



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

Gaowei Li^{2†}, Minshan Ma^{1†}, Guifang Wang¹, Xiaojuan Wang² and Xinxiang Lei^{1*}

¹ School of Pharmaceutical Sciences, South Central University for Nationalities, Wuhan, China, ² College of Chemistry and Chemical Engineering, Shangqiu Normal University, Shangqiu, China

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 ¹H 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 ¹H 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.

OPEN ACCESS

Edited by:

Guigen Li,
Texas Tech University, United States

Reviewed by:

Hongjian Lu,
Nanjing University, China
Andrea Gualandi,
University of Bologna, Italy

*Correspondence:

Xinxiang Lei
xxlei@mail.scuec.edu.cn

[†]These authors have contributed
equally to this work

Specialty section:

This article was submitted to
Organic Chemistry,
a section of the journal
Frontiers in Chemistry

Received: 05 December 2019

Accepted: 01 April 2020

Published: 04 May 2020

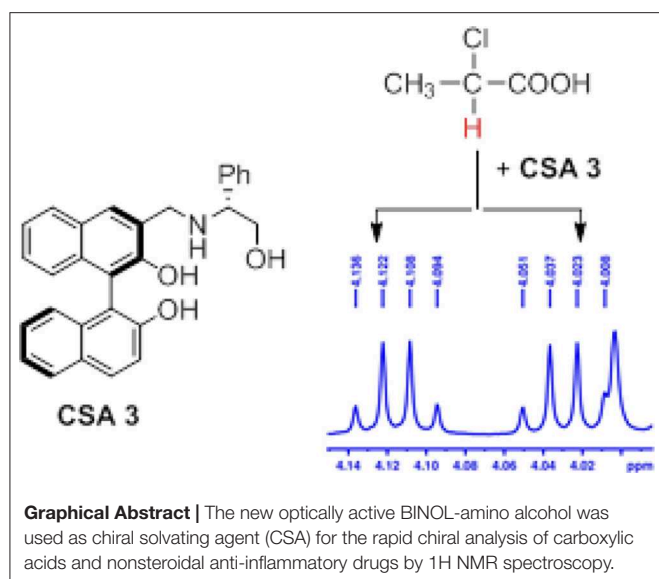
Citation:

Li G, Ma M, Wang G, Wang X and
Lei X (2020) Efficient
Enantiodifferentiation of Carboxylic
Acids Using BINOL-Based Amino
Alcohol as a Chiral NMR Solvating
Agent. *Front. Chem.* 8:336.
doi: 10.3389/fchem.2020.00336

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

INTRODUCTION

Chirality plays an important role in chemical, physical, pharmaceutical, and many biological events. The rapid and facial 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

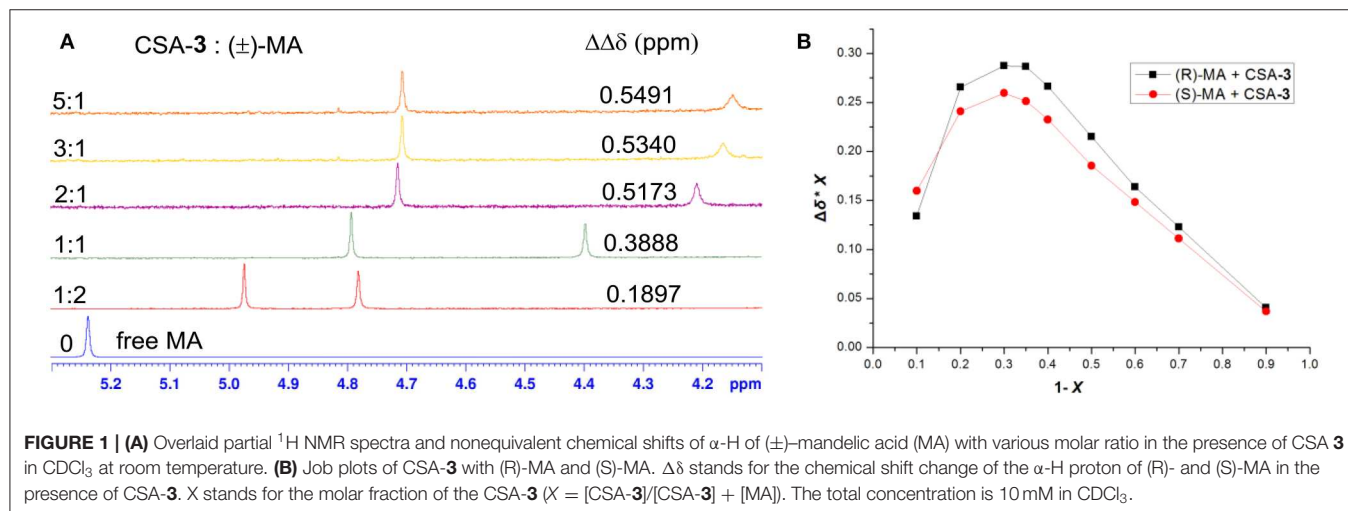
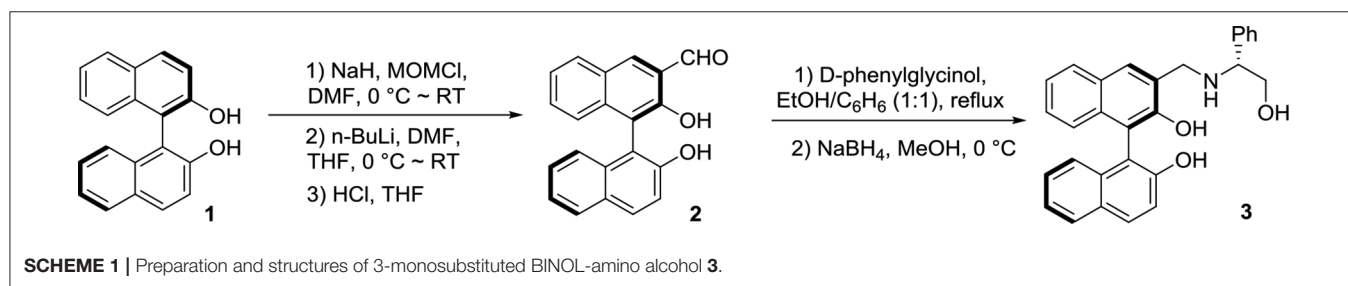


