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The Chirality Conversion Reagent for Amino Acids Based on Salicyl Aldehyde

Hoe-Jin Yoon, Hein Jung, Yun Soo Ahn,[†] Raju Nandhakumar,[‡] Jun Soo Kim, and Kwan Mook Kim[*]

Department of Chemistry and Nano Science (BK21), Ewha Womans University, Seoul 120-750, Korea
[*]E-mail: kkmook@ewha.ac.kr
[†]Aminolux R&D Center, #1022 Sicox Tower, Kyeonggi-do 462-806, Korea
[‡]Department of Chemistry, Karunya University,Coimbatore-641 114, TamilNadu, India
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2-Hydroxy-6-(1-(3-phenylurylphenyl)ethoxy)-benzaldehyde (**2**) has been synthesized in racemic form from 1,3-Dihydroxybenzene via formylation and reaction with 3-phenyluryl-methylbenzylbromide. The optically pure form of **2** was separated by normal silica column chromatography from the imine diastreomer which was obtained by the reaction of racemic mixture of **2** with optically pure leucinol. The absolute configuration of the separated enantiomer of **2** was decided from the energy calculation of the corresponding imine diastereomers. The activity of **2** as a chirality conversion reagent (CCR) for amino acids was determined by ^{1}H NMR analysis. The efficiency of **2** is not better than the previous CCRs based on binaththol. Compound **2**, however, has lower molecular weight compared to other CCRs. This work demonstrates that asymmetric carbon can control the selectivity of amino acids.

Key Words : Salicyl aldehyde, Chirality conversion, Amino acid, Enantioselective recognition

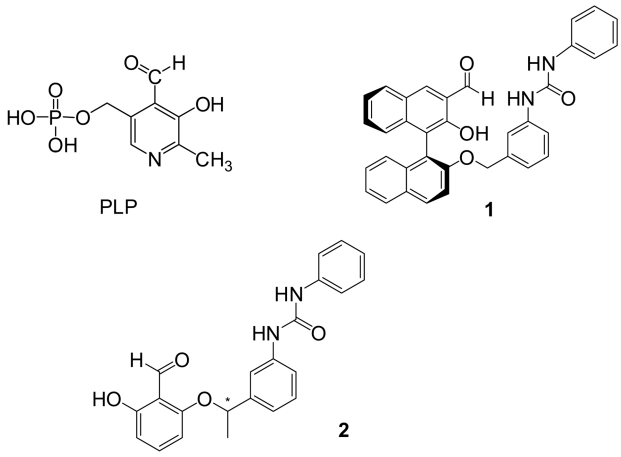
Introduction

Enantiomerically pure amino acids are useful starting materials or intermediates for the synthesis of a variety of biologically active chiral molecules.[1] They also serve as useful building blocks for ligand designs in the development of chiral catalysts.[2]

In nature, 5'-pyridoxal phosphate (PLP) plays an important role in amino acid racemization, transamination and decarboxylation processes.[3] The racemization occurs through the acidification of the α-proton of the amino acid in the Schiff base formed between the PLP and an amino acid.[4]

PLP, salicylic aldehyde (SA) and their derivatives have been widely studied as catalysts for amino acid racemization.[5] Chiral derivatives of PLP and SA can theoretically induce stereoselective deracemization of amino acids. Indeed, binaphthol-based chiral aldehyde **1** that was reported by our group converts stereoselectively L-amino acids to D-amino acids in its imine form.[6] The basis of the conversion has been well elucidated in our previous works.[7] The compound **1** and other related compounds developed in our group are chirality conversion reagents (CCR) for amino acids.[8] The compound **1** has the molecular weight much larger than normal amino acids, and thus, large amount of **1** is required in the L to D conversion process. In this context, we have searched for novel CCR with low molecular weight. It is rather surprising that it is hard to find out SA or PLP derivatives as CCR in literatures, even though some chiral SA or Pyridoxal derivatives were reported as catalysts for stereoselective transamination.[9]

