Efficient Enantiodifferentiation of Carboxylic Acids Using BINOL-Based Amino Alcohol as a Chiral NMR Solvating Agent

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A new optically active BINOL-amino alcohol has been designed and synthesized in a good yield and applied as chiral nuclear magnetic resonance (NMR) solvating agent for enantioselective recognition. Analysis by $^1$H NMR spectroscopy demonstrated that it has excellent enantiodifferentiation properties toward carboxylic acids and non-steroidal anti-inflammatory drugs (14 examples). The non-equivalent chemical shifts (up to 0.641 ppm) of various mandelic acids were evaluated by the reliable peak of well-resolved $^1$H NMR signals. In addition, enantiomeric excesses of the ortho-chloro-mandelic acid with different enantiomeric ratio were calculated based on integration of proton well-separated splitting signals.

Keywords: BINOL-amino alcohol, chiral-solvating agents, $^1$H NMR analysis, chiral discrimination, carboxylic acids

INTRODUCTION

Chirality plays an important role in chemical, physical, pharmaceutical, and many biological events. The rapid and facile methods to detect and discriminate chiral compounds are highly desirable and urgent to accelerate advance in modern asymmetric synthesis and chiral drug screening (Izake, 2007; Wenzel and Chisholm, 2011a). In this context, the exponentially growing detection demand in this intensive area of research drives the development of chiral analysis (Pu, 2004, 2012; Liu et al., 2010; Nieto et al., 2010; Leung et al., 2012; Cheng et al., 2013; Wolf and Bentley, 2013; Jo et al., 2014; Akdeniz et al., 2016; Yu and Yao, 2017). Among these direct and non-invasive spectroscopic methods of analysis, nuclear magnetic resonance (NMR) spectroscopy plays a leading role and enjoys a special status because it is a reliable, routine technique for monitoring the optical purity and analyzing the absolute configuration of chiral molecules, offering several advantages such as cost-effectiveness, operative convenience, small sample size, and also sensor responsiveness (Parker, 1991; Zalesskiy et al., 2014; Pérez-Trujillo et al., 2015; Silva, 2017; Xu et al., 2019). The general methods to NMR spectroscopic discrimination of enantiomers through chemical shift measurement and spectral splitting observed have been developed: first is to utilize an enantiomerically pure chiral derivatization agent taking advantage of a reactive moiety of the substrate to produce two diastereomers. However, the chiral derivatization agents require cumbersome and time-consuming synthetic procedures and may cause concerns of kinetic resolution and racemization (Seco and Riguera, 2015). The second, chiral-solvating agents (i.e., CSAs) or chiral lanthanide shift reagents (i.e., CLSRs) can form two NMR-observable diastereomeric complexes/mixtures with guests via non-covalent interaction (Wenzel and Wilcox, 2003; Seco et al., 2004; Pérez-Trujillo et al., 2013). In recent years, chiral liquid crystals are also employed for spectral enantiotopic discrimination due to the effect of magnetically induced anisotropic interactions.
the enantiomeric excess (ee) of enantiomeric hydroxy carboxylic acids, synthetic drugs, natural alkaloids, or flavanones via $^1$H NMR spectroscopy (Ardej-Jakubiska and Kawecki, 2008; Freire et al., 2008; Klika et al., 2010; Redondo et al., 2010, 2013; Chaudhari and Suryaprakash, 2013; Mishra et al., 2014; Yuste et al., 2014; Borowiecki, 2015; Du et al., 2015; Yi et al., 2016; Monteagudo et al., 2017) and bifunctional BINOL-macrocycles containing diacylamino pyridine moieties were developed by Ema et al. (2007, 2008, 2018); BINOL-derived disulfonimide extends the concept of CSA sensing to chiral recognition of O-heterocycles (Couffin et al., 2014); the crownphane and strapped calix[4]pyrrole containing built-in chiral BINOL were used for the enantioselective recognition of chiral amines and carboxylate anions, respectively (Tokuhisa et al., 2001; Miyaji et al., 2007). Chiral BINOL Brønsted acids were selected for determination of various indoloquinazoline alkaloid-type tertiary alcohols and various 3-arylquinazoliones (Liu et al., 2017; Wu et al., 2018), binaphthalen skeleton ureas as sensor for scanned various sulfoxides, phenylethanol, and arypropanoic acids (Holakovský et al., 2015; Čurinová et al., 2018, 2019). The results above indicated that highly active binaphthyl scaffold receptors containing multiple binding units could be used as an extremely versatile reagent for various analytes, and the large atropisomeric naphthyl rings also caused shielding effects through π-stacking stabilization that account for enantiomeric discrimination.

