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Stereoconversion of Amino Acids and Peptides in Uryl-Pendant Binol Schiff Bases

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Abstract: (*S*)-2-Hydroxy-2′-(3-phenyluryl-benzyl)-1,1′-binaphthyl-3-carboxaldehyde (**1**) forms Schiff bases with a wide range of nonderivatized amino acids, including unnatural ones. Multiple hydrogen bonds, including resonance-assisted ones, fix the whole orientation of the imine and provoke structural rigidity around the imine C=N bond. Due to the structural difference and the increase in acidity of the α proton of the amino acid, the imine formed with an L-amino acid (**1**–L-aa) is converted into the imine of the D-amino acid (**1**–D-aa), with a D/L ratio of more than 10 for most amino acids at equilibrium. N-terminal amino acids in dipeptides are also predominantly epimerized to the D form upon imine formation with **1**. Density functional theory calculations show that **1**–D-Ala is more stable than **1**–L-Ala by 1.64 kcal mol^{-1}, a value that is in qualitative agreement with the experimental result. Deuterium exchange of the α proton of alanine in the imine form was studied by ^{1}H NMR spectroscopy and the results support a stepwise mechanism in the L-into-D conversion rather than a concerted one; that is, deprotonation and protonation take place in a sequential manner. The deprotonation rate of L-Ala is approximately 16 times faster than that of D-Ala. The protonation step, however, appears to favor L-amino acid production, which prevents a much higher predominance of the D form in the imine. Receptor **1** and the predominantly D-form amino acid can be recovered from the imine by simple extraction under acidic conditions. Hence, **1** is a useful auxiliary to produce D-amino acids of industrial interest by the conversion of naturally occurring L-amino acids or relatively easily obtainable racemic amino acids.

Keywords: amino acids · chiral auxiliaries · epimerization · Schiff bases

Introduction

The guidelines for the marketing of chiral drugs issued by the Food and Drug Administration (FDA) in 1992 were a reminder of the importance of chirotechnology.[1] Amino acids, being the basic biocomponents, are useful as potential precursors in the manufacture of chiral drugs and as chiral pools in ligand design and total synthesis.[2,3] Peptides are known to exhibit bioactivities, for example, as high-intensity sweeteners, opioids, or enzyme inhibitors.[4] Over the years, there has been much interest in developing receptors for binding optically pure amino acids and peptides.[5–8]

Although L-amino acids dominate the natural world, D-serine and D-alanine have been found in biology as neurotransmitters and as building blocks for bacterial cell-wall synthesis.[9–11] Biologically, L-amino acids are converted into D-amino acids by pyridoxal phosphate (PLP) dependent enzymes that racemize amino acids (Scheme 1a).[12] This involves the formation of a Schiff base type imine with a resonance-assisted hydrogen bond (RAHB), which is well known to increase the acidity of the α proton.[13] From an industrial point of view, the induction of deracemization, which requires a combination of chirality, an RAHB, and additional interactions, is more interesting. The compound (*S*)-2-hydroxy-2′-(3-phenyluryl-benzyl)-1,1′-binaphthyl-3-carboxaldehyde (**1**) meets these necessary requirements (Scheme 1b). Chiral receptor **1** reacts with an amino acid to

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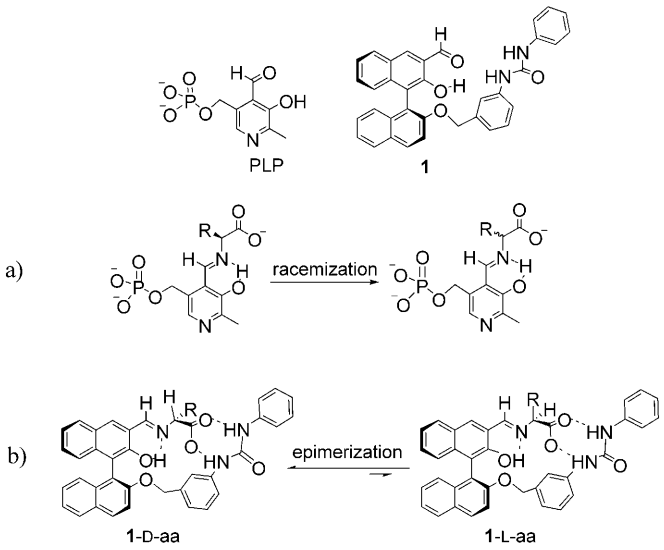


Scheme 1. a) Racemization of amino acids by achiral PLP and b) epimerization of amino acids by chiral **1**.

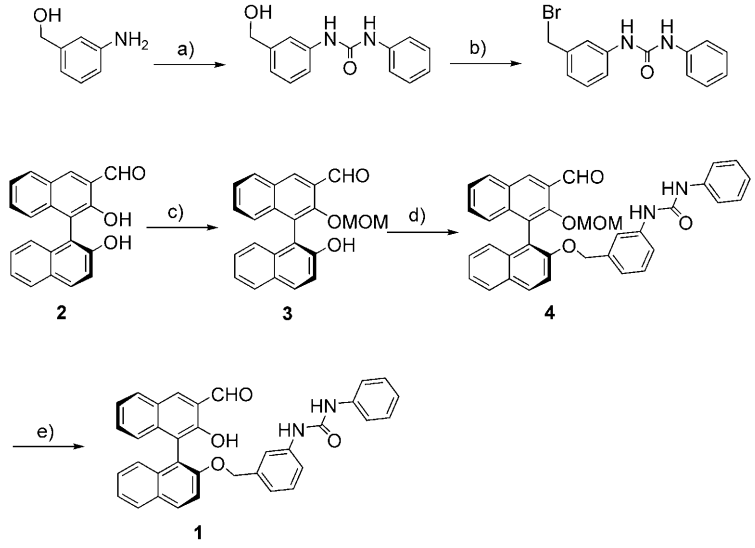
form the aldimine, in which the imine nitrogen atom is oriented toward the phenol OH group due to an RAHB and the carboxylate moiety is hydrogen bonded to the uryl group. This provokes stereoselectivity between the L-amino acid bound imine (**1**–L-aa) and the D-amino acid bound imine (**1**–D-aa), and the acidity of the α proton induces deracemization of the amino acid.