(Lesot et al., 2015; Farjon and Giraud, 2018). The CLSRs in the analyte solution are similar to CSAs with regard to the non-covalent interactions, but the major problem encountered in the use of CLSRs is enormous line broadening due to the paramagnetic interaction in poor resolution and sensitivity (Yang et al., 2005; Wenzel, 2012). In this regard, using CSAs as NMR-observable sensors for structural recognition has significant advantages over others mentioned above. Importantly, only a little amount of hosts (CSAs) and guest are needed without tedious derivatization and purification steps in test samples (Wenzel, 2007; Wenzel and Chisholm, 2011b; Chaudhari and Suryaprakash, 2012; Seco et al., 2012; Uccello-Barretta and Balzano, 2013a,b). In addition, it is not necessary to construct a calibration curve by using enantiopure samples compared with other spectroscopic apparatus, such as fluorescence spectroscopy and circular dichroism. Furthermore, the analytes are readily recovered because of non-covalent interactions, which is very important for difficult-access pharmaceutical compounds or drug samples (Holzgrabe et al., 1999; Uccello-Barretta and Balzano, 2013a,b). Thus, the further development of effective CSAs is highly desirable.

In recent years, various representative types of CSAs have been reported, such as Zwitterionic phosphorus heterocycles (Sheshenev et al., 2013), tetraaza macrocycles (Feng L. et al., 2018; Feng S. et al., 2018), C₂-symmetrical bistioureas (Chen et al., 2018), chiral squaramides (Yang et al., 2018), Kagan's amides (Jain et al., 2018), and so on. The binaphthyl-type and related compounds have been widely investigated in asymmetric catalysis, enantioselective fluorescence recognition, and new materials. The chiral binaphthyl units and multiple hydrogen bonding sites containing hydroxyl, or amino groups, can provide an excellent candidate for chiral receptor sensors development (Yu and Pu, 2015; Pu, 2017), especially, they are broadly applicable CSA. For instance, commercially available (R)- or (S)-BINOL and derivatives as chiral-solvating agents to assign

the enantiomeric excess (ee) of enantiomeric hydroxy carboxylic acids, synthetic drugs, natural alkaloids, or flavanones via ¹H NMR spectroscopy (Ardej-Jakubisiak 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 diacylaminopyridine 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-arylquinazolinones (Liu et al., 2017; Wu et al., 2018), binaphthalene skeleton ureas as sensor for scanned various sulfoxides, phenylethanol, and arylpropanoic acids (Holakovský et al., 2015; Curinová 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 discriminately 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 ^1H NMR spectroscopy. Herein these results are reported.

RESULTS AND DISCUSSION

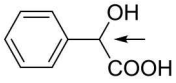
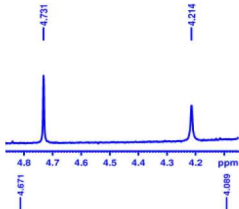
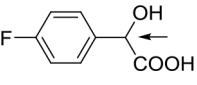
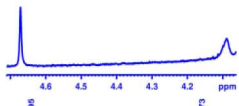
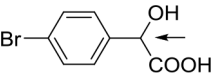
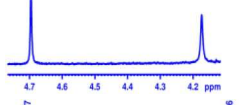
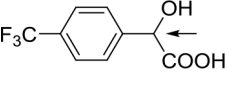
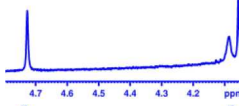
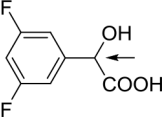
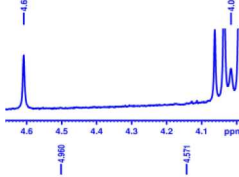
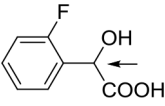
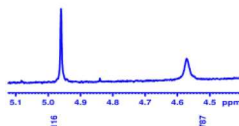
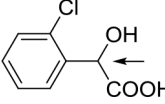
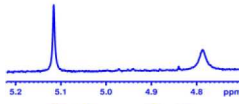
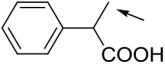
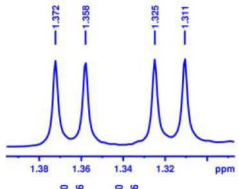
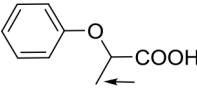
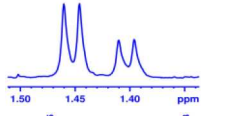
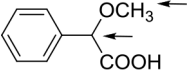
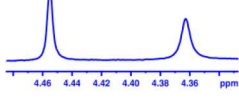
The chiral monosubstituted BINOL-amino alcohol can be readily carried out in five-step sequence according to the reported procedures starting from commercially available (R)-BINOL **1** (Matsunaga et al., 2000; DiMauro and Kozłowski, 2001; Dong et al., 2012; Xu et al., 2016). The key BINOL monoaldehyde 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 spectra 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 ^1H 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^αH proton resonance of MA to shift up-field in the ^1H 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 $\Delta\delta$ value of C^αH 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.

