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Optically Pure Aziridin-2-yl Methanols as Readily Available ^{1}H NMR Sensors for Enantiodiscrimination of α-Racemic Carboxylic Acids Containing Tertiary or Quaternary Stereogenic Centers

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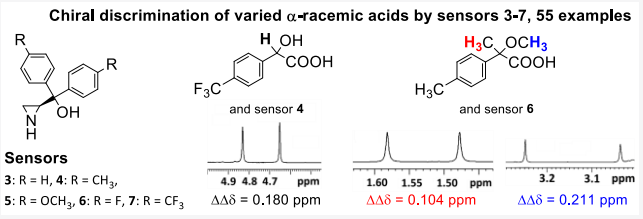
ABSTRACT: Enantiopure aziridin-2-yl methanols **3**−**7** are used as highly effective sensors for enantiodiscrimination of α-racemic carboxylic acids containing tertiary or quaternary stereogenic centers. A linear correlation between theoretical and observed % ee values for CSA-**3** and enantiomerically enriched samples of mandelic acid has been observed, indicating the possible application of these compounds in the ee determination. The free NH and OH groups in **3**−**7** ensure good recognition.



INTRODUCTION

The detection of enantiomeric purity is an important part of synthetic chemistry, pharmacology, biology, food industry, and materials science.[1] Among the methods used to measure the optical purity of chiral compounds, such as HPLC,[2] GC,[3] CD,[4] capillary electrophoresis (CE),[5] UV,[6] IR,[7] mass spectrometry,[8] electrophoresis,[9] or fluorescence spectroscopy,[10] NMR spectroscopy proved to be a fast, readily accessible and easy to use an attractive method to study the enantiomeric purity.[11] So-called chiral solvating agents (CSAs), associating with the racemic sample through noncovalent driving forces such as ion-pairing, hydrogen-bonding, $\pi-\pi$ or dipole−dipole interaction, form diastereoisomeric complexes showing differences in the chemical shifts of some signals. The study of the recognition of chiral carboxylic acids and their derivatives are of interest to many research groups due to the fact that such molecules are basic building blocks of many natural products and drug molecules.[12] In the past decades, various CSAs such as chiral and prochiral amines,[13] "calixarene-like" chiral amine systems[14] and other macrocyclic amines and amides,[15] amino alcohols,[16] salene derivatives,[17] crown or aza-crown ethers,[18] L-proline derivatives,[19] BINOL and their derivatives,[20] chiral shift reagents derived from squaramide and indanol,[21] 1,2-diaminocyclohexane derivatives,[22] and chiral bisthioureas[23] have been reported particularly for mandelic acid, its derivatives, and other α-hydroxy acids. Although variously modified amine systems have been successfully used as CSAs, just one example of an optically active aziridine-derived receptor for the enantiodiscrimination of α-racemic carboxylic acids can be found in the literature. Chiral imines prepared from 1-(2-aminoalkyl)aziridines proved to be effective CSAs for recognition of mandelic acid and its derivatives and *N*-protected amino acid.[24] Considering our results[24] and those described by Tan and Lei,[19e] regarding the use of diphenylprolinol as CSA for enantiodiscrimination of carboxylic acids and based on our experience in the field of the synthesis and catalytic activity in the asymmetric synthesis of chiral aziridines,[25] we decided to prepare a series of chiral aziridin-2-yl methanols to check their action as CSAs toward α-racemic carboxylic acids containing tertiary or quaternary stereogenic centers.

RESULTS AND DISCUSSION

The chiral aziridines **1**−**7** were synthesized in a good yield from L-serine, according to the literature (Figure 1).[26] In order to explore the enantiomeric discrimination ability, the aziridines **1**, **2**, and **3** were subjected to ^{1}H NMR analysis with DL-mandelic acid. The NMR experiments were performed with stoichiometric amounts of *rac*-mandelic acid and CSA (1:1) in $CDCl_3$ at room temperature.

Table 1 shows the values of chemical shift ($\Delta\delta$) on the C$^\alpha$H proton of mandelic acid after the addition of **1**−**3**, as well as nonequivalences signals corresponding to each enantiomer of the acid ($\Delta\Delta\delta$). The obtained results showed that **1** with an alkyl substituent at the C-2 atom of the aziridine ring indicated very poor recognition (Table 1, entry 1). The *N*-Tr derivative **2** was completely inactive, whereas (*S*)-**3** with NH and OH groups gave very good recognition, $\Delta\Delta\delta$ = 0.094 ppm (Table

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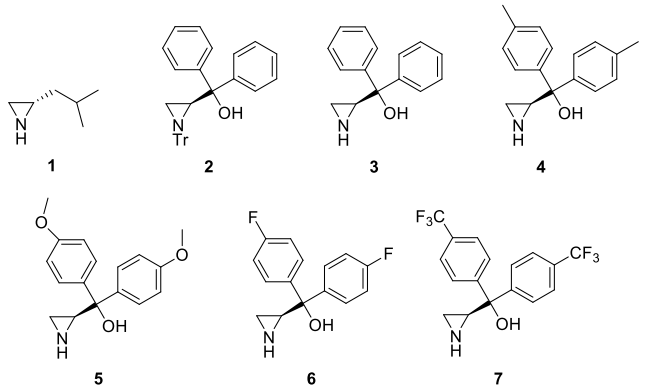

Figure 1. Structures of chiral 2-alkylaziridine **1** and aziridin-2-yl methanols **2**–**7**.