We recently demonstrated that **1** binds 1,2-amino alcohols with good stereoselectivity by formation of imines with an internal RAHB.[14] Furthermore, our preliminary communication proved that **1** converts the L-amino acid bound imine (**1**–L-aa) into the D-amino acid bound imine (**1**–D-aa).[15] Herein, we report detailed studies on the stereoselective molecular recognition and stereoconversion of amino acids, including unnatural ones and peptides, as well as mechanistic insights proposed by a deuterium-exchange study.

Results and Discussion

Synthesis of receptor 1: Receptor **1** can be prepared by direct reaction of 3-phenyluryl-benzyl bromide with (*S*)-2,2′-dihydroxy-1,1′-binaphthyl-3-carboxaldehyde (**2**).[14] However, the reaction produces a mixture of products that are not easily separable. Hence, a more advantageous modified procedure was employed (Scheme 2). The selective monoprotection of **2** with methoxymethyl chloride in DMF gave the mono-MOM-protected binol aldehyde **3** in 65% yield. Addition of 3-phenyluryl-benzyl bromide led to the formation of the MOM-protected compound **4**, which upon hydrolysis under acidic condition gave optically pure **1** in almost quantitative yield. The yellow compound **1** is freely soluble in organic solvents, such as DMF and dimethylsulfoxide (DMSO), and has been characterized by ^{1}H NMR and ^{13}C NMR spectroscopy and by HRMS. The signals of the aldehyde and phenol protons appear at $\delta = 10.30$ and 10.20 ppm, respectively, in the ^{1}H NMR spectrum; these signals are both significantly downfield shifted, which implies the presence of an intramolecular hydrogen bond.

Stereoselective imine formation of 1 with amino acids and epimerization: Stereoselective recognition of amino acids with receptor **1** was studied by ^{1}H NMR spectroscopy (Figure 1). Addition of [Bu_4N][L-Ala] and [Bu_4N][D-Ala] to **1** in [D_6]DMSO results in the formation of the corresponding imines within 10 min. Figures 1a and b show the partial ^{1}H NMR spectra for **1**–L-Ala and **1**–D-Ala, respectively. The signals of the uryl NH, imine CH, benzylic CH_2, and alanine α protons for **1**–L-Ala and **1**–D-Ala are all well resolved. Figure 1c shows the partial ^{1}H NMR spectrum for the mixture of **1**–L-Ala and **1**–D-Ala formed by addition of two equivalents of racemic alanine to **1**. Integration of the signals due to **1**–L-Ala and **1**–D-Ala in Figure 1c determines that the ratio of **1**–D-Ala/**1**–L-Ala is 2.7:1. This indicates the imine-formation constant for **1**–D-Ala is larger than that for **1**–L-Ala by a factor of about 2.7^2:1 or 7.4:1.[14] Even if **1**–L-Ala is formed first by addition of one equivalent of [Bu_4N][L-Ala], the above equilibrium ratio is obtained within 10 min upon addition of one equivalent of [Bu_4N][D-Ala] to the mixture. In this experiment, the epimerization of **1**–L-Ala into **1**–D-Ala is negligible, since the ^{1}H NMR spectra in Figures 1a and b do not change for a reasonable period of time.



Scheme 2. Synthesis of **1**. Reagents and conditions: a) Phenyl isocyanate, THF, 0.5 h, RT, 95%; b) PBr_3, THF, 1 h, RT, 90%; c) DMF, NaH, MOMCl, RT, 65%; d) DMF, NaH, 3-phenyluryl-benzyl bromide, RT, 84%; e) EtOH, HCl, 70°C, 95%. THF = tetrahydrofuran; DMF = *N*,*N*-dimethylformamide; MOM = methoxymethyl.

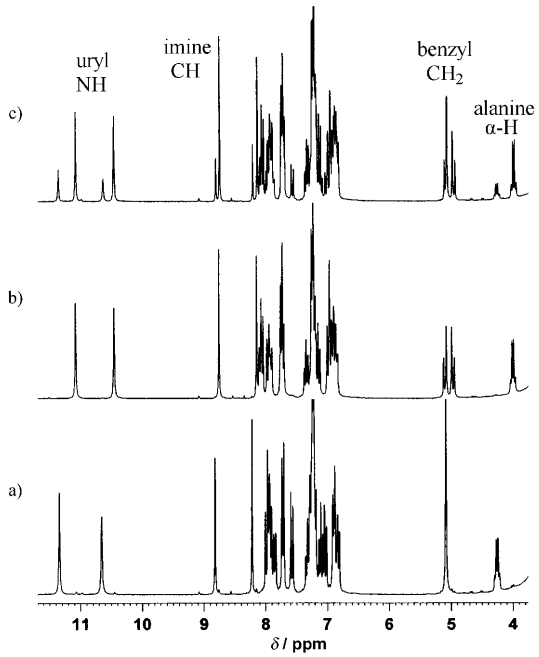


Figure 1. Partial ^{1}H NMR spectra indicating stereoselective imine formation of **1** with alanine in [D_6]DMSO. a) **1**+2[Bu_4N][L-Ala]; b) **1**+2[Bu_4N][D-Ala]; c) **1**+2[Bu_4N][DL-Ala].

