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A Novel Amine Receptor Based on the Binol Scaffold Functions as a Highly Effective Chiral Shift Reagent for Carboxylic Acids

Qingzhu Ma,[†] Minshan Ma,[†] Hongying Tian,[†] Xiaoxia Ye,[‡] Hongping Xiao,[†] Lian-hui Chen,*[,†] and Xinxiang Lei*[,†]

College of Chemistry & Materials Engineering, Wenzhou University, Wenzhou 325035, P. R. China, and Wenzhou Medical College, Wenzhou 325035, P. R. China

siocchenlh@yahoo.com.cn; xinxianglei@gmail.com

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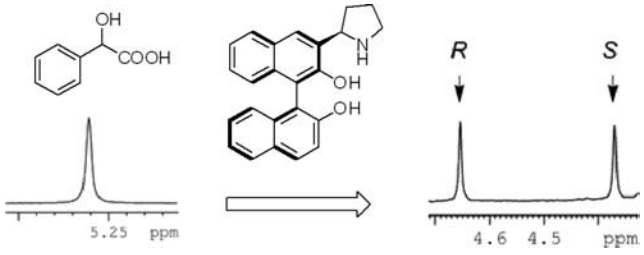
ABSTRACT



A "smart" receptor has been newly synthesized. NMR studies demonstrated that the receptor functions as a chiral shift reagent that is highly effective for determining the enantiomeric purity of a series of carboxylic acids, particularly those that have an α-oxygen atom.

Carboxylic acids are ubiquitous in nature and play a paramount role in many biological recognition processes. For their functional importance, great efforts have been dedicated toward understanding and mimicking their specific role and biochemical behavior.[1] Recognition of carboxylic acids by synthetic receptors is one of the most important research sectors due to the biological importance and versatile applications in drug discovery.[2] NMR spectroscopy provides a useful entry to fast ee determination. However, to date, few chiral shift reagents (CSRs) for enantiodifferentiation are known and protonic NMR shift inequivalencies between the diastereomeric adducts formed are often too small to realize baseline resolution.[3] This has been accomplished only in some rare cases developing very specific, highly selective synthetic receptors.[2e,4]

[†] Wenzhou University.
[‡] Wenzhou Medical College.

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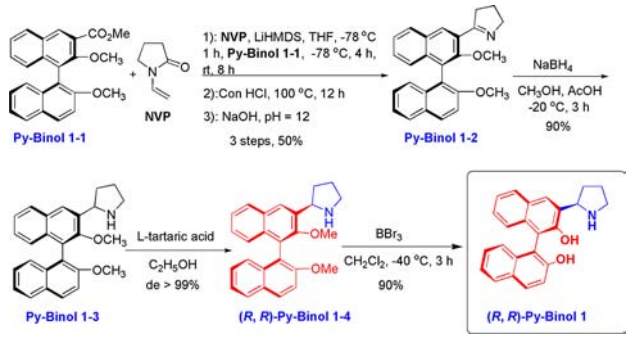
Binol is an important chiral building block and has been widely used in asymmetric catalysis[5] and for enantioselective fluorescence sensors bearing a variety of recognition elements.[6] This is because the unique chiral and aromatic structure of the 1,1′-binaphthyl scaffold could provide both excellent chiral recognition capability and a large ring-current effect. We have designed and synthesized a novel chiral receptor of 3-(2″-pyrrolidinyl)-Binol (**Py-Binol 1**) which has a 1,1′-binaphthyl chiral scaffold and a pyrrolidinyl group acting as the binding site for carboxylic acids. Herein, we report that the bifunctional receptor of (*R*,*R*)-Py-Binol **1** functions as a highly effective chiral shift reagent for enantiomeric excess determination for a series of chiral carboxylic acids by ^{1}H NMR.

Scheme 1. Synthesis of Chiral Amine Receptor of (*R*,*R*)-**Py-Binol 1**



The chiral (*R*, *R*)-**Py-Binol 1** can be readily prepared with over 99% de in the following six steps:[7] (1) a Claisen type of condensation of NVP with **Py-Binol 1-1**;[7a] (2) hydrolysis and a decarbonylation reaction of amide in concentrated HCl; (3) formation of cycloimine in aqueous NaOH; (4) reduction to imine with $NaBH_4$; (5) chiral resolution with L-tartaric acid to yield the receptor with the methyl protected in 99% de; (6) deprotection of the methyl group with BBr_3. The absolute configuration of **Py-Binol 1** was characterized by X-ray, and de data were determined by chiral HPLC.

