Supporting Information

Azaheterocyclic diphenylmethanol chiral solvating agents for the NMR chiral discrimination of alpha-substituted carboxylic acids

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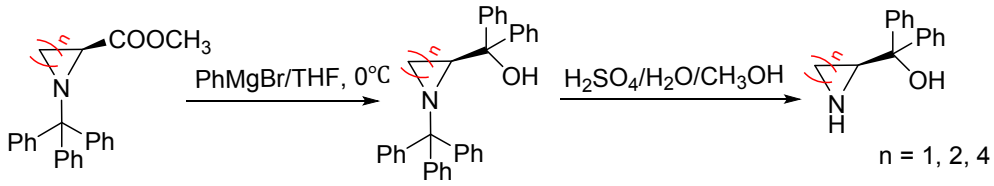
1. General methods

Solvents were dried with standard methods and freshly distilled prior to use if needed. Optical rotations were measured with Perkin Elmer, model 341 Polarimeter at 20 °C in $CHCl_3$. CSA **3** was prepared from commercial methyl 1-tritylaziridine-2-carboxylate, others chemicals were either purchased or purified by standard techniques. Melting pointswere obtained with a Yuhua X-5 micromelting point apparatus and uncorrected. ^1H NMR, ^{13}C NMR and ^{19}F NMR spectra were measured on 400 MHz Brucker spectrometer in $CDCl_3$ solutions with tetramethylsilane (TMS). *J* values are given in Hz. All spectra were recorded using 16 scans at 298 K. An exponential window function with a line-broadening factor of 1 Hz was applied to the FID before Fourier transformation. Column chromatography was performed using Silica gel (300-400 mesh).

2. General procedure for the synthesis of the chiral solvating agents

The chiral aza-heterocycle-containings diphenylmethanols can be readily carried out in a two-step sequence in good yield from commercially available methyl 1-aza-heterocycle-2-carboxylate with Grignard reagent and hydrolysis reaction, the route of synthesis as shown in Scheme S1.



Scheme S1. Preparation and structures of aza-heterocycle-containing diphenylmethanols.

2.1. Synthetic procedures of compound *N*-protected aza-heterocyclic diphenylmethanols

To a Grignard reagent solution prepared from 6.3 mL (60 mmol) of bromobenzene in 5 mL of THF and 1.46 g (60 mmol) of magnesium in 10 mL of THF was gradually added 15 mmol of methyl 1-aza-heterocycle- 2-carboxylate dissolved in 5 mL of THF at 20 °C. The mixture was then allowed to reach room temperature. After stirring for 12 h, the reaction was quenched with saturated aqueous NH_4Cl (8 mL) at 0 °C. The product was separated and the aqueous phase extracted with ethyl acetate (3×10 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by column chromatography with petroleum ether /ethyl acetate as the developing solvent to give the *N*-protected aza-heterocyclic diphenylmethanols.

2.2. General procedure for the deprotection by hydrolysis reaction

N-protected aza-heterocyclic diphenylmethanols (3 mmol) was dissolved in $H_2SO_4/H_2O/CH_3OH$ (3/8/60, 18 mL). The solution was stirred at room temperature for 24 h, the white precipitate formed was removed by filtration from the mixture, and then to the filtrate NaOH 30% w/w solution was carefully added simultaneously to adjust the solution mixture to around 10 pH and the solution was extracted with ethyl acetate (3 × 10 mL), the combined extracts were dried over Na_2SO_4. The organic phase was then concentrated in vacuo and the residue was purified by silica gel column chromatography with petroleum ether /ethyl acetate (4:1, v/v) as eluent to afford (*S*)-CSA-**1** as a white solid.

(*S*)-aziridinyl diphenylmethanol **1**: white solid, m. p. =162-163 °C; $[\alpha]^{25}_D$ = -20.5 (*c* 0.294, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.23 (m, 10H), 2.92 (s, 1H), 1.87 (d, J = 5.6 Hz, 1H), 1.75 (d, J = 3.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 145.2, 128.2, 128.1, 127.1, 127.1, 126.5, 126.3, 74.3, 37.0, 22.0; HRMS (EI-TOF): m/z Calculated for $C_{15}H_{15}NO$ (M^+): 225.1154; Found: 225.1167.

(*R*)-aziridinyl diphenylmethanol ***ent*-1**: white solid, m. p. =160-162 °C; $[\alpha]^{25}_D$ = +23.4 (*c* 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.23 (m, 10H), 2.92 (s, 1H), 1.88 (d, J = 5.6 Hz, 1H), 1.74 (d, J = 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 145.1, 128.2, 128.1, 127.18, 127.17, 126.5, 126.3, 74.3, 37.0, 22.1.

(*S*)-azetidinyl diphenylmethanol **2:** white solid, m. p. =112-113 °C; $[\alpha]^{25}_D$ = -73.4 (*c* 0.30, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 − 7.16 (m, 10H), 4.91 (t, J = 8.0 Hz, 1H), 3.61 (q, J = 7.2 Hz, 1H), 3.18 (ddd, J = 8.4, 7.2, 3.2 Hz, 1H), 2.42 − 2.33 (m, 1H), 198 − 1.90 (m, 1H); ^{13}C NMR (100 MHz,$CDCl_3$): δ 146.3, 143.3, 128.1, 128.0, 126.7, 126.6, 126.3, 125.9, 76.5, 64.7, 42.3, 21.9; HRMS (EI-TOF): m/z Calculated for $C_{16}H_{17}NO$ (M^+): 239.1310; Found:239.1322.

(*S*)-pyrrolidinyl diphenylmethanol **3:** The compound was purchased from J&K without purification.

(*S*)-piperidinyl diphenylmethanol **4**: white solid, m. p. =92-95 °C; $[\alpha]^{25}_D$ = -80.5 (*c* 0.250, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, J = 8.8, 1.6 Hz, 2H), 7.46 (dd, J = 8.8, 1.6 Hz, 2H), 7.39 – 7.10 (m, 6H), 4.31 (br, 1H), 3.53 (dd, J = 10.8, 2.8 Hz, 1H), 3.01 (dq, J = 10.8, 2.0 Hz, 1H), 2.72 (dt, J = 11.7, 2.7 Hz, 1H), 1.76 – 1.54 (m, 3H), 1.45 – 1.20 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.3, 144.2, 128.5, 127.9, 126.8, 126.3, 126.0, 125.5, 78.5, 61.7, 46.7, 25.6, 25.5, 24.5;

HRMS (EI-TOF): m/z Calculated for $C_{18}H_{21}NO$ (M^+): 267.1623; Found:267.1589.

3. Determination of enantiomeric purity of mandelic acid

To determine the enantiomeric purity of the carboxylic acids, ten 4-MeO-MA samples with -100%, -80%, -60%, -40%, -20%, 0%, 20%, 40%, 60%, 80%*ee* were prepared at a concentration of 10 mM in $CDCl_3$, respectively, expressed as % *R* in the data. The CAS **1** was also dissolved in $CDCl_3$ at a concentration of 10 mM. Then 250 μL of CAS **1** and 250 μL of 4-MeO-MA with different *ee*'s were mixed in the NMR tube generating a total concentration of 10 mM with a molar ratio of 1:1. Then the enantiomeric purity of the carboxylic acids was determined by ^1H NMR method. The plotting of gravimetric *ee* value (y axis) versus NMR observed *ee* value (x axis) presented excellent linearity with R^2 =0.99995.

4. Discrimination ability of CSA 1 toward racemic guests 1-25

At first, CSA **1**, and the guests were separately dissolved in $CDCl_3$ with a concentration of 10 mM. Then, 0.25 mL of CSA **1** and 0.25 mL guest were added to NMR tubes, so that the total volume was 0.5 mL, and the concentration of CSA **1** and guest was 10 mM. The ^1H NMR spectra of all samples were recorded on a 400 MHz spectrometer.

5. ^{1}H NMR, ^{13}C NMR spectra of CSAs

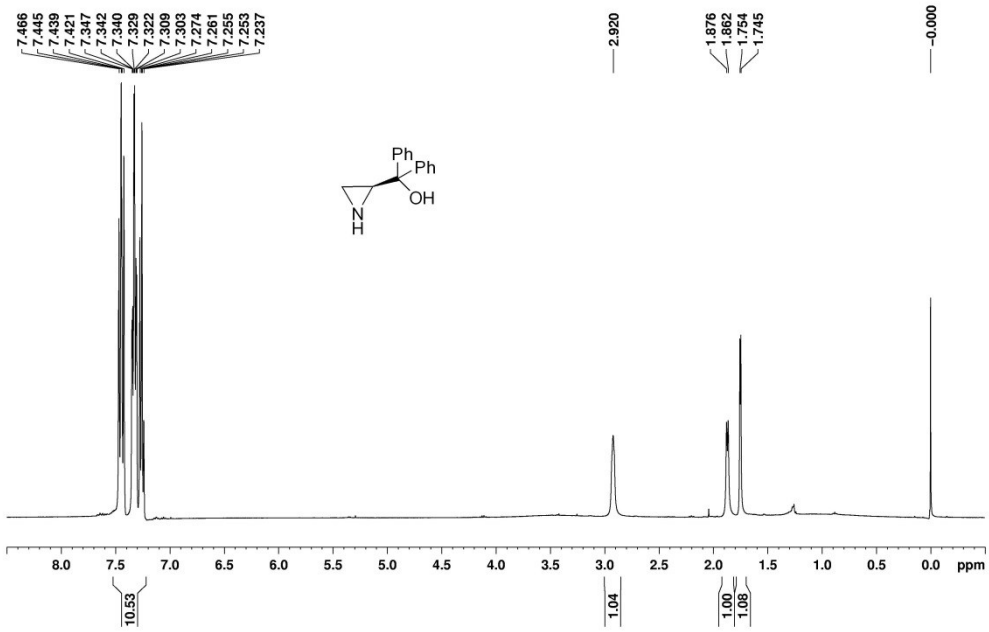


Figure S1. ^{1}H NMR (400 MHz, $CDCl_3$) of (*S*)-aziridinyl diphenylmethanol 1.

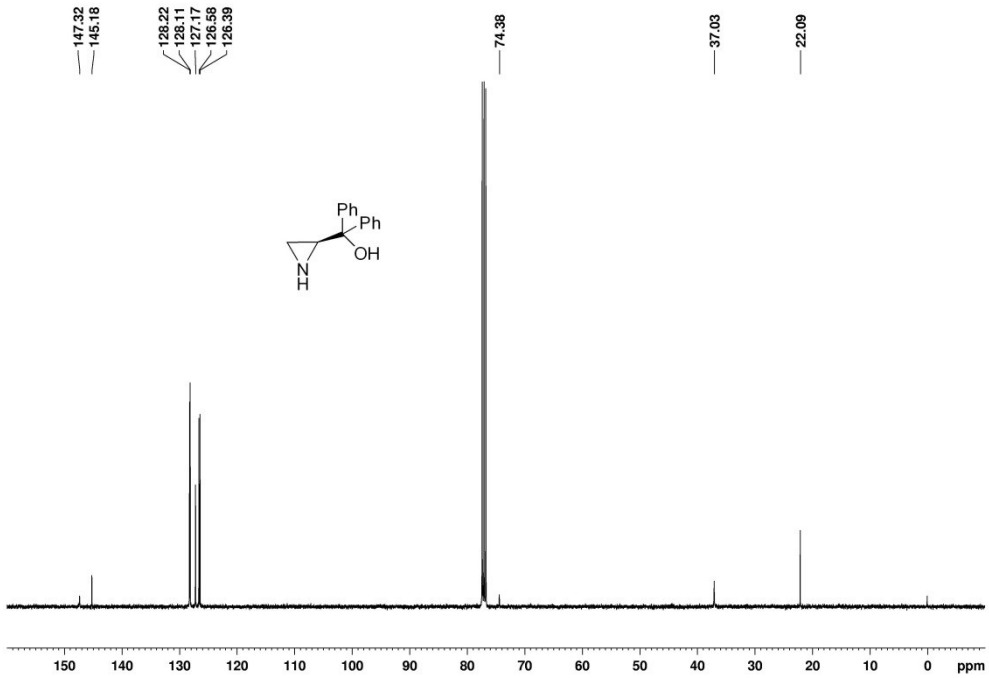


Figure S2. ^{13}C NMR (100 MHz, $CDCl_3$) of (*S*)-aziridinyl diphenylmethanol 1.

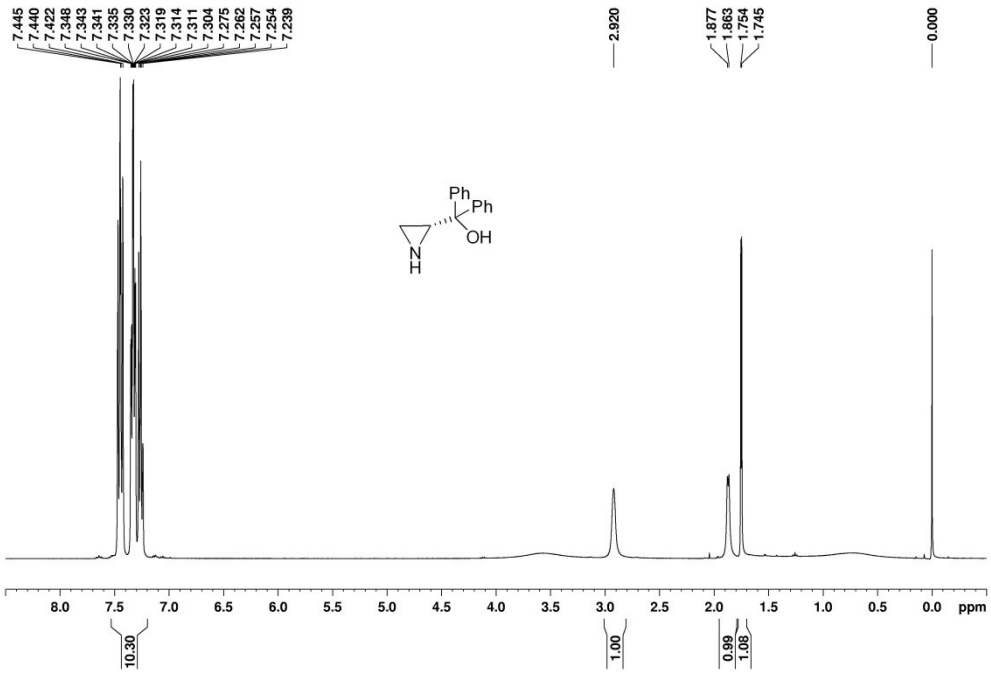


Figure S3. ^{1}H NMR (400 MHz, $CDCl_3$) of (*R*)-aziridinyl diphenylmethanol *ent*-1.