Table 1. Induced Chemical Shift ($\Delta\delta$) and Splitting ($\Delta\Delta\delta$) on the $C^{\alpha}H$ Proton for the Formation of Diastereomeric Complexes between CSA and Racemic Mandelic Acid

entry	chiral receptor	solvent	$\Delta\delta^{a}$ (ppm)	$\Delta\Delta\delta$ (ppm)	$\Delta\Delta\delta$ (Hz)
1	**1**	$CDCl_3$	−0.39	0.006	3.6
2	**2**	$CDCl_3$	−0.05	0.000	0.0
3	**3**	$CDCl_3$	−0.45	0.094	56.4
4	**3**	CD_3OD	−0.27	0.000	0.0
5	**3**	$(CD_3)_2CO$	−0.08	0.004	2.4
6	**3**	C_6D_6	−0.28	0.094	56.4

[a]Averaged between signals from both enantiomers.

1, entries 2 and 3). Considering the above results, it can be assumed that (i) the presence of free NH and OH groups is sufficient to form multiple intermolecular hydrogen bonds between these groups with tested acid, which provide good recognition and that (ii) the upfield change ($\Delta\delta < 0$) in the position of the signals from the acid suggests deprotonation of the carboxylic group additionally.[13c] The above conclusions have been drawn on the basis of previous literature reports. Tan and Lei observed that (*S*)-diphenyl(pyrrolidin-2-yl)-methanol with an unprotected NH group showed more than twice the recognition ability of mandelic acid than its *N*-benzyl derivative ($\Delta\Delta\delta$ = 0.062 ppm for NH and 0.028 ppm for *N*-Bn derivatives, respectively).[19e] We assumed that increasing the steric hindrance at the nitrogen atom should further reduce the possibility of recognition. Having in hands the *N*-Tr derivative, which is an intermediate in the synthesis of aziridinyl alcohols, we decided to check this thesis. Indeed a trityl derivative **2** having great steric hindrance could not form an effective hydrogen bond with mandelic acid, and the recognition effect was not effective. For this reason, we decided to synthesize NH derivatives **3**–**7** for our research. As for the hydroxyl group, Tan and Lei have already shown that diphenylprolinol, i.e., a compound containing the OH group, has the ability of enantiodiscrimination of racemic mandelic acid at the level of $\Delta\Delta\delta$ = 0.062 ppm, whereas literature data prove that (*S*)-2-(diphenylmethyl)pyrrolidine without the OH group has a much lower recognition capacity for this acid ($\Delta\Delta\delta$ = 0.028).[19a] It seems that the presence of the hydroxyl group will increase the possibility of multipoint interactions between aziridinyl alcohols and a carboxylic acid and will promote magnetic anisotropy, thereby improving their chiral recognition ability. We also assume that the formation of multipoint interactions will be favored by nonpolar solvents, while polar solvents will break down the formed agglomerates connected by hydrogen bonds, and thereby reduce recognition. The $\Delta\Delta\delta$ values for diastereomeric complexes between racemic mandelic acid and CSA-**3** in various solvents are summarized in Table 1. The obtained results confirmed that only nonpolar solvents provide good chiral recognition.

To determine the stoichiometry of the forming complex, ^1H NMR titrations were performed by adding incremental amounts of the most effective receptor (*S*)-**3** to the tubes containing a solution of (±)-MA in $CDCl_3$ (Figure 2). Upon

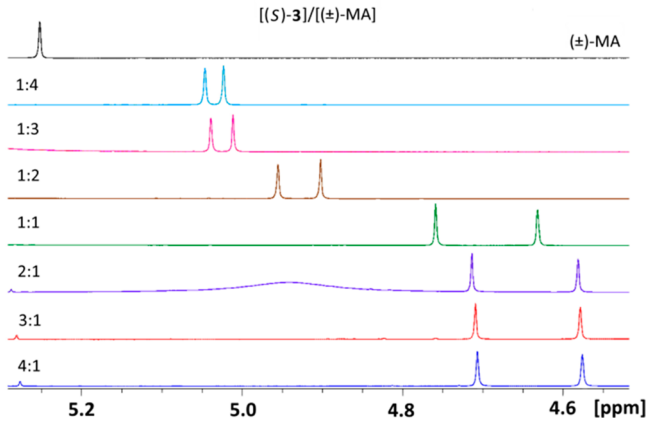

Figure 2. ^1H NMR spectra of the methine proton signal for various molar ratio mixtures of (*S*)-**3** and (±)-MA.

gradual addition of (*S*)-**3**, the ^1H NMR signal of the $C^{\alpha}H$ proton of racemic MA shifted upfield, and the chemical shift difference between the two enantiomers increased gradually, until the addition of stoichiometric quantities of (*S*)-**3** [(*S*)-**3**/(±)-MA = 1:1] to receive the best chiral recognition showing a 0.094 ppm difference. Subsequent addition of (*S*)-**3** only slightly shifts signals upfield but does not increase the chemical shift difference.