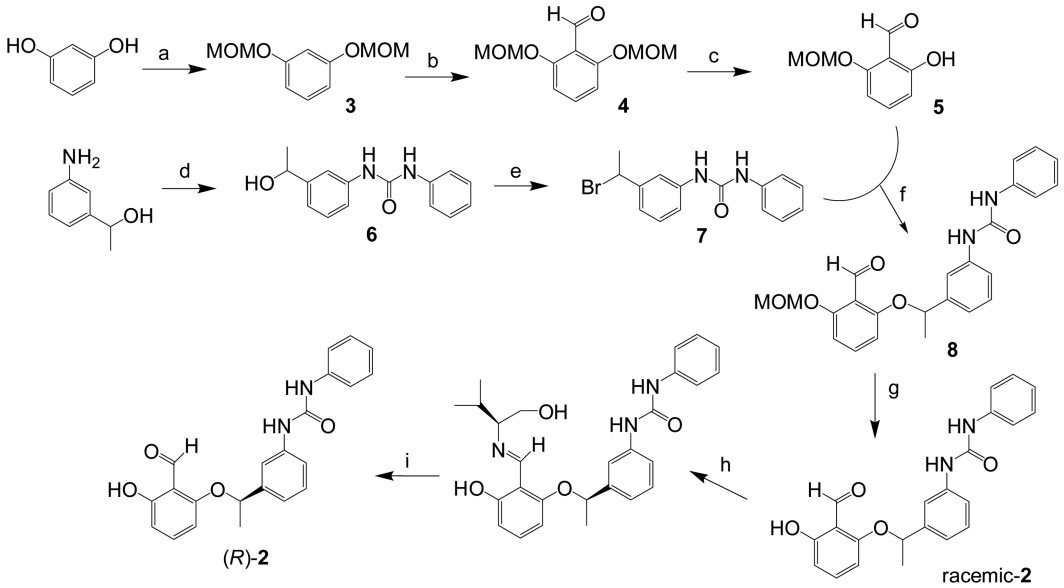
We designed the SA derivative **2** for the deracemization of amino acids. The asymmetric benzyl carbon was expected to control the stereoselectivity, and the uryl group was introduced because strong interaction with the carboxylate group of the amino acid in its imine form was considered to be important in providing the stereoselectivity.[6] Here we report the synthesis and efficiency of **2** as an L to D conversion reagent for amino acids.



Results and Discussion

Synthesis of 2. The synthetic route for the optically pure uryl-appended receptor **2** are described in Scheme 1. 1,3-Dihydroxybenzene was successfully formylated at 2-position with DMF/*n*-BuLi in THF and one hydroxy group was protected with MOM. The mono-MOM protected aldehyde was reacted with 3-phenyluryl-methylbenzylbromide to yield compound **8**, which on acid hydrolysis gave compound **2** in racemic form.

The optically pure form of **2** was separated by normal silica column chromatography from the imine diastreomer



Scheme 1. Reagents and conditions: (a) MOMCl, NaH, DMF, rt, 3 h, 92%; (b) *n*-BuLi/DMF, THF, –40 °C, 4 h, 92%; (c) HCl, ethanol, rt, 15 h, 75%; (d) Phenyl isocyanate, THF, rt, 1 h, 67%; (e) PBr_3, THF, rt, 3 h, 62%; (f) NaH, DMF, rt, 4 h, 90%; (g) HCl, THF, reflux, 80%; (h) (*S*)-leucinol, MC, rt, column separation, 75%; (i) HCl, ethanol, 70 °C, 83%.

which was obtained by the reaction of racemic mixture of **2** with optically pure leucinol. The absolute configuration of the separated enantiomer of **2** was decided from the energy calculation of the corresponding imine diastereomers using the program Spartan.[10] The calculation strongly supports that (*S*)-leucinol forms more stable imine with (*S*)-**2**. The diastereomer that forms more stable imine with (*S*)-leucinol was determined by ^{1}H NMR analysis. When the 0.5 eq (*S*)-leucinol was reacted with racemic mixture of **2**, more stable diastereomer was formed in larger ratio, and the corresponding compound **2** was decided to be (*S*)-form.

