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Binol Based Chirality Conversion Reagents for Underivatized Amino Acids

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Abstract

Four binol based pyrrole carboxamide chiral receptors has been synthesized and effectively used as a Chirality Conversion Reagent (CCR) for underivatized amino acids. Three points of interactions take place for the conversion process. They are the reversible imine formation, the internal resonance assisted Hydrogen Bonding (RAHB) and the additional hydrogen bonds between the amino acids and the heterocylic moiety of the pendant groups. The conversion efficiency of all the receptors was found to be comparable with those of the receptors reported earlier.

Keywords

Binol Based Receptors; Chiral Recognition; Amino Acids; Amino Alcohols; Chiral Inversion; ^{1}H-NMR

1. Introduction

Enantiomerically pure amino acids emerged as an interesting and rewarding synthetic target during the past decade, because of their increasing industrial importance as chiral building blocks in ligand design and total synthesis. In particular, preparation of D-amino acids has attracted considerable attention not only because of their importance in the synthesis of pharmaceuticals, food ingredients, and drug intermediates but also due to the lack of natural resources and preparation requires high cost [1]-[8]. Even though a wealth of organic, biological, polymeric and metal based amino acid receptors have been developed during the past years [9]-[15], there has been a rare example of a chirality conversion reagent(CCR) for a wide range of underivatized amino acids [16].

Earlier, we showed several binol based receptors as able CCR's which convert amino acids [17]-[19] and peptides [20] [21] from L-form to D-form by the reversible imine formation [22] [23]. Multiple hydrogen bonding

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dur- ing the imine formation along with internal Resonance-Assisted H-bonds (RAHBs) play important roles in de- termining the stereoselective ratio (D/L) during the Chirality Conversion (CC). Recently, we reported pyrrole- 2-carboxamide [24] based binol receptors and their analogues **1 - 4** for chiral discrimination and enantioselective recognition of chiral amino alcohols (**Scheme 1**). Herein, we report the pyrrole-2-carboxamide based binol re- ceptors for enantioselective recognition and also as potential CCR's for chiral amino acids.

2. Experimental

2.1. General

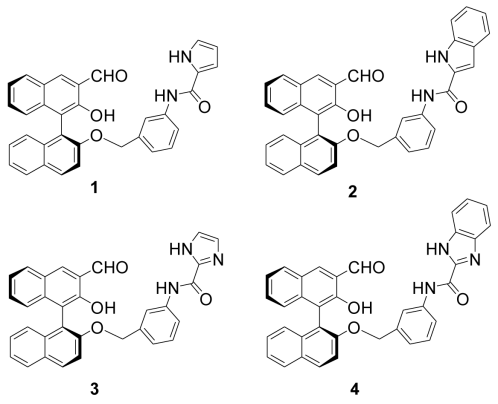
Imidazole-2-carboxylic acid and benzimidazole carboxylic acid were prepared according to the literature procedures [24]. All other chemicals were commercially available and used without further purifications. The solvents for dry reactions were dried with appropriate desiccants and distilled prior to use. NMR spectra were recorded on a BrukerAM 250 spectrometer in $CDCl_3$ solution containing tetramethylsilane as internal standard. Melting points were measured with Electrothermal IA 9000 digital melting point apparatus and are uncorrected. HRMS spectra were obtained on FAB mode. EA was determined using vario EL Elemental Analyser. For column chromatography, silica gel of 230 - 400 mesh was used.