Additionally, the stoichiometry was determined according to the Job's method of continuous variation.

Figure 3 shows the Job plots of $\Delta\delta$*X versus the molar fraction X of (*R*)- and (*S*)-MA. A maximum was observed

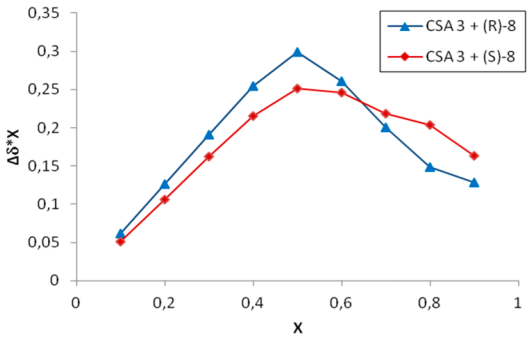

Figure 3. Job plots of (*S*)-**3** with (*R*)- and (*S*)-MA.

when the ratio of (*S*)-**3** to (*R*)- or (*S*)-MA was 1:1 (X = 0.5), which indicates that the (*S*)-**3** and the mandelic acid form a 1:1 complex under these conditions.

After determining the stoichiometry of the complex, we tested the ability of enantiodiscrimination of aziridin-2-yl

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methanols **3**–**7** (Figure 1) for various α-racemic carboxylic acids **8**–**18** (Figure 4).

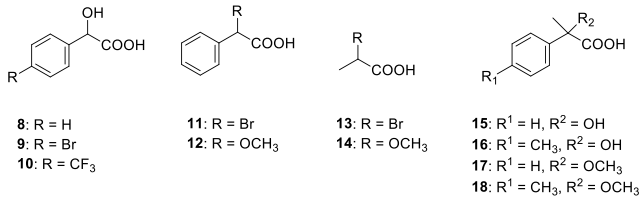

Figure 4. Structures of *rac*-carboxylic acids **8**–**18**.

Carboxylic acids containing tertiary stereogenic centers **8**–**14** were subjected to the first tests, and the results are summarized in Table 2. For easy observation, we have marked the ability to chiral recognition using colors. Green was used for very good values of $\Delta\Delta\delta \geq 0.1$ ppm, orange for good ($0.05 < \Delta\Delta\delta < 0.1$ ppm), yellow for average ($0.02 < \Delta\Delta\delta < 0.05$ ppm), and white for weak ($\Delta\Delta\delta < 0.02$ ppm). Generally, all CSAs **3**–**7** showed a high ability of enantiodiscrimination for racemic mandelic acid **8** and its derivatives **9**–**12** (Table 2). The largest $\Delta\Delta\delta$ values of 0.111–0.180 ppm exhibited aziridine **4** used as the CSA, while the *p*-CF_3 substituted aziridine-alcohol **7** showed the lowest $\Delta\Delta\delta$ values from 0.028 to 0.052 ppm. It should be noted that chiral discriminations were also observed for the OCH_3 signals of (±)-**12**. In the presence of (*S*)-CSAs **3**–**7**, comparable or higher $\Delta\Delta\delta$ values were obtained for protons of the methoxy group compared to $\Delta\Delta\delta$ values of α-H signals of this acid. Aliphatic α-*rac*-bromopropionic acid **13** in the presence of **3**–**7** gave poor results of enantiodiscrimination, both for the methine proton $C^{\alpha}H$ and for the methyl group protons.

Interestingly, (*S*)-CSAs **3**–**7** can effectively discriminate against the enantiomers of α-methoxypropionic acid **14**.

Although the $\Delta\Delta\delta$ values of $C^{\alpha}H$ signals were unsatisfactory, the methoxy, and in particular CH_3 protons, can be well recognized with $\Delta\Delta\delta$ values up to 0.106 ppm. Considering the obtained results, in particular for mandelic acid **8** and its derivatives **9**–**12**, it can be assumed that the recognition of these acids is based on the formation of the hydrogen bond between CSAs and the carboxyl group of mandelic acid, and the chemical shift difference is caused by the different shielding effect of CSAs on carboxylic acid. It would seem that the electron-donating group (**3**) helps the amino group to provide electrons to form a stronger hydrogen bond, thus enhancing the recognition effect. On the contrary, the electron-withdrawing group (**7**) is not conducive to form a hydrogen bond, and the recognition effect becomes poor. However, the lower $\Delta\Delta\delta$ values obtained in the presence of **5** containing the stronger electron-donating OCH_3 group suggest a more complex mechanism of enantiodiscrimination of the tested acids by aziridin-2-yl methanols **3**–**7**. Table 2 also includes literature $\Delta\Delta\delta$ values for most structurally similar (*S*)-diphenyl(pyrrolidin-2-yl) methanol and other amino alcohols. The pyrrolidine derivative showed a much lower enantiodiscriminating ability of the following racemic acids: **8** $\Delta\Delta\delta$ = 0.062 ppm (0.094 ppm for **3**), **10** = 0.076 ppm (0.140 ppm for **3**), **12** = 0.023 for α-H and 0.003 ppm for OCH_3 protons (0.079 and 0.085 ppm, respectively, for sensor **3**), and **13** = 0.006 ppm for α-H and 0.012 for OCH_3 protons (0.012 and 0.012 ppm, respectively, for aziridin-2-yl methanol **3**. The literature data for other amino alcohols indicate their