The structures of reaction intermediates and final compound **2** were confirmed by spectroscopic studies such as ^{1}H NMR, ^{13}C NMR. Compound **2** is freely soluble in various organic solvents including DMSO, $CHCl_3$ and benzene.

Conversion of L-Amino Acid to D-Amino Acid by (*R*)-2. The activity of (*R*)-**2** as CCR for amino acids was determined by ^{1}H NMR analysis. Figure 1 shows the time-dependent change of ^{1}H NMR spectra of the imine (*R*)-**2**-L-Ala formed between (*R*)-**2** (10 mM) and L-Ala (10 mM) in the presence of 4 equiv triethylamine in DMSO-d_6. The mixing of the reagents and stirring for 1 h led to the complete imine formation. The two peaks at 10.33 and 10.09 ppm correspond to the two urea hydrogen signals of the imine, (*R*)-**2**-L-Ala. The quartets at 5.59 ppm and 4.21 ppm are ascribed to the benzyl methine proton and the a proton of alanine, respectively, in the imine. The intensity of these peaks decrease as time goes, while new peaks corresponding to urea (10.65 and 10.33 ppm) and benzyl methine (5.68 ppm) and a proton of alanine (4.11 ppm) signals of (*R*)-**2**-D-Ala are growing. This clearly shows the chirality conversion of (*R*)-**2**-L-Ala to (*R*)-**2**-D-Ala. The apparent downfield shift of uryl NH protons of (*R*)-**2**-D-Ala compared to (*R*)-**2**-L-Ala is probably due to the stronger hydrogen bond between the

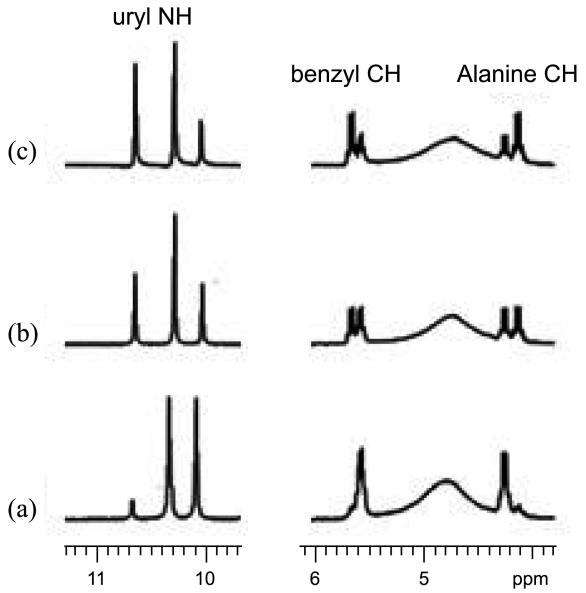


Figure 1. ^{1}H NMR spectra showing the conversion of L-alanine to D-alanine in the imine, (*R*)-**2**-L-Ala, formed by the reaction of (*R*)-**2** and L-alanine in the presence of excess TEA in DMSO-d_6. (a) after 1 hr (b) after 2 days (d) after 4 days.

uryl group of (*R*)-**2** and carboxylate group of D-alanine. The intensities of the resonance signals reach the equilibrium in 4 days. The stereoselectivity defined by the ratio of ((*R*)-**2**-D-Ala)/((*R*)-**2**-L-Ala) is measured by the integration of the corresponding signals.