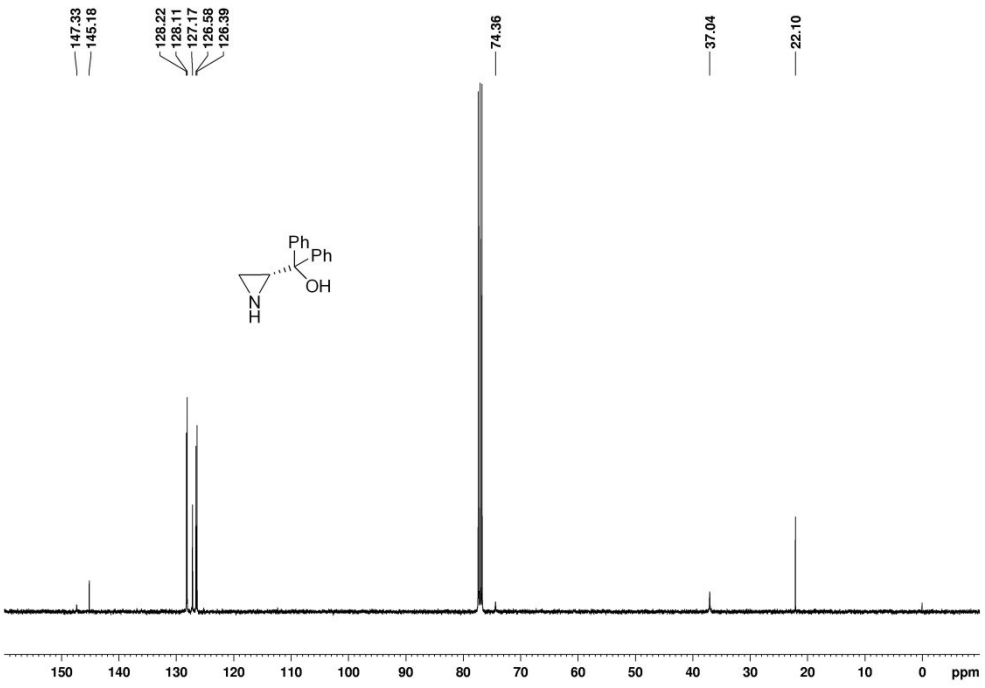


Figure S4. ^{13}C NMR (100 MHz, $CDCl_3$) of (*R*)-aziridinyl diphenylmethanol *ent*-1.

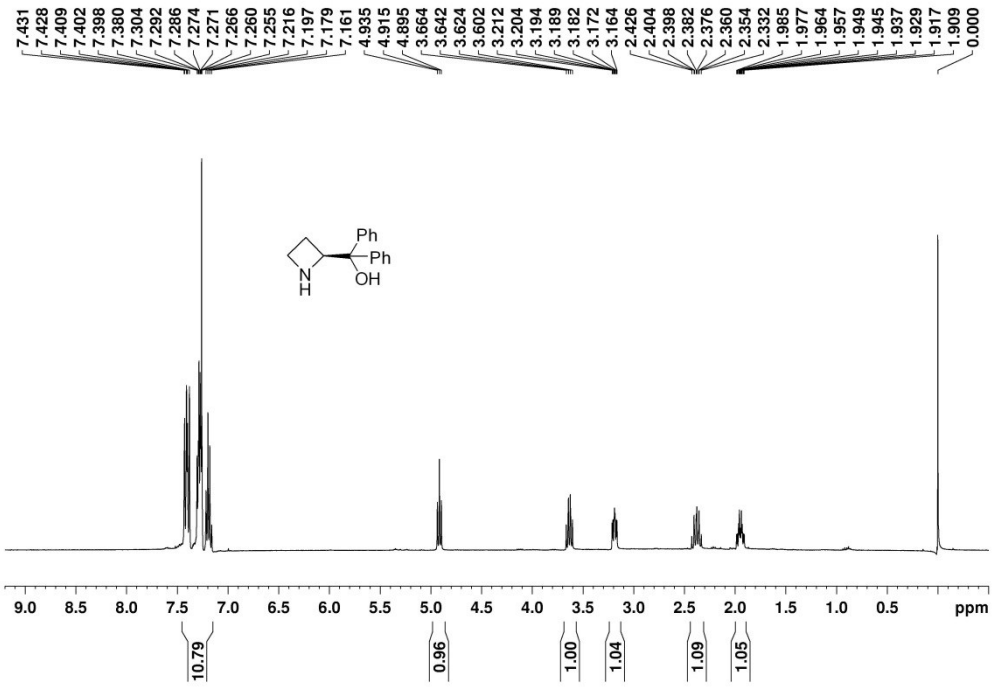


Figure S5. ^{1}H NMR (400 MHz, $CDCl_3$) of (*S*)-azetidinyl diphenylmethanol 2.

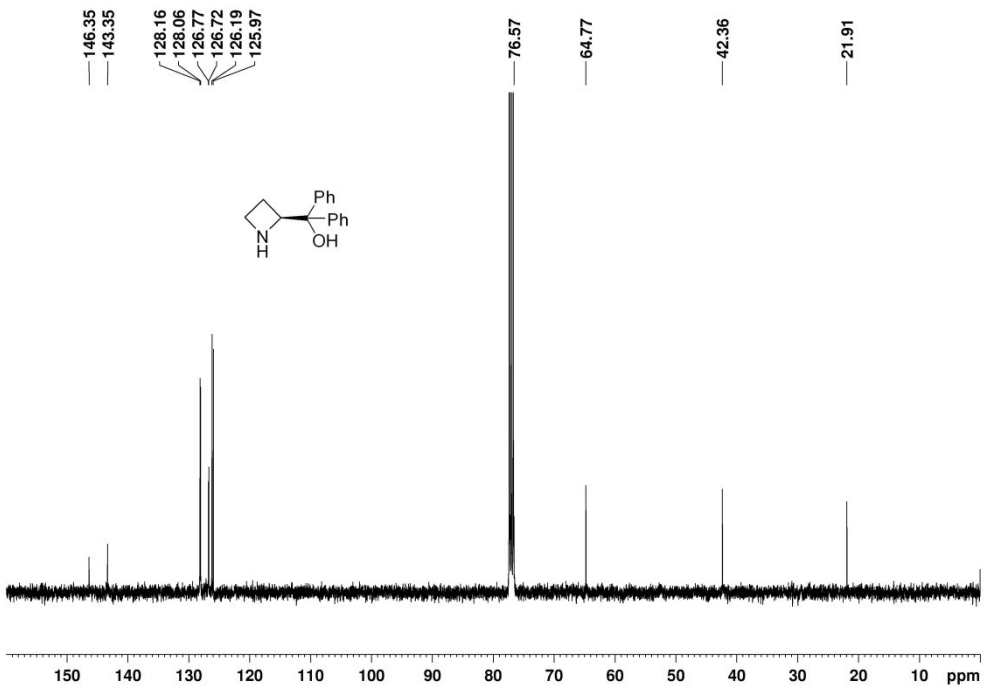


Figure S6. ^{13}C NMR (100 MHz, $CDCl_3$) of (*S*)-azetidinyl diphenylmethanol 2.

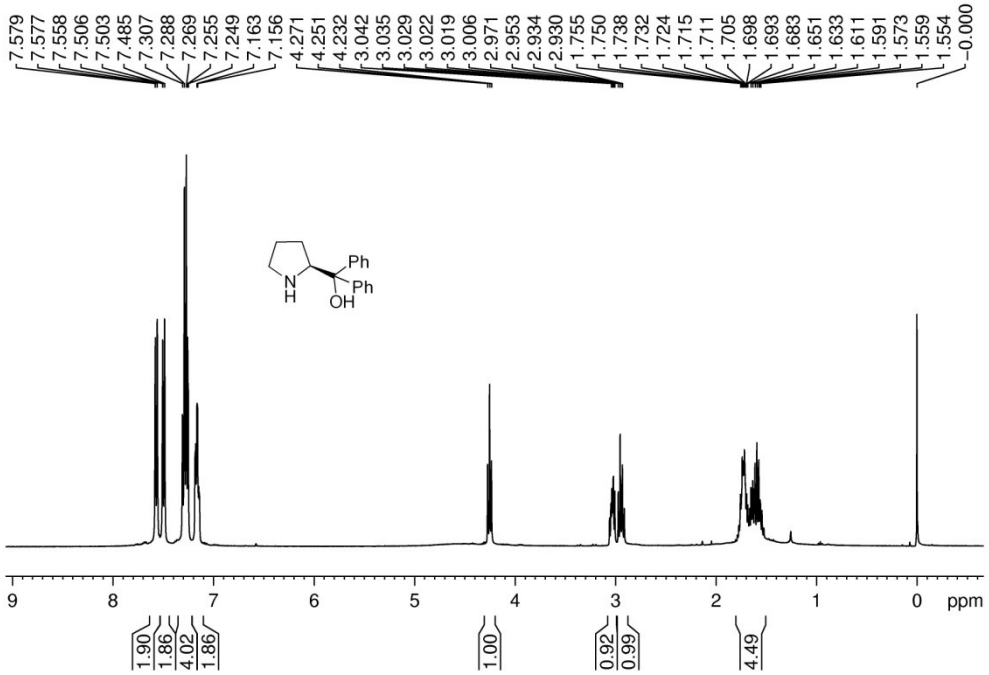


Figure S7. ^{1}H NMR (400 MHz, $CDCl_3$) of (*S*)-pyrrolidinyl diphenylmethanol 3.

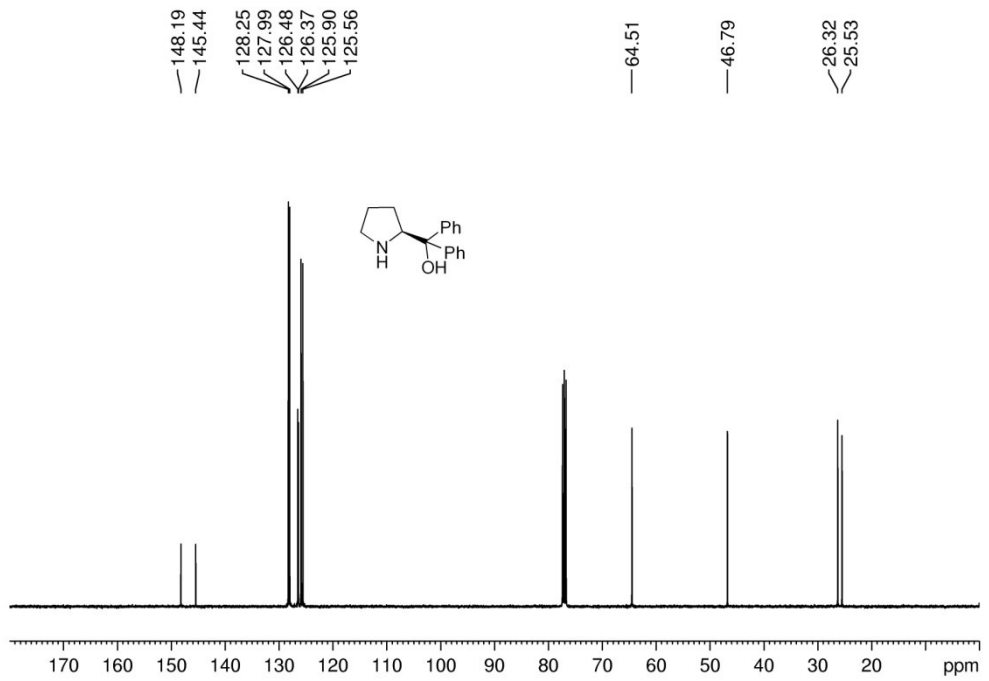


Figure S8. ^{13}C NMR (100 MHz, $CDCl_3$) of (*S*)-pyrrolidinyl diphenylmethanol 3.

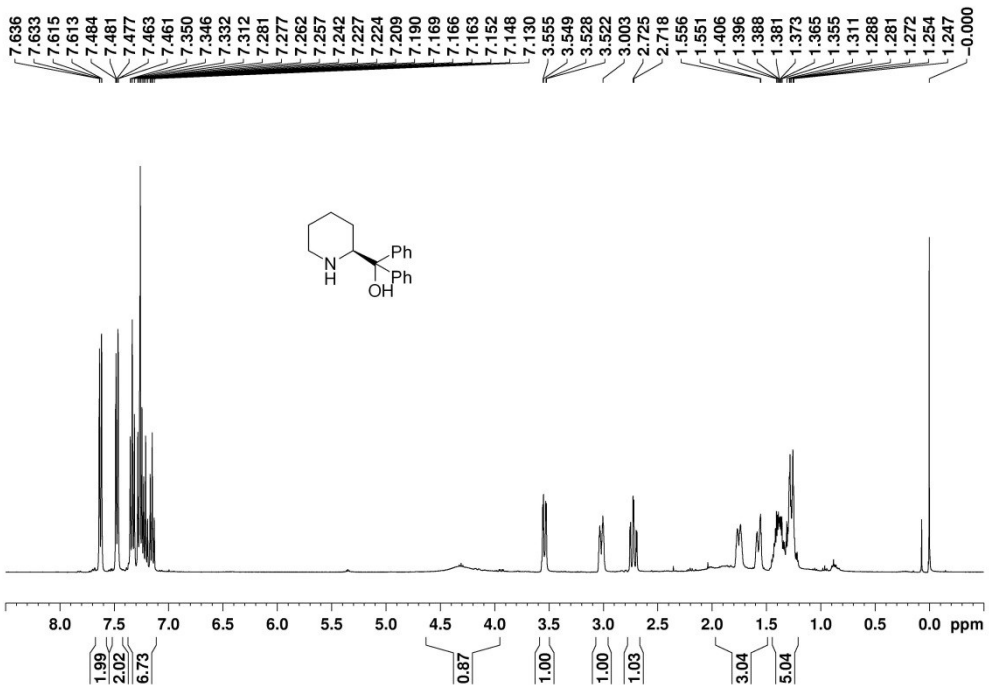


Figure S9. ^{1}H NMR (400 MHz, $CDCl_3$) of (*S*)-piperidinyl diphenylmethanol 4.