2.2. (*S*)-3-Hydroxymethyl-2-Methoxymethoxy-2'-(3-(1*H*-Pyrrole-2-Carboxamido) -Benzyl)-1,10-Binaphthalene (6)

A mixture of the 2-pyrrole carboxylic acid (0.49 g, 4.4 mmol), PyBOP (2.3 g, 4.4 mmol), and N-methyl morpholine (NMP, 2 ml) in DMF (40 ml) was stirred at room temperature for 15 min. Amine 5 (2.0 g, 3.7 mmol) was added and the mixture was stirred over night. The mixture was hydrolyzed with water, extracted with ethyl acetate, and silica gel column chromatography (EA/Hexane, 1:1) afforded **6**. Isolated yield: 81% (mp 105˚C). ^{1}H NMR ($CDCl_3$, 250 MHz): δ (ppm) = 9.77 (br s, 1H), 8.20 (s, 1H), 8.04 - 7.84 (m, 5H), 7.52 - 7.00 (m, 7H), 6.74 - 6.38 (m, 5H), 6.12 (s, 1H), 5.00 - 4.90 (m, 3H), 4.66 - 4.51 (m, 4H), 3.47 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ (ppm) = 162.7, 158.2, 157.2, 148.6, 141.4, 136.1, 132.5, 128.9, 128.3, 128.1, 127.6, 127.4, 125.7, 124.1, 123.3, 122.8, 122.3, 119.4, 119.3, 111.7, 95.7, 71.2, 64.9, 55.6. Anal. Calcd for $C_{35}H_{30}N_2O_5$: C, 75.25; H, 5.41; N, 5.01. Found: C, 75.34; H, 5.53; N, 4.92.

2.3. (*S*)-3-Hydroxymethyl-2-Methoxymethoxy-2'-(3-(1*H*-Indole-2-Carboxamido)-Benzyl) -1,10-Binaphthalene (7)

It was prepared similar to **6**, but with indole-2-carboxylic acid. Isolated yield: 86% (mp 158˚C). ^{1}H NMR ($CDCl_3$, 250 MHz): δ (ppm) = 10.55 (s, 1H), 9.04 (s, 1H), 7.95 - 7.77 (m, 8H), 7.47 - 7.07 (m, 11H), 6.80 (d, 1H), 5.18 - 5.04 (dd, 2H), 4.96 (d, 2H), 4.60 (q, 2H), 4.35 (br s, 1H), 3.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ (ppm) = 160.5, 57.9, 156.7, 144.3, 141.5, 138.5, 136.1, 134.7, 131.2, 129.9, 129.8, 129.2, 128.7, 128.3, 128.0, 127.4, 126.0, 125.7, 124.1, 123.9, 122.8, 122.2, 120.1, 119.0, 115.6, 111.1, 97.6, 70.5, 65.5, 54.6; Anal. Calcd for $C_{39}H_{32}N_2O_5$: C, 76.96; H, 5.30; N, 4.60. Found: C, 76.85; H, 5.21; N, 4.71.



Scheme 1. pyrrole-2-carboxamide based binol receptors.

2.4. (*S*)-3-Hydroxymethyl-2-Methoxymethoxy-2'-(3-(1*H*-Imidazole-2-Carboxamido)-Benzyl)-1,10-Binaphthalene (8)

It was prepared similar to **6**, but with imidazole-2-carboxylic acid. Isolated yield: 76% (mp 70˚C). ^{1}H NMR ($CDCl_3$, 250 MHz): δ (ppm) = 12.55 (br s, 1H), 9.34 (s, 1H), 8.38 (s, 1H), 8.07 - 7.85 (m, 5H), 7.47 - 7.15 (m, 9H), 7.09 (s, 1H), 6.97 (d, 1H), 5.55 (br s, 1H), 5.23 - 4.90 (m, 4H), 4.62 (s, 2H), 2.99 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ (ppm) = 163.0, 156.6, 154.0, 152.8, 141.8, 138.4, 137.4, 134.0, 134.1, 133.7, 131.9, 130.3, 129.3, 129.0, 128.6, 128.1, 126.9, 126.3, 125.7, 125.5, 125.1, 120.3, 118.7, 115.3, 99.3, 70.4, 61.5, 56.8. Anal. Calcd for $C_{34}H_{29}N_3O_5$: C, 72.97; H, 5.22; N, 7.51. Found: C, 72.81; H, 5.36; N, 7.43.