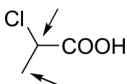
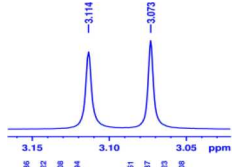
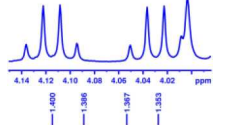
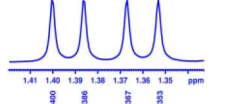
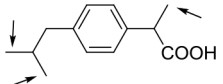
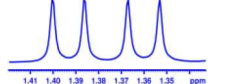
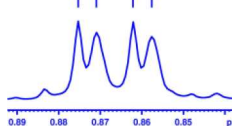
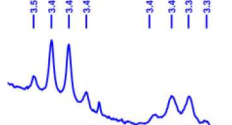
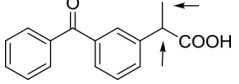
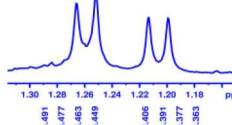
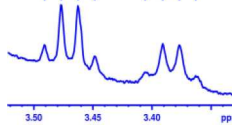
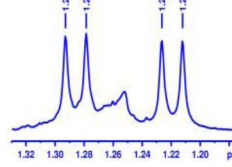
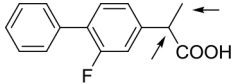
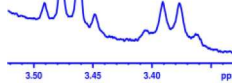

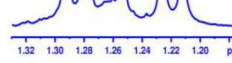
With optimized conditions in hand and encouraged by above satisfactory enantiodiscriminating results, next, we examined the scope of other derivatives of MA. The structure, $\Delta\delta$ values of examined guests, and related spectra are displayed in **Table 1**. Because of the multiple hydrogen–bond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

TABLE 1 | Non-equivalence chemical shift ($\Delta\Delta\delta$) and partial spectra of racemic carboxylic acids (guests) in presence of receptor by ^1H NMR (500 MHz) in CDCl_3 at 25°C .

Entry	Guest ^a	$\Delta\Delta\delta$ (ppm) ^b	$\Delta\Delta\delta$ (Hz)	Spectra
1		0.517	258.5	
2		0.582	291.0	
3		0.522	261.0	
4		0.641	320.5	
5		0.592	296.0	
6		0.389	194.5	
7		0.329	164.5	
8		0.047 ^c	23.5	
9		0.050 ^c	25.0	
10		0.092	46.0	

(Continued)

TABLE 1 | Continued

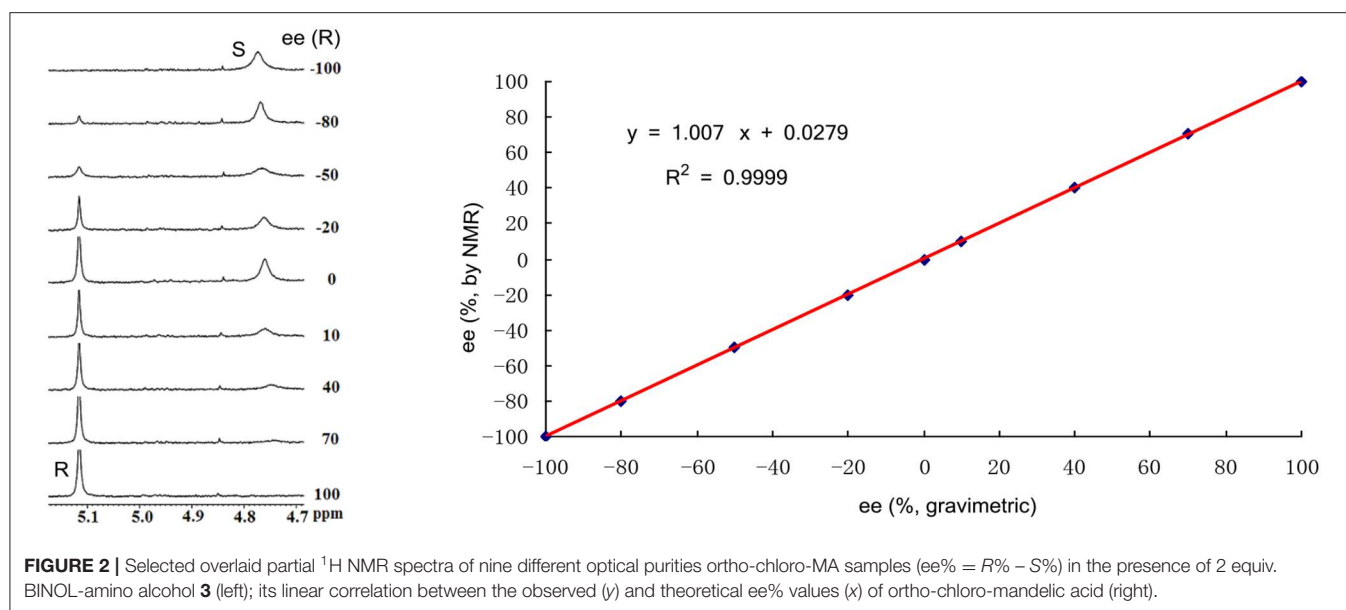
Entry	Guest ^a	$\Delta\Delta\delta$ (ppm) ^b	$\Delta\Delta\delta$ (Hz)	Spectra
11		0.041 ^c	20.5	
		0.086	43.0	
		0.033 ^c	16.5	
12		0.033 ^c	16.5	
		0.013 ^d	6.5	
		0.099	49.5	
13		0.052 ^c	26.0	
		0.086	43.0	
		0.067 ^c	33.5	
14		0.086	43.0	
		0.086	43.0	
		0.067 ^c	33.5	