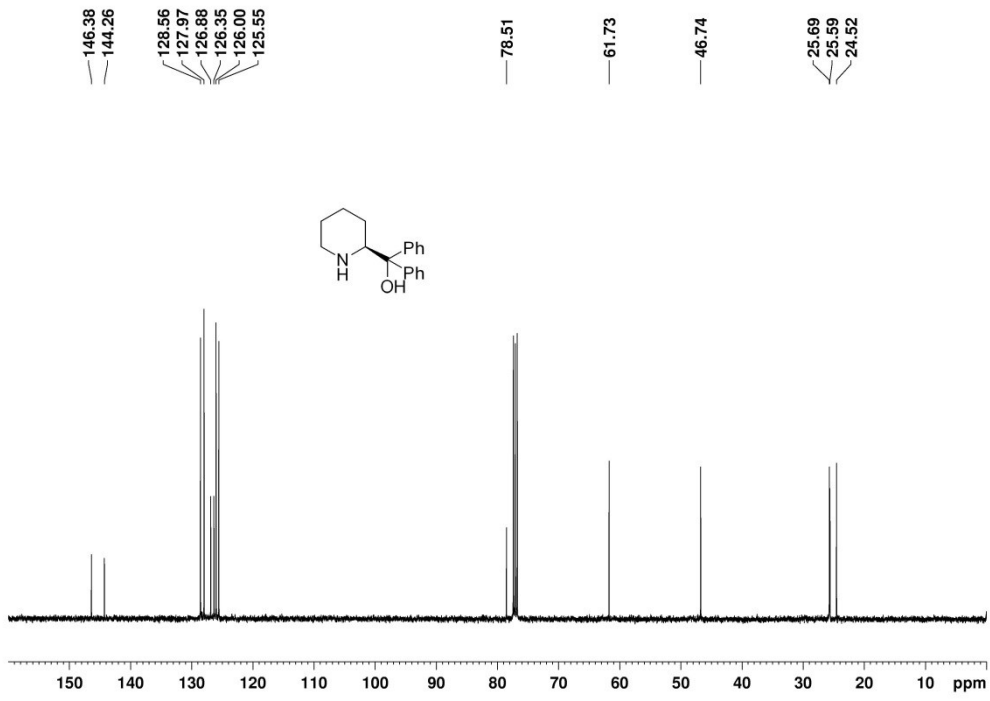


Figure S10. ^{13}C NMR (100 MHz, $CDCl_3$) of (*S*)-piperidinyl diphenylmethanol 4.

6. ^{1}H NMR spectroscopy CSA 1-4 and racemic 3,5-difluoro-mandelic acid

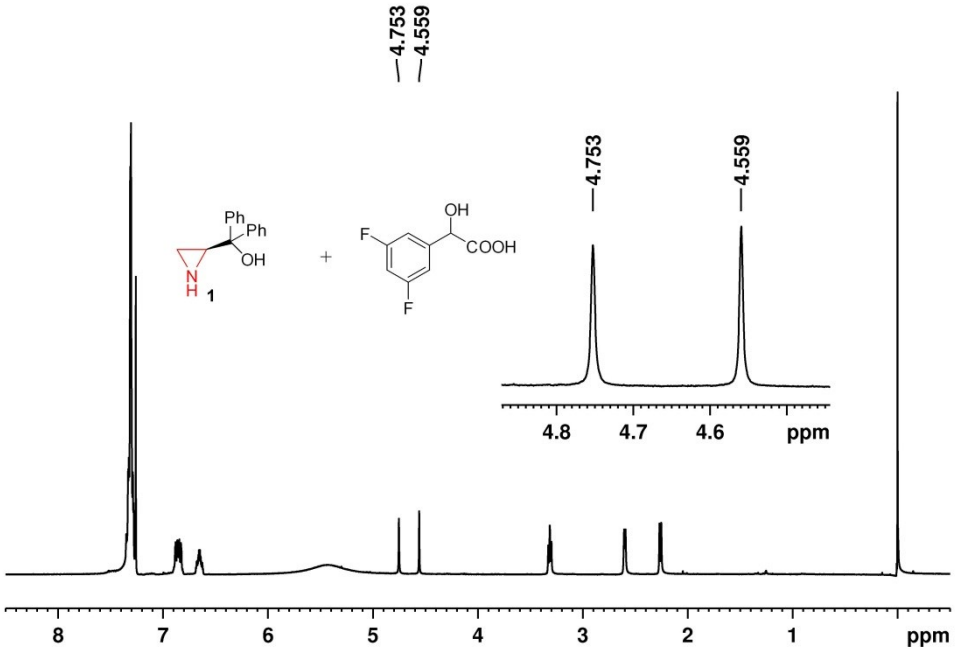


Figure S11. ^{1}H NMR Spectra (400 MHz, $CDCl_3$) of (*S*)-aziridinyl diphenylmethanol 1 and (±)-3,5-difluoro-mandelic acid.

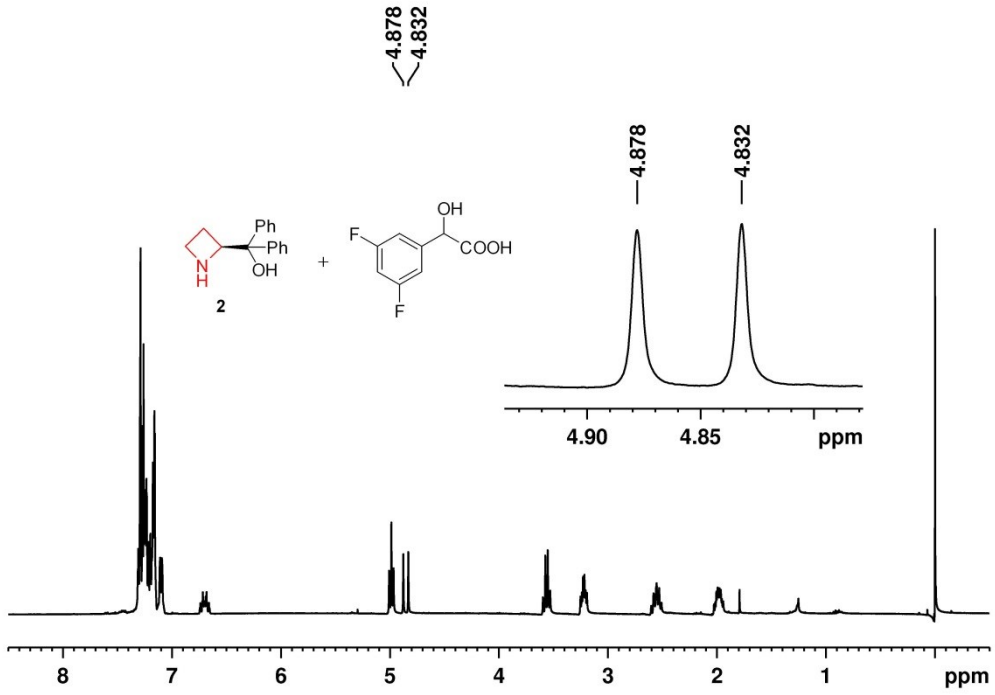


Figure S12. ^{1}H NMR Spectra (400 MHz, $CDCl_3$) of (*S*)-azetidinyl diphenylmethanol 2 and (±)-3,5-difluoro-mandelic acid.

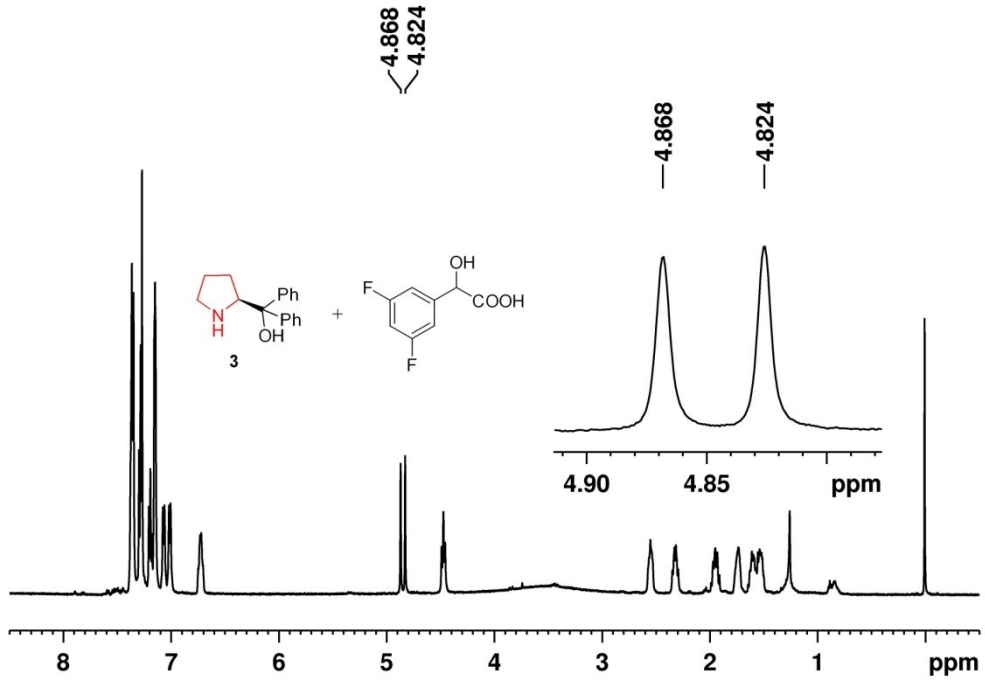


Figure S13. ^{1}H NMR Spectra (400 MHz, $CDCl_3$) of (*S*)-pyrrolidinyl diphenylmethanol 1 and (±)-3,5-difluoro-mandelic acid.

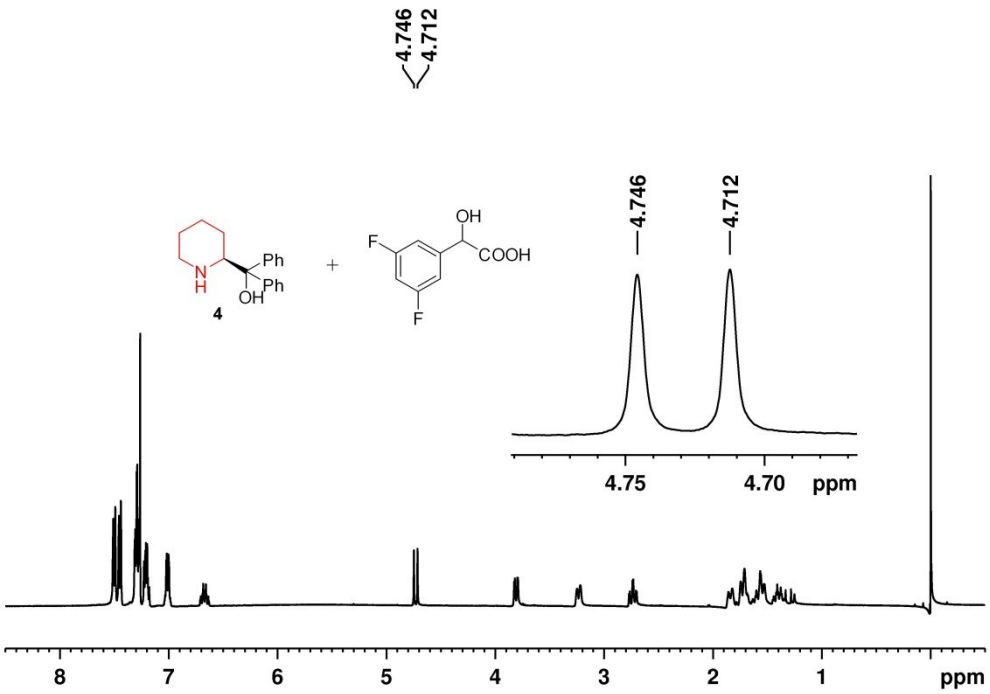


Figure S14. ^{1}H NMR Spectra (400 MHz, $CDCl_3$) of (*S*)-piperidinyl diphenylmethanol 4 and (±)-3,5-difluoro-mandelic acid.

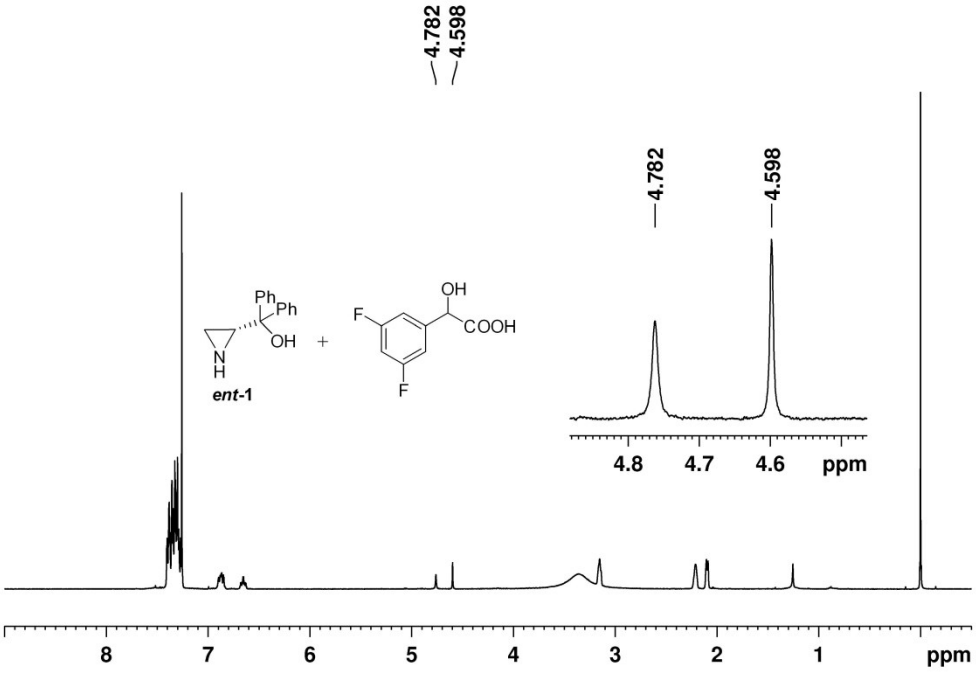


Figure S15. ^{1}H NMR Spectra (400 MHz, $CDCl_3$) of (*R*)-aziridinyl diphenylmethanol *ent*-1 and (±)-3,5-difluoro-mandelic acid.