The efficiency of (*R*)-**2** for representative other amino acids such as alanine, asparagine, glutamine, histidine, phenyl alanine, serine, tyrosine and leucine were measured by the same method. As shown in Table 1, diastereomeric ratio ranges from 1.02 to 3.29. This ratio is relatively not so

Table 1. The conversion efficiency of (*R*)-**2** for amino acids determined by ^{1}H NMR anaylsis

Amino acid	Diastereomeric ratio	
	(*R*)-**2**	**1**[6]
Alanine	2.21	7
Serine	1.85	11
Phenylalanine	2.32	11
Glutamine	1.31	15
Asparagine	3.29	13
Histidine	1.81	14
Tyrosine	2.28	12
Leucine	1.02	-

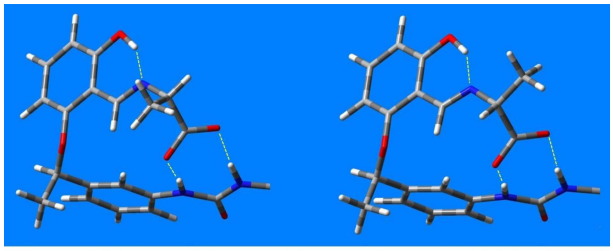
Table 2. The stereoselectivities (K_R/K_S) for the imine formation of (*R*)-**2** in $CDCl_3$ determined by ^{1}H NMR analysis

Amino alcohols	K_R/K_S	
	(*R*)-**2**	**1**[11]
2-amino-1-propanol	2.0	3.7
2-amino-1-butanol	2.2	3.1
2-amino-2-phenylethanol	4.2	4.8
phenyl alaninol	3.4	3.7
valinol	2.6	-
leucinol	2.6	-

remarkable as the ratio of compound **1** which was reported previously by our group, however, this is noticeable because **2** is SA derivative, a non-axially chiral compound.

Enantioselective Recognition of 1,2-Amino Alcohols with (*R*)-2. The stereoselective imine formation of (*R*)-**2** with various amino alcohols such as 2-amino-1-propanol, 2-amino-1-butanol, 2-amino-3-phenyl-1-propanol (phenylalaninol), 2-amino-3-methyl-1-butanol (valinol), and 2-amino-4-methyl-1-pentanol (leucinol) were studied by ^{1}H NMR analysis in $CDCl_3$ following the same protocol used in our previous work.[11] The results are summarized in Table 2, in which the selectivities obtained with binaphthol-based receptors **1**[11] were also included for comparison.

Modeling for the Chiral Selectivity Calculated by Molecular Mechanics. The energy optimized structures for (*R*)-**2**-L-Ala and (*R*)-**2**-D-Ala calculated by density functional theory (DFT) with the program Gaussian 09 are shown in Figure 2.[10] Two structures are first optimized with molecular mechanics and further optimized with DFT calculations at the B3LYP/6-31G* level.



(a) (*R*)-**2**-L-Ala (b) (*R*)-**2**-D-Ala

Figure 2. The energy optimized structures for (a) (*R*)-**2**-L-Ala and (b) (*R*)-**2**-D-Ala calculated by DFT calculations at the B3LYP/6-31G* level. The phenyl ring connected to the urea group in each figure was omitted for clarity.

The energy of the (*R*)-**2**-D-Ala is lower by 1.12 kcal/mol than that of (*R*)-**2**-L-Ala, and thus (*R*)-**2**-D-Ala is expected to be more stable than (*R*)-**2**-L-Ala. The optimized structures for their (*S*)-form counterparts, (*S*)-**2**-D-Ala and (*S*)-**2**-L-Ala, are just mirror images of (*R*)-form diastereomers. The energy difference between the optimized (*R*)-form diastereomers seems to originate in the steric environments around the imine bonds.

Conclusion

In summary, new salicyl-based chirality conversion reagent (CCR) for amino acids, **2**, has been developed in this work. The efficiency of **2** is not better than compound **1** which has been developed previously by our group. Compound **2**, however, has lower molecular weight compared to compound **1**. Moreover, this work demonstrates that asymmetric carbon can control the selectivity of amino acids, which is noticeable considering that the CCRs for amino acids developed so far are all based on axially chiral compounds such as binaphthol and 1,8-octahydro-binaphthol.