^aAll 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 CDCl₃).

^bChemical shift non-equivalences of the methine group.

^cChemical shift non-equivalences of the α -methyl group.

^dChemical shift non-equivalences of the α -methyl protons of the isopropyl group.



group, the CSA associated with all tested aromatic carboxylic acids through ion-pairing interaction and exhibited good baseline resolution for large-enough α -H signals on a 500-MHz instrument (Table 1, entries 1–7 and Figures S11–S17). As a whole, these carboxylic acids with a para- or meta-substituent on the phenyl group gave higher $\Delta\Delta\delta$ values than those bearing ortho-substituted ones, the ¹H chemical shift non-equivalences of methane protons reached hundreds of Hertz. In light of the above observation, the para-substituted aromatic carboxylic acids (Table 1, entries 2–4) almost showed good baseline resolution and much bigger $\Delta\Delta\delta$ value compared with the ortho-substituted aromatic carboxylic acids (Table 1, entries 6–7); in particular, the MAs with strong electron-donating groups (F-, CF₃-) gave better results (0.582 ppm, 291.0 Hz and 0.641 ppm, 320.5 Hz; Table 1, entries 2 and 4). However, the ortho-substituted group on the MAs displayed weaker values (0.582 ppm, 291.0 Hz vs. 0.389 ppm, 194.5 Hz; Table 1, entries 2 and 6); ortho-chloro-MA displayed similar enantiodiscriminating ability (0.329 ppm, 164.5 Hz; Table 1, entry 7); the above results indicated that the discriminating ability of CAS 3 could be weakened presumably due to being more sterically hindered in ortho-substituted MAs. However, meta-difluoro-substituted aromatic carboxylic acid showed the relatively bigger $\Delta\Delta\delta$ value as 0.592 ppm compared with the ortho-fluoro-substituted one (Table 1, entry 5). The results suggested the stronger electron-withdrawing effects, the larger the corresponding $\Delta\Delta\delta$ values. In order to further explore enantiodiscriminating abilities of CAS 3, the α -methyl protons of the carboxylic acids were also discriminated by the corresponding host only moderately (0.047 ppm, 23.5 Hz; 0.050 ppm, 25.0 Hz; 0.041 ppm, 20.5 Hz; and 0.033 ppm, 16.5 Hz; Table 1, entries 8–11 and Figures S18–S21). We can observe a minor separation of the CH₃ proton signal when using propionic acid derivatives instead of phenylacetic acid derivatives (Table 1, entries 9 and 11).

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequently used for patients with low-back pain and inflammation. Among these phenylacetic acid analogs, the BINOL-amino alcohol 3 also exhibited clear and good chiral discrimination of signals for NSAIDs. The signals of α -CH₃ ibuprofen, ketoprofen, and flurbiprofen were large enough with peaks identifiable (Table 1, entries 12–14 and Figures S22–S24).

Finally, encouraged by above good enantiodiscriminating results, and to explore the practical quantitative applicability of BINOL-amino alcohol 3 for enantiomeric determination of various non-racemic samples, nine non-racemic samples containing ortho-chloro-MA with 0, 10, 40, 70, 100, –20, –50, –80, and –100% ee values were accurately calculated by integration of α -H signals of ortho-chloro-MA in ¹H NMR analysis. The results are shown in Figure 2. The linear relationship between the NMR-determined values (y) and those gravimetry-determined values (x) is excellent with $R^2 = 0.999$ ($y = 1.007x + 0.0279$, $R^2 =$ correlation coefficient).

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 ($\Delta\Delta\delta$) 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 conducted the experiments and characterized the samples. 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.