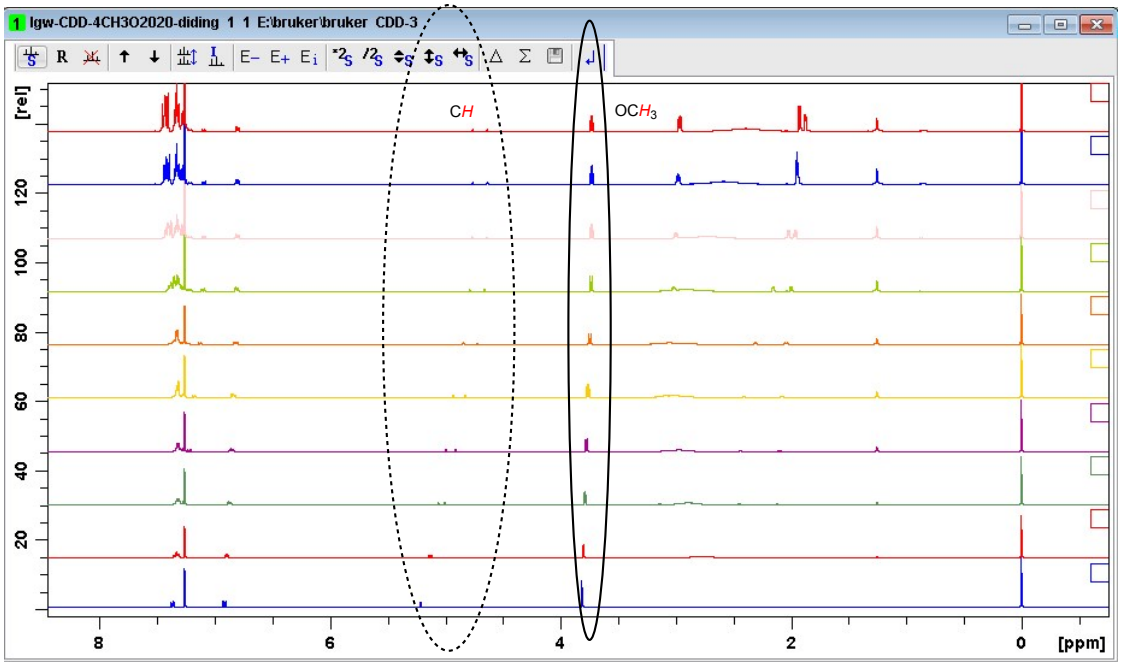


Figure S16. Evolution of ^{1}H NMR (400 MHz, $CDCl_3$) signals of methine and methoxy group of (*rac*)-4-MeO-MA by NMR titration experiments.

7. ^{1}H NMR spectroscopy (*S*)-aziridinyl diphenylmethanol and various racemic α-substituted carboxylic acids

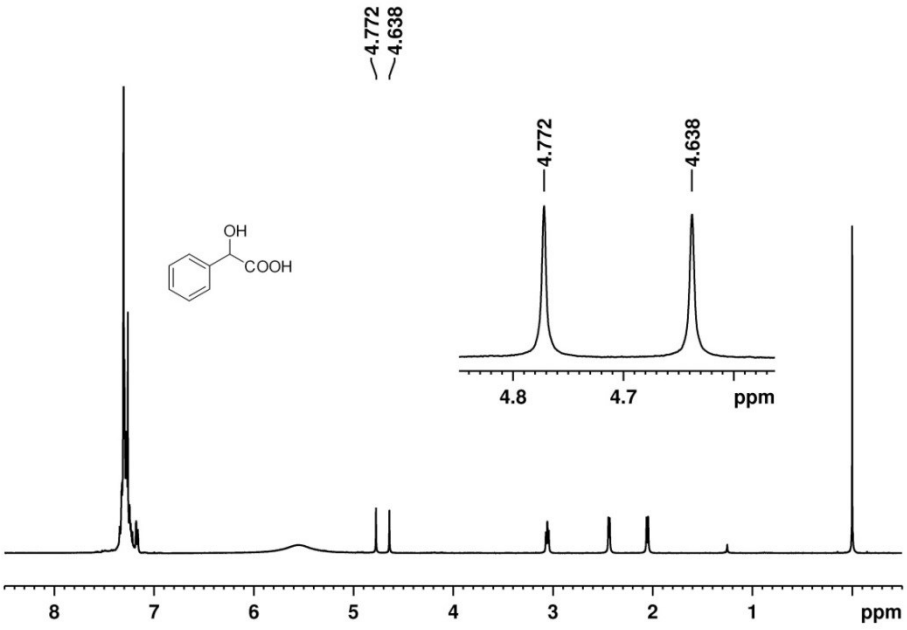


Figure S1a. ^{1}H NMR Spectra (400 MHz, $CDCl_3$) of (*S*)-aziridinyl diphenylmethanol 1 and (±)-mandelic acid.

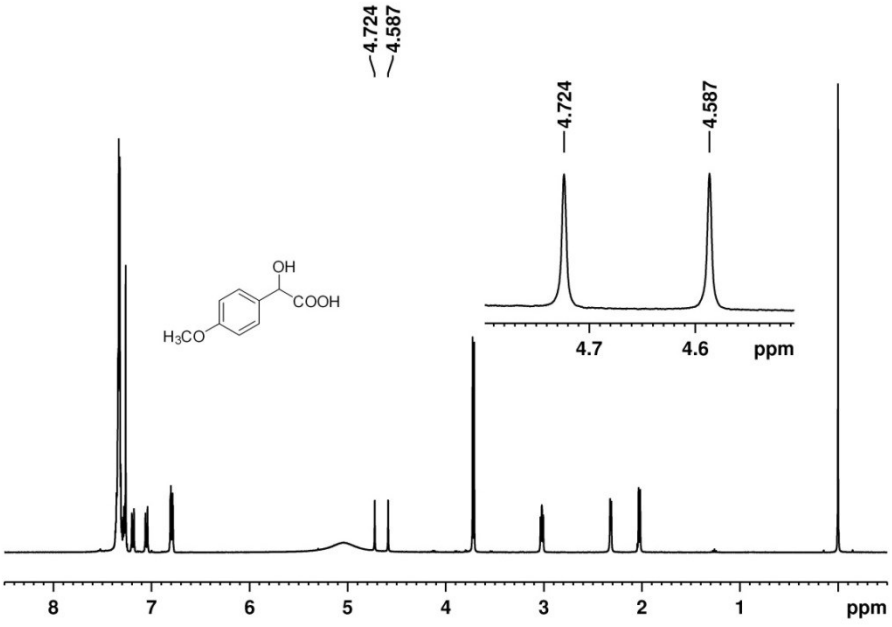


Figure S1b. ^{1}H NMR Spectra (400 MHz, $CDCl_3$) of (*S*)-aziridinyl diphenylmethanol 1 and (±)-4-methoxy-mandelic acid.

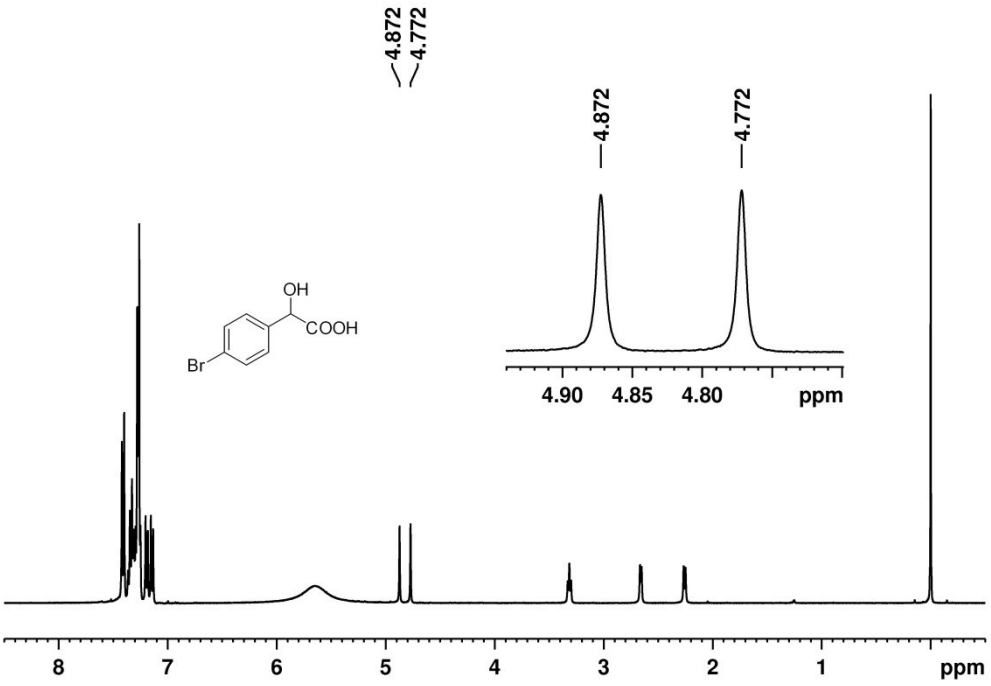


Figure S1c. ^{1}H NMR Spectra (400 MHz, $CDCl_3$) of (*S*)-aziridinyl diphenylmethanol 1 and (±)-4-bromo-mandelic acid.

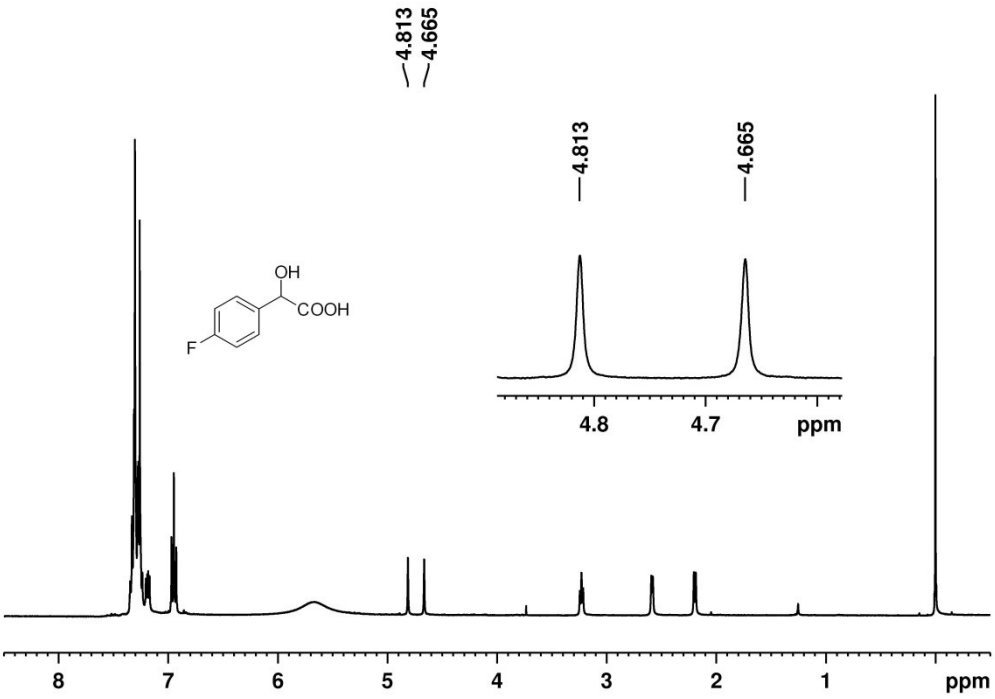


Figure S1d. ^{1}H NMR Spectra (400 MHz, $CDCl_3$) of (*S*)-aziridinyl diphenylmethanol 1 and (±)-4-fluoro-mandelic acid.

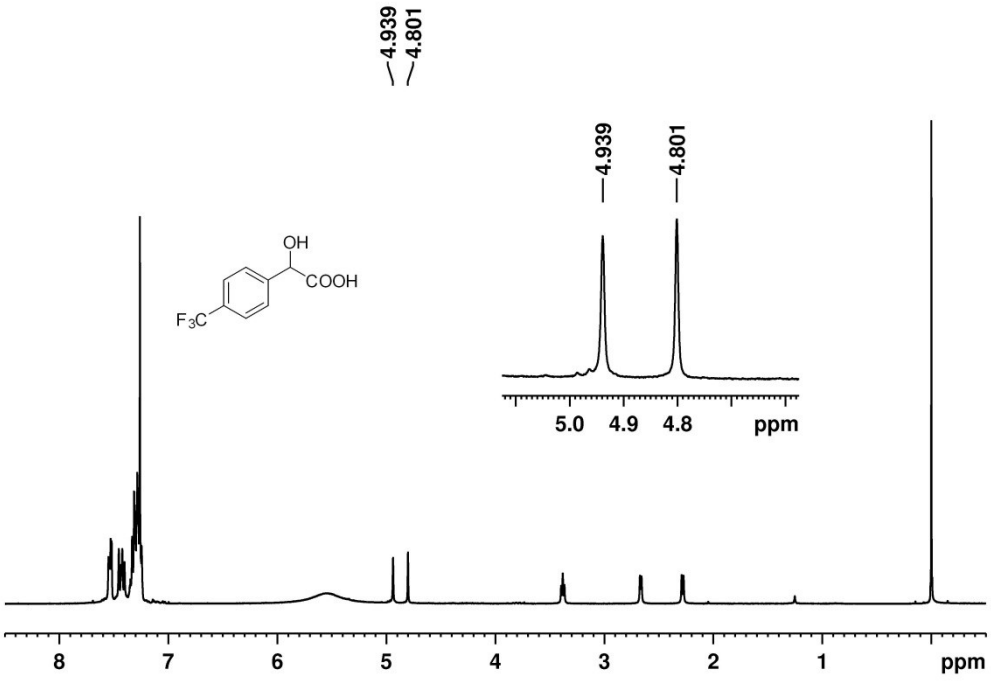


Figure S1e. ^{1}H NMR Spectra (400 MHz, $CDCl_3$) of (*S*)-aziridinyl diphenylmethanol 1 and (±)-4-trifluoromethyl-mandelic acid.

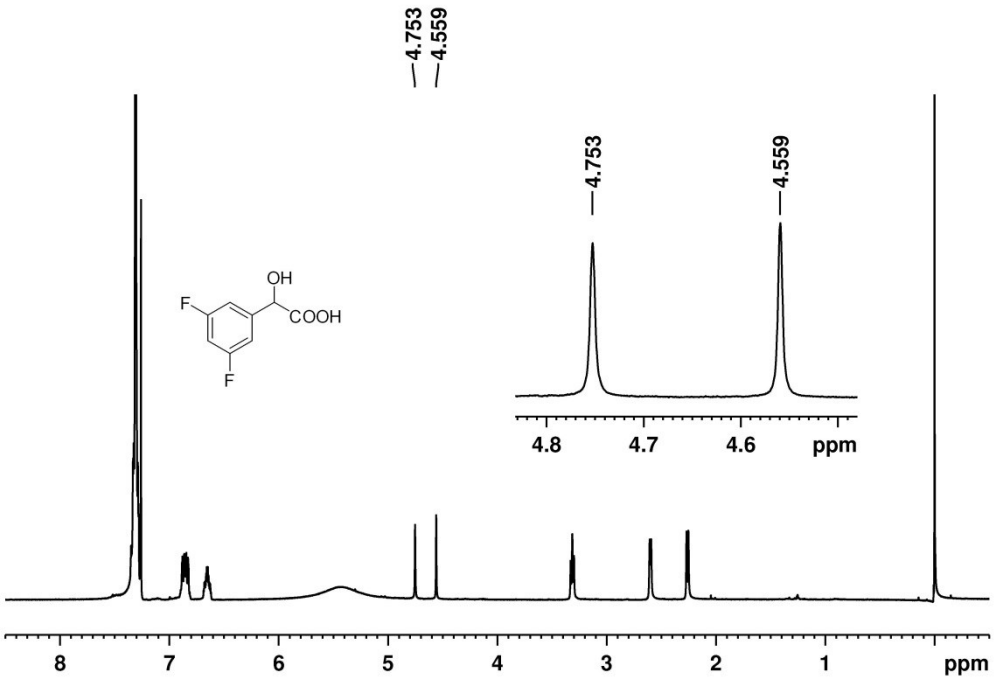


Figure S1f. ^{1}H NMR Spectra (400 MHz, $CDCl_3$) of (*S*)-aziridinyl diphenylmethanol 1 and (±)-3,5-difluoro-mandelic acid.