Experimental

General. The reagents and solvents were purchased from Aldrich and TCI. All chemicals were used as received without further purifications. NMR spectra were recorded on Bruker AM 250 spectrometer in $CDCl_3$ and DMSO-d_6 solutions containing tetramethylsilane as internal standard. Melting points were measured with Electrothermal IA 9000 digital melting point apparatus and are uncorrected. For column chromatography, silica gel of 230-400 mesh was used.

3-(1-Hydroxyethyl)phenyl-phenylurea (6). Compound (1-hydroxyethyl)-3-aniline (10.0 g, 72.9 mmol) was added dropwise to phenylisocyanate (8.86 g, 72.9 mmol) in THF (50 mL) following vigorous stirring for 2 hr, and the resultant solid was filtered off washed with diethylehter. Yield: 12.5 g (67%). ^{1}H NMR (DMSO-d_6, 250 MHz) δ 8.64-8.60 (br, 2H, -NH), 7.5-6.8 (m, 9H), 5.14 (d, 1H, -OH), 4.70-4.61 (m, 1H, -CH), 1.29 (d, 3H, $-CH_3$).

(1-Bromoethyl)phenyl-3-phenylurea (7). Phosphorus tribromide (4.84 g, 17.9 mmol) was added to (1-hydroxyethyl)phenyl-3-phenylurea (12.5 g, 101 mmol) in THF (100 mL) and stirred for 3 h. The precipitate, (1-bromoethyl)-phenyl)-3-phenylurea, was filtered out and washed with diethyl ether. Yield: 9.65 g (62%); ^{1}H NMR (DMSO-d_6, 250 MHz) δ 8.74 (s, -NH), 8.69 (s, -NH), 7.63 (s, 1H), 7.45-7.42 (d, 2H), 7.33-7.22 (m, 4H), 7.10-7.07 (d, 1H), 6.98-6.92 (t, 1H), 5.48-5.40 (m, 1H, -CH), 1.96-1.94 (d, 3H, $-CH_3$).

1,3-Di(methoxymethoxy)benzene (3). NaH (4.58 g, 60%, 115 mmol) was added portionwise to 1,3-dihydroxybezene (5.25 g, 47.7 mmol) in DMF (50 mL) cooled on ice bath. After stirring for 2 h, chloromethyl methyl ether (MOMCl,

7.45 g, 105 mmol) was added for 30 min and stirred for 3 h at room temperature. The reaction mixture was extracted with EA and water. The column chromatography for the organic layer with eluent EA/hexane (1/3) obtained the product. Yield: 8.90 g (92%); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.18 (t, 1H), 6.74-6.68 (m, 3H), 5.16 (s, 4H, -OCH_2), 3.47 (s, 6H, -OCH_3); mp 56 °C.

2,6-Bis(methoxymethoxy)benzaldehyde (4). To the solution of 1,3-bis(methoxymethoxy)benzene (8.90 g, 44.9 mmol) in anhydrous THF (100 mL), *n*-BuLi of 1.6 N solution in Hexane (31 mL, 49 mmol) was added for 1 h at −40 °C. After raising the temperature of the solution to −20 °C, anhydrous DMF (6.95 mL, 89.8 mmol) was added for 2 h and stirred for 1 h at room temperature. The reaction mixture was extracted with EA and water. The column chromatography for the organic layer with the eluent of EA and hexane (1:5) obtained the product. Yield: 9.55 g (92%); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 10.54 (s, 1H, -CHO), 7.40 (t, 1H), 6.85 (d, 2H), 5.27 (s, 4H, -OCH_2), 3.50 (s, 6H, -OCH_3); mp 102 °C.