2.5. (*S*)-3-Hydroxymethyl-2-Methoxymethoxy-2'-(3-(1*H*-Benzo[*d*]Imidazole-2-Carboxamido)-Benzyl)-1,10-Binaphthalene (9)

It was prepared similar to **6**, but with benzimidazole-2-carboxylic acid. Isolated yield: 81% (mp 246˚C). ^{1}H NMR ($CDCl_3$, 250 MHz): δ (ppm) = 12.01 (br s, 1H), 9.15 (s, 1H), 8.52 (s, 1H), 8.12 - 7.80 (m, 4H), 7.58 - 7.11 (m, 13H), 6.73 (d, 1H), 5.10 - 4.87 (m, 3H), 4.72 - 4.55 (m, 4H), 3.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ (ppm) = 161.3, 158.3, 149.8, 145.5, 141.7, 138.9, 138.5, 136.1, 132.1, 129.8, 129.5, 129.0, 128.5, 128.0, 127.9, 120.4, 126.8, 125.7, 124.1, 123.6, 123.3, 120.5, 120.1, 119.5, 115.6, 115.3, 98.6, 74.8, 66.0, 58.4. Anal. Calcd for $C_{38}H_{31}N_3O_5$: C, 74.86; H, 5.13; N, 6.89. Found: C, 74.97; H, 5.01; N, 6.78.

2.6. (*S*)-2-Methoxymethoxy-2'-(3-(1*H*-Pyrrole-2-Carboxamido)-Benzyl)-1,10-Binaphthyl-3-Carboxaldehyde (10)

A mixture of **6** (2.0 g, 3.6 mmol) and pyridinium chlorochromate (PCC) (1.5 g, 7.2 mmol) was dissolved in methylene chloride and stirred for 5 h. The reaction mixture was filtered, and after evaporation and column chromatography with EA and hexane 1:2 mixture provided compound **10**. Isolated yield: 79% (mp 185˚C). ^{1}H NMR ($CDCl_3$, 250 MHz): δ (ppm) = 10.54 (s, 1H) 10.17 (br s, 1H), 8.46 (s, 1H), 8.89 - 7.74 (m, 4H), 7.37 - 7.01 (m, 10H), 6.83 - 6.72 (m, 3H), 6.18 (s, 1H), 5.01 (s, 2H), 4.68 (q, 2H), 2.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ (ppm) = 194.1, 159.6, 158.5, 142.4, 137.4, 135.7, 134.5, 132.7, 132.3, 129.9, 129.4, 128.7, 128.1, 127.8, 127.1, 126.8, 125.7, 125.0, 124.6, 120.3, 120.1, 114.5, 112.6, 97.3, 73.5, 56.1. Anal. Calcd for $C_{35}H_{28}N_2O_5$: C, 75.52; H, 5.07; N, 5.03. Found: C, 75.43; H, 5.15; N, 5.12.

2.7. (*S*)-2-Methoxymethoxy-2'-(3-(1*H*-Indole-2-Carboxamido)-Benzyl)-1,10-Binaphthyl-3-Carboxaldehyde (11)

Same procedures as that of **10**. Isolated yield: 82% (mp 201˚C). ^{1}H NMR ($CDCl_3$, 250 MHz): δ (ppm) = 10.59 (s, 1H), 10.33 (br s, 1H), 8.53 (s, 1H), 8.11 - 7.63 (m, 6H), 7.47 - 7.10 (m, 13H), 6.87 (d, 1H), 5.14 (q, 2H), 4.77 (q, 2H), 2.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ (ppm) = 192.5, 159.7, 158.5, 152.8, 145.2, 144.1, 139.5, 138.6, 135.9, 134.6, 134.1, 132.5, 131.2, 129.8, 128.9, 128.6, 126.5, 125.0, 124.5, 122.2, 121.6, 120.5, 120.1, 119.6, 119.2, 114.4, 108.0, 96.3, 71.2, 55.3. Anal. Calcd for $C_{39}H_{30}N_2O_5$: C, 77.21; H, 4.98; N, 4.62. Found: C, 77.14; H, 5.08; N, 4.69.

