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Chirality conversion and enantioselective extraction of amino acids by imidazolium-based binol-aldehyde

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ABSTRACT

A novel imidazolium-based binol receptor **4** has been synthesized and used as a chirality conversion reagent for general amino acids with higher D-form selectivity compared to other guanidinium-based receptors. Favorable solubility in chloroform enabled **4** as an effective chiral extractant for the resolution of racemic amino acids.

Optically pure D-amino acids are of increasing industrial importance as chiral building blocks for the synthesis of pharmaceuticals, food ingredients, and drug intermediates.[1] Preparation of most D-amino acids requires high cost due to the lack of natural sources.[2] Even though a wealth of organic, biological, polymeric, and metal-based amino acid chiral receptors had been developed during the past years,[3] there has been a rare example of a chirality conversion reagent (CCR) for underivatized amino acids.[4]

We recently reported[5] that uryl-based binol compound **1** is a CCR that converts a wide range of L-amino acids to D-amino acids via the imine formation (Scheme 1). Hydrogen bonding between the carboxylate group and the uryl group along with internal resonance-assisted H-bonds (RAHBs) play important roles in determining the stereoselective ratio (D/L) during the chirality conversion. Considering the origin of the stereoselectivity of **1**, one can envision that incorporation of strong hydrogen bond donors in the receptor will enhance the stereoselectivity. In this context, we have developed a new guanidinium-based receptor **2** which provides the charge-reinforced hydrogen bond (CRHB)[6] and high enantioselective recognition toward amino alcohols.[7] We report herein the synthesis of other novel guanidinium-based receptors **3** and **4** as potential CCRs. Furthermore, we also found that compound **4** is an effective enantioselective extractant for amino acids. Extractive resolution of enantiomers is a chirotechnology of current industrial interest for large-scale production due to time-saving and cost-effective process.[8]

Synthesis of receptors **3** and **4** are described in Schemes 2 and 3, respectively.[9,10] Reaction of binol-based aminobenzyl derivative **5**[7] with phenylisothiocyanate and subsequent treatment with mercuric chloride provided the guanidinyl compound **7**. Pyridinium chloromate (PCC) oxidation and deprotection of MOM under acidic conditions gave the optically pure receptor **3**. Similarly, receptor **4** was readily prepared from compound **5** via guanilation through a three-step protocol. Reaction of **5** with *N*-Boc-2-methylthio-2-imidazoline[11] in a co-solvent of ethanol and acetic acid afforded guanidine compound **8**. PCC oxidation and acid hydrolysis gave receptor **4** (see Schemes 2 and 3).

Partial ^{1}H NMR spectra in Figure 1 demonstrate the chiral conversion of **4**-L-Leu (the imine formed between **4** and L-leucine) to **4**-D-Leu 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. The singlet peak at 8.58 ppm assigned to the imine CH proton of **4**-L-Leu decreases, and the singlet peak at 8.48 ppm ascribed to the imine CH of **4**-D-Leu increases concomitantly. Besides imine –CH peak, benzyl –CH_2- peaks (centered at 4.85 and 4.9 ppm) and leucine α proton peaks (centered at 3.95 and 3.65 ppm) also indicate the chirality conversion. The chirality conversion reaches the equilibrium at ~48 h. The stereoselectivity, which is defined by the ratio of (**4**-D-Leu)/(**4**-L-Leu), is measured by the integration of the –CH=N– signals. Table 1 compares the stereoselectivities of the uryl-based receptor **1** and the guanidinium-based receptors **2**, **3,** and **4**, for eight different amino acids assessed by the same procedures.

Table 1 indicates that the receptors **2** and **3** show lower stereoselectivities to amino acids than **1**, whereas **4** exhibits higher