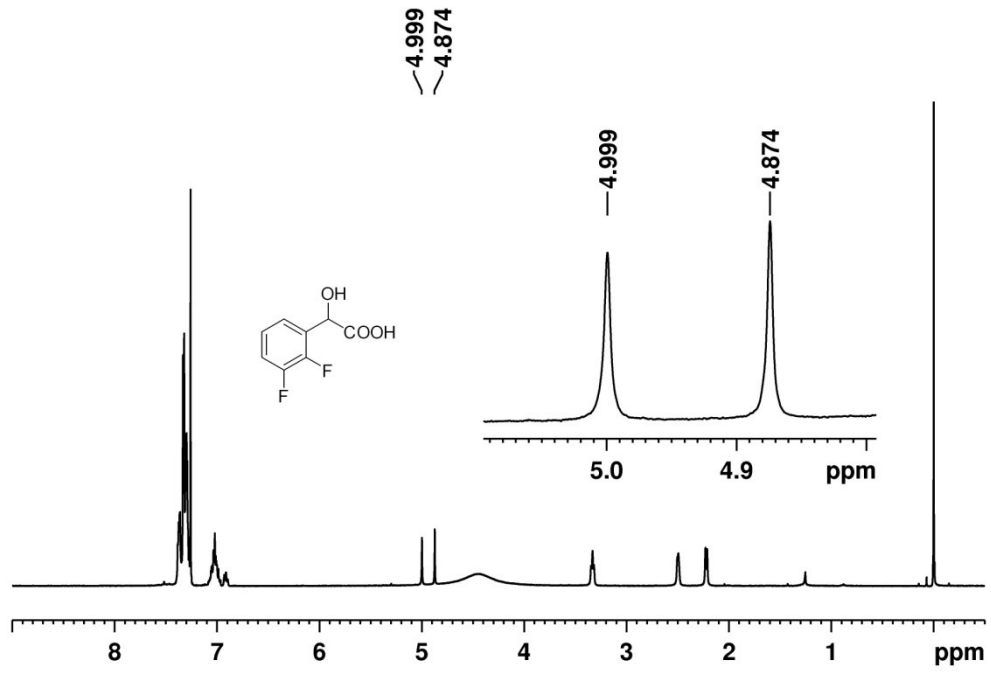


Figure S1g. ^{1}H NMR Spectra (400 MHz, $CDCl_3$) of (*S*)-aziridinyl diphenylmethanol 1 and (±)-2,3-difluoro-mandelic acid.

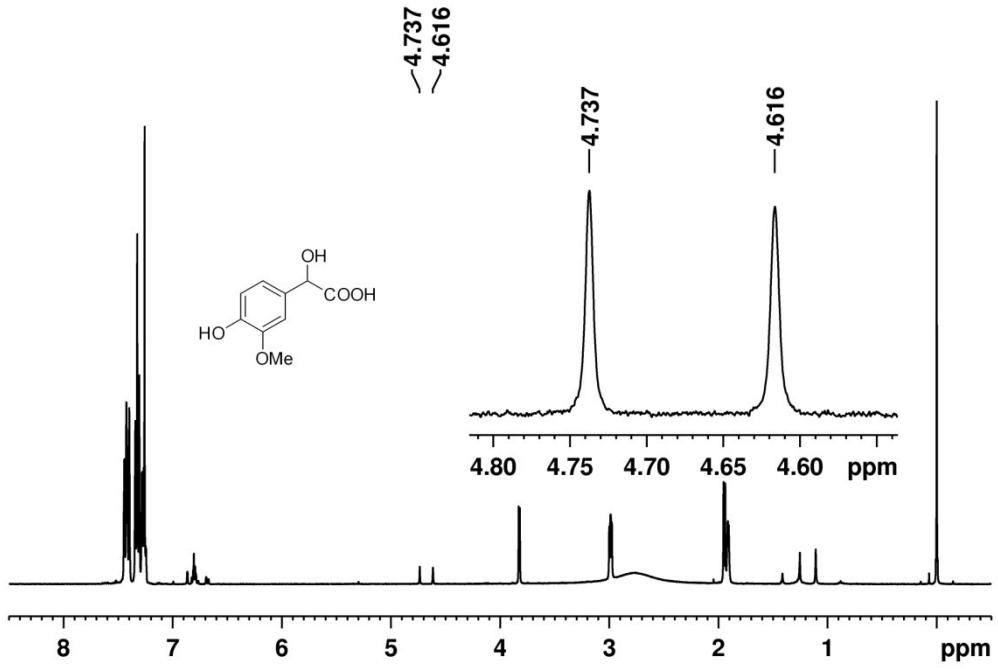


Figure S1h. ^{1}H NMR Spectra (400 MHz, $CDCl_3$) of (*S*)-aziridinyl diphenylmethanol 1 and (±)-4-hydroxy-3-methoxy-mandelic acid.

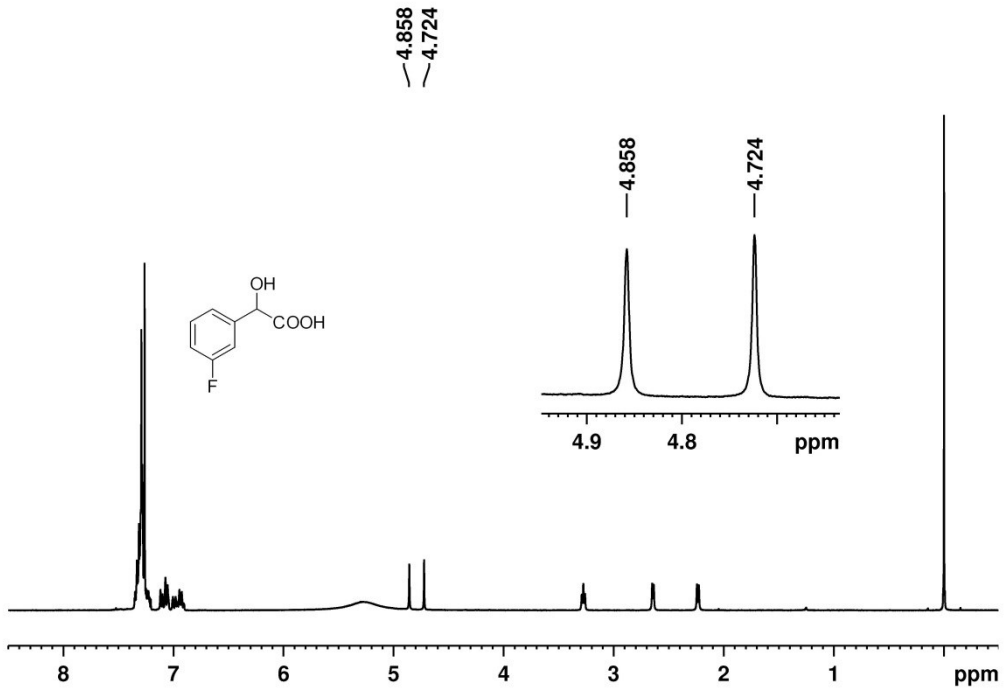


Figure S1i. ^{1}H NMR Spectra (400 MHz, $CDCl_3$) of (*S*)-aziridinyl diphenylmethanol 1 and (±)-3-fluoro-mandelic acid.

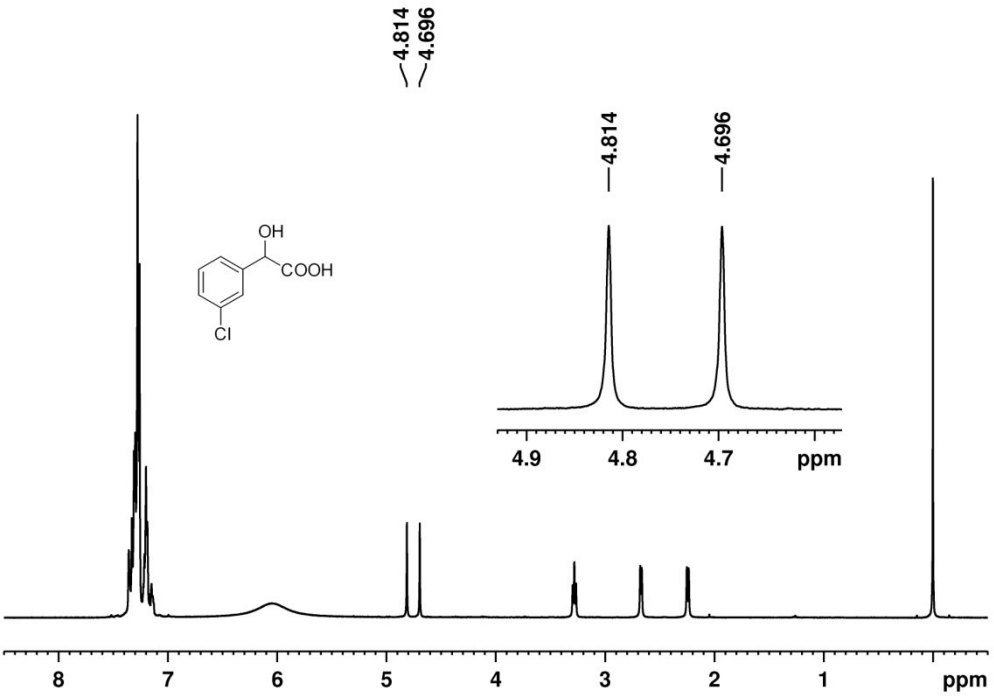


Figure S1j. ^{1}H NMR Spectra (400 MHz, $CDCl_3$) of (*S*)-aziridinyl diphenylmethanol 1 and (±)-3-chloro-mandelic acid.

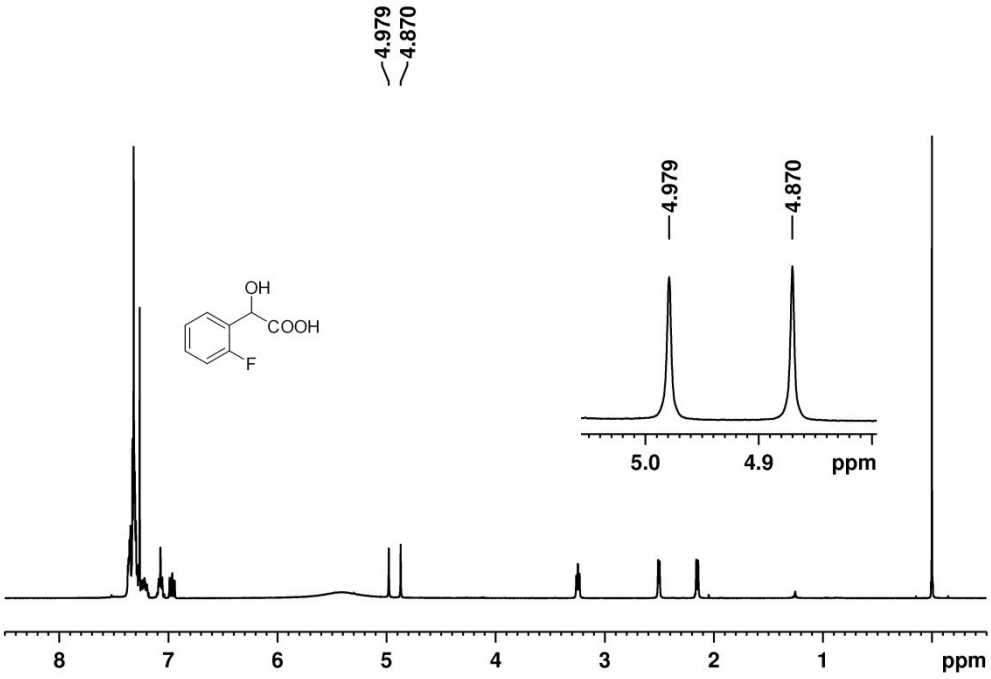


Figure S1k. ^{1}H NMR Spectra (400 MHz, $CDCl_3$) of (*S*)-aziridinyl diphenylmethanol 1 and (±)-2-fluoro-mandelic acid.

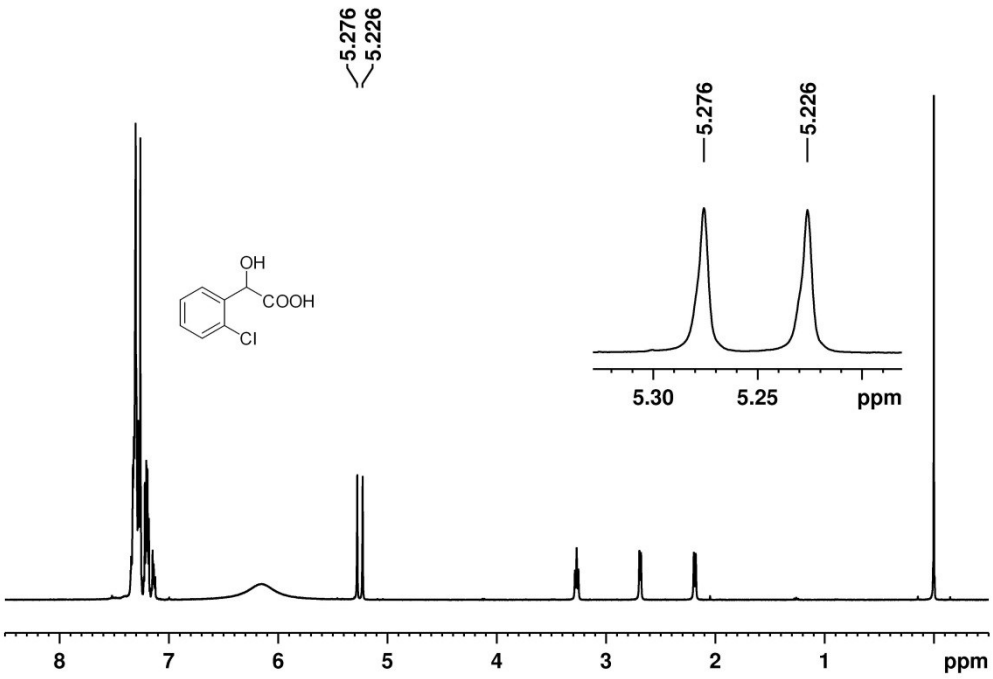


Figure S1l. ^{1}H NMR Spectra (400 MHz, $CDCl_3$) of (*S*)-aziridinyl diphenylmethanol 1 and (±)-2-chloro-mandelic acid.