Under different experimental conditions, with the weak base triethylamine, epimerization of the imine **1**–L-Ala into **1**–D-Ala has been observed by ^{1}H NMR studies. In a typical experiment, L-Ala (10 mM) and **1** (10 mM) were mixed in [D_6]DMSO to form the imine, **1**–L-Ala, then triethylamine (40 mM) was added. Figure 2a shows the time-dependent changes in the ^{1}H NMR spectrum due to epimerization of the imine from **1**–L-Ala into **1**–D-Ala. The phenolic hydrogen signal of the RAHB shifts upfield from $\delta = 14.69$ to 14.55 ppm as **1**–L-Ala epimerizes into **1**–D-Ala. The two urea hydrogen signals shift dramatically downfield from $\delta =$ 9.65 and 10.37 to 10.22 and 10.85 ppm, and the imine CH signal shifts upfield from $\delta = 8.78$ to 8.70 ppm as the epimerization proceeds. The apparent downfield shift of the signal for the uryl NH protons upon epimerization from **1**–L-Ala into **1**–D-Ala is certainly due to the strong hydrogen bond between the uryl group of **1** and the carboxylate group of alanine. At equilibrium, established in approximately 20 h, the ratio of [**1**–D-Ala] to [**1**–L-Ala] is about 7 to 1, which is comparable to the stereoselectivity of 7.4 to 1 calculated from the study with [Bu_4N][Ala] described above.

Figure 2b shows the epimerization of the imine of glutamate with two asymmetric carboxylate groups. The ^{1}H NMR spectra of **1**–L-Glu, when compared with those of other amino acids, suggest two different conformations, whereas **1**–D-Glu has only one. Interestingly, both conformers of **1**–L-Glu are epimerized to a single conformer of **1**–D-Glu. Figure 2c shows that the imine of a hydroxy-group-containing amino acid, serine, also epimerizes.

The ratios of [**1**–D-aa] to [**1**–L-aa] at equilibrium for various amino acids are listed in Table 1. The side chains of the amino acids in Table 1 include basic (His) and acidic (Glu) ones, as well as hydrophobic (Tyr, Trp, Phe, Leu, Ala) and hydrophilic (Ser, Thr, Gln, Arg, Asn, Met) ones. Further-

Table 1. The stereoselective ratios of [**1**–D-aa] to [**1**–L-aa] at equilibrium, as determined by the integration of the ^{1}H NMR spectra.

Amino acid	D/L ratio	Amino acid	D/L ratio
threonine	20	methionine	11
glutamine	15	glutamic acid	11
histidine	14	serine	11
arginine	14	leucine	9
asparagine	13	tryptophan	8
tyrosine	12	alanine	7
phenylalanine	11	valine	0
3-(2-thienyl)alanine	18	4-nitrophenylalanine	14
norleucine	13	H-Lys(Cbz)-OH	14
O-methyltyrosine	10	N_ω-nitroarginine	12

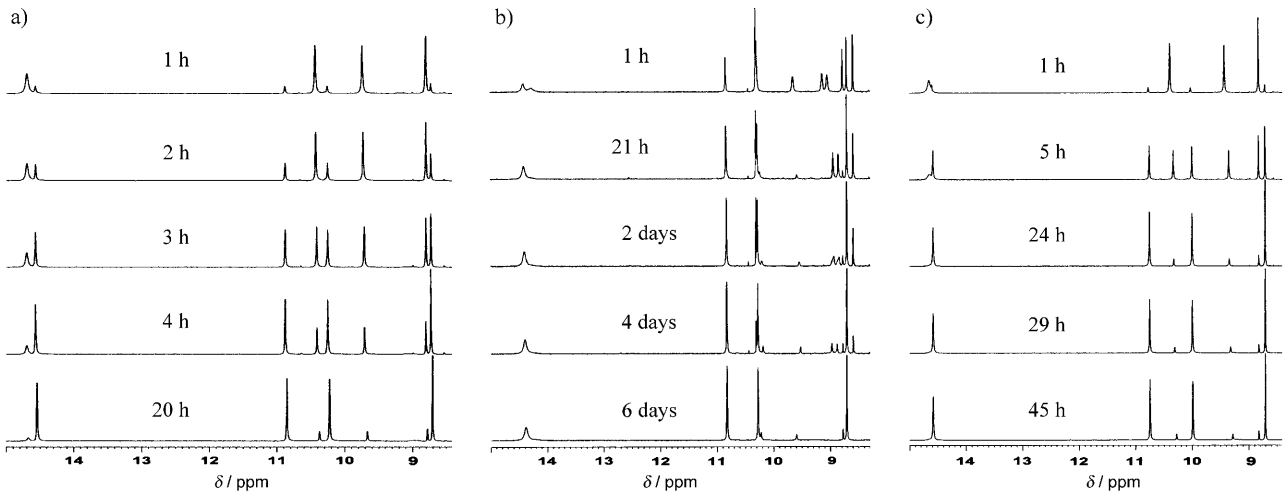
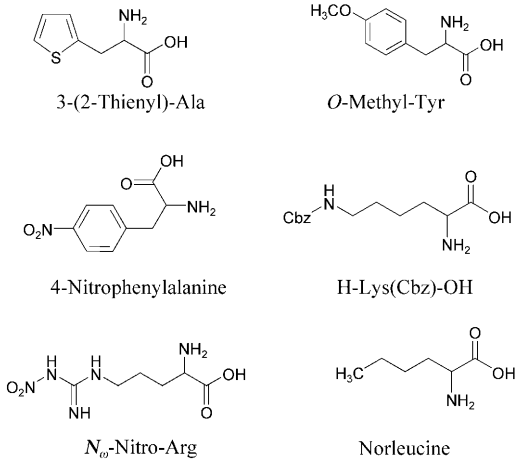


Figure 2. Partial ^{1}H NMR spectra indicating the conversion of **1**–L-aa into **1**–D-aa. The peaks corresponding to **1**–L-aa decrease while those corresponding to **1**–D-aa increase (from top to bottom). a) Conversion of L-Ala into D-Ala; b) conversion of L-Glu into D-Glu; c) conversion of L-Ser into D-Ser.

more, six representative unnatural amino acids, 3-(2-thienyl)alanine, *O*-methyltyrosine, 4-nitrophenylalanine, H-Lys-(Cbz)-OH, N_ω-nitroarginine, and norleucine (Scheme 3),



Scheme 3. Unnatural amino acids tested. Cbz: benzyloxycarbonyl.

have also been observed to form aldimines with **1** and to participate in the epimerization. It is clear from the table that the receptor binds all amino acids with the same sense of stereoselectivity. Although the sense of the receptor stereoselectivity for binding α-amino acids is the same as that for binding 1,2-amino alcohols,[14] the magnitude of the receptor stereoselectivity is considerably greater for binding α-amino acids. Stronger H-bonding between the urea group and the carboxylate group over the H-bonding between the urea group and the alcohol group may contribute to the greater receptor streoselectivity in binding α-amino acids over that in binding 1,2-amino alcohols.

