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A chiral aluminum solvating agent (CASA) for ^{1}H NMR chiral analysis of alcohols at low temperature†

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A chiral aluminum solvating agent (CASA) was demonstrated to be a general and efficient reagent for ^{1}H NMR chiral analysis of alcohols. The sodium salt of the CASA (CASA-Na) showed a complete baseline peak separation of the hydroxyl group for various chiral alcohols including primary, secondary, and tertiary alcohols with alkyl and aryl substituents in CD$_3$CN. Due to the weak intermolecular interaction, ^{1}H NMR measurement at low temperature (−40 to 10 °C) was required.

Chiral analysis such as determination of the absolute configuration and the relative ratio of enantiomers is indispensable in the asymmetric synthesis of chiral compounds.[1,2] Quantitative chiral analysis has largely relied on chromatographic techniques using high-performance liquid chromatography (HPLC) or gas chromatography (GC) with a column coated or immobilized with chiral stationary phases.[3] In addition, NMR spectroscopy can be a complementary analytical technique for chiral analysis because it is the most conveniently and widely used method for the structural determination of compounds. However, for the NMR chiral analysis, chiral analytes should be converted to diastereomeric mixtures by covalent bond formation or non-covalent interactions with chiral reagents,[1] or by self-association with achiral reagents[4] in order to generate anisochronous chemical shifts. Among these NMR chiral analyses, the use of chiral solvating agents (CSAs) using non-covalent interactions is operationally simple and convenient because the sample can be directly analyzed by mixing with a CSA. The reported CSAs include unsaturated metal complexes,[5] Brønsted–Lowry acids/bases,[6] hydrogen bonding reagents,[7] supramolecular receptors,[8] and others.[9] However, analytes are mainly limited to amines or carboxylic acids because they can form relatively strong charged hydrogen bonding. Although several efficient CSAs

have been reported, it is still quite challenging to use CSAs for other polar compounds. Indeed, for example, chiral alcohols are common structural motifs synthesized by many stereoselective reactions, but only a few cases of chiral analysis using CSAs have been reported and moreover, they tend to exhibit insufficient peak separation and narrow analyte scope.[10,11] We recently introduced negatively charged octahedral aluminum complexes as an efficient CSA for charged compounds including amines (Fig. 1a).[12] Here, we demonstrate that our chiral aluminum complexes can be generally applicable for chiral solvation of alcohols (Fig. 1b).

A chiral aluminum solvating agent (CASA), a negatively charged octahedral ate complex, was readily prepared by a stereoselective assembly of the N$_2$O$_4$ ligand with AlCl$_3$. We demonstrated that the protonated form, CASA-H, can be used for chiral solvation of amines and the sodium form, CASA-Na, can be used for chiral solvation of carboxylic acids. The CASA is one of the most efficient CSAs efficiently working with almost all types of charged compounds including amines and carboxylic acids in polar and nonpolar solvents.[13] In order to test the chiral solvation ability of
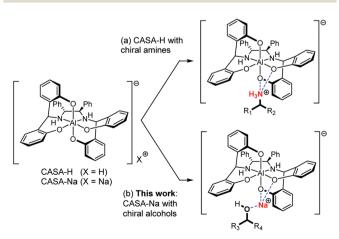
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† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic and calculation data, and crystallographic details. CCDC 1816058. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8cc00574e

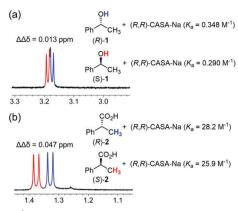Fig. 1 CASA for (a) chiral solvation of amines and (b) chiral solvation of alcohols.

Fig. 2 Partial ^{1}H NMR spectra and measured binding constants for chiral solvation of (a) 1-phenylethanol (**1**) and (b) 2-phenylpropionic acid (**2**) with (*R*,*R*)-CASA-Na at 25 °C in CD$_3$CN.

the CASA for chiral alcohols, we initially compared the chiral solvation of an alcohol, 2-phenylethanol (**1**), and a structurally related carboxylic acid, 2-phenylpropionic acid (**2**), with CASA-Na.