2.8. (*S*)-2-Methoxymethoxy-2'-(3-(1*H*-Imidazole-2-Carboxamido)-Benzyl)-1,10-Binaphthyl-3-Carboxaldehyde (12)

Same procedures as that of **10**. Isolated yield: 74% (mp 185˚C). ^{1}H NMR ($CDCl_3$, 250 MHz): δ (ppm) = 10.60 (s, 1H), 10.45 (br s, 1H), 8.79 (s, 1H), 8.01 - 7.84 (m, 4H), 7.35 - 7.16 (m, 9H), 6.73 - 6.58 (m, 3H), 6.35 (s, 1H), 5.13 (s, 2H), 4.75 (q, 2H), 3.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ (ppm) = 195.4, 160.7, 159.4, 142.8, 139.9, 136.7, 135.1, 132.8, 132.2, 129.8, 129.1, 128.6, 128.2, 127.9, 127.3, 126.4, 125.2, 125.3, 124.9, 121.4, 120.5, 115.7, 112.9, 97.7, 74.1, 57.2. Anal. Calcd for $C_{34}H_{27}N_3O_5$: C, 73.24; H, 4.88; N, 7.54. Found: C, 73.31; H, 5.01; N, 7.44.

2.9. (*S*)-2-Methoxymethoxy-2'-(3-(1*H*-Benzo[*d*] Imidazole-Carboxamido)-Benzyl)-1,10-Binaphthyl-3-Carboxaldehyde (13)

Same procedures as that of **10**. Isolated yield: 82% (mp 168˚C); ^{1}H NMR ($CDCl_3$, 250 MHz): δ (ppm) = 12.14

(br s, 1H), 10.60 (s, 1H), 9.4 (s, 1H), 8.61 (s, 1H), 8.01 - 7.90 (m, 4H), 7.65 - 7.19 (m, 13H), 6.91 (d, 1H), 5.16 (q, 2H), 4.76 (q, 2H), 2.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ (ppm) = 194.3, 160.8, 159.0, 158.1, 152.8, 145.6, 144.0, 138.7, 136.9, 135.7, 133.5, 131.9, 130.0, 129.9, 129.6, 128.8, 128.4, 127.6, 126.8, 124.3, 123.6, 123.1, 122.5, 121.1, 120.6, 118.9, 116.1, 115.9, 97.5, 73.5, 57.6. Anal. Calcd for $C_{38}H_{29}N_3O_5$: C, 75.11; H, 4.81; N, 6.92. Found: C, 75.01; H, 4.73; N, 7.02.

2.10. (*S*)-2-Hydroxy-2'-(3-(1*H*-Pyrrole-2-Carboxamido) -Benzyl)-1,10-Binaphthyl-3-Carboxaldehyde (1)

To an ethanolic solution of **10** a few drops of conc. hydrochloric acid was added and refluxed for 30 min. The solvent was evaporated and extracted with ethyl acetate to afford the desired receptor **1**. Isolated yield: 98% (mp 240˚C). ^{1}H NMR ($CDCl_3$, 250 MHz): δ (ppm) = 10.50 (s, 1H), 10.18 (s, 1H), 9.45 (br s, 1H), 8.30 (s, 1H), 7.99 - 7.87 (m, 3H), 7.48 - 7.16 (m, 10H), 7.00 - 6.71 (m, 4H), 6.35 (s, 1H), 5.12 (s, 2H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ (ppm) = 196.9, 158.8, 154.0, 153.4, 138.3, 137.9, 130.3, 130.1, 129.7, 128.9, 128.2, 127.5, 126.7, 125.5, 124.8, 124.2, 124.0, 122.5, 122.4, 122.1, 119.2, 115.6, 110.1, 109.5, 70.8; HRMS (FAB) calcd for $C_{33}H_{24}N_2O_4$: 512.1736, found: 512.1731.