Compound **1** reacts with a wide variety of natural and unnatural amino acids and changes their chirality sense, except with proline, which has a secondary amine group, and cysteine, the thiol group of which is involved in attacking the aldehyde moiety. In the case of valine, the bulky *tert*-butyl group hinders epimerization even though the imine is formed stereoselectively. Aspartic acid showed low stereoselectivity (D/L≈2:1), probably due to competition of the side-chain carboxylate group for effective H-bonding to the urea NH moiety. To our knowledge, **1** represents the most stereoselective small-molecule organic receptor for binding and epimerizing a wide range of chiral amino acids.

Epimerization of peptides: Figure 3 illustrates the epimerization of the dipeptide L-Ala-Gly and the tripeptide L-Phe-Gly-Gly after the formation of the imine with **1**. The signals for the uryl NH protons appear at $\delta = 10.62$ and 11.04 ppm for **1**–L-Ala-Gly and at $\delta = 11.14$ and 11.60 ppm for **1**–D-Ala-Gly. Significantly, much stronger hydrogen bonds are assumed between the carboxylate and uryl groups for **1**–D-Ala-Gly than for **1**–L-Ala-Gly. The stereoselectivity of **1** for the dipeptide is comparable to that for alanine. However, the stereoselectivity is only marginal and the epimerization

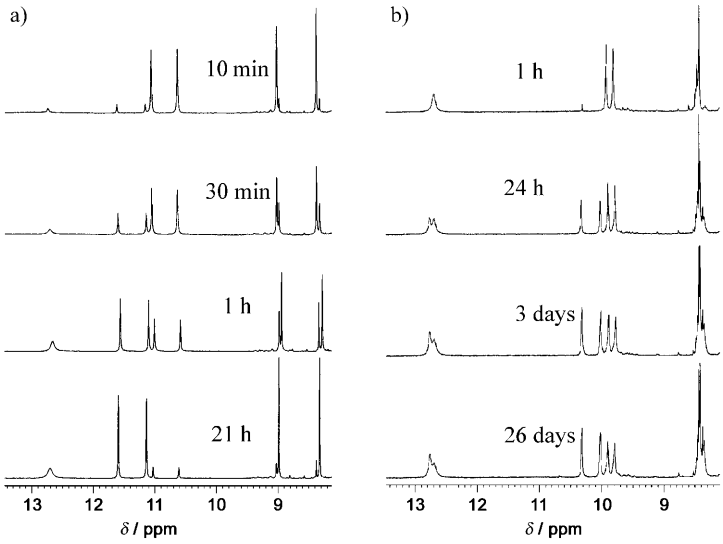


Figure 3. Partial ^{1}H NMR spectra indicating the stereoconversion of peptides in [D$_6$]DMSO. a) **1**+L-Ala-Gly; b) **1**+L-Phe-Gly-Gly.

rate is much slower in the case of the tripeptide. Other dipeptides, like L-Met-Gly, L-His-Gly, and L-Leu-Gly, have also been studied for the epimerization in the imine form. All of the amino acid residues in the peptides are achiral glycine, except for the N-terminal ones; this was chosen for simplicity. It is not unreasonable to assume that a similar epimerization behavior would be applied to other peptides if any other amino acids replaced the glycine residues. The epimerization rates and stereoselective ratios for the dipeptides are not much different those of the corresponding amino acids (Table 1).

It is noteworthy that compound **1** can be used as a chiral shift agent (CSA) for discriminating the chirality sense of a C-terminal amino acid by ^{1}H NMR spectroscopy, as illustrated with Gly-L-Phe and Gly-D-Phe in Figure 4. One uryl NH proton signal appears at $\delta = 10.68$ ppm for **1**–Gly-D-Phe and at $\delta = 10.58$ ppm for **1**–Gly-L-Phe, and these signals are well base-line resolved. Additionally, the signal of the benzylic CH_2 protons of **1**–Gly-D-Phe appears as a distinct doublet of doublets (dd) at $\delta = 4.15$ ppm whereas that of **1**–Gly-L-Phe appears as an obscured dd pattern at $\delta = 4.20$ ppm (not shown). Under these experimental conditions, the stereoconversion of phenylalanine in the peptide was not detected at all.

Dipeptides are prepared either chemically or enzymatically.[16,17] Enzymatic syntheses may have limitations in application to a wide variety of stereoisomers of dipeptides, and chemical syntheses require protection and deprotection processes. Therefore, **1** may be practically helpful in the preparation of some stereoisomers of dipeptides.

