-resolution mass spectrometry (HRMS) data were obtained in electron impact (EI) or fast atom bombardment (FAB) mode.

Synthesis of (*S*)-3-Acetyl-2,2′-dihydroxy-1,1′-binaphthyl. To a solution of (*S*)-BINOL-3-carboxylic acid (990 mg, 3.0 mmol) in tetrahydrofuran (THF) (30 mL) was slowly added methyllithium (3 M in diethoxymethane, 5.0 mL, 15.0 mmol) at 0 °C. The mixture was stirred for 6 h between 0 °C and room temperature and then quenched with 0.5 N HCl (10 mL), after which THF was evaporated in vacuo. The mixture was poured into water and extracted with ethyl acetate (3 × 25 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by recrystallization from ethyl acetate (885.6 mg, 90%). $[\alpha]_D$ = −1.41 (*c* 0.41 $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.01 (s, 1H), 8.62 (s, 1H), 7.88−7.98 (m, 3H), 7.07−7.45 (m, 7H), 5.02 (s, 1H), 2.91 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.8, 155.6, 151.4, 128.3, 127.1, 126.6, 124.8, 124.6, 124.5, 123.4, 121.2, 117.7, 115.1, 113.9, 27.06. HRMS-EI (*m*/*z*): calcd for $C_{22}H_{16}O_3$, 328.1099; found, 328.1097.

Synthesis of (*S*)-3. (*S*)-3-Acetyl-2,2′-dihydroxy-1,1′-binaphthyl (885.6 mg, 2.7 mmol) in *N*,*N*-dimethylformamide (DMF) (20 mL) was added dropwise to a slurry of NaH (0.30 g, 7.43 mmol) in DMF (50 mL) with stirring under ice-cooled conditions. After 2 h of stirring, 3-(phenyluryl)benzyl bromide (820.8 mg, 2.7 mmol) was added, and the stirring was continued at room temperature overnight. The reaction was then quenched with saturated NH_4Cl solution, extracted with ethyl acetate, and washed with water. The crude product was purified by silica column chromatography with 4:1:5 dicholoromethane/ethyl acetate/hexane as the eluent, which furnished the product (*S*)-**3** as a yellow solid (598 mg, 41%). $[\alpha]_D$ = −15.42 (*c* 0.26 $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.82 (s, 1H), 8.55 (s, 1H), 7.83−7.95 (m, 3H), 7.09−7.45 (m, 16H), 4.94−5.05 (dd, 2H), 2.87 (s, 3H). HRMS-EI (*m*/*z*): calcd for $C_{36}H_{28}N_2O_4$, 553.2127; found, 553.2128.

DFT Calculations. All of the DFT calculations were performed with the B3LYP hybrid functional, as implemented in the Gaussian 03 program package.[14] Geometries were fully optimized with the 3-21G* basis set and characterized by frequency analysis. Unless otherwise specified, energies corrected for zero-point vibrational energy were used in the discussion.

ASSOCIATED CONTENT

Supporting Information

Experimental details, ^{1}H NMR spectra showing the ELLE of general amino acids, and details of the DFT calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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