Optically Pure Aziridin-2-yl Methanols as Readily Available $^1$H NMR Sensors for Enantiodiscrimination of $\alpha$-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 $\alpha$-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 attractive method to study the enantiomeric purity.$^1$ 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 diastereomeric 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,$^{18}$ $\alpha$-proline derivatives,$^{19}$ BINOL and their derivatives,$^{20}$ chiral shift reagents derived from squaramide and indanone,$^{21}$ 1,2-diaminocyclohexane derivatives,$^{22}$ and chiral bisthioureas$^{23}$ have been reported particularly for mandelic acid, its derivatives, and other $\alpha$-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 $\alpha$-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 $\alpha$-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$^\text{H}$ 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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enantiodiscrimination of racemic mandelic acid at the level of compound containing the OH group, has the ability of Tan and Lei have already shown that diphenylprolinol, i.e., a twice the recognition ability of mandelic acid than its methanol with an unprotected NH group showed more than Tan and Lei observed that (have been drawn on the basis of previous literature reports.

We also assume that the formation of multipoint magnetic anisotropy, thereby improving their chiral recognition. The formation of multipoint interactions between these groups with tested acid, which 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 CDCl₃ (Figure 2). Upon gradual addition of (S)-3, the 1H NMR signal of the C'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 ΔδX versus the molar fraction X of (R)- and (S)-MA. A maximum was observed 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 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 ΔΔδ 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.

| entry | chiral receptor | solvent | Δδ* (ppm) | ΔΔδ (ppm) | ΔΔΔδ (Hz) |
|-------|----------------|---------|-----------|-----------|-----------|
| 1     | 1              | CDCl₃   | -0.39     | 0.006     | 3.6       |
| 2     | 2              | CDCl₃   | -0.05     | 0.000     | 0.0       |
| 3     | 3              | CDCl₃   | -0.45     | 0.094     | 56.4      |
| 4     | 3              | CD₃OD   | -0.27     | 0.000     | 0.0       |
| 5     | 3              | (CD₃)₂CO| -0.08     | 0.004     | 2.4       |
| 6     | 3              | (CD₃)₂CO| -0.28     | 0.094     | 56.4      |

*Averaged between signals from both enantiomers.

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

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

Figure 3. Job plots of (S)-3 with (R)- and (S)-MA.
methanols 3–7 (Figure 1) for various \( \alpha \)-racemic carboxylic acids 8–18 (Figure 4).

![Figure 4. Structures of rac-carboxylic acids 8–18.](image)

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 poor (\( \Delta \Delta \delta < 0.02 \) 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 (\( \alpha \))-H and 0.012 ppm (0.012 and 0.012 ppm, respectively, for sensor 3), and 13 = 0.006 ppm for \( \alpha \)-H and 0.012 for OCH\(_3\) protons (0.012 and 0.012 ppm, respectively, for aziridin-2-yl methanol 9. The literature data for other amino alcohols indicate their results of enantiodiscrimination, both for the methine proton \( \mathrm{C}^\beta \)H and for the methyl group protons.

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

Although the \( \Delta \Delta \delta \) values of \( \mathrm{C}^\beta \)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 carbonyl 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 enantiomeric discrimination 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(pyrrrolidin-2-yl) methanol and other amino alcohols. The pyrrolidine derivative showed a much lower enantiomeric discrimination 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 \( \alpha \)-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 \( \alpha \)-H and 0.012 for OCH\(_3\) protons (0.012 and 0.012 ppm, respectively, for aziridin-2-yl methanol 9. The literature data for other amino alcohols indicate their

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**Table 2. Color-Coded \(^1\)H NMR \( \Delta \Delta \delta \) Values of Racemic Carboxylic Acids 8–18 in the Presence of (S)-CSA 3–7**