Deuteration of the α proton and insight into the mechanism: Figure 5 displays time-dependant ^{1}H NMR spectra of the imine **1**–DL-Ala in [D$_6$]DMSO containing 10% D_2O. The α proton of L-Ala ($\delta = 4.25$ ppm) is deuterated faster than that of D-Ala ($\delta = 3.98$ ppm). The half life of the L-Ala

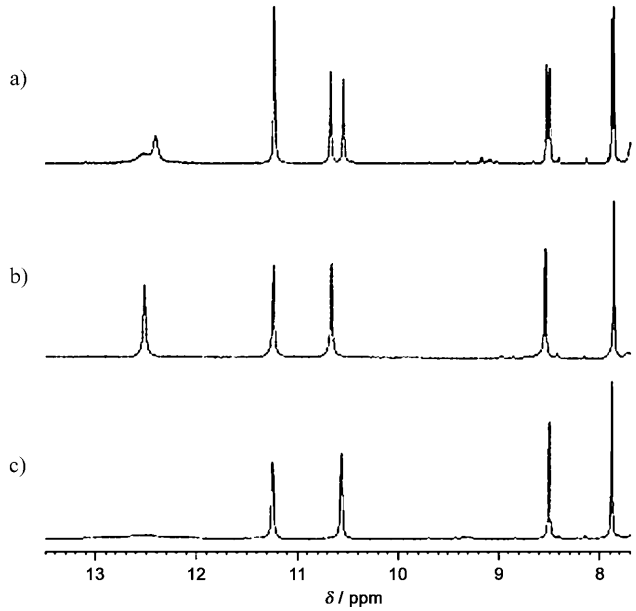


Figure 4. Partial ^{1}H NMR spectra indicating the ability of **1** as a chiral shift reagent for Gly-Phe. a) **1**+Gly-DL-Phe; b) **1**+Gly-D-Phe; c) **1**+Gly-L-Phe.

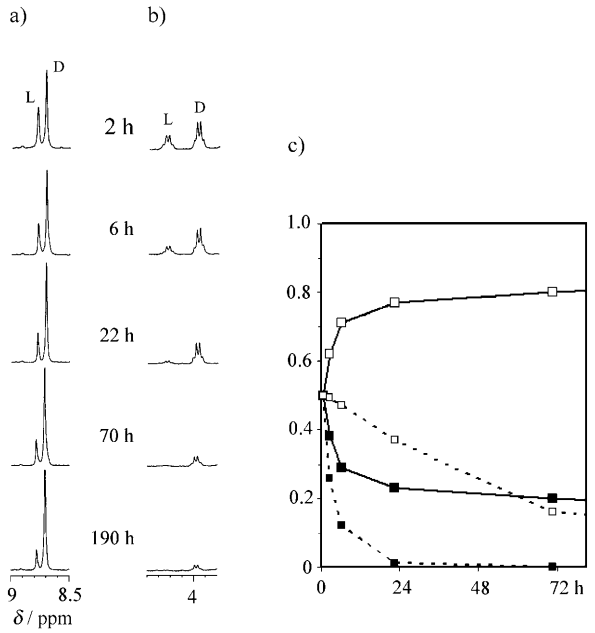


Figure 5. Time-dependent deuterium-exchange ^{1}H NMR spectra for a) the imine CH proton and b) the α proton of Ala in the imine. The ^{1}H NMR spectra were measured in [D_6]DMSO and D_2O (90:10) with **1**–DL-Ala. c) Deuterium-exchange study for the α proton of Ala in **1**–DL-Ala. ——: relative amounts of the L- and D-Ala in the imine; -----: relative amounts of nondeuterated α proton. ■: L-Ala; □: D-Ala.

α proton ($t_{1/2,L}$) is approximately 3 h and that of the D-Ala α proton ($t_{1/2,D}$) is approximately 48 h. Upon deuteration, the amount of D-Ala increases and the reaction requires more than ten days to reach equilibrium, at which point the D/L ratio is around four. The D_2O content tends to decrease the selectivity and retards the reaction rate.

The epimerization may occur in a concerted way or a stepwise way. In the concerted mechanism where deprotonation and deuteration occurs simultaneously, L-Ala is expected to convert into D-Ala and vice versa upon deuterium exchange. Hence, in the concerted mechanism, the relative amount of D-Ala in the imine will be higher than at least 0.9 in 1 day due to the fast deuteration of the L-Ala α proton. But, as determined from Figure 5, the relative amount of D-Ala observed in 1 day is less than 0.8, which does not support the concerted mechanism.

In the stepwise mechanism, sequential steps of deprotonation and deuteration are supposed. If both L-Ala and D-Ala are produced by the same probability in the deuteration step, and if the deuterated alanines are not deuterated again, then the relative amount of D-Ala in one day will be approximately 0.7. However, when it is taken into account that the deuterated alanines must be deuterated again, the expected relative amount of D-Ala in the imine will be even higher than the observed value of 0.78. Such analysis of the data in Figure 5 supports the conclusion that L-Ala is formed more favorably than D-Ala in the deuteration step; this is considered to have an adverse effect for obtaining higher D/L ratios in the final equilibrium.

The energy-minimized structures of imines **1**–L-Ala and **1**–D-Ala are shown in Figures 6a and b, respectively. The density functional theory (DFT) calculations predict that **1**–D-Ala is more stable than **1**–L-Ala by 1.64 kcal mol^{-1}, a result that is in qualitative agreement with the experimental stereoselectivity. In **1**–L-Ala, there appears to be considerable steric hindrance between the methyl group of the alanine and the imine CH moiety of the receptor. By contrast,

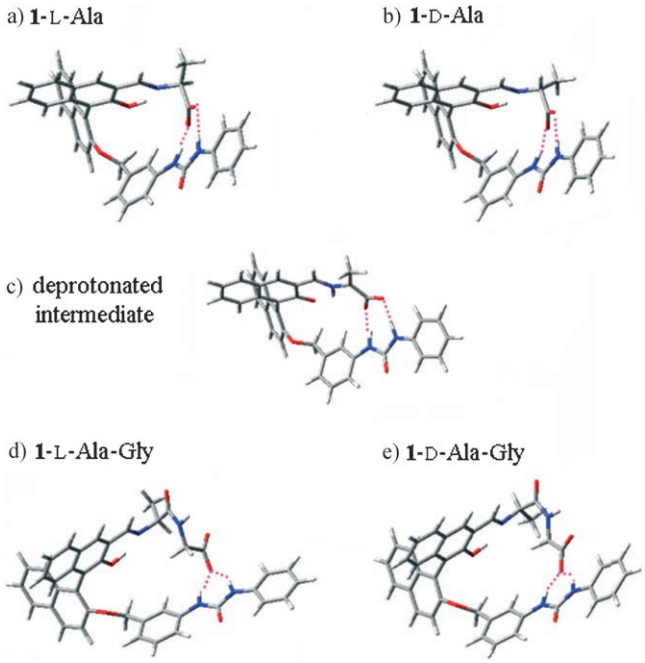


Figure 6. Energy-minimized geometries at the B3LYP/6-31G* level. The pink dotted lines represent hydrogen bonding. Red: oxygen atoms; blue: nitrogen atoms.