Table 2. Color-Coded ^{1}H NMR $\Delta\Delta\delta$ Values of Racemic Carboxylic Acids 8–14 in the Presence of (*S*)-CSA 3–7[a]

	CSAs[b]					
Analyte	**3**	**4**	**5**	**6**	**7**	**Other amino alcohols [Ref.]**
8	0.094; (56.4) α-H *0.062; (31.0)*[d]	0.127; (76.2) α-H	0.116; (69.6) α-H	0.108; (64.8) α-H	0.049; (29.4) α-H	0.25 α-H [16a] 0.004-0.092 α-H [16b] 0.058-0.131 α-H [16c] 0.003-0.027 α-H [16d] 0.024-0.005 α-H [16e]
9	0.122; (73.2) α-H	0.149; (89.4) α-H	0.029; (17.4)[c] α-H	0.110; (66) α-H	0.044; (26.4) α-H	
10	0.140; (84.0) α-H *0.076; (38.0)*[d]	0.180; (108) α-H	0.117; (70.2) α-H	0.113; (67.8) α-H	0.028; (16.8) α-H	
11	0.028; (16.8) α-H	0.114; (68.4) α-H	0.092; (55.2) α-H	0.080; (48) α-H	0.052; (31.2) α-H	
12	0.079; (47.3) α-H *0.023; (11.5)*[d] 0.085; (51.0) OCH_3 *0.003; (1.5)*[d]	0.111; (66.6) α-H 0.085; (51.0) OCH_3	0.058; (34.8) α-H 0.056; (33.6) OCH_3	0.077; (46.2) α-H 0.104; (62.4) OCH_3	0.038; (22.8) α-H 0.079; (47.4) OCH_3	0.066-0.281 α-H [16c] 0.04 OCH_3 [16a] 0.045-0.078 OCH_3 [16c]
13	0.012; (7.2) α-H *0.006; (3.0)*[d] 0.012; (7.2) CH_3 *0.014; (7.0)*[d]	0.012; (7.2) α-H 0.015; (9.0) CH_3	0.012; (7.2) α-H 0.011; (6.6) CH_3	0.012; (7.2) α-H 0.011; (6.6) CH_3	0.017; (10.2) α-H 0.016 (9.6) CH_3	
14	0.011; (6.6) α-H 0.024; (14.4) OCH_3 0.023; (13.8) CH_3	0.018; (10.8) α-H 0.040; (24.0) OCH_3 0.083; (49.8) CH_3	0.011; (6.6) α-H 0.044; (26.4) OCH_3 0.058; (34.8) CH_3	0.002; (1.2) α-H 0.040; (24.0) OCH_3 0.082; (49.2) CH_3	0.023; (13.8) α-H 0.020; (12.0) OCH_3 0.106; (63.6) CH_3	

	Excellent $\Delta\Delta\delta \geq 0.1$ ppm		Good $0.05 < \Delta\Delta\delta < 0.1$ ppm		Average $0.02 < \Delta\Delta\delta < 0.05$ ppm		Weak $\Delta\Delta\delta < 0.02$ ppm

[a](±)-Carboxylic acid/(*S*)-CSA = 1:1 and the spectra are recorded on a 600 MHz spectrometer in $CDCl_3$ at 25 °C. [b]$\Delta\Delta\delta$ values [ppm; (Hz)] for α-H or CH_3 or OCH_3 are shown. [c]10% of acetone-d_6 was added due to the crystallization of diastereomeric complexes in $CDCl_3$. [d]Data for (*S*)-diphenyl(pyrrolidin-2-yl)methanol (ref 19e).

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Table 3. Color-Coded ^{1}H NMR $\Delta\Delta\delta$ Values of Racemic Carboxylic Acids 15−18 Containing Quaternary Stereogenic Centers Using Chiral Sensors 3−7[a]

	CSAs[b]				
Analyte	**3**	**4**	**5**	**6**	**7**
15	0.049; (29.4) CH_3	0.043; (25.8) CH_3	0.039; (23.4) CH_3	0.024; (15.6) CH_3	0.0; (0.0) CH_3
16	0.033; (19.8) CH_3	0.026; (15.6) CH_3 0.030; (18.0) CH_3Ar	0.030; (18.0) CH_3	0.017; (10.2) CH_3 0.016; (9.8) CH_3Ar	0.0; (0.0) CH_3 0.010; (6.12) CH_3Ar
17	0.115; (69.0) CH_3 0.246; (147.6) OCH_3	0.013; (7.8) CH_3 0.281; (168.6) OCH_3	0.123; (73.8) CH_3 0.136; (81.6) OCH_3	0.116; (69.6) CH_3 0.193; (115.8) OCH_3	0.087; (52.2) CH_3 0.214; (128.4) OCH_3
18	0.090; (54.0) CH_3 0.212; (127.2) OCH_3 0.020, (12.0) CH_3Ar	0.074; (44.4) CH_3 0.192; (115.2) OCH_3 0.018, (10.8) CH_3Ar	0.120; (72.0) CH_3 0.162; (97.2) OCH_3 0.013, (7.8) CH_3Ar	0.104; (62.4) CH_3 0.211; (126.6) OCH_3	0.122; (73.2) CH_3 0.189; (113.4) OCH_3 0.069, (41.4) CH_3Ar