The designed, synthetic new hosts that are capable of discriminating more substrate are often challenging and an important goal for prochiral substrates and have attracted increasing attention in recent years. However, most of existing CSAs are not usually practical because of the splitting of chemical shift non-equivalences too weak to realize baseline resolution, thereby hampering the chemical analysis. Therefore, the development of new CSAs for NMR chiral analysis is still highly desirable. In the last years, our group has successfully developed a different class of CSAs for the determination of enantiomeric ratio and the application of enantiodiscrimination (Lei et al., 2010; Liu et al., 2011; Bai et al., 2019). Among reported CSAs, chiral amino alcohols are especially suitable to be used as chiral sensors as they pose proper nature of non-covalent interactions with substrates. In our previous study, we found that pyrrolidine-functionalized BINOL could be used as a highly effective chiral sensor for the resolution of discrimination and measurement of carboxylic acids. Recently, the simple β-amino alcohol was also developed as a CSA for discrimination of the signals of some carboxylic acid molecules (Ma et al., 2012; Li et al., 2016). In order to know the incorporation of BINOL-derived scaffold in the CSA enantiodifferentiation capacity, we decided to design and explore the possibility to introduce monosubstituted amino alcohol by choosing attached hydroxyl and amino groups with an aim to form multiple hydrogen bonding in the form of π-stacking. Based on this goal, the enlargement of the enantiodistinctive capacity of target BINOL-derived amino alcohol depended on incorporated structural modification that was generalized and developed. In addition, taking it into account commercially available and relatively cheap chiral amino alcohols, we decided to synthesize our target CSA of BINOL derivatives with chiral phenylglycinol...
as an attached side chain. The convenient and powerful CSA containing chiral phenylglycinol can be utilized to carry out the enantiodifferentiation of carboxylic acids based on well-resolved splitting signals by $^1$H NMR spectroscopy. Herein these results are reported.

RESULTS AND DISCUSSION

The chiral monosubstituted BINOL-amino alcohol can be readily carried out in five-step sequence according to the reported procedures starting from commercially available (R)-BINOL 1 (Matsunaga et al., 2000; DiMauro and Kozlowski, 2001; Dong et al., 2012; Xu et al., 2016). The key BINOL monoaldehyde was readily generated by lithiation, acylation of the bisprotected BINOL, and cleavage of the MOM ethers starting from the source of commercial (R)-BINOL; subsequently, the requisite monoaldehyde 2 was condensed with ready D-phenylglycinol and followed by reduction with NaBH$_4$. The 3-monosubstituted BINOL-amino alcohol 3 was obtained as a yellow solid in 89% yield. The synthetic route leading to chiral 3-monosubstituted BINOL-amino alcohol 3 is shown in Scheme 1 (the general synthesis procedure is illustrated in Scheme S1 and details of all NMR spectras are provided in Figures S1–S10).

With the desired synthetic host in hand, to investigate the discriminating ability of BINOL-amino alcohol 3 as a CSA for the analysis of carboxylic acids, we first performed $^1$H NMR experiment of the racemic mandelic acid (MA) as a test sample in 0.5 mL CDCl$_3$. The results of these experiments are shown in Figure 1; the addition of CSA 3 to racemic MA in CDCl$_3$ caused non-equivalence C$_2^\alpha$H proton resonance of MA to shift up-field in the $^1$H NMR spectrum; the good signal resolution was collected. The observed two peaks suggest that the host compound was able to interact with racemate guests to convert the enantiomer into different diastereomeric complexes. To find out the suitable stoichiometries of the host–guest complex, the regarding chemical shift $\Delta\Delta\delta$ value of C$_2^\alpha$H resonance ranged from 0.1879 to 0.5491 ppm (93.95–274.55 Hz), when the molar ratio of CSA 3 and racemic MA varied from 1:2 to 5:1. By considering cost-efficiency, we know commercially available hosts are often very expensive, and the discriminating ability of 3 to resolve enantiomers at the host:guest molar ratio 2:1 is a clear improvement as a minimum of 1.0 eq. (and in some cases an excess up to 24 eq.) of the host is needed to obtain a maximal resolution (Ema et al., 2007; Uccello-Barretta and Balzano, 2013). From the above detailed analysis, therefore, the molar ratio of 2:1 was finally utilized to select the application in the NMR differentiation of MA derivatives. The stoichiometry of host–guest complex was also determined according to Job’s method of continuous variation. As shown in Figure 1B, it showed a probable maximum at 1 – $X$ = 0.35; this indicates that CSA 3 and the acid bind in a 2:1 complex under these conditions.