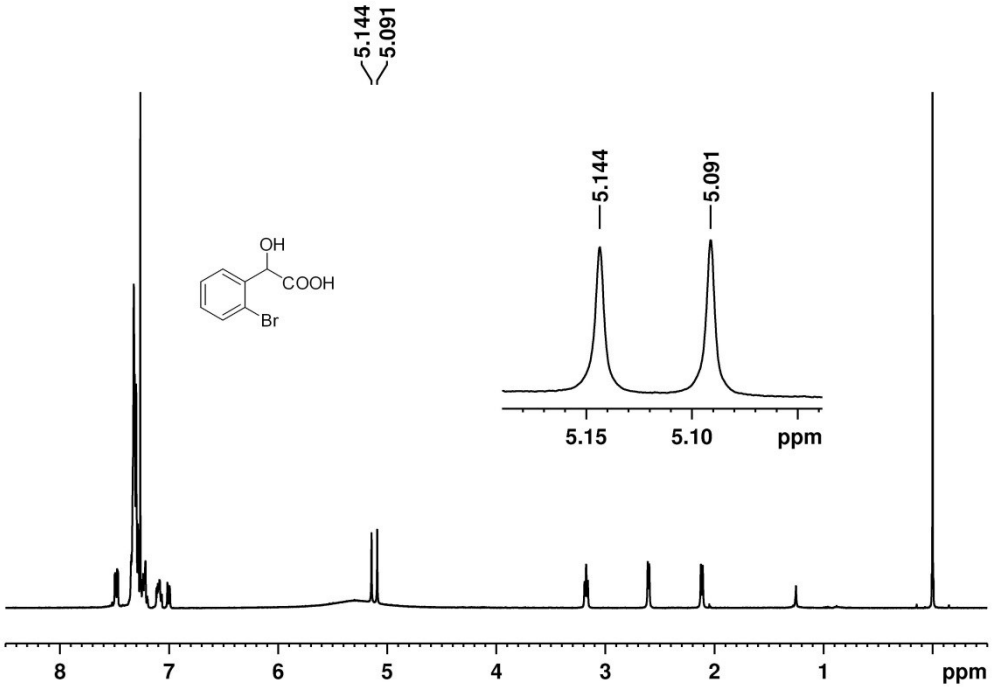


Figure S1m. ^{1}H NMR Spectra (400 MHz, $CDCl_3$) of (*S*)-aziridinyl diphenylmethanol 1 and (±)-2-bromo-mandelic acid.

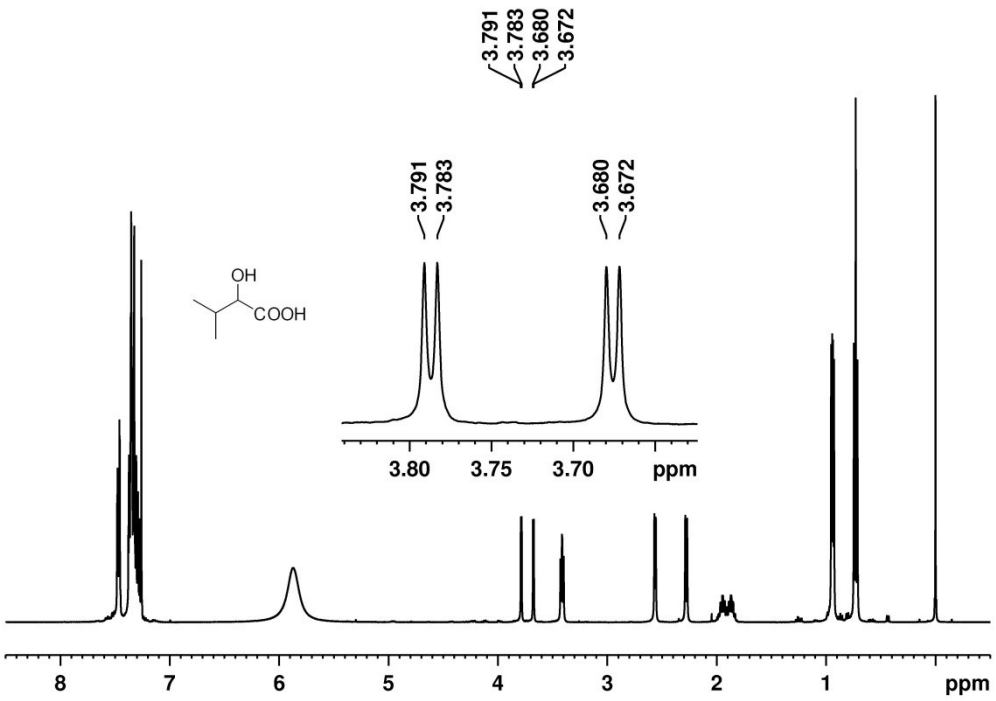


Figure Sln. ^{1}H NMR Spectra (400 MHz, $CDCl_3$) of (*S*)-aziridinyl diphenylmethanol 1 and (±)-2-hydroxy-3-methylbutyric acid.

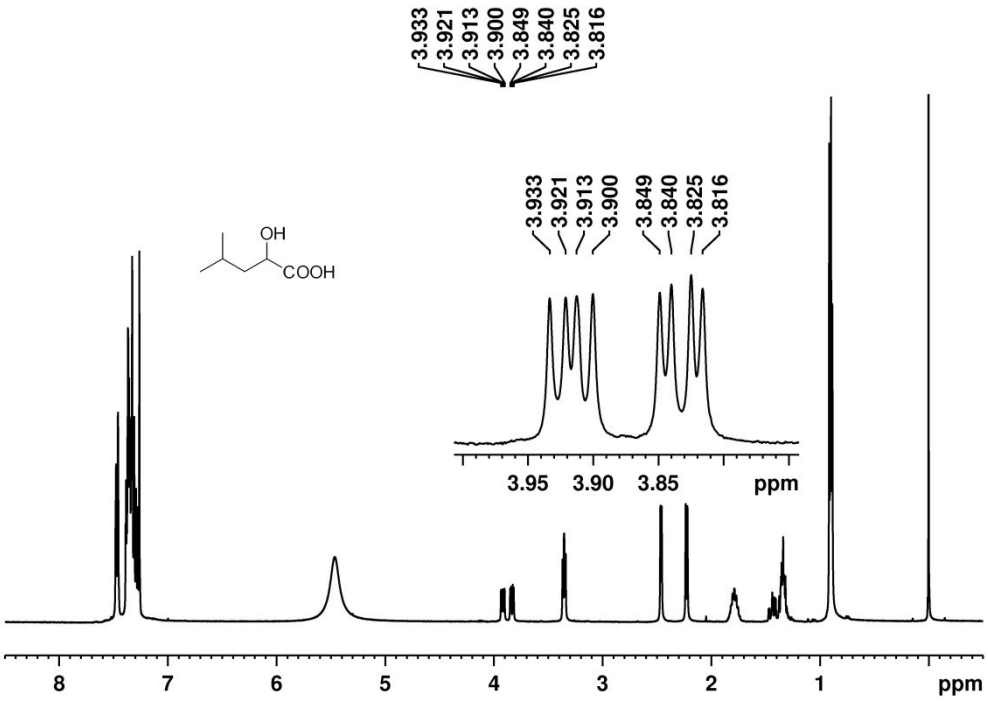


Figure S1o. ^{1}H NMR Spectra (400 MHz, $CDCl_3$) of (*S*)-aziridinyl diphenylmethanol 1 and (±)-2-hydroxyisocaproic acid.

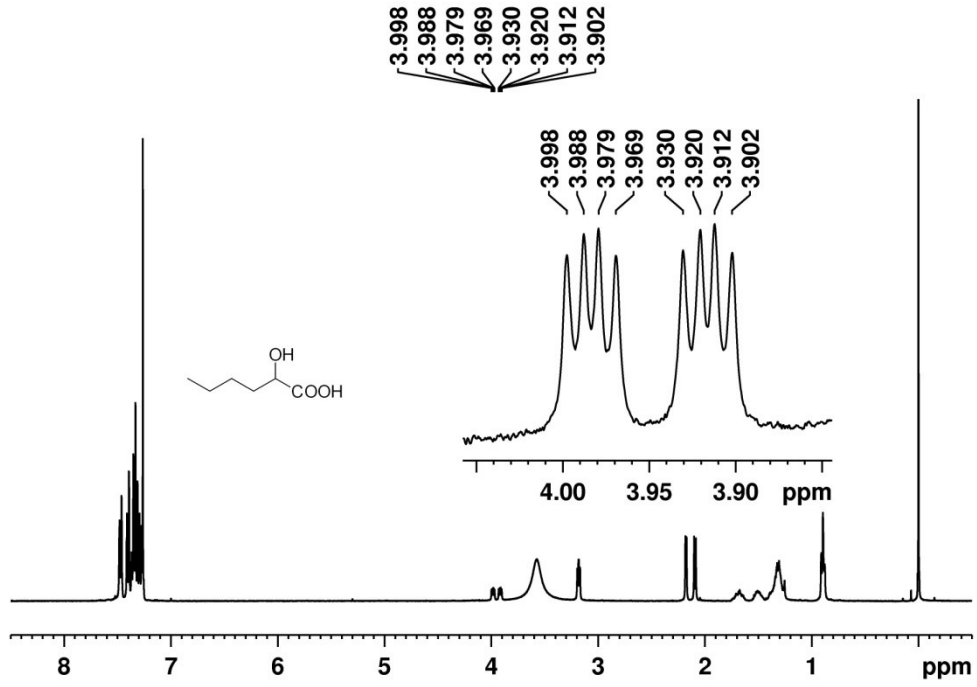


Figure S1p. ^{1}H NMR Spectra (400 MHz, $CDCl_3$) of (*S*)-aziridinyl diphenylmethanol 1 and (±)-2-hydroxyhexanoic acid.

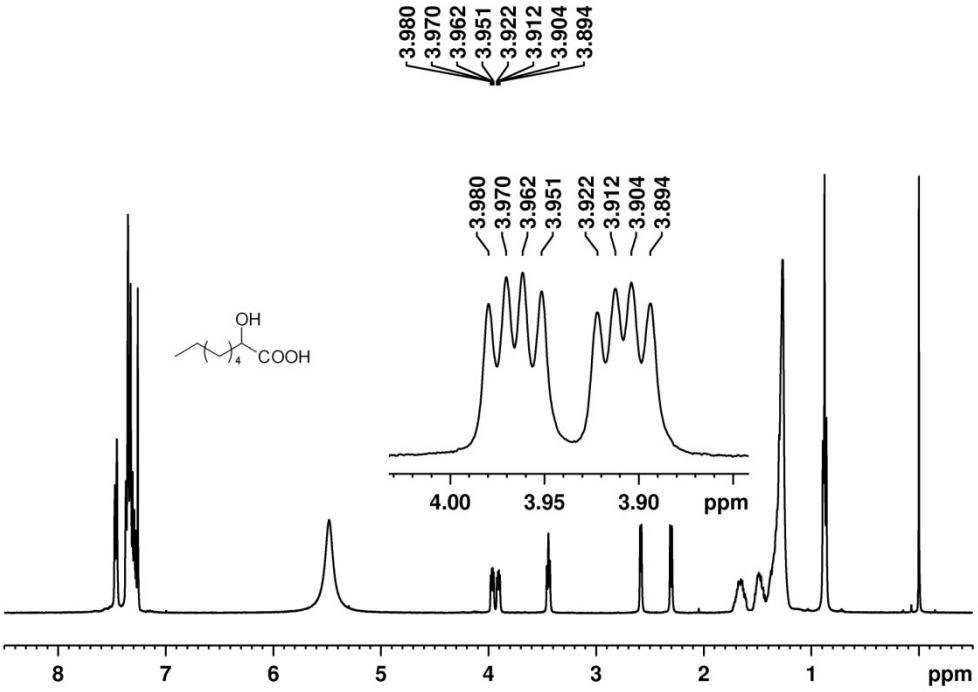


Figure S1q. ^{1}H NMR Spectra (400 MHz, $CDCl_3$) of (*S*)-aziridinyl diphenylmethanol 1 and (±)-2-hydroxyoctanoic acid.

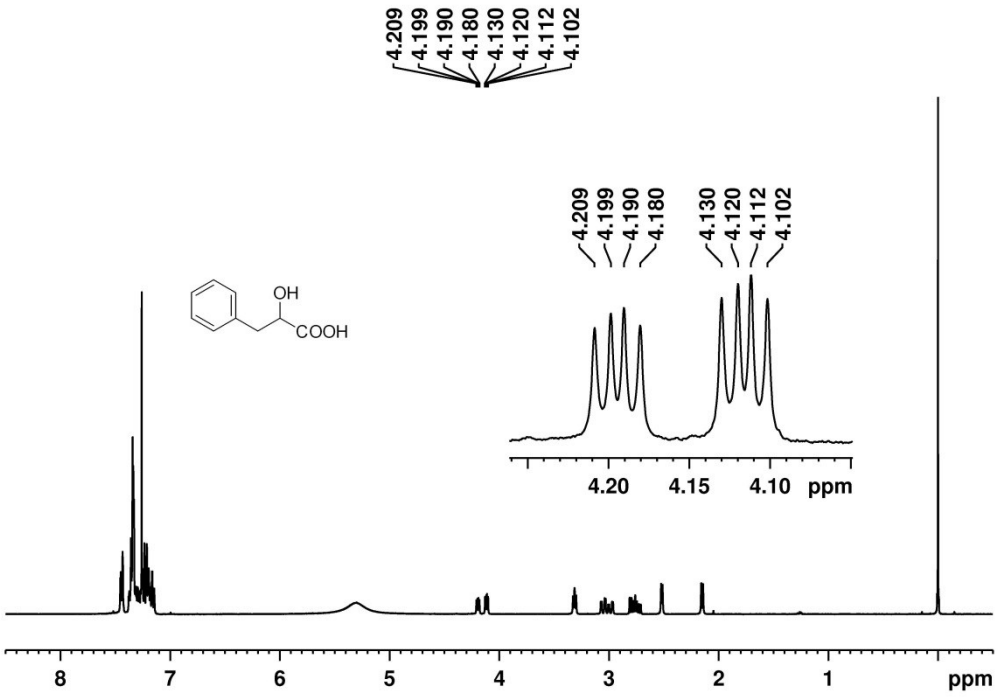


Figure S1r. ^{1}H NMR Spectra (400 MHz, $CDCl_3$) of (*S*)-aziridinyl diphenylmethanol 1 and (±)-2-hydroxy-3-phenylpropanoic acid.