1-Hydroxy-6-methoxymethoxy-benzaldehyde (5). To the solution of 2,6-bis(methoxymethoxy)benzaldehyde (12 g, 53 mmol) in ethanol (200 mL), 3 N HCl (18 mL, 54 mmol) was added, and the reaction solution was stirred for 15 h at room temperature. The reaction solution was wholly evaporated and extracted with EA and water. The product was isolated from the organic layer by column chromatography with eluent, EA and hexane of 1:5 ratio. Yield: 7.76 g (75%); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 12.24 (s, 1H, -OH), 10.42 (s, 1H, -CHO), 7.40 (t, 1H), 6.59 (d, 1H), 6.57 (d, 1H), 5.27 (s, 2H, -OCH_2), 3.49 (s, 3H, -OCH_3); mp 125 °C.

2-Methoxymethoxy-6-(1-(3-phenyluryl-phenyl)ethoxy)-benzaldehyde (8). To the solution of 1-hydroxy-6-methoxymethoxy-benzaldehyde (1.0 g, 5.5 mmol) in DMF (10 mL) on ice bath, 60% NaH (0.22 g, 5.5 mmol) was added and the reaction solution was stirred for 1 h followed by the addition of 1-bromoethyl-phenyl-3-phenylurea (1.75 g, 5.49 mmol) and stirring for 4 h. The reaction mixture was extracted with EA and water. The product was isolated by column chromatography with eluent EA and hexane in 1:1 ratio. Yield: 2.0 g (90%); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 10.4 (s, 1H, -CHO), 7.5-6.4 (m, 14H, aromatic and ury hydrogens), 5.15 (q, 1H, -CH), 5.47 (s, 2H, -OCH_2), 3.49 (s, 3H, -OCH_3), 1.22 (d, 3H, -CH_3); mp 138 °C.

2-Hydroxy-6-(1-(3-phenyluryl-phenyl)ethoxy)-benzaldehyde (2). Compound 2-methoxymethoxy-6-(1-(3-phenyluryl-phenyl)ethoxy)-benzaldehyde (2.0 g, 4.9 mmol) was added to THF (20 mL) with 2.0 N HCl (2.5 mL, 5.0 mmol), and the solution was stirred for 6 h at 50-60 °C. The solution was wholly evaporated and was extracted with EA and water. Column chromatography with an eluent of EA and hexane in 1:5 ratio gave the product. Yield: 1.5 g (83%); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 11.9 (s, 1H, -OH), 10.4 (s, 1H, -CHO), 7.6-4.4 (m, 14H, aromatic and uryl hydrogens), 5.32 (q, 1H, -CH), 1.62 (d, 3H, -CH_3); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 194.4, 165.5, 163.7, 154.3, 143.5, 139.8, 139.6, 139.3, 129.7, 129.2, 128.1, 124.1, 121.5, 120.9, 120.7, 119.8, 117.0, 111.2, 109.2, 103.7, 77.0, 24.5; mp 152 °C.

Enantiomeric Resolution of 2-Hydroxy-6-(1-(3-phenyluryl-phenyl)ethoxy)-benzaldehyde. Compound 2-hydroxy-6-(1-(3-phenyluryl-phenyl)ethoxy)-benzaldehyde (4.0 g, 1.14 mmol) was reacted with (*S*)-leucinol (0.14 g, 1.15 mmol) in $CHCl_3$ (20 mL) to form imine diastereomers. The two imine diastereomers was separated by column chromatography with an eluent of EA and hexane in 1:3 ratio. Each diastereomer was hydrolyzed in ethanol with excess HCl. The enantiomerically pure form of compound **2** was obtained by the extraction with EA and water. The yield of (*R*)-**2**: 1.05 g (50%); The yield of (*S*)-**2**: 0.26 g (13 %); $[\alpha]_D$ = −215 (*c* 17.6, $CHCl_3$) (***S***-form), $[\alpha]_D$ = 216 (*c* 10.3, $CHCl_3$) (*R*-form).

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