	Excellent $\Delta\Delta\delta \geq 0.1$ ppm		Average $0.02 < \Delta\Delta\delta < 0.05$ ppm		Weak $\Delta\Delta\delta < 0.02$ ppm

[a](±)-Carboxylic acid/(*S*)-CSA = 1:1 and the spectra are recorded on a 600 MHz spectrometer in $CDCl_3$ at 25 °C. [b]$\Delta\Delta\delta$ values [ppm; (Hz)] for CH_3 or OCH_3 are shown.

significantly lower recognition than aziridin-2-yl methanols **3**−**7** (Table 2, last column). Only the amino alcohols of Pericàs[16a] and Fu[16c] provided better recognition of (±)-**8** and (±)-**12**, respectively.

In the second part of the research, we decided to test the ability of chiral aziridin-2-yl methanols **3**−**7** as CSAs for enantiomeric discriminating for *α-rac*-carboxylic acids containing quaternary stereogenic centers (Figure 4, **15**−**18**). On the basis of the available databases, we can conclude that such studies for racemic *α*-tetrasubstituted acids have not yet been realized. For *α*-CH_3- and *α*-OH-substituted carboxylic acid **15** and **16**, better $\Delta\Delta\delta$ values for methyl protons were obtained in the presence of chiral sensors **3**−**5** containing electron-donating groups in the position *para* of the aromatic ring (∼0.04 ppm for **15** and ∼0.03 ppm for **16**) (Table 3), while the (*S*)-CSAs **6**−**7** with electron-withdrawing groups were practically ineffective. The *α*-Me- and *α*-OCH_3-substituted acid **17** and **18** showed the biggest $\Delta\Delta\delta$ values in the presence of all tested CSAs. In particular, high chiral discrimination was observed for the OCH_3 signals of (±)-**17** and (±)-**18**, $\Delta\Delta\delta$ = 0.281 ppm for (±)-**17** and chiralsensor (*S*)-**4**, or $\Delta\Delta\delta$ = 0.212 ppm for (±)-**18** and (*S*)-**3**. It is noteworthy that enantiodiscrimination was observed in several cases for the *para*-CH_3 substituent in the aromatic ring of acids **16** and **18**.

Finally, we demonstrated the practicality of aziridin-2-yl methanols **3**−**7** as a CSAs for the determination of enantiomeric excess (% ee) of chiral carboxylic acids. Samples containing different ee's of mandelic acid (**8**) were prepared, and their ^{1}H NMR spectra in the presence of (*S*)-**3** were measured (Figure 5). The excellent linear relationship (R = 0.9999) between the gravimetry-determined values and those NMR-determined % ee values was observed (Figure 6).

Moreover, an experiment with **3** and an enantiomerically enriched sample of 2-methoxy-2-phenylacetic acid (**12**) showed that aziridin-2-yl methanols **3**−**7** allow identifying individual enantiomers of carboxylic acids containing tertiary or quaternary stereogenic centers and determining their ratio based on the proton signals from CH_3 or OCH_3 groups (Supporting Information, Figure S80a,b).

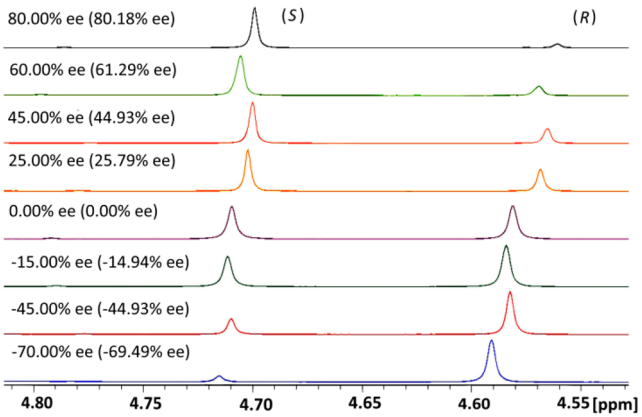

Figure 5. Selected regions of the ^{1}H NMR spectra of nonracemic 8 samples (varied ee values) with (*S*)-CSA **3** in $CDCl_3$.

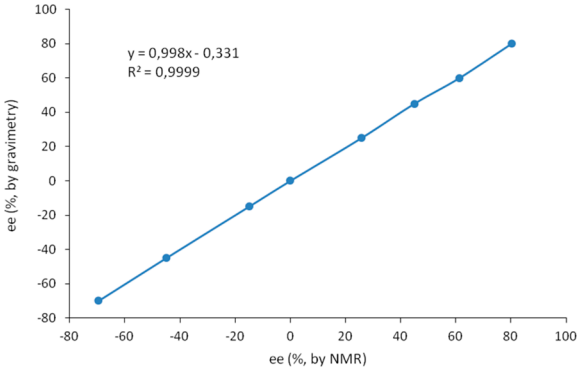

Figure 6. Linear relationship between measured ee values versus the gravimetrically determined ee values.