REFERENCES

- Akdeniz, A., Minami, T., Watanabe, S., Yokoyama, M., Ema, T., and Anzenbacher, J. P. (2016). Determination of enantiomeric excess of carboxylates by fluorescent macrocyclic sensors. *Chem. Sci.* 7, 2016–2022. doi: 10.1039/c5sc04235f
- Ardej-Jakubisiak, M., and Kawecki, R. (2008). NMR method for determination of enantiomeric purity of sulfinimines. *Tetrahedron Asymmetry* 19, 2645–2647. doi: 10.1016/j.tetasy.2008.11.023
- Bai, L., Chen, P., Xiang, J., Sun, J., and Lei, X. X. (2019). Enantiomeric NMR discrimination of carboxylic acids using actinomycin D as a chiral solvating agent. *Org. Biomol. Chem.* 17, 1466–1470. doi: 10.1039/c8ob03012j
- Borowiecki, P. (2015). Enantiodifferentiation of promethazine using (S)-(-)-BINOL as the NMR chiral solvating agent: determination of the enantiomeric purity and performance comparison with traditional chiral HPLC. *Tetrahedron Asymmetry* 26, 16–23. doi: 10.1016/j.tetasy.2014.11.018
- Chaudhari, S. R., and Suryaprakash, N. (2012). Simple and efficient methods for discrimination of chiral diacids and chiral alpha-methyl amines. *Org. Biomol. Chem.* 10, 6410–6419. doi: 10.1039/c2ob25599e
- Chaudhari, S. R., and Suryaprakash, N. (2013). Ternary ion-pair complexation: a protocol for chiral discrimination and the assignment of absolute configuration of chiral hydroxy acids. *New J. Chem.* 37, 4025–4030. doi: 10.1039/C3NJ00779K
- Chen, Z., Fan, H., Yang, S., Bian, G., and Song, L. (2018). Chiral sensors for determining the absolute configurations of α -amino acid derivatives. *Org. Biomol. Chem.* 16, 6933–8317. doi: 10.1039/c8ob01933a
- Cheng, C., Cai, Z. W., Peng, X. S., and Wong, H. N. C. (2013). Enantiomeric recognition of amino acid salts by macrocyclic crown ethers derived from enantiomerically pure 1,8,9,16-tetrahydroxytetraphenylenes. *J. Org. Chem.* 78, 8562–8573. doi: 10.1021/jo401240k
- Couffin, A., Thillaye, O., Boullay, D., Vedrenne, M., Navarro, C., Martin-Vaca, B., et al. (2014). Enantio-differentiation of O-heterocycles using a binol-derived disulfonimide as a chiral solvating agent. *Chem. Commun.* 50, 5997–6000. doi: 10.1039/c4cc00466c
- Curínová, P., Dračinský, M., Jakubec, M., Tlustý, M., Janku, K., Izák, P., et al. (2018). Enantioselective complexation of 1-phenylethanol with chiral compounds bearing urea moiety. *Chirality* 30, 798–806. doi: 10.1002/chir.22855
- Curínová, P., Hájek, P., Janku, K., and Holakovský, R. (2019). Method for determination of optical purity of 2-arylpropanoic acids using urea derivatives based on a 1,1'-binaphthalene skeleton as chiral NMR solvating agents: advantages and limitations thereof. *Chirality* 31, 410–417. doi: 10.1002/chir.23067
- DiMauro, E. F., and Kozlowski, M. C. (2001). BINOL-Salen metal catalysts incorporating a bifunctional design. *Org. Lett.* 3, 1641–1644. doi: 10.1021/ol0158213
- Dong, M., Dong, Y. M., Ma, T. H., Wang, Y. W., and Peng, Y. (2012). A highly selective fluorescence-enhanced chemosensor for Al^{3+} in aqueous solution based on a hybrid ligand from BINOL scaffold and β -amino alcohol. *Inorg. Chim. Acta* 381, 137–142. doi: 10.1016/j.ica.2011.08.043

FUNDING

This work was supported by the National Natural Science Foundation of China (21874158, 21804086, 21572164) and Natural Science Foundation of Hubei Province (2019CFA072).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fchem.2020.00336/full#supplementary-material>