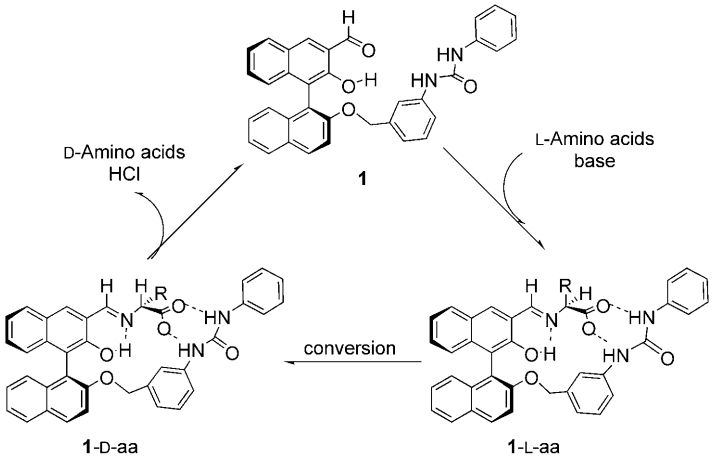
there is less steric hindrance between the α proton of the alanine and the imine CH group of the receptor in **1**–D-Ala. The weaker steric interactions in **1**–D-Ala should be the origin of the stability. The easier deprotonation of the L-alanine α proton is probably due to the instability of **1**–L-Ala.

Why is L-Ala production favored in the deuteration step? Figure 6c demonstrates the structure of the deprotonated species determined by DFT calculations. The structure shows almost perfect planar geometry of the deprotonated alanine motif. Deuteration on this plane will lead to L-Ala and D-Ala with the same probability. However, the structure illustrates that the deuterium attacking space is more open to the position leading to L-Ala, which may be the reason why more L-Ala than D-Ala is produced in the deuteration step.

The structure of the deprotonated species may, furthermore, be a clue to an explanation for the sluggish stereoconversion of valine in the imine form. The acidity of the α proton of amino acids in the imine form would have some correlation with the structure of their deprotonated intermediates, which must be present during the stereoconversion. The energy-minimized structure for the deprotonated form of the alanine-bound imine (Figure 6c) shows that the imine CH proton and the alanine methyl group are in close proximity. With the *tert*-butyl group of valine, the imine would suffer more steric hindrance in its deprotonated intermediate, which may be the reason for the low acidity of the α proton and, thus, the sluggish stereoconversion.

The DFT calculations for the imine with the dipeptide revealed that **1**–L-Ala-Gly suffers more steric hindrance around the imine bond than **1**–D-Ala-Gly (Figures 6d and e). The energy difference is 1.20 kcal mol^{-1}, which again is in qualitative agreement with the experimental result. On the other hand, the marginal stereoselectivity for the tripeptide that was shown by the ^{1}H NMR study may be attributed to the large degree of freedom in conformations of the peptide.

Recycling of 1: Imine formation between **1** and an amino acid is a thermodynamic equilibrium process, and catalytic deracemization of the amino acid cannot be accomplished with substoichiometric amounts of **1**. Despite the thermodynamic limitation, deracemization of amino acids can be practically realized by using **1** as an auxiliary, as shown in Scheme 4. Mixing of **1** and racemic amino acid in the presence of the weak base triethylamine in DMSO led to reversible formation of the imine followed by stereoselective epimerization. At equilibrium, the reaction mixture was extracted with chloroform and water. Compound **1** and the amino acids were separated into the organic and aqueous phases, respectively. In a representative one-cycle experiment with **1** (3.0 g) and racemic phenylalanine (1 equiv), we recovered all of the **1** and 89% of the phenylalanine. The D/L ratio of recovered phenylalanine was investigated by HPLC and found to be 11.8:1, which is comparable to the value (11:1) in Table 1.



Scheme 4. The cycle process for conversion of an L-amino acid to a D-amino acid with **1** as an auxiliary.

Conclusion

In the past few decades, there has been much interest in deracemization of amino acids as a method for large-scale production of D- or L-amino acids. Chemoenzymatic dynamic-kinetic-resolution processes have recently been developed for the deracemization of amino acids.[18] Many interesting models of pyridoxamine, including chiral ones, have been developed to convert α-keto acids into α-amino acids.[19] Our receptor, **1**, is a convenient auxiliary, which requires mild conditions for binding and releasing its substrates. Thus, the small organic receptor **1** may be industrially useful for the production of D-amino acids from naturally obtainable L-amino acids or chemically synthesized DL-amino acids.

We have designed and synthesized (*S*)-2-hydroxy-2′-(3-phenyluryl-benzyl)-1,1′-binaphthyl-3-carboxaldehyde (**1**), which forms a chiral Schiff base type imine with a wide range of amino acids, including unnatural ones, and converts bound L-amino acids into D-amino acids. The ratio of **1**–D-aa/**1**–L-aa was observed to be more than 10 at equilibrium for most amino acids. The deuteration data for the α proton of alanine in its imine form suggest a stepwise mechanism rather than a concerted one in the L-into-D conversion reaction. We have demonstrated that the N-terminal amino acids in dipeptides are also predominantly converted into the D form upon imine formation. Computer-modeling studies on the imine forms have provided useful information that gives explanations for the D-form stereoselectivity. We have also demonstrated that **1** can be a practical auxiliary converter of L- or DL-amino acids into D-amino acids by showing the complete recovery of **1** under mild conditions through an extraction process.