With optimized conditions in hand and encouraged by above satisfactory enantiodiscriminating results, next, we examined the scope of other derivatives of MA. The structure, $\Delta\Delta\delta$ values of examined guests, and related spectra are displayed in Table 1. Because of the multiple hydrogen–bond interactions of OH/NH moiety and incorporated anisotropic aromatic

![Scheme 1](image)

**Scheme 1** Preparation and structures of 3-monosubstituted BINOL-amino alcohol 3.

![Figure 1](image)

**Figure 1** (A) Overlaid partial $^1$H NMR spectra and nonequivalent chemical shifts of $\alpha$-H of (±)–mandelic acid (MA) with various molar ratio in the presence of CSA 3 in CDCl$_3$ at room temperature. (B) Job plots of CSA-3 with (R)-MA and (S)-MA. $\Delta\delta$ stands for the chemical shift change of the $\alpha$-H proton of (R)- and (S)-MA in the presence of CSA-3. X stands for the molar fraction of the CSA-3 ($X = [\text{CSA-3}]/[\text{CSA-3} + \text{[MA]}]$). The total concentration is 10 mM in CDCl$_3$. 

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| Entry | Guest | $\Delta \Delta \delta$ (ppm) | $\Delta \Delta \delta$ (Hz) | Spectra |
|-------|-------|-----------------|-----------------|---------|
| 1     | ![Benzoic Acid](image) | 0.517 | 258.5 |
| 2     | ![Fluorinated Benzoic Acid](image) | 0.582 | 291.0 |
| 3     | ![Brominated Benzoic Acid](image) | 0.522 | 261.0 |
| 4     | ![Trifluoromethylated Benzoic Acid](image) | 0.641 | 320.5 |
| 5     | ![Fluorinated Benzoic Acid](image) | 0.592 | 296.0 |
| 6     | ![Fluorinated Benzoic Acid](image) | 0.389 | 194.5 |
| 7     | ![Chlorinated Benzoic Acid](image) | 0.329 | 164.5 |
| 8     | ![Benzoic Acid](image) | 0.047$^c$ | 23.5 |
| 9     | ![Benzoic Acid](image) | 0.050$^c$ | 25.0 |
| 10    | ![Benzoic Acid](image) | 0.092 | 46.0 |

(Continued)
| Entry | Guest | $\Delta \Delta \delta$ (ppm)$^c$ | $\Delta \Delta \delta$ (Hz) | Spectra |
|-------|-------|-------------------------------|----------------|---------|
| 11    | ![Guest11](image1) | 0.041$^c$ | 20.5 | ![Spectra1](image2) |
| 12    | ![Guest12](image3) | 0.086 | 43.0 | ![Spectra2](image4) |
| 13    | ![Guest13](image5) | 0.033$^c$ | 16.5 | ![Spectra3](image6) |
| 14    | ![Guest14](image7) | 0.099 | 49.5 | ![Spectra4](image8) |
| 15    | ![Guest15](image9) | 0.052$^c$ | 26.0 | ![Spectra5](image10) |

$^a$All analytes were prepared by mixing 2:1 of the host 3 with various carboxylic acids in NMR tubes (20 mM host and 10 mM guests in CDCl$_3$). 
$^b$Chemical shift non-equivalences of the methine group.
$^c$Chemical shift non-equivalences of the $\alpha$-methyl group.
$^d$Chemical shift non-equivalences of the $\alpha$-methyl protons of the isopropyl group.
CONCLUSIONS

In summary, a new chiral amino alcohol containing BINOL subunit had been prepared in a five-step sequence and enantiomerically pure form starting from commercially available (R)-BINOL. The CSA 3, which was a successfully solvating agent that was effective for carboxylic acids including some NSAIDs. In the presence of two equivalent of BINOL-amino alcohols, carboxylic acid racemates showed the chemical shift non-equivalences (Δδ) large enough for the discrimination of the enantiomers (up to 320.5 Hz). Furthermore, excellent split signals were revealed in 1H NMR spectroscopy. The quantitative applicability of CSA 3 for enantiomeric determination of non-racemic samples was also explored based on the integration of α-H signals.
DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/Supplementary Material.

AUTHOR CONTRIBUTIONS

XL conceived the project and supervised the study. MM and GL wrote the draft manuscript and prepared the supporting information. All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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SUPPLEMENTARY MATERIAL

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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