2.11. (*S*)-2-Hydroxy-2'-(3-(1*H*-Indole-2-Carboxamido) -Benzyl)-1,10-Binaphthyl-3-Carboxaldehyde (2)

It was prepared similar to receptor **1**. Isolated yield: 98% (mp 130˚C). ^{1}H NMR ($CDCl_3$, 250 MHz): δ (ppm) = 10.55 (s, 1H), 10.10 (s, 1H), 9.83 (s, 1H), 8.18 (1H, s), 7.94 - 7.73 (m, 4H), 7.46 - 7.15 (m, 15H), 6.98 (d, 1H), 5.09 (s, 2H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ (ppm) = 196.9, 159.7, 154.0, 153.4, 138.3, 137.9, 136.9, 130.5, 130.3, 130.1, 129.7, 129.5, 128.9, 128.2, 127.5, 126.7, 125.4, 124.9, 124.8, 124.2, 122.0, 120.8, 115.4, 112.2, 103.1, 70.7; HRMS (FAB) calcd for $C_{37}H_{26}N_2O_4$: 562.1893, found: 562.1899.

2.12. (*S*)-2-Hydroxy-2'-(3-(1*H*-Imidazole-2- Carboxamido)-Benzyl)-1,10-Binaphthyl-3-Carboxaldehyde (3)

It was prepared similar to receptor **1**. Isolated yield: 75% (mp 110˚C); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 12.37 (br s, 1H), 10.51 (s, 1H), 10.12 (s, 1H), 9.14 (s, 1H), 8.28 (s, 1H), 7.97 - 7.86 (m, 3H), 7.63 (d, 1H), 7.45 - 7.11 (m, 11H), 6.83 (d, 1H), 5.09 (s, 2H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ 196.9, 156.8, 154.0, 153.4, 138.4, 138.0, 137.1, 133.7, 130.3, 130.1, 129.8, 129.5, 128.2, 127.5, 126.7, 125.3, 125.0, 124.3, 124.0, 122.0, 118.7, 118.6, 115.7, 70.8; HRMS (FAB) calcd for $C_{32}H_{23}N_3O_4$: 513.1689, found: 513.1683.

2.13. (*S*)-2-Hydroxy-2'-(3-(1*H*-Benzo[*d*]Imidazole- 2-Carboxamido)-Benzyl)-1,10-Binaphthyl-3-Carboxaldehyde (4)

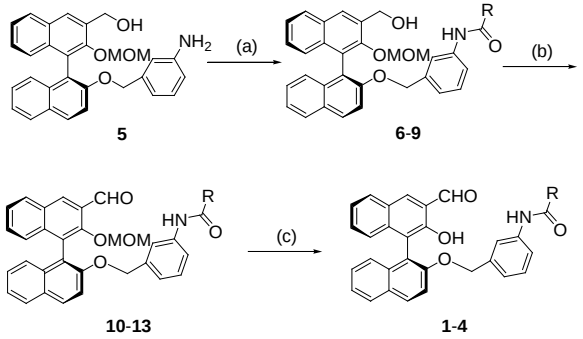
It was prepared similar to receptor **1**. Isolated yield: 98% (mp 145˚C). ^{1}H NMR ($CDCl_3$, 250 MHz): δ (ppm) = 12.31 (br s, 1H), 10.52 (s, 1H), 10.16 (s, 1H), 9.46 (s, 1H), 8.51 (s, 1H), 8.19 - 7.88 (m, 4H), 7.71 - 7.22 (m, 13H), 6.96 (d, 1H), 5.19 (s, 2H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ (ppm) = 194.7, 161.6, 159.8, 158.6, 151.5, 147.32, 146.1, 140.5, 138.9, 138.6, 136.9, 136.2, 132.7, 131.9, 129.9, 129.7, 128.7, 128.0, 126.6, 124.8, 123.7, 123.1, 122.8, 120.1, 116.5, 116.1, 72.6; HRMS (FAB) calcd for $C_{36}H_{25}N_3O_4$: 563.1845, found: 563.1840.