Experimental Section

Materials and methods: Melting points were obtained on an Electrothermal IA 9000 digital melting-point apparatus. Optical rotations were mea-

sured on an ADP 220 digital polarimeter. NMR spectra were measured on a Bruker AM 250 spectrometer. Chemical shifts (δ) are given in ppm with tetramethylsilane (TMS) as an internal standard. HRMS data were obtained on Jeol-JMS 700 spectrometer in EI mode. HPLC was performed with an Agilent 1100 instrument. (*S*)-2,2′-dihydroxy-1,1′-binaphthyl-3-carboxaldehyde (**2**) was prepared according to the literature procedure.[20] All other chemicals including amino acids and peptides are commercially available and were used without further purification. The solvents for dry reactions were dried with appropriate desiccants and distilled prior to use. For column chromatography, silica gel of 230–400 mesh was used.

Synthesis of 3-phenyluryl-benzyl alcohol: Phenylisocyanate (9.0 g, 75 mmol) was added to a solution of 3-aminobenzyl alcohol (9.3 g, 75 mmol) in THF (100 mL), and the mixture was stirred at ambient temperature. The precipitate formed was filtered, washed with THF, and dried in vacuo to give the desired product as a white solid (17.4 g, 95% yield): m.p. 161°C; ^{1}H NMR ([D$_6$]DMSO, 250 MHz): δ = 8.65 (s, 1H), 8.63 (s, 1H), 7.52–6.95 (m, 9H), 5.21 (t, 1H), 4.45 ppm (d, 2H); ^{13}C NMR ([D$_6$]DMSO, 62.5 MHz): δ = 152.9, 143.7, 140.2, 140.0, 129.2, 129.0, 128.9, 122.2, 120.4, 118.5, 116.9, 116.6, 63.3 ppm.

Synthesis of 3-phenyluryl-benzyl bromide: Phosphorus tribromide (2.2 mL, 23 mmol) was added to a slurry of 3-phenyluryl-benzyl alcohol (15 g, 62 mmol) in THF (100 mL) and the mixture was stirred at room temperature. The precipitate formed was filtered, washed with THF, and dried in vacuo to give the product as a white solid (18 g, 90% yield): m.p. 186°C; ^{1}H NMR ([D$_6$]DMSO, 250 MHz): δ = 8.73 (s, 1H), 8.65 (s, 1H), 7.59–6.93 (m, 9H), 4.66 ppm (d, 2H); ^{13}C NMR ([D$_6$]DMSO, 62.5 MHz): δ = 152.9, 140.4, 140.0, 139.0, 129.6, 129.2, 123.1, 122.3, 119.8, 119.2, 118.6, 118.5, 35.2 ppm.

Synthesis of (*S*)-2-methoxymethoxy-2′-hydroxy-1,1′-binaphthyl-3-carboxaldehyde (3): Sodium hydride (0.45 g, 11 mmol) was added portionwise to a stirred solution of (*S*)-2,2′-dihydroxy-1,1′-binaphthyl-3-carboxaldehyde (**2**; 3.9 g, 12.4 mmol) in DMF (40 mL). The mixture was stirred for another 1 h, and a solution of MOM chloride (1.08 mL, 12.4 mmol) in DMF (40 mL) was added dropwise. After being stirred overnight at ambient temperature, the resulting mixture was extracted with ethyl acetate several times. The combined organic layers were dried with anhydrous magnesium sulfate, and the solvent was evaporated. The crude product was purified by column chromatography with ethyl acetate/hexane (1:5) as the eluent to give the product **3** as a yellow solid (2.9 g, 65% yield): m.p. 164°C; $[\alpha]_D = -108.2$ (c = 0.42 in EtOH); ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 10.59 (s, 1H), 8.62 (s, 1H), 8.09 (d, 1H), 7.99–7.88 (m, 2H), 7.54–7.27 (m, 6H), 7.07 (d, 1H), 5.08 (s, 1H), 4.74 (dd, 2H), 3.03 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 154.4, 151.0, 136.6, 133.3, 132.7, 130.0, 130.7, 130.3, 129.7, 128.2, 128.5, 127.3, 126.1, 125.4, 124.3, 124.7, 123.4, 118.5, 114.2, 100.8, 57.3 ppm; HRMS (EI): calcd for $C_{23}H_{18}O_4$: 358.1205; found: 358.1198.

Synthesis of (*S*)-2-methoxymethoxy-2′-(3-phenyluryl-benzyl)-1,1′-binaphthyl-3-carbxaldehyde (4): Compound **3** (2.42 g, 6.75 mmol) in 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 1 h of stirring, 3-phenyluryl-benzyl bromide (2.26 g, 7.42 mmol) was added, and the stirring was continued at room temperature. After an additional 5 h of stirring, the reaction mixture was extracted with ethyl acetate and washed with water. The crude product was purified by silica column chromatography with ethyl acetate/hexane as the eluent (1:1) to furnish the product **4** as a yellow solid (3.3 g, 84% yield): m.p. 140°C; $[\alpha]_D = -43.4$ (c = 0.42 in EtOH); ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 10.48 (s, 1H), 8.51 (s, 1H), 7.98–7.09 (m, 20H), 6.87 (s, 1H), 6.75 (d, 1H), 5.07 (d, 2H), 4.71 (dd, 2H), 2.66 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 192.9, 153.9, 152.8, 152.0, 138.9, 138.7, 137.7, 137.3, 135.0, 133.4, 130.3, 130.2, 129.8, 129.0, 128.1, 127.0, 126.2, 125.0, 124.0, 123.1, 120.1, 119.7, 118.5, 118.3, 117.8, 114.5, 100.0, 69.8, 56.8 ppm; HRMS (EI): calcd for $C_{37}H_{30}N_2O_5$: 582.2155; found: 582.2147.