CONCLUSION

In conclusion, easy to synthesize enantiopure aziridin-2-yl methanols, **3**−**7**, were proven to be effective CSAs for the easy enantiodiscrimination of *α*-racemic carboxylic acids containing tertiary stereogenic centers. A linear correlation observed between theoretical and observed % ee values indicates the possible application of these compounds for analysis of enantiomerically enriched samples. All performed experiments showed that the unsubstituted NH and OH groups in CSAs **3**−**7** are sufficient for good recognition of *α*-chiral acids. Noteworthy, aziridinyl alcohols **3**−**7** are also very effective sensors for some carboxylic acids containing quaternary stereogenic centers.

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EXPERIMENTAL SECTION

Commercially available chemicals used in this work were purchased from Sigma-Aldrich and were used as supplied, without additional purification. NMR spectra were recorded in $CDCl_3$ on a Bruker Avance III (600 MHz for ^1H NMR, 150 MHz for ^{13}C NMR); coupling constants are reported in hertz (Hz). The rotations were measured using an Anton Paar MCP 500 polarimeter. Melting points are uncorrected. Chromatographic purification of compounds was achieved with 230−400 mesh size silica gel. The progress of reactions was monitored by silica gel thin-layer chromatography plates (Merck TLC Silicagel 60 F_{254}).

Materials. Racemic carboxylic acids used in this protocol, **8**−**11** and **13**, were purchased from Sigma-Aldrich. Other carboxylic acids, *rac*-**12**, (*S*)-**12**, *rac*-**14**−**18**, and aziridines **1**−**7**, were synthesized by reported procedures.

Synthesis of (S)-2-Isobutylaziridine (1). The 2-alkylaziridine was synthesized according to a literature procedure[26a] using L-leucine. The product was purified by distillation affording the desired aziridine **1** as a colorless oil: 1.15 g, 45% yield; bp = 128 °C, $[\alpha]_D^{20}$ −17.1 (*c* 5, ethanol); lit.[26b] $[\alpha]_D^{20}$ −16.8 (*c* 5.4, ethanol); ^1H NMR ($CDCl_3$, 600 MHz) δ 1.81−1.87 (m, 1H, C*H*N), 1.60−1.71 (m, 2H, C*H*, C*H*N), 1.22 (d, 1H, *J* = 3.6, C*H*N), 1.07−1.13 (m, 2H, CH_2), 0.85 (d, 6H, *J* = 6.7, CH_3), 0.52 (s, 1H, NH).

^1H NMR spectral data matched that reported by Effenberger.[26b]

General Procedure for Aziridine-2-carbinols 2−7. *N*-Tritylmethylesters of L-serine as a starting material from which the compounds **2**−**7** could be prepared, by a convenient multigram "one-pot procedure", were obtained using methansulfonyl chloride and triethylamine.[26c] The obtained aziridine ester was next converted into the corresponding aziridine carbinols by reaction with Grignard reagents[26c,d] (CSA **2**) followed by detritylation with sulfuric acid in MeOH/THF (CSAs **3**−**7**).[26c]

(S)-Diphenyl(1-tritylaziridin-2-yl)methanol (2): white solid, 1.5 g, 67% yield; mp = 131.6−132.5 °C, lit.[26d] mp = 133.5−134.5 °C; $[\alpha]_D^{20}$ −80.5 (*c* 1, $CHCl_3$); lit.[26d] $[\alpha]_D^{20}$ −78.8 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 7.45 (d, 2H, *J* = 7.3 H_{ar}) 7.30−7.37 (m, 8H, H_{ar}), 7.12−7.25 (m, 15H, H_{ar}), 4.47 (s, 1H, OH), 2.39 (dd, 1H, *J* = 6.3, 3.2 C*H*N), 2.12 (d, 1H, *J* = 3.2 C*H*N), 1.36 (d, 1H, *J* = 6.3 C*H*N).

^1H NMR spectral data matched that reported by Wessjohann.[26e]

(S)-Aziridin-2-yl(diphenyl)methanol (3): white solid, 1.25 g, 71% yield; mp = 154.5−156.2 °C, lit.[26f] mp = 155−157 °C; $[\alpha]_D^{20}$ −23.3 (*c* 1, $CHCl_3$); lit.[26f] $[\alpha]_D^{20}$ −22.6 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 7.47 (d, 2H, *J* = 7.4 H_{ar}), 7.44 (d, 2H, *J* = 7.4, H_{ar}), 7.30−7.36 (m, 4H, H_{ar}), 7.26 (t, 2H, *J* = 7.9, H_{ar}), 2.94 (dd, 1H, *J* = 6.1, 3.6 C*H*N), 1.89 (d, 1H, *J* = 6.1 C*H*N), 1.73 (d, 1H, *J* = 3.6, C*H*N).