3. Results and Discussion

Synthesis of the Receptors 1 - 4

The synthesis of receptors **1 - 4** were previously reported by our group [24] which is described in **Scheme 2**. The receptors were prepared from (*S*)-3-hydroxymethyl-2-methoxymethoxy-2'-(3-aminobenzyloxy)-1,1'-binaphthol (**5**) [20] [21] in dimethylformamide (DMF) and N-methyl morpholine (NMP) using the appropriate carboxylic acids. Subsequent oxidation and hydrolysis under the acidic conditions gave the final products. The synthesized compounds were confirmed by spectroscopic and analytical data which are in good agreement with the presented structures. All the receptors are freely soluble in solvents such as DMSO, $CHCl_3$, benzene etc. (**Scheme 2**).

Stereoselective recognition of amino acids with receptor **1** was studied by ^{1}H NMR spectroscopy (**Figure 1**). Addition of [Bu_4N][L-PheAla] and [Bu_4N][D-PheAla] to **1** in DMSO-d_6 results in the formation of the corres-



6,**10** & **1** : R = 2-pyrrole
7,**11** & **2** : R = 2-indole
8,**12** & **3** : R = 2-imidazole
9,**13** & **4** : R = 2-benzimidazole

Scheme 2. Reagents and conditions: (a) PyBOP, DMF, NMP, R-COOH, rt, 15 h; (b) PCC, CH_2Cl_2, rt, 5 h; (c) HCl, EtOH, reflux, 0.5 h.

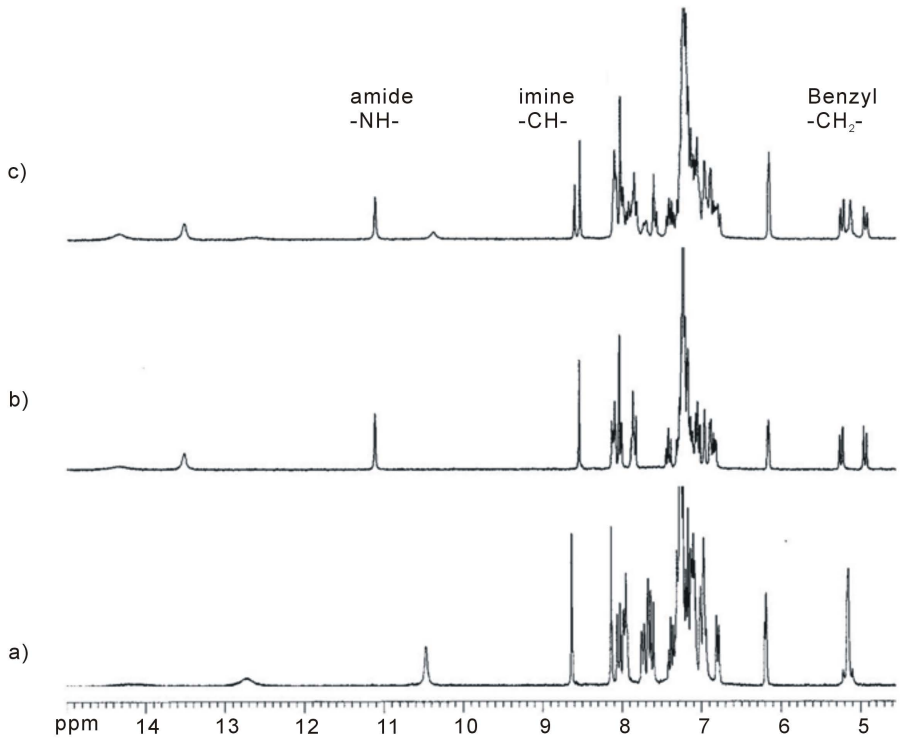


Figure 1. Partial ^{1}H NMR spectra indicating stereoselective imine formation of **1** with phenylalanine in DMSO [D_6]. a) **1** + **2**[Bu_4N][L-PheAla]; b) **1** + **2**[Bu_4N][D-PheAla]; c) **1** + **2**[Bu_4N][DL-PheAla].