| Analyte | CSAs\(^3\) | \( \Delta \Delta \delta \) Values | Other amino alcohols [Ref.] |
|---------|-------------|---------------------------------|-----------------------------|
| 8       | 0.094; (56.4) \( \alpha \)-H; 0.062; (31.0)\(^3\) | 0.112; (76.2) \( \alpha \)-H; 0.116; (69.6) \( \alpha \)-H; 0.108; (68.4) \( \alpha \)-H; 0.049; (29.4) \( \alpha \)-H | \( \alpha \)-H [16a]; 0.004; (0.092) \( \alpha \)-H [16b]; 0.058; (0.131) \( \alpha \)-H [16c]; 0.003; (0.027) \( \alpha \)-H [16d]; 0.024; (0.056) \( \alpha \)-H [16c] |
| 9       | 0.122; (73.2) \( \alpha \)-H; 0.149; (89.4) \( \alpha \)-H; 0.029; (17.4) \( \alpha \)-H; 0.110; (66) \( \alpha \)-H; 0.044; (26.4) \( \alpha \)-H | | |
| 10      | 0.140; (84.0) \( \alpha \)-H; 0.076; (38.0)\(^3\) | 0.117; (70.2) \( \alpha \)-H; 0.113; (67.8) \( \alpha \)-H; 0.028; (16.8) \( \alpha \)-H | |
| 11      | 0.028; (16.8) \( \alpha \)-H; 0.114; (68.4) \( \alpha \)-H; 0.092; (55.2) \( \alpha \)-H; 0.080; (48) \( \alpha \)-H; 0.052; (31.2) \( \alpha \)-H | | |
| 12      | 0.079; (47.3) \( \alpha \)-H; 0.023; (11.5)\(^3\); 0.085; (51.0) OCH\(_3\); 0.003; (1.5)\(^3\) | 0.111; (66.6) \( \alpha \)-H; 0.085; (51.0) OCH\(_3\); 0.058; (34.8) \( \alpha \)-H; 0.056; (33.6) OCH\(_3\); 0.077; (46.2) \( \alpha \)-H; 0.104; (62.4) OCH\(_3\); 0.079; (47.4) OCH\(_3\); 0.066; (0.28) \( \alpha \)-H [16c]; 0.04 OCH\(_3\) [16a]; 0.045; 0.078 OCH\(_3\) [16c] | |
| 13      | 0.012; (7.2) \( \alpha \)-H; 0.006; (3.0)\(^3\); 0.012; (7.2) CH\(_3\); 0.014; (7)\(^3\) | 0.012; (7.2) \( \alpha \)-H; 0.015; (9) CH\(_3\); 0.012; (7.2) \( \alpha \)-H; 0.011; (6.6) CH\(_3\); 0.012; (7.2) \( \alpha \)-H; 0.011; (6.6) CH\(_3\); 0.017; (10.2) \( \alpha \)-H; 0.016 (9.6) CH\(_3\) | |
| 14      | 0.011; (6.6) \( \alpha \)-H; 0.024; (14.4) OCH\(_3\); 0.023; (13.8) CH\(_3\) | 0.018; (10.8) \( \alpha \)-H; 0.040; (24.0) OCH\(_3\); 0.083; (49.8) CH\(_3\); 0.011; (6.6) \( \alpha \)-H; 0.046; (26.4) OCH\(_3\); 0.058; (34.8) CH\(_3\); 0.002; (12.1) \( \alpha \)-H; 0.040; (24.0) OCH\(_3\); 0.082; (49.2) CH\(_3\); 0.023; (13.8) \( \alpha \)-H; 0.020; (12.0) OCH\(_3\); 0.106; (63.6) CH\(_3\) | |

\(^4\)(\(\pm\))-Carboxylic acid/(S)-CSA = 1:1 and the spectra are recorded on a 600 MHz spectrometer in CDCl\(_3\) at 25 °C. \(^5\)\(\Delta \Delta \delta \) values [ppm; (Hz)] for \( \alpha \)-H or CH\(_3\) or OCH\(_3\) are shown. \(^6\)10% of acetone-\(d_6\) was added due to the crystallization of diastereomeric complexes in CDCl\(_3\). \(^7\)Data for (S)-diphenyl(pyrrrolidin-2-yl)methanol (ref 19a).
studies for racemic ing quaternary stereogenic centers (Figure 4, realized. For enantiomeric discriminating for 3 ability of chiral aziridin-2-yl methanols 0.281 ppm for (±)
(Supporting Information, Figure S80a,b).

Using Chiral Sensors 3 observed for the OCH3 signals of (±) 17 acid 16 and 17 showed that the unsubstituted NH and OH groups in CSAs 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-OCH3-substituted acid 17 and 18 showed the biggest ΔΔδ values in the presence of all tested CSAs. In particular, high chiral discrimination was observed for the OCH3 signals of (±)-17 and (±)-18, ΔΔδ = 0.281 ppm for (±)-17 and chiral sensor (S)-4, or ΔΔδ = 0.212 ppm for (±)-18 and (S)-3. It is noteworthy that enantiodiscrimination was observed in several cases for the para-CH3 substituent in the aromatic ring of acids 16 and 18.

Finally, we demonstrated the practicality of aziridin-2-yl methanols 3−7 as 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 1H 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 CH3 or OCH3 groups (Supporting Information, Figure S80a,b).