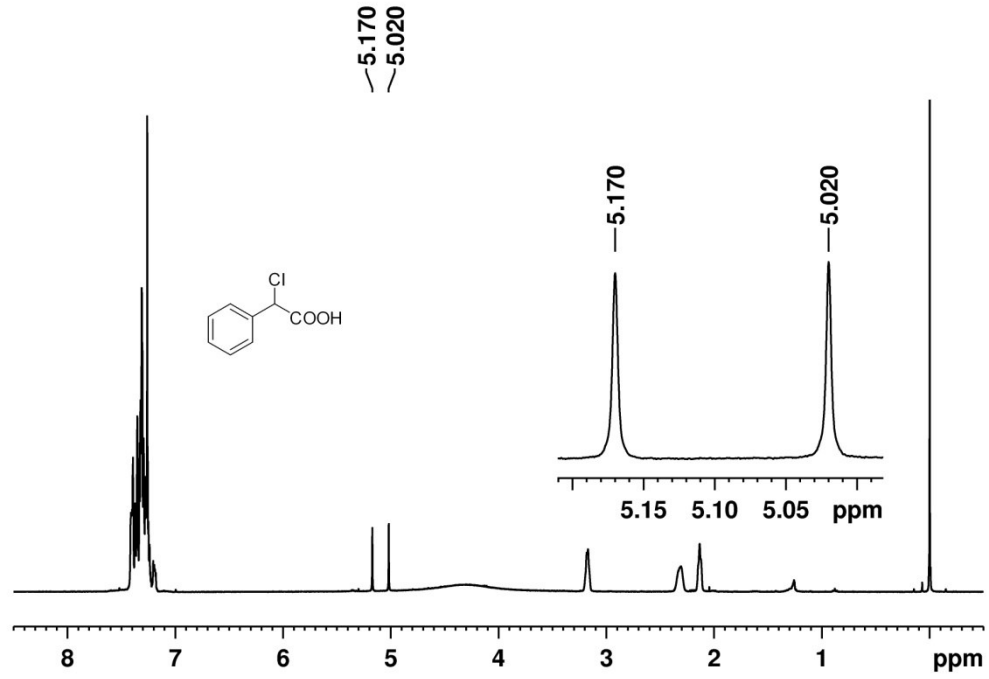


Figure S1s. ^{1}H NMR Spectra (400 MHz, $CDCl_3$) of (*S*)-aziridinyl diphenylmethanol 1 and (±)-α-chloro-phenylacetic acid .

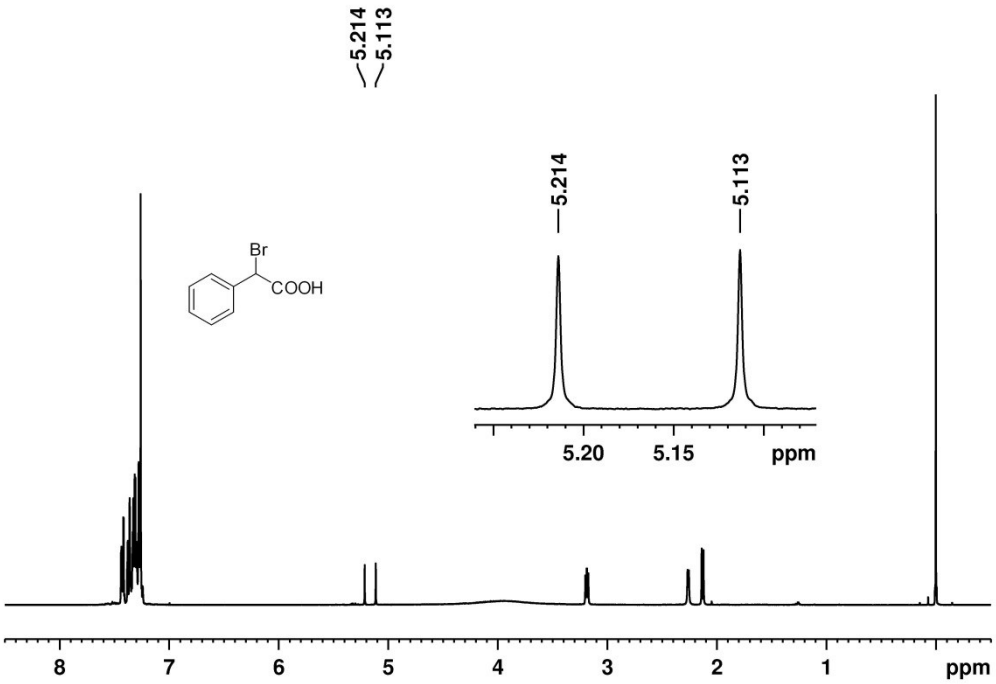


Figure S1t. ^{1}H NMR Spectra (400 MHz, $CDCl_3$) of (*S*)-aziridinyl diphenylmethanol 1 and (±)-α-bromo-phenylacetic acid.

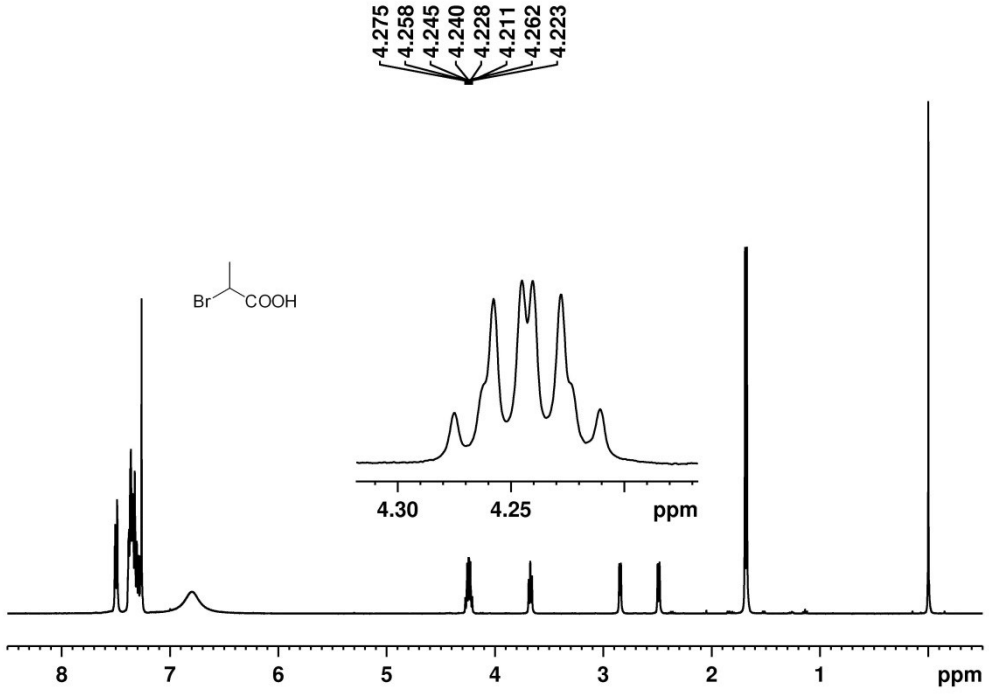


Figure S1u. ^{1}H NMR Spectra (400 MHz, $CDCl_3$) of (*S*)-aziridinyl diphenylmethanol 1 and (±)-2-bromopropanoic acid.

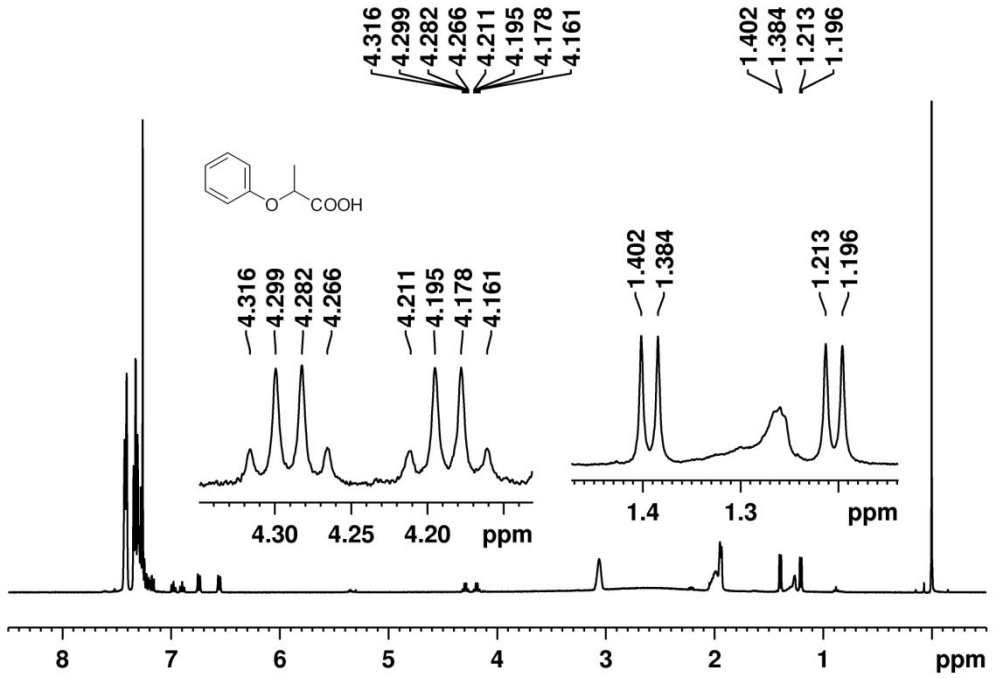


Figure S1v. ^{1}H NMR Spectra (400 MHz, $CDCl_3$) of (*S*)-aziridinyl diphenylmethanol 1 and (±)-2-phenoxypropanoic acid.

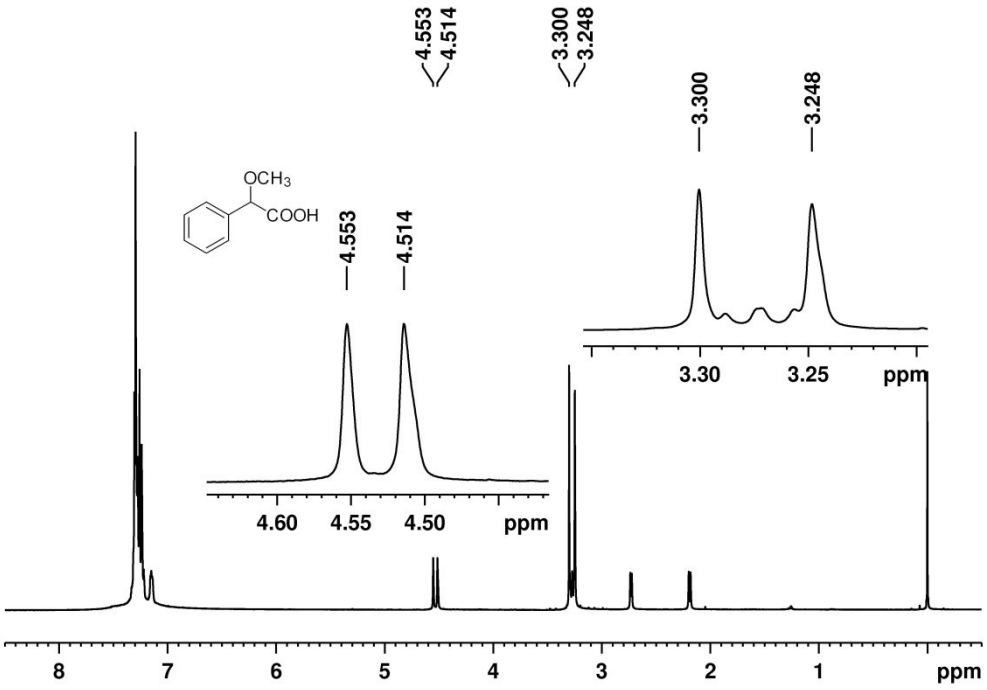


Figure S1w. ^{1}H NMR Spectra (400 MHz, $CDCl_3$) of (*S*)-aziridinyl diphenylmethanol 1 and (±)-2-methoxy-2-phenylacetic acid.

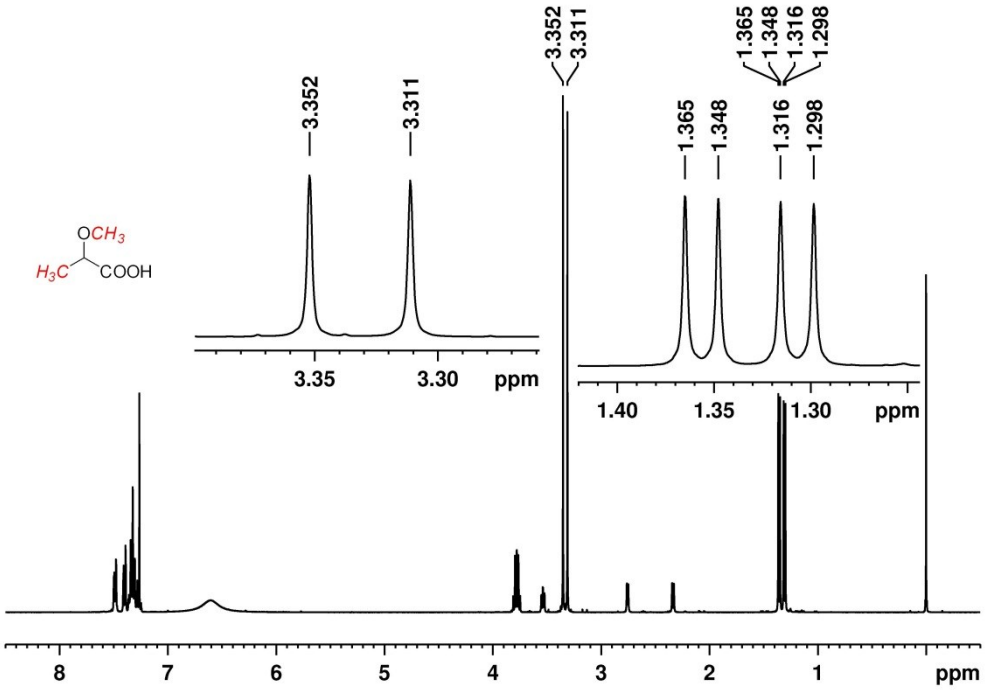


Figure S1x. ^{1}H NMR Spectra (400 MHz, $CDCl_3$) of (*S*)-aziridinyl diphenylmethanol 1 and (±)-2-methoxypropanoic acid.