Preliminary studies were designed to probe the enantioselective recognition characteristics of receptor (*R*,*R*)-**Py-Binol 1**, which was carried out by ^{1}H NMR spectroscopy. Specifically, receptor (*R*,*R*)-**Py-Binol 1** was studied in the presence of the chiral guests (*R*)- and (*S*)-mandelic acid (MA) in deuterated chloroform at 298 K. As shown in Figure 1, analysis of the ^{1}H NMR spectra obtained from a 1:1 mixture of host and guest (*R*)- and (*S*)-mandelic acid

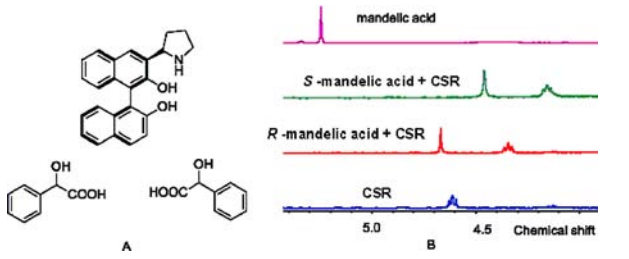


Figure 1. (A) Structures of receptor and mandelic acid. (B) Overlaid ^{1}H NMR spectra of free receptor, free mandelic acid, and the 1:1 mixture of receptor (10 mM) with (*R*)- and (*S*)-mandelic acid (10 mM).

showed that the chemical shift of (*R*)- and (*S*)-mandelic acid exhibits a 0.58 and 0.79 ppm upfield shift, respectively. This result suggests different chemical environments for different enantiomers of mandelic acid. This conclusion could also be drawn from the characteristic peak changes associated with anion binding and the corresponding outcome that occurred after the addition of the enantiomers of 2-methoxy-2-phenylacetic acid (entry 12) as the guest, as shown in Figure 2.

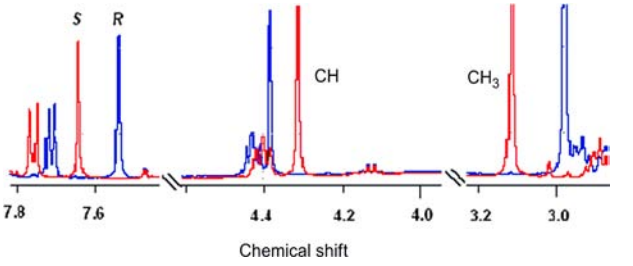


Figure 2. Overlaid ^{1}H NMR spectra of the 1:1 mixture of receptor (10 mM) with (*R*)- and (*S*)-2-methoxy-2-phenylacetic acid (10 mM). (*S*) = red; (*R*) = blue.

The difference in chemical shifts of the corresponding protons of two enantiomeric mandelates in the presence of receptor **1** inspired us to compare the enantiomeric discriminating ability of **1** with that of other chiral carboxylic acids. These carboxylic acids were different from one another in their structure and functionality, including some derivatives of mandelic acid, α-halo acids, etc. as guests to screen the potential of **1** as a chiral shift reagent by using ^{1}H NMR spectroscopy. As shown in Table 1, in the presence of receptor **1**, the chemical shift nonequivalences of appropriate protons are broad enough to give baseline resolution for most of the tested carboxylic acids on a 500 MHz NMR instrument at 25 °C. The carboxylic acids with methyl (entry 9) and halo (entry 13) groups show smaller nonequivalences than a hydroxyl or ether group (entry 11) on the α-positions, which means that the α-oxygen atoms play an important role in the recognition of the receptor. On the other hand, when the hydroxyl