When the (*R*,*R*)-form of CASA-Na was used in CD$_3$CN, *rac*-2-phenylpropionic acid (**2**) showed a sufficient baseline peak separation of $\Delta\Delta\delta^{14}$ = 0.047 ppm, but *rac*-1-phenylethanol (**1**) showed only a small peak separation of $\Delta\Delta\delta$ = 0.013 ppm (Fig. 2). Because of the structural similarity of **1** and **2**, we proposed that the binding strength of carboxylic acid and alcohol functionality to the CASA may be related to the chiral solvation ability. Indeed, the binding constants between (*R*,*R*)-CASA-Na and chiral alcohols (*R*)-**1** and (*S*)-**1** were measured to be 0.348 and 0.290 M^{-1}, while those between (*R*,*R*)-CASA-Na and chiral acids (*R*)-**2** and (*S*)-**2** were measured to be 28.2 and 25.9 M^{-1}, respectively (Fig. 2, ESI†). The binding constants for alcohol **1** are about 80–90 times weaker than those for carboxylic acid **2**. Interestingly, (*R*,*R*)-CASA-Na binds 1.1–1.2 times stronger with the (*R*)-enantiomer than with the (*S*)-enantiomer. Such a weak intermolecular interaction between a receptor and an alcohol analyte is the reason why efficient CSAs for chiral alcohol have not been developed so far.

We then attempted to improve the peak separation ability of the CASA for chiral alcohols. Changing solvents or counter cations was not successful. In a series of analyte tests, we found that 1-phenylbutanol (**3**) showed a peak separation ($\Delta\Delta\delta$ = 0.020 ppm) at 25 °C in CD$_3$CN. Because 1-phenylbutanol is an extended structure of 1-phenylethanol by substituting a methyl group with an *n*-propyl group, we proposed that the increase of hydrophobic interaction would improve the peak separation of diastereomeric mixtures of chiral alcohols and CASA-Na. Indeed, when *rac*-1-phenyldodecanol (**4**) was used, a better peak separation ($\Delta\Delta\delta$ = 0.028 ppm) was observed (Fig. 3a). Thus, increasing hydrophobicity is a method to achieve a baseline peak separation for chiral solvation of alcohols with CASA-Na. In addition, we wanted to develop a more general method applicable to most chiral alcohol analytes. As a reduction in temperature can shift the equilibrium towards the formation of the complex, we lowered the temperature to increase the enantiodifferentiation. To our delight, an increase of peak separation of *rac*-1-phenylethanol (**1**) was
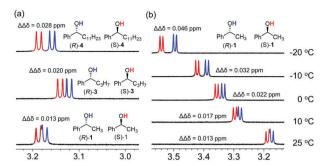

Fig. 3 The effect of (a) hydrophobicity and (b) temperature for chiral solvation of hydroxyl groups of alcohols with CASA-Na in CD$_3$CN.

observed with CASA-Na and a sufficient baseline peak separation was obtained at −10 °C ($\Delta\Delta\delta$ = 0.032 ppm) and −20 °C ($\Delta\Delta\delta$ = 0.046 ppm) (Fig. 3b). Because the temperature control is a simple operation in modern NMR spectroscopy, the chiral solvation with CASA-Na can be conveniently used for most chiral alcohols.

In order to understand the origin of chiral solvation of alcohols with a CASA, we first obtained a Job plot to find the 1:1 adduct formed between CASA-Na and 1-phenyldodecanol (**4**) (Fig. 4a). All our efforts to obtain an X-ray structure of such a 1:1 adduct with CASA-Na and alcohol analyte failed, but we obtained the X-ray structure of the Sc(III) complex from methanolic solution (Fig. 4b). In the crystal structure of the Sc complex, two MeOH and two H$_2$O molecules coordinate to the Na$^+$ ion in the unit cell.[13] Thus, the Job plot and the crystal structure provided us insight to propose a 1:1 binding model between CASA-Na and 1-phenylethanol (**1**). We then calculated the energy minimum structures of (*R*,*R*)-CASA-Na/(*R*)-**1** and (*R*,*R*)-CASA-Na/(*S*)-**1** (Fig. 4c and d). The DFT computation showed that both complexes have
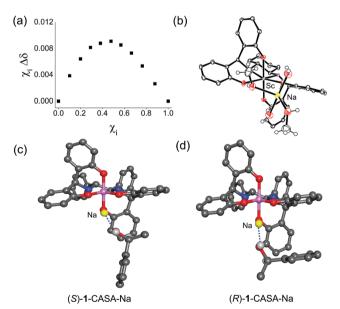