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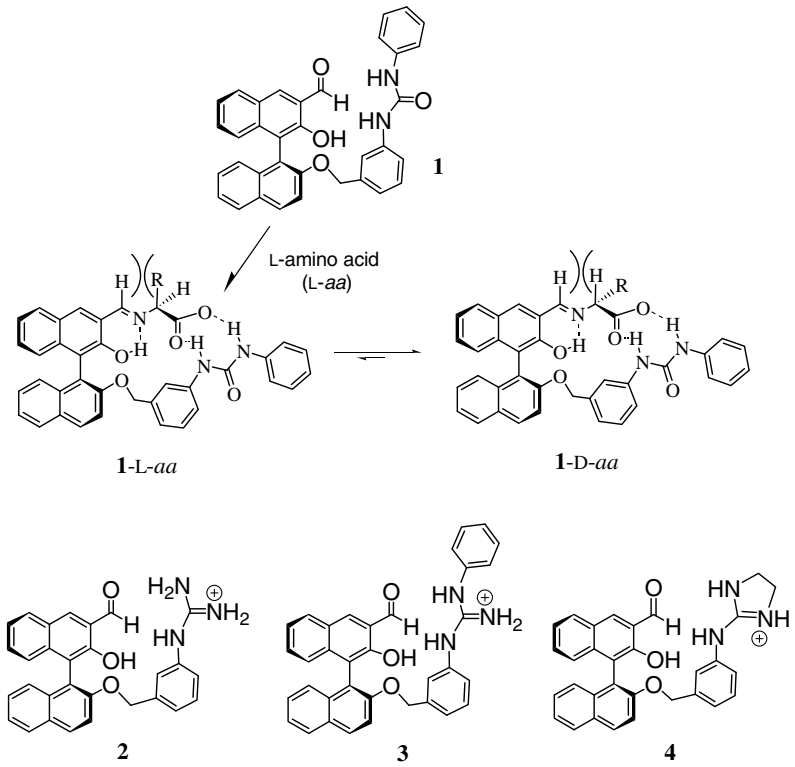
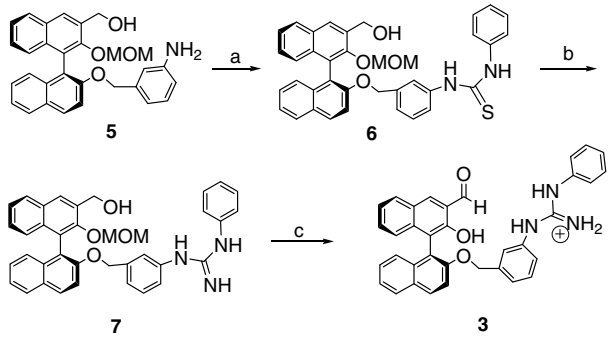
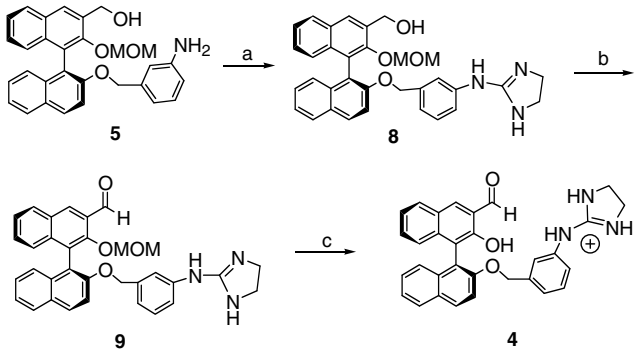


Scheme 1.



Scheme 2. Reagents and conditions: (a) Phenylisothiocyanate, THF, rt, 5h, 75%; (b) $HgCl_2$, NH_3/EtOH, rt, 3h, 98%; (c) (i) PCC/CH_2Cl_2, rt, 5h, 79%, (ii) HCl/EtOH, 70 °C, 0.5 h, 90%.



Scheme 3. Reagents and conditions: (a) *N*-Boc-2-methylthio-2-imidazoline, EtOH/AcOH, reflux, 30 h, 85%; (b) PCC/CH_2Cl_2, rt, 12 h, 91%; (c) HCl/Et_2O/EtOH, rt, 5 h, (Quant).

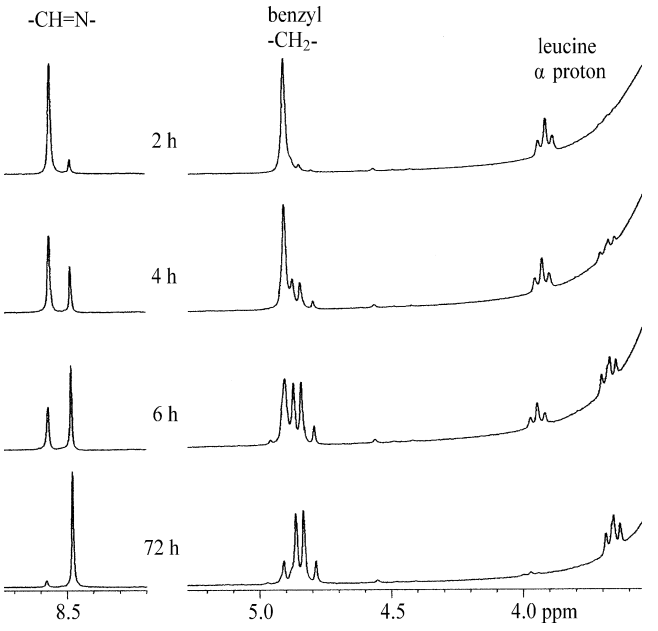


Figure 1. Time-dependent ^1H NMR of 4-L-Leu in DMSO-d_6 in the presence of 4 equiv triethylamine.