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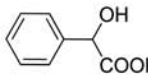
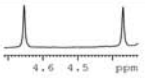
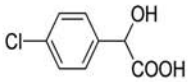
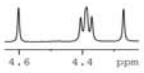
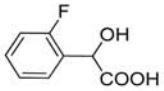
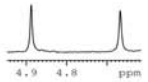
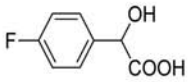
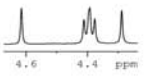
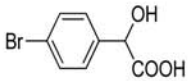
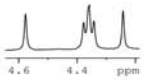
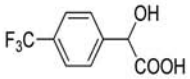
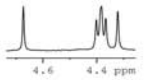
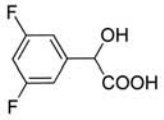
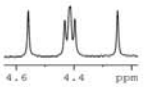
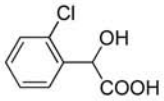
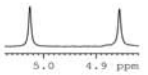
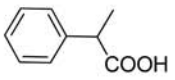
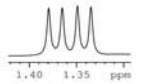
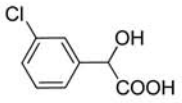
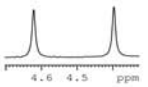
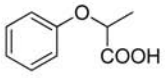
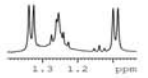
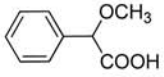
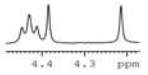
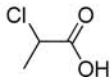
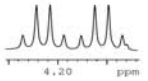
Table 1. Measurements of ^{1}H Chemical Shift Nonequivalences ($\Delta\Delta\delta$) of Racemic Carboxylic Acids in Presence of Receptor by ^{1}H NMR (500 MHz) in $CDCl_3$ at 25 °C

entry	carboxylic acid [a]	$\Delta\Delta\delta$ (ppm) [b]	spectra
1		0.284	
2		0.332	
3		0.220	
4		0.337	
5		0.334	
6		0.351	
7		0.310	
8		0.170	
9		0.030 [c]	
10		0.225	
11		0.238 [c]	
12		0.171	
13		0.060	

[a] All samples were prepared by mixing 2:1 of receptor (10 mM) with carboxylic acids (5 mM in CDCl3) in NMR tubes. [b] Chemical shift nonequivalences of the methine protons on the chiral centers of the acids unless otherwise indicated. [c] Chemical shift nonequivalences of the *R*-methyl protons of the acids.

group is protected in the receptor ((*R*,*R*)-Py-Binol **1**–**4**, Scheme 1), as expected, it shows an inability to distinguish racemic mandelic acid by ^{1}H NMR spectroscopy (see Supporting Information), which indicates that the hydroxyl group of the receptor is a key functional group for interacting with carboxylic acids to obtain chiral discrimination.

To demonstrate the practical utility of the receptor as a CSR, ee values of multiple nonracemic MA samples were determined by integration of the enantiomeric benzylic C−H resonances in the presence of the receptor. Figure 3 shows that the receptor maintains analytical resolution over a wide ee range and yields an excellent linear relationship between the ee values detemined by NMR and those determined gravimetrically. The average absolute error in the ee measurements plotted in Figure 3 is within 2%.

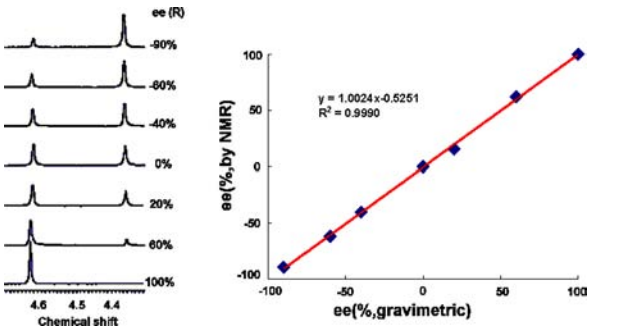


Figure 3. Selected region of the ^{1}H NMR spectra of nonracemic mandelic acid samples (10 mM) (various ee values) and the receptor (10 mM) in $CDCl_3$. Linear correlation between ee values determined gravimetrically and by integration of signals shown on left side; ee defined in terms of (*R*)-MA.

In conclusion, we have synthesized a new "smart and concise" molecular receptor, named binol-pyrrolidine (*R*,*R*) which shows an excellent ability to discriminate the enantiomers of a series of carboxylic acids, particularly those that have an α-oxygen atom. It combines the practical resolution of diastereomeric complexes due to effective signal separation and signal sharpness. Furthermore, compared with chromatographic methods, our method is rapid and convenient, requiring *no prior chemical derivatization*. Further work is in progress to expand the application to assign the absolute configuration of carboxylic acids.

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Supporting Information Available. Experimental procedures along with copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.