- Du, G., Li, Y., Ma, S., Wang, R., Li, B., Guo, F., et al. (2015). Efficient determination of the enantiomeric purity and absolute configuration of flavanones by using (S)-3,3'-dibromo-1,1'-bi-2-naphthol as a chiral solvating agent. *J. Nat. Prod.* 78, 2968–2974. doi: 10.1021/acs.jnatprod.5b00690
- Ema, T., Tanida, D., Hamada, K., and Sakai, T. (2008). Tuning the chiral cavity of macrocyclic receptor for chiral recognition and discrimination. Enantio-differentiation of O-heterocycles using a binol-derived disulfonimide as a chiral solvating agent. *J. Org. Chem.* 73, 9129–9132. doi: 10.1021/jo801584b
- Ema, T., Tanida, D., and Sakai, T. (2007). Versatile and practical macrocyclic reagent with multiple hydrogen-bonding sites for chiral discrimination in NMR. *J. Am. Chem. Soc.* 129, 10591–10596. doi: 10.1021/ja073476s
- Ema, T., Yamasaki, T., Watanabe, S., Hiyoshi, M., and Sakai, T. (2018). Cross-coupling approach to an array of macrocyclic receptors functioning as chiral solvating agents. *J. Org. Chem.* 83, 10762–10769. doi: 10.1021/acs.joc.8b01327
- Farjon, J., and Giraud, N. (2018). 1H NMR analyses of enantiomeric mixtures using chiral liquid crystals. *Curr. Opin. Colloid. Interface. Sci.* 33, 1–8. doi: 10.1016/j.cocis.2017.11.001
- Feng, L., Gao, G., H., Zhao, L., Zheng, Y., Wang, P., Stavropoulos, P., et al. (2018). Synthesis of tripeptide derivatives with three stereogenic centers and chiral recognition probed by tetraaza macrocyclic chiral solvating agents derived from d-Phenylalanine and (1S,2S)-(+)-1,2-diaminocyclohexane via 1H NMR spectroscopy. *J. Org. Chem.* 83, 13874–13887. doi: 10.1021/acs.joc.8b02212
- Feng, S., Yao, L., Liu, F., Zang, X., and Wang, J. J. (2018). Synthesis of noval chiral tridentate amino alcohols as chiral solvating agents under ball-milling conditions. *Tetrahedron Lett.* 59, 4305–4310. doi: 10.1016/j.tetlet.2018.10.049
- Freire, F., Quinoa, E., and Riguera, R. (2008). In tube determination of the absolute configuration of α - and β -hydroxy acids by NMR via chiral BINOL borates. *Chem. Commun.* 35, 4147–4149. doi: 10.1039/B806529B
- Holakovský, R., März, M., and Cibulka, R. (2015). Urea derivatives based on a 1,1'-binaphthalene skeleton as chiral solvating agents for sulfoxides. *Tetrahedron Asymmetry* 26, 1328–1334. doi: 10.1016/j.tetasy.2015.10.011
- Holzgrabe, U., Wawer, I., and Diehl, B. (1999). *NMR Spectroscopy in Drug Development and Analysis*. New York, NY: Wiley Press.
- Izake, E. L. (2007). Chiral discrimination and enantioselective analysis of drugs: an overview. *J. Pharm. Sci.* 96, 1659–1676. doi: 10.1002/jps.20820
- Jain, N., Khanvilkar, A. N., Sahoo, S., and Bedekar, A. V. (2018). Modification of kagan's amide for improved activity as chiral solvating agent in enantiodiscrimination during NMR analysis. *Tetrahedron* 74, 68–76. doi: 10.1016/j.tet.2017.11.036
- Jo, H. H., Lin, C. Y., and Anslyn, E. V. (2014). Rapid optical methods for enantiomeric excess analysis: from enantioselective indicator displacement assays to exciton-coupled circular dichroism. *Acc. Chem. Res.* 47, 2212–2221. doi: 10.1021/ar500147x
- Klika, K. D., Budovská, M., and Kutschy, P. (2010). Enantiodifferentiation of phytoalexin spirobrassinin derivatives using the chiral solvating agent (R)-(+)-1,1'-bi-2-naphthol in conjunction with molecular modeling. *Tetrahedron Asymmetry* 21, 647–658. doi: 10.1016/j.tetasy.2010.03.035