## 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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### Table 3. Color-Coded 1H NMR ΔΔδ Values of Racemic Carboxylic Acids 15−18 Containing Quaternary Stereogenic Centers Using Chiral Sensors 3−7a

| Analyte | CSAs2 | 3 | 4 | 5 | 6 | 7 |
|---------|-------|---|---|---|---|---|
| 15      | 0.049; (29.4) CH3 | 0.043; (25.8) CH3 | 0.039; (23.4) CH3 | 0.024; (15.6) CH3 | 0.00; (0.0) CH3 |
| 16      | 0.033; (19.8) CH3 | 0.026; (15.6) CH3 | 0.030; (18.0) CHAr | 0.017; (10.2) CH3 | 0.00; (0.0) CH3 |
| 17      | 0.115; (69.0) CH3 | 0.246; (147.6) OCH3 | 0.013; (7.8) CH3 | 0.123; (73.8) CH3 | 0.116; (69.6) CH3 |
| 18      | 0.090; (54.0) CH3 | 0.212; (127.2) OCH3 | 0.020; (12.0) CHAr | 0.074; (44.4) CH3 | 0.120; (72.0) CH3 |

**a**(±)-Carboxylic acid/(S)-CSA = 1:1 and the spectra are recorded on a 600 MHz spectrometer in CDCl3 at 25 °C. **b** ΔΔδ values [ppm; (Hz)] for CH3 or OCH3 are shown.

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**Figure 5.** Selected regions of the 1H NMR spectra of nonracemic 8 samples (varied ee values) with (S)-CSA 3 in CDCl3.

**Figure 6.** Linear relationship between measured ee values versus the gravimetrically determined ee values.
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 CDCl₃ on a Bruker Avance III (600 MHz for ¹H NMR, 150 MHz for ¹³C NMR); coupling constants are reported in hertz (Hz). The rotations were measured using an Antos 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 F₂₅₄). 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 procedure²⁶ using l-teucine. The product was purified by distillation affording the desired aziridine 1 as a colorless oil: 1.15 g, 45% yield; bp = 128 °C (literature: 118 °C) [1]; lit.²⁶c,d [δH] = 1.18 (s, 6H, 2xC₃H₃), 2.01 (d, 1H, 1H, J = 6.9, CH₃), 4.81 (s, 1H, CH₂) [δC] = 15.6 (6H, 2xC₃H₃), 32.8 (CH₃), 49.9 (CH₂), 207.0 (CO). ¹H NMR (CDCl₃, 600 MHz) δ 1.09 (s, 6H, 2xC₃H₃), 2.03 (d, 1H, 1H, J = 5.9, CH₃), 4.96 (s, 1H, CH₂). ¹³C NMR (CDCl₃, 150 MHz) δ 15.6 (6H, 2xC₃H₃), 30.0 (CH₃), 49.7 (CH₂), 207.0 (CO).

H NMR spectral data matched that reported by Wessjohann.²⁶e

Synthesis of (S)-2-Methoxy-2-phenylacetic Acid (12). (S)-Methoxy-2-phenylacetic acid was synthesized according to a literature procedure using (S)-(−)-mandelic acid and dimethyl sulfate:²⁶f colorless oil, 0.65 g, 70% yield; mp = 69–70 °C; ¹H NMR (CDCl₃, 600 MHz) δ 7.45–7.49 (m, 9H, H₃), 7.37–7.44 (m, 3H, H₃), 4.82 (s, 1H, CH₂), 3.45 (s, 3H, CH₃).

H NMR spectral data matched that reported by Brown.²⁷a

Synthesis of (S)-2-Methoxy-2-phenylacetic Acid (12). (S)-2-Methoxy-2-phenylacetic acid was synthesized according to a literature procedure using (S)-(−)-mandelic acid and dimethyl sulfate:²⁶f colorless oil, 0.65 g, 90% yield; ¹H NMR (CDCl₃, 600 MHz) δ 3.95 (q, 1H, J = 6.9 CH₂), 3.47 (s, 3H, OCH₃), 1.49 (d, 3H, J = 6.9 CH₃).