Fig. 4 (a) Job plot between **4** and CASA-Na measured in CD$_3$CN. (b) Crystal structure of the Sc(III) complex (thermal ellipsoids at the 50% probability: all hydrogens except for those in water and methanol are omitted for clarity). Optimized structures of (c) (*S*)-**1**-CASA-Na and (d) (*R*)-**1**-CASA-Na.
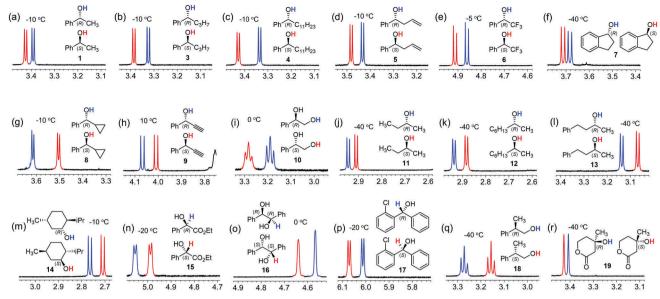
Fig. 5 Chiral solvation of various chiral alcohols with CASA-Na in CD$_3$CN.

comparable energy with a free energy difference of 0.04 kcal mol^{-1}. In both optimized structures, chiral alcohols (R)-**1** and (S)-**1** bind to the sodium cation with a geometry where the proton at the chiral carbon center is placed toward the CASA in order to minimize the steric repulsion. Thus, the methyl group of (S)-**1** is placed toward the phenol groups of the CASA, whereas that of (R)-**1** is placed away from the phenol groups. On the basis of the proposed **1**-CASA complexes, the methyl group of (S)-**1** is expected to be more shielded than that of (R)-**1**. Indeed the calculated methyl peaks (1.71 and 1.15 ppm for (R)-**1** and (S)-**1**, respectively) relatively agree with the measured methyl peaks (1.41 and 1.40 ppm for (R)-**1** and (S)-**1**, respectively). Moreover, the calculated chemical shifts for the proton of the OH groups were found to be 1.49 and 1.59 ppm for (R)-**1** and (S)-**1**, respectively, which also agreed with the observed ^{1}H NMR spectra.

The utility of the CASA for chiral solvation of alcohols was demonstrated with various chiral alcohols **1** and **3–19** as shown in Fig. 5. To our delight, we could achieve baseline peak separation for all of the chiral alcohols tested. In many cases, the proton peak of the hydroxy group was well-separated in the ^{1}H NMR spectra in the presence of CASA-Na. The recorded temperature ranged from −40 °C to 10 °C based on the substituents of the chiral alcohols related to hydrophobicity. First, we successfully differentiated secondary alcohols with one phenyl substituent at the chiral carbon center. All OH peaks from (R)-phenyl-substituted alcohols **1** and **3–7** with linear alkyl, allyl, CF$_3$, and cyclic alkyl groups are located at more upfield positions than those from (S)-alcohols (Fig. 5a–f). However, the relative peak pattern was inverted with substituents of cyclopropyl and alkynyl groups (Fig. 5g and h). Thus, it is still primitive to generally apply chiral solvation with a CASA to predict the absolute chirality of chiral alcohols. In addition, CASA-Na was also effective for alkyl substituted secondary alcohols **11–14**. In cases of chiral secondary alcohols with alkyl substituents, a low temperature of −40 °C was generally required to achieve

baseline peak separation and all OH peaks of (R)-alcohols appeared in more downfield positions than those of (S)-alcohols. Finally, other chiral alcohols including diol **16**, diaryl-substituted secondary alcohol **17**, primary alcohol **18**, and tertiary alcohol **19** were well resolved in the ^{1}H NMR spectra with CASA-Na in CD$_3$CN. Thus, the chiral solvation with CASA-Na can be a general method for chiral solvation of chiral alcohols.

We next investigated the quantitative chiral analysis of a chiral alcohol. As shown in Fig. 6a, 1-phenylbutanol **3** with various % ee was analyzed with CASA-Na. The chemical shifts of the resolved peaks were almost constant, implying that K_a values are rather close.[15] Accordingly, reliable integration of major and minor peaks can be achieved. In order to ensure a fair comparison, we measured % ee with both NMR and HPLC, and both measurements showed an excellent linear relationship (Fig. 6b). Accordingly, ^{1}H NMR chiral analysis of alcohols with CASA-Na can be a complementary analytical tool together with classical chromatographic methods. In addition, when compared with several reported CSAs,[11] CASA-Na showed better peak separation of the hydroxyl groups in CD$_3$CN (ESI†).