^1H NMR spectral data matched that reported by Xichun.[26f]

(S)-Aziridin-2-yldi-p-tolylmethanol (4): white solid, 0.76 g, 65% yield; mp = 134.3−136.1 °C; $[\alpha]_D^{20}$ −20.1 (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$, 600 MHz) δ 7.34 (d, 2H, *J* = 8.2, H_{ar}), 7.31 (d, 2H, *J* = 8.2, H_{ar}), 7.16 (dd, 4H, *J* = 7.8, 4.9, H_{ar}), 2.89−2.95 (m, 1H, C*H*N), 2.36 (s, 6H, 2xCH_3), 1.89 (d, 1H, *J* = 6.0, C*H*N), 1.77 (d, 1H, *J* = 3.6, C*H*N). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 144.5, 142.6, 136.8, 136.7, 128.9, 128.8, 126.5, 126.3 (C_{ar}), 74.2 (*C*OH), 37.2 (*C*HN), 22.1 (CH_3), 21.1 (CH_3), 21.0 (*C*HN). Anal. Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.73; H, 7.69; N, 5.74.

(S)-Aziridin-2-yl(bis(4-methoxyphenyl))methanol (5): colorless oil, 0.55 g, 78% yield; $[\alpha]_D^{20}$ +66.1 (*c* 1, THF); Lit.[26g] $[\alpha]_D^{20}$ +67.0 (*c* 9, THF). ^1H NMR ($CDCl_3$, 600 MHz) δ 7.37 (d, 2H, *J* = 8.6, H_{ar}), 7.33 (d, 2H, *J* = 8.6, H_{ar}), 6.85 (dd, 4H, *J* = 8.6, 4.1, H_{ar}), 3.80 (s, 6H, 2xOCH_3), 2.86 (dd, 1H, *J* = 5.9, 3.3 C*H*N), 1.87 (d, 1H, *J* = 5.9 C*H*N), 1.75 (d, 1H, *J* = 3.3, C*H*N).

^1H NMR spectral data matched that reported by Xichun.[26f]

(S)-Aziridin-2-ylbis(4-fluorophenyl)methanol (6): white solid, 0.87 g, 70% yield; mp = 94.7−96.4 °C; $[\alpha]_D^{20}$ −19.4 (*c* 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$, 600 MHz) δ 1.75 (d, 1H, *J* = 3.6 C*H*N), 1.91 (d, 1H, *J* = 6.1 C*H*N), 2.89 (dd, 1H, *J* = 6,1, 3.6, C*H*N), 7.01−7.08 (m, 4H, H_{ar}), 7.38−7.46 (m, 4H, H_{ar}). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 22.1 (CHN), 37.0 (CHN), 73.7 (COH), 114.9 (d, *J* = 9.2, C_{ar}), 115.1 (d, *J* = 8.8, C_{ar}), 128.1 (d, *J* = 11.2, C_{ar}), 128.3 (d, *J* = 8.0, C_{ar}), 140.8 (d, *J* = 3.1, C_{ar}), 143.0 (d, *J* = 3.1, C_{ar}), 161.2, 1628 (C_{ar}). Anal. Calcd for $C_{17}H_{19}NO$: C, 68.96; H, 5.02; N, 5.36. Found: C, 68.88; H, 5.16; N, 5.58.

(S)-Aziridin-2-ylbis(4-(trifluoromethyl)phenyl)methanol (7): white solid, 0.75 g, 85% yield; mp = 151.0−152.3 °C, lit.[26c] mp = 151−153 °C; $[\alpha]_D^{20}$ −14.2 (*c* 0.5, $CHCl_3$); lit.[26c] $[\alpha]_D^{20}$ −14.7 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 7.57−7.62 (m, 8H, H_{ar}), 3.00 (dd, 1H, *J* = 6.1, 3.5, C*H*N), 1.96 (d, 1H, *J* = 6.1, C*H*N), 1.73 (d, 1H, *J* = 3.5, C*H*N).

^1H NMR spectral data matched that reported by Bonini.[26c]

Synthesis of (±)-2-Methoxy-2-phenylacetic Acid (12). 2-Methoxy-2-phenylacetic acid was synthesized according to a literature procedure using 2-bromo-2-phenylacetic acid and sodium methoxide in methanol:[27a] white solid, 1.28 g, 98% yield; mp = 69.6−71.0 °C; lit.[27a] mp = 69−70 °C; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.45−7.49 (m, 2H, H_{ar}), 7.37−7.44 (m, 3H, H_{ar}), 4.82 (s, 1H, C*H*), 3.45 (s, 3H, CH_3).

^1H NMR spectral data matched that reported by Brown.[27a]

Synthesis of (S)-(+)-2-Methoxy-2-phenylacetic Acid (S)-12. (*S*)-2-Methoxy-2-phenylacetic acid was synthesized according to a literature procedure using (*S*)-(+)-mandelic acid and dimethyl sulfate:[27b] colorless oil, 0.57 g, 46% yield; $[\alpha]_D^{20}$ +21.2 (*c* 1, ethanol); lit.[27b] $[\alpha]_D^{20}$ +20.8 (*c* 2.12, ethanol).