ponding imines within 10 min. **Figures 1(a)** and **(b)** show the partial ^{1}H NMR spectra for **1**—L-PheAla and **1**—D-PheAla, respectively. The signals of the amide NH, imine CH and benzylic CH_2 protons for **1**—L-PheAla and **1**—D-PheAla are all well resolved. **Figure 1(c)** shows the partial ^{1}H NMR spectrum for the mixture of **1**—L-PheAla and **1**—D-PheAla formed by addition of two equivalents of racemic alanine to **1**. Integration of the signals due to **1**—L-PheAla and **1**—D-PheAla in **Figure 1(c)** determines that the ratio of **1**—D-PheAla/**1**–L-PheAla is 1.74:1. This indicates the imine formation constant for **1**—d-Ala is larger than that for **1**—l-Ala by a factor of about 1.74^2:1 or 3.03:1. Even if **1**–L-PheAla 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-PheAla into **1**—D-PheAla is negligible, since the ^{1}H NMR spectra in **Figures 1(a)** and **(b)** do not change for a reasonable period of time.

Partial ^{1}H NMR spectra in **Figure 2(a)** demonstrates the CC of **1**-L-PheAla (the imine formed between **1** and L-phenylalanine) to **1**-D-PheAla in the presence of triethylamine in DMSO-d_6 as a representative. The imine CH signals are conveniently monitored as it is free from other signals. Therefore, the singlet peak at 8.69 ppm assigned to the imine CH proton of **1**-L-PheAla decreases and the singlet peak at 8.48 ppm ascribed to the imine CH of **1**-D-PheAla, increases concomitantly. The CC reaches the equilibrium at 48 h where the stereoselectivity, which is defined by the ratio of (**1**-D-PheAla)/(**1**-L-PheAla) is measured by the integration of the ^{1}H NMR signals.

Table 1 compares the stereoselectivities of the pyrrole based receptors **1 - 4** for six different amino acids, *i.e.* Alanine, Glutamine, Histidine, Phenylalanine, Serine and Tyrosine assessed by the same procedures. The results from the table indicates that the receptors **1** and **3** show higher conversion efficiency to amino acids than receptors **2** and **4.** The lower stereoselectivities of **2** and **4** compared to **1** and **3** may be presumably due to the lower hydrogen bond donor capability and steric hindrance of the additional benzene moiety [25]. The stereoselectivity and chirality conversion, depends on the degree of the difference of steric energies around imine bonds between **1-L-aa** and **1-D-aa** (**Scheme 3**). This will be maximized in the condition that the whole imine complex is rigid by hydrogen bonds (resonance assisted hydrogen bond between imine nitrogen and phenolic -OH, and the hydrogen bond between heterocyclic -NH and carboxylic acid -COOH).