selectivity ratio comparable to **1**. In the case of amino acids, the lower selectivities of **2** and **3** may be explicable by neutralization of the compounds by base triethylamine, which is required for conversion of L-amino acid to D-amino acid. The neutralization of the charges in the guanidinyl groups may weaken the CRHB. Compound **4**, however, has relatively more basic imidazoline unit, which increases the effect of CRHB and the stereoselectivities for the amino acids.

Table 1
Selectivities of the L to D conversion in the imine forms of **1**–**4** with amino acids

Amino acid	Receptors			
	1	**2**	**3**	**4**
Histidine	14	9.6	3.0	13
Tyrosine	12	10.0	3.2	14
Phenylalanine	11	7.4	2.2	13
Serine	11	8.0	2.2	11
Glutamine	15	5.9	3.3	19
Asparagine	13	11.0	2.9	15
Leucine	9	5.5	2.6	16
Alanine	7	5.6	1.9	5

The selectivity is defined by the ratio, (D-amino acid bound imine)/(L-amino acid imine).

Charged receptors **2**–**4** are freely soluble in organic solvent $CHCl_3$ unlike the uryl-based compound **1**. Hence, we tested the stereoselective extraction of amino acids with compound **4**. Excess racemic leucine (0.1 g) in 1.0 ml water at pH 8 was stirred with **4** (0.015 g) in 1.0 ml $CDCl_3$. ^1H NMR of the chloroform layer at 1 h confirmed the imine formation between **4** and leucine, where **4**-D-Leu is more than **4**-L-leu by a factor of 4.5. The stereoselectivities for the extraction of alanine and valine under the same conditions were observed to be 3.3. Under these experimental conditions, L to D conversion of amino acids is very slow and negligible. The selectivities of representative three amino acids for the extractions are remarkable when compared to those of other receptors so far developed such as crown ether, and cholesteryl L-glutamates.[8] An advantage of **4** as a chiral extractor is that the amino acid and **4** are easily separated from the imine by convenient pH control. Treatment of the $CDCl_3$ layer containing the imine of **4**-Leu with 0.1 N HCl dissociated the imine immediately to **4** in the organic layer and amino acid in the aqueous layer. Therefore, compound **4** is a new type of effective stereoselective extractant for enantiomeric separation of amino acids.

In summary, we have shown that imidazolium derivative **4** converts L-amino acids to D-amino acids with higher selectivities compared to other guanidinyl derivatives. The basic nature of imidazoline motif may be an important reason for the high selectivity. The favorable solubility in chloroform enabled **4** as an useful chiral extractant for amino acids such as alanine, valine, and leucine with enantioselectivities of 3.3–4.5.