In summary, we have demonstrated a general and efficient chiral solvation of chiral alcohols with a sodium salt of negatively
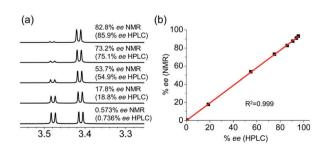

Fig. 6 (a) Partial ^{1}H NMR spectra showing the methyl peaks of 1-phenyl-butanol (**3**, 10 mM) with various enantiomeric excess in the presence of a CASA (10 mM) in CD$_3$CN and (b) a linear plot between the % ee values determined by HPLC and NMR.

charged octahedral Al complex, CASA-Na. Baseline peak separation of hydroxyl groups has been achieved at low temperature by simple addition of CASA-Na. We have shown that low temperature measurement is necessary due to the small binding constants between CASA-Na and chiral alcohols and that the hydrophobicity of chiral alcohols enhances the peak resolution. The origin of chiral discrimination of chiral alcohols has been proposed by DFT computation together with ^{1}H NMR and X-ray crystallographic data. Because the CASA provides well resolved and sharp signals of various chiral alcohols including aryl- and alkyl-substituted primary, secondary, and tertiary alcohols, it can be a general method for the determination of the % ee and absolute configuration of alcohols. As we have successfully extended the analyte scope of the CASA, we anticipate that the CASA will be used as a universal chiral solvating agent for amines, carboxylic acids, and alcohols.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 For reviews on chiral analysis by NMR: (a) T. J. Wenzel, *Tetrahedron: Asymmetry*, 2017, **28**, 1212; (b) T. J. Wenzel and C. D. Chisholm, *Chirality*, 2011, **23**, 190; (c) J. Lacour and D. Moraleda, *Chem. Commun.*, 2009, 7073; (d) T. J. Wenzel, *Discrimination of Chiral Compounds Using NMR Spectroscopy*, Wiley-VCH, Weinheim, 2007; (e) J. M. Seco, E. Quiñoá and R. Riguera, *Chem. Rev.*, 2004, **104**, 17; (f) H. Schneider, F. Hacket and V. Rudiger, *Chem. Rev.*, 1998, **98**, 1755; (g) D. Parker, *Chem. Rev.*, 1991, **91**, 1441.
2 For reviews on chiral analysis using optical sensing: (a) L. You, D. Zha and E. V. Anslyn, *Chem. Rev.*, 2015, **115**, 7840; (b) Z. Chen, Q. Wang, X. Wu, Z. Li and Y.-B. Jiang, *Chem. Rev.*, 2015, **44**, 4249; (c) D. Leung, S. O. Kang and E. V. Anslyn, *Chem. Soc. Rev.*, 2012, **41**, 448; (d) E. B. Bauer, *Chem. Soc. Rev.*, 2012, **41**, 3153; (e) G. A. Hembury, V. V. Borovkov and Y. Inoue, *Chem. Rev.*, 2007, **108**, 1.
3 (a) S. M. Han, *Biomed. Chromatogr.*, 1997, **11**, 259; (b) V. Schurig and H.-P. Nowotny, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 939.
4 (a) R. García-Rodríguez, S. Hanf, A. D. Bond and D. S. Wright, *Chem. Commun.*, 2017, **53**, 1225; (b) J. Labuta, J. P. Hill, S. Ishihara, L. Hanykova and K. Ariga, *Acc. Chem. Res.*, 2015, **48**, 521; (c) J. Labuta, S. Ishihara, T. Sikorsky, Z. Futera, A. Shundo, L. Hanykova, J. V. Burda, K. Ariga and J. P. Hill, *Nat. Commun.*, 2013, **4**, 1.
5 For recent examples, see: (a) L.-P. Li and B.-H. Ye, *Inorg. Chem.*, 2017, **56**, 10717; (b) Y. Zhao and T. M. Swager, *J. Am. Chem. Soc.*, 2015, **139**, 3321; (c) F. Freire, E. Quiñoá and R. Riguera, *Chem. Commun.*, 2008, 4147.