H NMR spectral data matched that reported by Zakarian.²⁷e

General Procedure for (S)-Carybic Acids 15–18. 2-Hydroxymethyl esters as starting materials from which the compounds 15–18 could be prepared were obtained using methyl pyruvate and appropriate Grignard reagents. Obtained hydroxymethyles were hydrolyzed (15–16) or converted into the corresponding carybic carbinols by reaction with Grignard reagents²⁶d (CS₂) 2 followed by detritylation with sulfuric acid in MeOH/THF (CS₂S 3–7).²⁶e

(S)-Aziridin-2-yl(di-p-tolyl)methanol (2): white solid, 1.28 g, 98% yield; mp = 69–70 °C; ¹H NMR (CDCl₃, 600 MHz) δ 7.45 (d, 2H, J = 7.3 H₃), 7.30–7.37 (m, 8H, H₃), 7.12–7.25 (m, 15H, H₃), 4.47 (s, 1H, OH), 2.39 (dd, 1H, J = 6.3, 1H), 2.12 (d, 1H, J = 6.3 CH₃), 1.36 (d, 1H, J = 6.3 CH₃).

H NMR spectral data matched that reported by Wessjohann.²⁶d

(S)-Aziridin-2-yl(di-p-tolyl)methanol (2): white solid, 1.28 g, 98% yield; mp = 69–70 °C; ¹H NMR (CDCl₃, 600 MHz) δ 7.45 (d, 2H, J = 7.3 H₃), 7.30–7.37 (m, 8H, H₃), 7.12–7.25 (m, 15H, H₃), 4.47 (s, 1H, OH), 2.39 (dd, 1H, J = 6.3, 1H), 2.12 (d, 1H, J = 6.3 CH₃), 1.36 (d, 1H, J = 6.3 CH₃).

H NMR spectral data matched that reported by Wessjohann.²⁶d

(S)-2-Methoxy-2-phenylacetic Acid (12): white solid, mp = 113.5–114.8 °C; lit.²⁷c mp = 114–116 °C; ¹H NMR (CDCl₃, 600 MHz) δ 7.58 (d, 2H, J = 7.5, H₃), 7.37 (t, 2H, J = 7.3, H₃), 7.32–7.35 (m, 1H, H₃), 1.83 (s, 1H, CH₂).

H NMR spectral data matched that reported by Iglesissi-Markopoulou.²⁷b

2-Hydroxy-(p-tolyl)propionic Acid (16): white solid; mp = 100–101.8 °C; lit.²⁷c mp = 100–103 °C; ¹H NMR (CDCl₃, 600 MHz) δ 7.47 (d, 2H, J = 8.1, H₃), 7.18 (d, 2H, J = 8.1, H₃), 2.35 (s, 3H, CH₃), 1.82 (s, 3H, CH₃), 1.68 (s, 3H, CH₃).

H NMR spectral data matched that reported by Aramini.²⁷e

2-Methoxy-2-phenylpropionic Acid (17): white solid; mp = 35.1–36.9 °C; lit.²⁷c mp = 35.5–37.5 °C; ¹H NMR (CDCl₃, 600 MHz) δ 7.46 (d, 2H, J = 7.4, H₃), 7.39 (t, 2H, J = 7.2, H₃), 7.34 (t, 1H, J = 7.2, H₃), 3.28 (s, 3H, OCH₃), 1.86 (s, 3H, CH₃).

H NMR spectral data matched that reported by Kasumi.²⁷d

2-Methoxy-2-phenylpropionic Acid (17): white solid; mp = 35.1–36.9 °C; lit.²⁷c mp = 35.5–37.5 °C; ¹H NMR (CDCl₃, 600 MHz) δ 7.46 (d, 2H, J = 7.4, H₃), 7.39 (t, 2H, J = 7.2, H₃), 7.34 (t, 1H, J = 7.2, H₃), 3.28 (s, 3H, OCH₃), 1.86 (s, 3H, CH₃).

H NMR spectral data matched that reported by Kasumi.²⁷d

2-Methoxy-2-phenylpropionic Acid (17): white solid; mp = 35.1–36.9 °C; lit.²⁷c mp = 35.5–37.5 °C; ¹H NMR (CDCl₃, 600 MHz) δ 7.46 (d, 2H, J = 7.4, H₃), 7.39 (t, 2H, J = 7.2, H₃), 7.34 (t, 1H, J = 7.2, H₃), 3.28 (s, 3H, OCH₃), 1.86 (s, 3H, CH₃).

H NMR spectral data matched that reported by Kasumi.²⁷d

Determination of Stoichiometry of the Host–Guest Complex (Job plots). Compound (S)-3 and (S)- and (R)-mandelic acid 8 were separately dissolved in CDCl₃, 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
to 1.0, and the total concentration of (S)-3 and (S)- and (R)-8 was 0.046 mmol/mL. The complex induction shifts (Δδ) 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**

**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 1H NMR method. All samples were prepared by adding 1 equiv of host 3 in these conditions.

**Notes**

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

**Author Contributions**

All authors have given approval to the final version of the manuscript.

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