- Lei, X. X., Liu, L., Chen, X. J., Yu, X. C., Ding, L. S., and Zhang, A. J. (2010). Pattern-based recognition for determination of enantiomeric excess, using chiral auxiliary induced chemical shift perturbation NMR. *Org. Lett.* 12, 2540–2543. doi: 10.1021/ol100773s
- Lesot, P., Aroulanda, C., Zimmermann, H., and Luz, Z. (2015). Enantiotopic discrimination in the NMR spectrum of prochiral solutes in chiral liquid crystals. *Chem. Soc. Rev.* 44, 2330–2375. doi: 10.1039/c4cs00260a
- Leung, D., Kang, S. O., and Anslyn, E. V. (2012). Rapid determination of enantiomeric excess: a focus on optical approaches. *Chem. Soc. Rev.* 41, 448–479. doi: 10.1039/c1cs15135e
- Li, G. W., Cao, J. M., Zong, W., Lei, X. X., and Tan, R. X. (2016). Enantiodiscrimination of carboxylic acids using the diphenylprolinol NMR chiral solvating agents. *Org. Chem. Front.* 3, 96–102. doi: 10.1039/C5QO00264H
- Liu, C. X., Zheng, L., Zhu, L., Xiao, H. P., Li, X., and Jiang, J. (2017). Efficient chiral ^1H NMR analysis of indoloquinazoline alkaloids phaitanthrin A, cephalanthrin-A and their analogues with a chiral phosphoric acid. *Org. Biomol. Chem.* 15, 4314–4319. doi: 10.1039/c7ob00823f
- Liu, H. L., Peng, Q., Wu, Y. D., Chen, D., Hou, X. L., Sabat, M., et al. (2010). Highly enantioselective recognition of structurally diverse α -hydroxycarboxylic acids using a fluorescent sensor. *Angew. Chem. Int. Ed.* 49, 602–606. doi: 10.1002/anie.200904889
- Liu, L., Ye, M. D., Hu, X. G., Yu, X. C., Zhang, L. X., and Lei, X. X. (2011). Chiral solvating agents for carboxylic acids based on the salen moiety. *Tetrahedron Asymmetry* 22, 1667–1671. doi: 10.1016/j.tetasy.2011.09.022
- Ma, Q. Z., Ma, M. S., Tian, H. Y., Ye, X. X., Xiao, H. P., Chen, L. H., et al. (2012). A novel amine receptor based on the binol scaffold functions as a highly effective chiral shift reagent for carboxylic acids. *Org. Lett.* 14, 5813–5815. doi: 10.1021/ol3027686
- Matsunaga, S., Das, J., Roels, J., Vogl, E. M., Yamamoto, N., Iida, T., et al. (2000). Catalytic enantioselective meso-epoxide ring opening reaction with phenolic oxygen nucleophile promoted by gallium heterobimetallic multifunctional complexes. *J. Am. Chem. Soc.* 122, 2252–2260. doi: 10.1021/ja993650f
- Mishra, S. K., Chaudhari, S. R., and Suryaprakash, N. (2014). *In situ* approach for testing the enantiopurity of chiral amines and amino alcohols by ^1H NMR. *Org. Biomol. Chem.* 12, 495–502. doi: 10.1039/C3OB41671B
- Miyaji, H., Hong, S. J., Jeong, S. D., Yoon, D. W., Na, H. K., Hong, J., et al. (2007). A binol-strapped calix[4]pyrrole as a model chirogenic receptor for the enantioselective recognition of carboxylate anions. *Angew. Chem. Int. Ed.* 46, 2508–2511. doi: 10.1002/anie.200604161
- Monteagudo, E., March, P. D., Álvarez-Larena, Á., and Virgili, A. (2017). A new chirally organized trifluoromethylanthrylmethanol derivative and its application as chiral solvating agent. *ChemistrySelect* 2, 7362–7367. doi: 10.1002/slct.201701429
- Nieto, S., Dragana, J. M., and Anslyn, E. V. (2010). A facile circular dichroism protocol for rapid determination of enantiomeric excess and concentration of chiral primary amines. *Chem. Eur. J.* 16, 227–232. doi: 10.1002/chem.200902650
- Parker, D. (1991). NMR determination of enantiomeric purity. *Chem. Rev.* 91, 1441–1457. doi: 10.1021/cr00007a009
- Pérez-Trujillo, M., Monteagudo, E., and Parella, T. (2013). ^{13}C NMR spectroscopy for the differentiation of enantiomers using chiral solvating agents. *Anal. Chem.* 85, 10887–10894. doi: 10.1021/ac402580j
- Pérez-Trujillo, M., Parella, T., and Kuhn, L. T. (2015). NMR-aided differentiation of enantiomers: signal antioresolution. *Anal. Chim. Acta* 876, 63–70. doi: 10.1016/j.aca.2015.02.069
- Pu, L. (2004). Fluorescence of organic molecules in chiral recognition. *Chem. Rev.* 104, 1687–1716. doi: 10.1021/cr030052h
- Pu, L. (2012). Enantioselective fluorescent sensors: a tale of BINOL. *Acc. Chem. Res.* 45, 150–163. doi: 10.1021/ar200048d
- Pu, L. (2017). Simultaneous determination of concentration and enantiomeric composition in fluorescent sensing. *Acc. Chem. Res.* 50, 1032–1040. doi: 10.1021/acs.accounts.7b00036
- Redondo, J., Capdevila, A., and Ciudad, S. (2013). Determination of the enantiomeric purity of the antiasthmatic drug montelukast by means of ^1H NMR spectroscopy. *Chirality* 25, 780–786. doi: 10.1002/chir.22213
- Redondo, J., Capdevila, A., and Latorre, I. (2010). Use of (S)-BINOL as NMR chiral solvating agent for the enantiodiscrimination of omeprazole and its analogs. *Chirality* 22, 472–478. doi: 10.1002/chir.20766
- Seco, J. M., Quiñoá, E., and Riguera, R. (2004). The assignment of absolute configuration by NMR. *Chem. Rev.* 104, 17–118. doi: 10.1021/cr000665j
- Seco, J. M., Quinoa, E., and Riguera, R. (2012). Assignment of the absolute configuration of polyfunctional compounds by NMR using chiral derivatizing agents. *Chem. Rev.* 112, 4603–4641. doi: 10.1021/cr2003344