6 For recent examples, see: (a) C.-X. Liu, L. Zheng, L. Zhu, H.-P. Xiao, X. Li and J. Jiang, *Org. Biomol. Chem.*, 2017, **15**, 4314; (b) R. Gupta, R. G. Gonnade and A. V. Bedekar, *J. Org. Chem.*, 2016, **81**, 7384; (c) A. Lakshmipriya, S. R. Chaudhari and N. Suryaprakash, *New J. Chem.*, 2016, **40**, 8118; (d) H. Huang, G. Bian, H. Zong, Y. Wang, S. Yang, H. Yue, L. Song and H. Fan, *Org. Lett.*, 2016, **18**, 2524.
7 For recent examples, see: (a) Y. Li, G.-H. Yang, C. Q. He, X. Li, K. N. Houk and J.-P. Cheng, *Org. Lett.*, 2017, **15**, 4314; (b) E. Monteagudo, P. March, A. Alvarez-Larena and A. Virgili, *ChemistrySelect*, 2017, **2**, 7362; (c) G. Bian, H. Fan, H. Huang, S. Yang, H. Zong, L. Song and G. Yang, *Org. Lett.*, 2015, **17**, 1369; (d) G. Bian, H. Fan, S. Yang, H. Yue, H. Huang, H. Zong and L. Song, *J. Org. Chem.*, 2013, **78**, 9137.
8 For recent examples, see: (a) S. Ito, M. Okuno and M. Asami, *Org. Biomol. Chem.*, 2018, **16**, 213; (b) N. Jain, A. N. Khanvilkar, S. Sahoo and A. V. Bedekar, *Tetrahedron*, 2018, **74**, 68; (c) S. K. Mishra and N. Suryaprakash, *Tetrahedron: Asymmetry*, 2017, **28**, 1220; (d) A. Lakshmipriya, G. Sumana and N. Suryaprakash, *Tetrahedron: Asymmetry*, 2017, **28**, 1290; (e) B. E. Dalvano and T. J. Wenzel, *Tetrahedron: Asymmetry*, 2017, **28**, 1061; (f) C. Lv, L. Feng, H. Zhao, G. Wang, P. Stavropoulos and L. Ai, *Org. Biomol. Chem.*, 2017, **15**, 1642; (g) L. Fang, C. Lv, G. Wang, L. Feng, P. Stavropoulos, G. Gao, L. Ai and J. Zhang, *Org. Chem. Front.*, 2016, **3**, 1716; (h) S. Ito, K. Ikeda and M. Asami, *Chem. Lett.*, 2016, **45**, 1379; (i) T. Ema, D. Tanida and T. Sakai, *J. Am. Chem. Soc.*, 2007, **129**, 10591; (j) A. E. Lovely and T. J. Wenzel, *J. Org. Chem.*, 2006, **71**, 9178.
9 L. Yang, T. Wenzel, R. T. Williamson, M. Christensen, W. Schafer and C. J. Welch, *ACS Cent. Sci.*, 2016, **2**, 332.
10 (a) G. Bian, S. Yang, H. Huang, H. Zong, L. Song, H. Fan and X. Sun, *Chem. Sci.*, 2016, **7**, 932; (b) L. S. Moon, M. Pal, Y. Kasetti, P. V. Bharatam and R. S. Jolly, *J. Org. Chem.*, 2010, **75**, 5487; (c) L. S. Moon, R. S. Jolly, Y. Kasetti and P. V. Bharatam, *Chem. Commun.*, 2009, 1067.
11 (a) G. Bian, S. Yang, H. Huang, H. Zong and L. Song, *Sens. Actuators, B*, 2016, **231**, 129; (b) I. Pal, S. R. Chaudhari and N. R. Suryaprakash, *Magn. Reson. Chem.*, 2015, **53**, 142; (c) I. Pal, S. R. Chaudhari and N. Suryaprakash, *New J. Chem.*, 2014, **38**, 4908; (d) C. Wolf, A. M. Cook and J. E. Dannatt, *Tetrahedron: Asymmetry*, 2014, **25**, 163.
12 M.-S. Seo and H. Kim, *J. Am. Chem. Soc.*, 2015, **137**, 14190.
13 CCDC 1816058 contain the supplementary crystallographic data for this paper†.
14 $\Delta\Delta\delta = |\Delta\delta_R - \Delta\delta_S|$, $\Delta\delta_R = |\delta_{R\,\text{with CSA}} - \delta_R|$, and $\Delta\delta_S = |\delta_{S\,\text{with CSA}} - \delta_S|$.
15 K. D. Klika, *Tetrahedron: Asymmetry*, 2009, **20**, 1099.