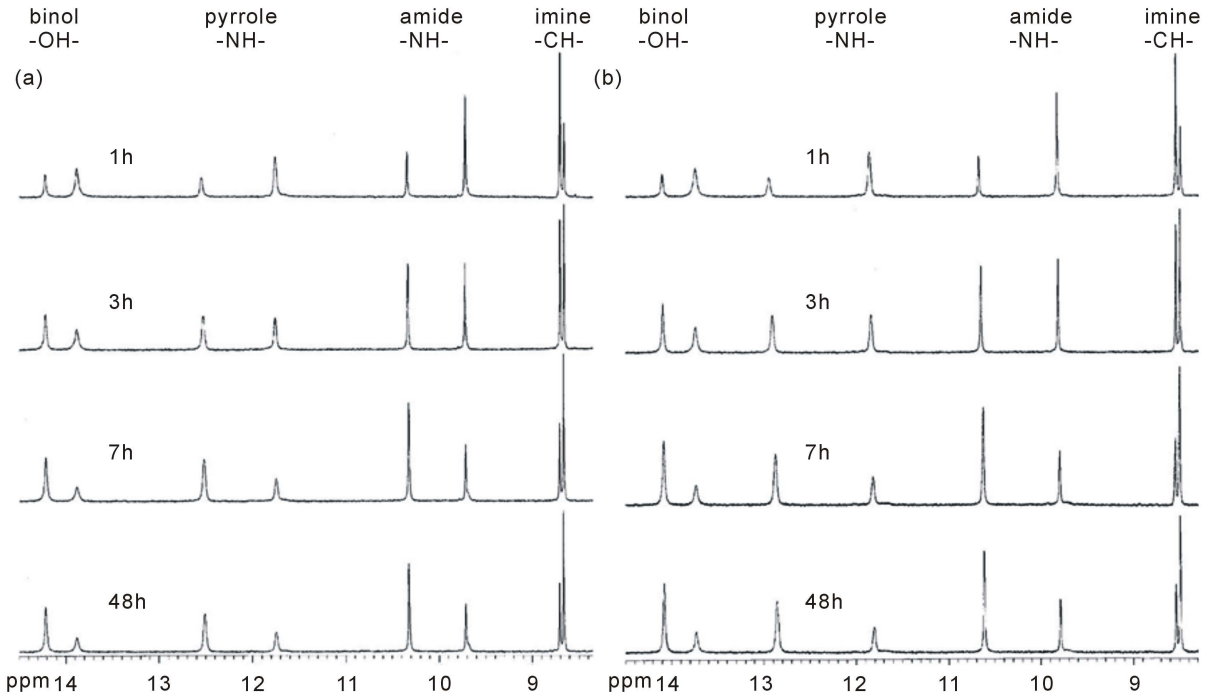
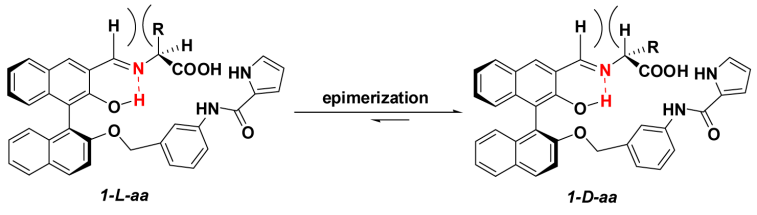


Figure 2. Partial ^{1}H NMR spectra indicating the conversion of 1—L-aa into 1—D-aa. The peaks corresponding to 1—L-aa decrease while those corresponding to 1—D-aa increase (from top to bottom). (a) conversion of L-PheAla into D-PheAla; (b) conversion of L-Ser into D-Ser.



Scheme 3. Difference of steric energies around imine bonds between 1-L-aa and 1-D-aa.

Table 1. L to D conversion efficiency of the receptors for amino acid.

	Receptors			
Amino acid	**1**	**2**	**3**	**4**
Alanine	2.45	1.95	2.25	1.41
Glutamine	2.77	2.36	2.86	1.13
Histidine	2.67	2.18	2.42	1.25
Phenylalanine	2.93	2.22	2.65	1.16
Serine	2.35	2.17	2.12	1.47
Tyrosine	2.77	2.24	2.81	1.37

The Diastereomeric ratio, (D-amino acid bound imine)/(L-amino acid imine), was determined by ^{1}H-NMR in DMSO-d_6 at equilibrium.

4. Conclusion

In summary, four pyrrole carboxamide based receptors were explored as Chirality conversion reagents for six underivatized amino acids. Though these receptors were not efficient as that of the Binol based receptors reported earlier, they are the first receptors based on the heterocyclic moiety which can be utilized as Chirality Conversion Reagents. Receptors **1** and **3** show higher conversion efficiency than the receptors **2** and **4**.

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