- Seco, J. M., and Riguera, R. (2015). NMR methods for the assignment of absolute stereochemistry of bioactive compounds. *eMagRes.* 4, 1–30. doi: 10.1002/9780470034590.emrstm1398
- Sheshenev, A. E., Boltukhina, E. V., Grishina, A. A., Cisarova, I., Lyapkalo, I. M., and Hii, K. K. (2013). New chiral zwitterionic phosphorus heterocycles: synthesis, structure, properties and application as chiral solvating agents. *Chem. Eur. J.* 19, 8136–8143. doi: 10.1002/chem.201300062
- Silva, M. S. (2017). Recent advances in multinuclear NMR spectroscopy for chiral recognition of organic compounds. *Molecules* 22:247. doi: 10.3390/molecules22020247
- Tokuhisa, H., Ogihara, T., Nagawa, Y., and Hiratani, K. (2001). Synthesis of chiral crownphanes having two phenolic groups via tandem claisen rearrangement and their chiral recognition. *J. Incl. Phenom. Macro. Chem.* 39, 347–352. doi: 10.1023/A:1011122827281
- Uccello-Barretta, G., and Balzano, F. (2013a). “Chiral NMR solvating additives for differentiation of enantiomers,” in *Differentiation of enantiomers II. Topics in Current Chemistry*, Vol. 341, ed V. Schurig (Berlin: Springer), 69–131.
- Uccello-Barretta, G., and Balzano, F. (2013b). Chiral NMR solvating additives for differentiation of enantiomers. *Top. Curr. Chem.* 341, 69–131. doi: 10.1007/128_2013_445
- Wenzel, T. J. (2007). *Discrimination of Chiral Compounds Using NMR Spectroscopy*. Hoboken, NJ: John Wiley & Sons, Inc.
- Wenzel, T. J. (2012). Spectroscopic analysis: NMR and shift reagents. *Comput. Chirality* 8, 545–570. doi: 10.1016/B978-0-08-095167-6.00844-2
- Wenzel, T. J., and Chisholm, C. D. (2011a). Assignment of absolute configuration using chiral reagents and NMR spectroscopy. *Chirality* 23, 190–214. doi: 10.1002/chir.20889
- Wenzel, T. J., and Chisholm, C. D. (2011b). Using NMR spectroscopic methods to determine enantiomeric purity and assign absolute stereochemistry. *Prog. Nucl. Magn. Reson. Spectrosc.* 59, 1–63. doi: 10.1016/j.pnmrs.2010.07.003
- Wenzel, T. J., and Wilcox, J. D. (2003). Chiral reagents for the determination of enantiomeric excess and absolute configuration using NMR spectroscopy. *Chirality* 15, 256–270. doi: 10.1002/chir.10190
- Wolf, C., and Bentley, K. W. (2013). Chirality sensing using stereodynamic probes with distinct electronic circular dichroism output. *Chem. Soc. Rev.* 42, 5408–5424. doi: 10.1039/c3cs35498a
- Wu, C., Liu, H., Li, J., Xiao, H. P., Li, X., and Jiang, J. (2018). Chiral ^1H NMR of atropisomeric quinazolinones with enantiopure phosphoric acids. *Front Chem.* 6:300. doi: 10.3389/fchem.2018.00300
- Xu, Y., Yu, S., Chen, Q., Chen, X., Xiao, M., Chen, L., et al. (2016). Greatly enhanced fluorescence by increasing the structural rigidity of an imine: enantioselective recognition of 1,2-Cyclohexanediamine by a chiral aldehyde. *Chem. Eur. J.* 22, 5963–5968. doi: 10.1002/chem.201504686
- Xu, Z. C., Liu, C., Zhao, S. J., Chen, S., and Zhao, Y. C. (2019). Molecular sensors for NMR-based detection. *Chem. Rev.* 119, 195–230. doi: 10.1021/acs.chemrev.8b00202
- Yang, D., Li, X., Fan, Y., and Zhang, D. (2005). Enantioselective recognition of carboxylates: a receptor derived from α -aminoxy acids functions as a chiral shift reagent for carboxylic acids. *J. Am. Chem. Soc.* 127, 7996–7997. doi: 10.1021/ja051072z
- Yang, G. H., Li, Y., and Li, X. (2018). Chirality sensing of molecules with diverse functional groups by using N-tert-butyl sulfanyl squaramide. *Asian J. Org. Chem.* 7, 770–775. doi: 10.1002/ajoc.201700671
- Yi, J., Du, G., Yang, Y., Li, Y., Li, Y., and Guo, F. (2016). Chiral discrimination of natural isoflavanones using (R)- and (S)-BINOL as the NMR chiral solvating agents. *Tetrahedron Asymmetry* 27, 1153–1159. doi: 10.1016/j.tetasy.2016.09.002
- Yu, S., and Pu, L. (2015). Recent progress on using BINOLs in enantioselective molecular recognition. *Tetrahedron* 71, 745–772. doi: 10.1016/j.tet.2014.11.007

- Yu, X. Y., and Yao, Z. P. (2017). Chiral recognition and determination of enantiomeric excess by mass spectrometry: a review. *Anal. Chim. Acta* 968, 1–20. doi: 10.1016/j.aca.2017.03.021
- Yuste, F., Sánchez-Obregón, R., Díaz, E., and García-Carrillo, M. A. (2014). Enantiodifferentiation of the antitumor alkaloid crispine a using the NMR chiral solvating agents (R)- and (S)-BINOL. *Tetrahedron Asymmetry* 25, 224–228. doi: 10.1016/j.tetasy.2013.12.006
- Zaleskiy, S. S., Danieli, E., Blümich, B., and Ananikov, V. P. (2014). Miniaturization of NMR systems: desktop spectrometers, microcoil spectroscopy, and “NMR on a chip” for chemistry, biochemistry, and industry. *Chem. Rev.* 114, 5641–5694. doi: 10.1021/cr400063g

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.

Copyright © 2020 Li, Ma, Wang, Wang and Lei. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.