Synthesis of (*S*)-2-hydroxy-2′-(3-phenyluryl-benzyl)-1,1′-binaphthyl-3-carboxaldehyde (1): Concentrated hydrochloric acid (37%, 0.28 mL, 3.43 mmol) was added to a solution of **4** (2.00 g, 3.43 mmol) in ethanol (200 mL), and the mixture heated to 70°C for 1 h. The solution was evaporated to dryness, and the crude product was further purified by column chromatography with ethyl acetate/hexane (1:1) as the eluent to give **1** as a yellow solid (1.76 g, 95% yield): m.p. 217°C; $[\alpha]_D = -215.2$ (c = 0.58 in EtOH); ^{1}H NMR ([D$_6$]DMSO, 250 MHz): δ = 10.30 (s, 1H), 10.20 (s, 1H), 8.68 (s, 2H), 8.60 (s, 1H), 8.15–7.03 (m, 16H), 6.67 (s, 1H), 5.20 ppm (d, 2H); ^{13}C NMR ([D$_6$]DMSO, 62.5 MHz): δ = 196.9, 154.0, 152.9, 152.3, 139.6, 139.5, 137.9, 136.9, 136.7, 133.2, 130.1, 130.0, 129.7, 128.9, 128.7, 128.5, 128.1, 127.1, 126.6, 124.4, 124.3, 124.0, 123.6, 122.6, 121.7, 120.2, 118.1, 117.6, 117.3, 116.8, 115.6, 70.0 ppm; HRMS (EI): calcd for $C_{35}H_{26}N_2O_4$: 538.1893; found: 538.1898.

Preparation of [Bu$_4$N][L-Ala], [Bu$_4$N][D-Ala], and [Bu$_4$N][DL-Ala]: L-Ala (1.0 g, 11 mmol) was stirred in methanol, and a 1.0 N [Bu$_4$N][OH] methanol solution (10.0 mL, 10.0 mmol) was added. The unreacted precipitate (L-Ala) was removed by filtration. The filtrate was evaporated to dryness under high vacuum, which left [Bu$_4$N][L-Ala] as a white solid. [Bu$_4$N][D-Ala] and [Bu$_4$N][DL-Ala] were prepared by the same method.

Energy calculations for the imines and the deprotonated intermediate: To perform conformational searches for each molecular system, constant-temperature molecular dynamics simulations were executed by using the SANDER module of the AMBER program package and employing the parm99 force field.[21] The molecular system was subjected to 1000 steps of conjugate gradient energy minimization and then brought into an equilibrium state for 100 ps by using the Berendsen coupling algorithm. In all calculations, an 8.0 Å nonbonded interaction cut-off was used and nonbonded pair lists were updated every 20 integration steps. A 2 fs timestep was used for the simulation. The simulations were performed for 1 ns at 3 different temperatures, and the structures were saved every 5 ps for analyses. Thus, a total of 600 structures was collected during 3 trajectories. Geometry optimizations were then performed for those structures by using the AM1 semiempirical method[22,23] to find the energy minima that would be used as initial structures for a high-level geometry optimization. By using this method, energy-minima structures were collected for each conformation and the structures were then confirmed by vibrational-frequency analysis at the AM1 level. Geometry optimization was then performed for those structures with DFT calculations at the B3LYP/6-31G* level[24] followed by MPWB1K/6-31$^+$G**//B3LYP/6-31G* calculations[25] by using Gaussian 03 package.[26] Frequency calculations were performed to verify the identity of each stationary point as a minimum. All energies discussed here are at the MPWB1K/6-31$^+$G**//B3LYP/6-31G* level unless otherwise noted.

^{1}H NMR study for epimeric conversion of amino acids and peptides: In a typical experiment, enantiomerically pure L-Ala (1.1 equiv, 2.0 mg, 22 μmol) and triethylamine (8.9 mg, 88 μmol) were added to **1** (11 mg, 20 μmol) in [D$_6$]DMSO (1.0 mL). The reaction mixture was stirred at room temperature. After complete imine formation (within 10 min), ^{1}H NMR spectra were taken periodically. The integration ratio was carefully measured, and the D/L ratio of the equilibrated solution was determined. Epimerizations for other amino acids were tested by the same method.

Recovery of receptor 1 and D-amino acids: This experiment was carried out with phenylalanine as a representative amino acid. L-Phenylalanine (0.93 g, 5.57 mmol) and triethylamine (3.1 mL, 22 mmol) were added to **1** (3.0 g, 5.57 mmol) dissolved in [D$_6$]DMSO (30 mL). The reaction mixture was stirred for 24 h at 40°C. The ^{1}H NMR spectrum for the solution confirmed that the ratio of **1**–D-Phe/**1**–L-Phe had reached equilibrium. The solution was extracted with $CHCl_3$ (300 mL) and washed 7 times with brine (30 mL), which removed remaining DMSO from the organic layer. The organic layer was then extracted 3 times with a 1.0 N HCl (50 mL) solution to hydrolyze the imine. Evaporation of the organic layer gave **1** (3.0 g, 100% yield), the ^{1}H NMR spectrum of which confirmed that the purity has not been changed. Complete evaporation of the combined aqueous layers gave triethylamine HCl and phenylalanine HCl salts. The triethylamine HCl could be removed by washing with $CHCl_3$, and the phenylalanine HCl salt was recovered (1.01 g, 89% yield). The D/L ratio of the recovered phenylalanine was assessed by HPLC to be 11.8:1. A Chirosil RCA column was used, the mobile phase was a mixture of ethanol and water (7:3), and UV detection was performed at 210 nm. The re-

tention times of the enantiomers were 3.21 (D-Phe; 92.2%) and 4.74 min (L-Phe; 7.8%).

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