Acknowledgments

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9. *Data for compound* **6**: mp 80 °C. ^1H NMR ($CDCl_3$, 250 MHz) δ 8.19 (d, 2H), 7.84–7.98 (m, 4H), 7.11–7.45 (m, 14H), 6.88 (d, 1H), 6.62 (s, 1H), 5.04–4.92 (m, 4H), 4.45–4.54 (dd, 2H), 3.77 (br s, 1H), 3.02 (s, 3H). ^{13}C NMR ($CDCl_3$, 63 MHz) 179.57, 153.96, 153.67, 152.83, 138.77, 137.62, 134.33, 133.95, 133.69, 131.06, 129.41, 129.38, 129.00, 128.80, 128.17, 126.41, 125.69, 125.44, 125.38, 125.26, 124.88, 123.33, 120.21, 115.45, 99.27, 70.51, 61.89, 56.99 Anal. Calcd for $C_{37}H_{32}N_2O_4S$: C, 73.98; H, 5.37; N, 4.66. Found: C, 73.87; H, 5.29; N, 4.73.
Data for compound **7**: mp 65 °C. ^1H NMR ($CDCl_3$, 250 MHz) δ 7.38–7.73 (m, 4H), 7.16–6.74 (m, 16H), 6.55 (d, 2H), 6.18 (s, 1H), 4.35–4.71 (m, 4H), 4.17 (dd, 2H), 2.66 (s, 3H). ^{13}C NMR ($CDCl_3$, 63 MHz) 154.31, 153.66, 152.62, 139.57, 134.29, 133.83, 133.80, 133.77, 130.89, 130.32, 130.20, 129.54, 128.73, 128.09, 128.01, 127.71, 125.81, 125.55, 125.45, 125.34, 124.39, 120.34, 115.06, 99.25, 70.14, 61.25, 56.92. Anal. Calcd for $C_{37}H_{33}N_3O_4$: C, 76.14; H, 5.70; N, 7.20. Found: C, 76.21; H, 5.83; N, 7.05.
Data for compound **3:** mp 94 °C. ^1H NMR ($CDCl_3$, 250 MHz) δ 10.20 (s, 1H, –CHO), 8.63 (s, 1H), 8.22 (d, 2H), 7.98 (d, 1H), 7.01–7.52 (m, 17H), 6.77 (d, 1H), 6.54 (s, 1H), 4.99–5.19 (dd, 2H). ^{13}C NMR ($CDCl_3$, 63 MHz) 197.42, 154.14, 153.60, 153.11, 139.16, 138.551, 137.74, 134.16, 133.49, 130.57, 130.20, 130.06, 129.92, 129.58, 128.19, 127.53, 126.85, 125.11, 124.96, 124.44, 124.25, 121.75, 118.09, 115.88, 70.56 HRMS (FAB) calcd for $C_{35}H_{27}N_3O_3$: 537.2052; found: 537.2061.
10. *Data for compound* **8**: mp 43 °C. ^1H NMR ($CDCl_3$, 250 MHz): δ 8.11 (s, 1H), 7.96 (d, 1H), 7.87 (s, 2H), 7.47 (d, 1H), 7.38–7.02 (m, 7H), 6.83 (d, 1H), 6.66 (d, 1H), 6.57 (s, 1H), 5.13–4.79 (m, 4H), 4.51 (s, 2H), 4.16 (br s, 3H), 3.43 (s, 4H), 2.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) 158.50, 154.28, 152.30, 148.95, 138.10, 135.29, 134.00, 133.31, 131.02, 129.77, 129.19, 128.81, 128.02, 127.94, 126.74, 125.89, 125.67, 125.45, 125.04, 124.81, 121.72, 120.27, 115.65, 99.10, 76.75, 60.57, 56.65, 42.43. Anal. Calcd for $C_{33}H_{31}N_3O_4$: C, 74.28; H, 5.86; N, 7.87. Found: C, 74.20; H, 5.95; N, 7.78.
Data for compound **9**: mp 106 °C. ^1H NMR ($CDCl_3$, 250 MHz): δ 10.58 (s, 1H, –CHO), 8.55 (s, 1H), 8.05–7.85 (m, 3H), 7.48–7.01 (m, 8H), 6.81–6.60 (m, 3H), 5.02 (dd, 2H), 4.68 (dd, 2H), 4.05 (br s, 2H), 3.40 (s, 4H), 2.97 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ 191.3, 157.7, 154.2, 153.9, 138.0, 137.1, 133.8, 130.9, 130.2, 129.8, 129.2, 129.1, 129.0, 128.0, 127.0, 126.1, 125.9, 125.3, 125.0, 124.0, 122.4, 121.3, 120.7, 118.8, 115.2, 100.2, 71.0, 57.2, 42.3. Anal. Calcd for $C_{33}H_{29}N_3O_4$: C, 74.56; H, 5.50; N, 7.90. Found: C, 74.67; H, 5.62; N, 7.81.
Data for compound **4:** mp 164 °C. ^1H NMR (DMSO-d_6, 250 MHz): δ 10.40 (br s, 1H), 10.36 (s, 1H, –CHO), 10.15 (br s, 1H), 8.68 (s, 1H), 8.23–8.07 (m, 4H), 7.97 (d, 1H, J = 8.0 Hz), 7.64 (d, 1H, J = 9.0 Hz), 7.45–7.22 (m, 5H), 7.55–6.99 (m, 4H), 6.87 (s, 1H), 5.21 (s, 2H), 3.63 (s, 4H); ^{13}C NMR (DMSO-d_6, 63 MHz): δ 140.1, 137.9, 137.5, 136.6, 134.2, 131.1, 130.9, 130.4, 129.9, 129.1, 128.2, 127.7, 125.6, 125.4, 125.1, 124.7, 123.7, 122.7, 118.6, 118.4, 116.4, 70.1, 43.6; HRMS (FAB) calcd for $C_{31}H_{26}N_3O_3$ 488.1974; found: 488.1981.
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