Synthesis of (±)-2-Methoxypropionic Acid (14). 2-Methoxypropionic acid was synthesized according to a literature procedure using 2-bromopropionic acid and sodium methoxide in methanol:[27c] colorless oil, 0.65 g, 0.90% yield; ^1H NMR ($CDCl_3$, 600 MHz) δ 3.95 (q, 1H, *J* = 6.9 C*H*), 3.47 (s, 3H, OCH_3), 1.49 (d, 3H, *J* = 6.9, CH_3).

^1H NMR spectral data matched that reported by Zakarian.[27c]

General Procedure for (±)-Carboxylic Acids 15−18. 2-Hydroxymethylesters as starting materials from which the compounds **15**−**18** could be prepared were obtained using methyl pyruvate and appropriate Grignard reagents. Obtained hydroxyesters were hydrolyzed (**15**−**16**) or converted into the corresponding 2-methoxymethylesters by reaction with iodomethane in the presence of sodium hydride followed by hydrolysis (**17**−**18**).[27d]

2-Hydroxy-2-phenylpropionic Acid (15): white solid, mp = 113.5−114.8 °C, lit.[27e] mp = 114−116 °C; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.58 (d, 2H, *J* = 7.5, H_{ar}), 7.37 (t, 2H, *J* = 7.3, H_{ar}), 7.32−7.35 (m, 1H, H_{ar}), 1.83 (s, 1H, CH_3).

^1H NMR spectral data matched that reported by Igglessi-Markopoulou.[27e]

2-Hydroxy-2-(p-tolyl)propionic Acid (16): white solid; mp = 100.0−101.8 °C, lit.[27f] mp = 100−103 °C; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.47 (d, 2H, *J* = 8.1, H_{ar}), 7.18 (d, 2H, *J* = 8.1, H_{ar}), 2.35 (s, 3H, CH_3), 1.82 (s, 3H, CH_3).

^1H NMR spectral data matched that reported by Aramini.[27g]

2-Methoxy-2-phenylpropionic Acid (17): white solid; mp = 35.1−36.9 °C, lit.[27h] mp = 35.5−37.5 °C; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.46 (d, 2H, *J* = 7.4, H_{ar}), 7.39 (t, 2H, *J* = 7.2, H_{ar}), 7.34 (t, 1H, *J* = 7.2, H_{ar}), 3.28 (s, 3H, OCH_3), 1.86 (s, 3H, CH_3).

^1H NMR spectral data matched that reported by Kusumi.[27i]

2-Methoxy-2-(p-tolyl)propionic Acid (18): white solid; mp = 42.8−45.2 °C; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.34 (d, 2H, *J* = 8.0, H_{ar}), 7.19 (d, 2H, *J* = 8.0, H_{ar}), 3.25 (s, 3H, OCH_3), 2.35 (s, 3H, CH_3), 1.83 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 175.6 (CO), 138.4, 135.7, 129.7, 126.2, (C_{ar}), 81.2 (C_q), 51.6 (OCH_3), 21.1 (CH_3), 20.5 (CH_3); MS-EI 192.9 $[M - H]^-$. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.98; H, 7.21.

^1H NMR Host−Guest Titration. ^1H NMR titrations were performed by adding incremental amounts of (*S*)-**3** to seven NMR tubes containing a solution of *rac*-**8** (3.5 mg, 0.023 mmol) in $CDCl_3$ (0.5 mL).

Determination of Stoichiometry of the Host−Guest Complex (Job plots). Compound (*S*)-**3**, and (*S*)- and (*R*)-mandelic acid **8** were separately dissolved in $CDCl_3$ with a concentration of 0.046 mmol/mL. These solutions were distributed among nine NMR tubes, with the molar fraction X of **8** in the resulting solutions increasing from 0.1

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to 1.0, and the total concentration of (*S*)-**3** and (*S*)- and (*R*)-**8** was 0.046 mmol/mL. The complexation induced shifts ($\Delta\delta$) were multiplied by X and plotted against X itself to afford a 1:1 (host/guest) complex under these conditions.

*Typical Procedure for Enantiodiscrimination of rac-Carboxylic Acids **8**–**18** Using Chiral Sensors **1**–**7**.* Sensors **1**–**7** (0.023 mmol) and carboxylic acid (0.023 mmol) were mixed in 0.5 mL $CDCl_3$. Then ^{1}H NMR was recorded on a 600 MHz spectra at room temperature.

*Determination of Enantiomeric Purity of Mandelic Acid **8**.* To evaluate the accuracy of our determining method, we prepared eight samples containing mandelic acid with 0, 25, 45, 60, and 80% ee (in favor of the *S* enantiomer) and 15, 45, 70% ee (in favor of the *R* enantiomer) and determined their enantiomeric purities in the presence of host **3** by using ^{1}H NMR method. All samples were prepared by adding 1 equiv of host **3** in the solutions of mandelic acid (0.023 mmol in 0.5 mL of $CDCl_3$). The results, which were calculated based on the integrations of the NMR signals, are shown in Figure 5, and the linear correlation between the theoretical and observed% ee values is shown in Figure 6.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01564.

Experimental procedures, copies of NMR spectra, and recorded Job plots data (PDF)

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Notes

The authors declare no competing financial interest.

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