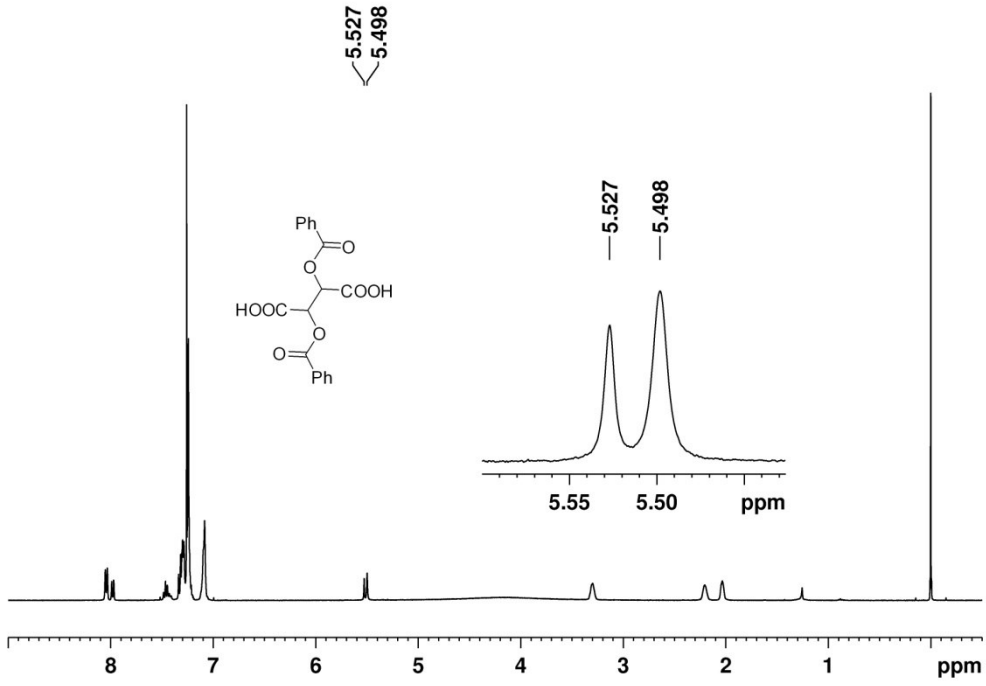


Figure S1y. ^{1}H NMR Spectra (400 MHz, $CDCl_3$) of (*S*)-aziridinyl diphenylmethanol 1 and (±)-2,3-bis(benzoyloxy)succinic acid.

8. ^{19}F NMR spectroscopy (*S*)-aziridinyl diphenylmethanol and fluorine-containing *α*-substituted carboxylic acids

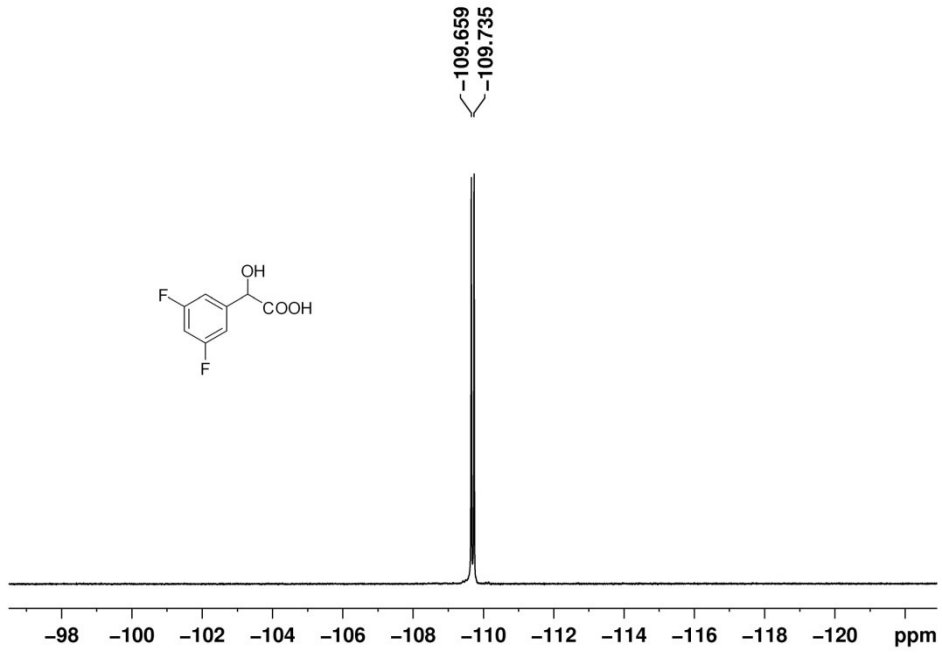


Figure S2a. ^{19}F NMR Spectra (376 MHz, $CDCl_3$) of (*S*)-aziridinyl diphenylmethanol 1 and (±)-3,5-difluoro-mandelic acid

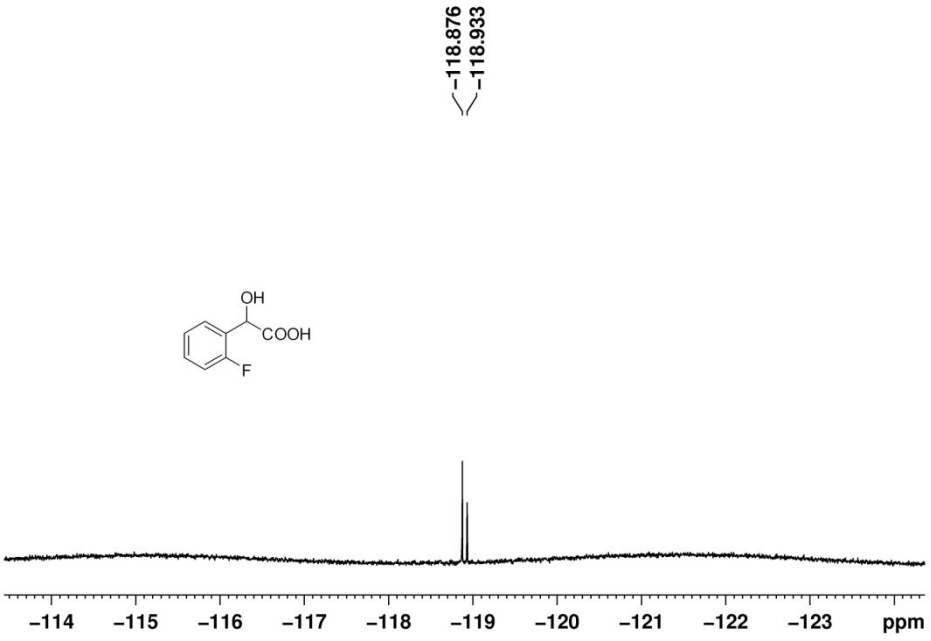


Figure S2b. ^{19}F NMR Spectra (376 MHz, $CDCl_3$) of (*S*)-aziridinyl diphenylmethanol 1 and (±)-2-fluoro-mandelic acid

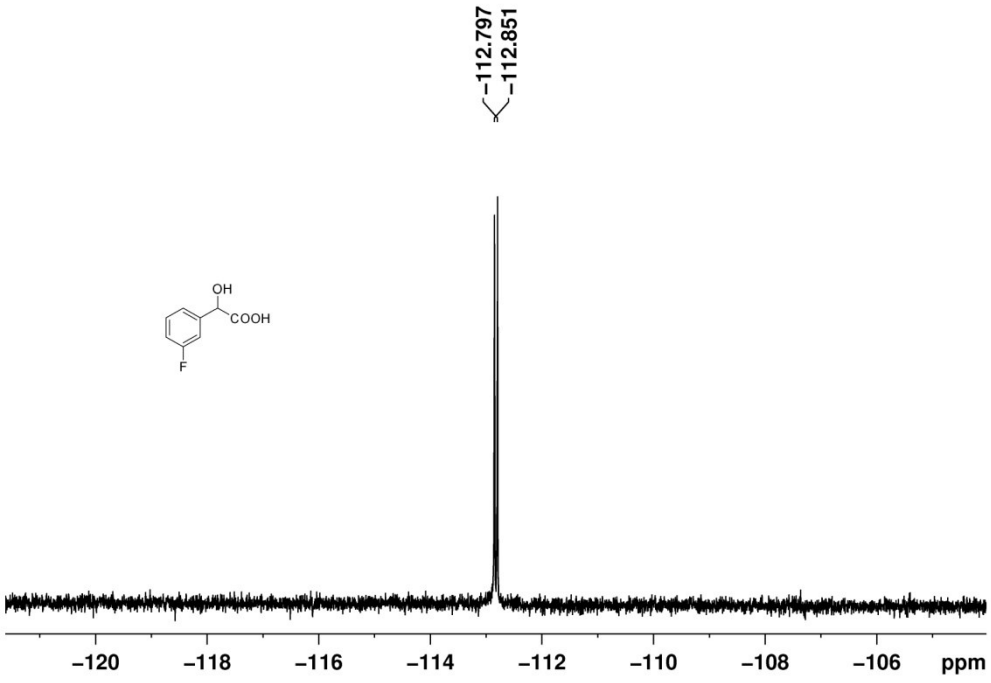


Figure S2c. ^{19}F NMR Spectra (376 MHz, $CDCl_3$) of (*S*)-aziridinyl diphenylmethanol 1 and (±)-3-fluoro-mandelic acid

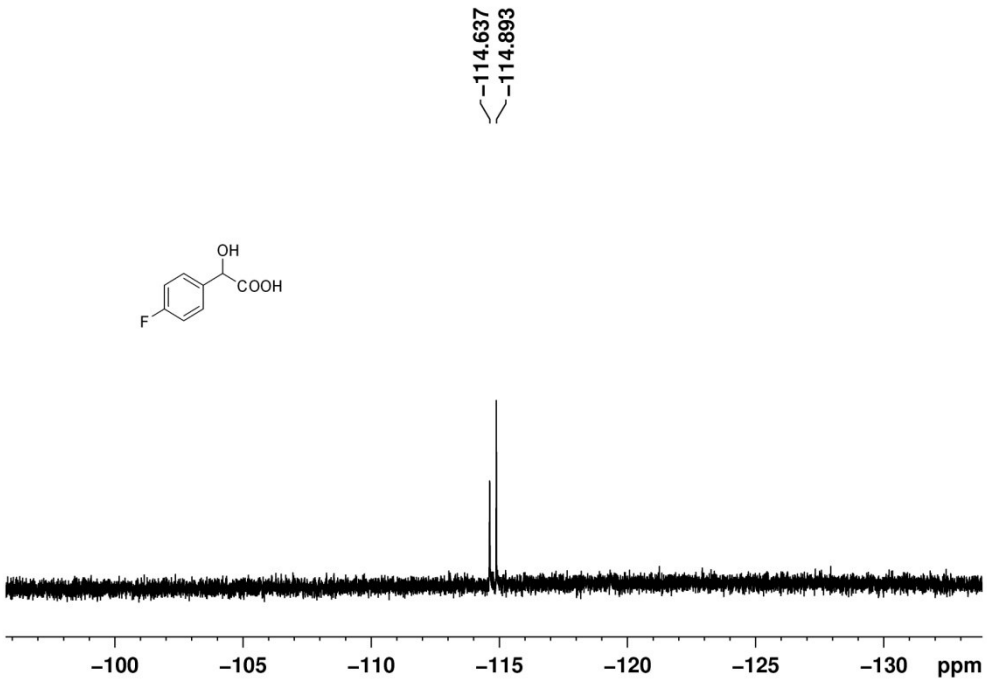


Figure S2d. ^{19}F NMR Spectra (376 MHz, $CDCl_3$) of (*S*)-aziridinyl diphenylmethanol 1 and (±)-4-fluoro-mandelic acid

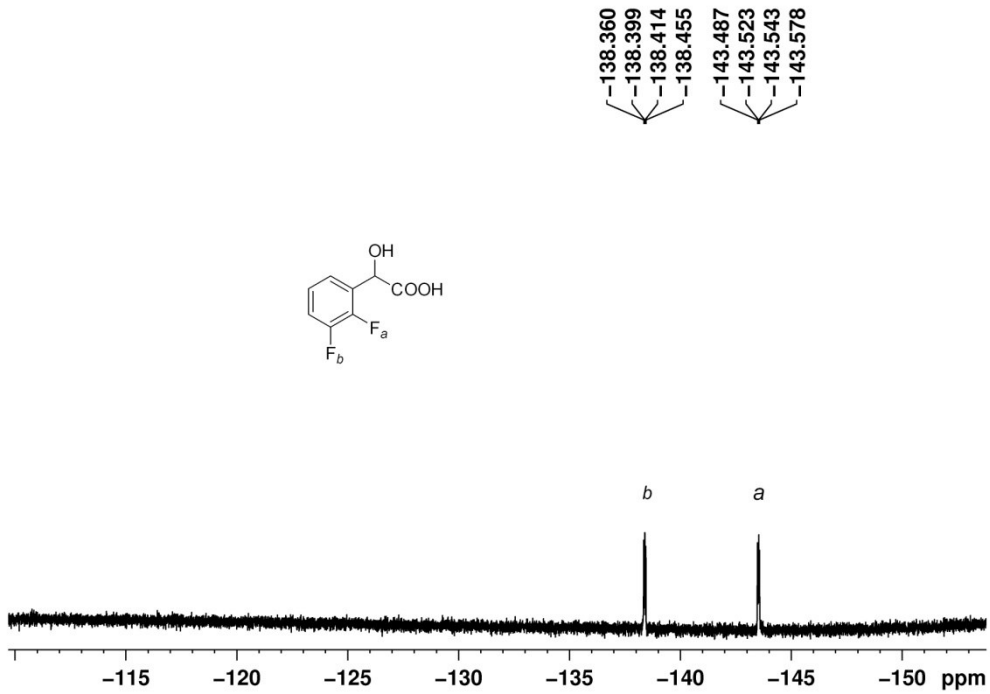


Figure S2e. ^{19}F NMR Spectra (376 MHz, $CDCl_3$) of (*S*)-aziridinyl diphenylmethanol 1 and (±)-2,3-difluoro-mandelic acid

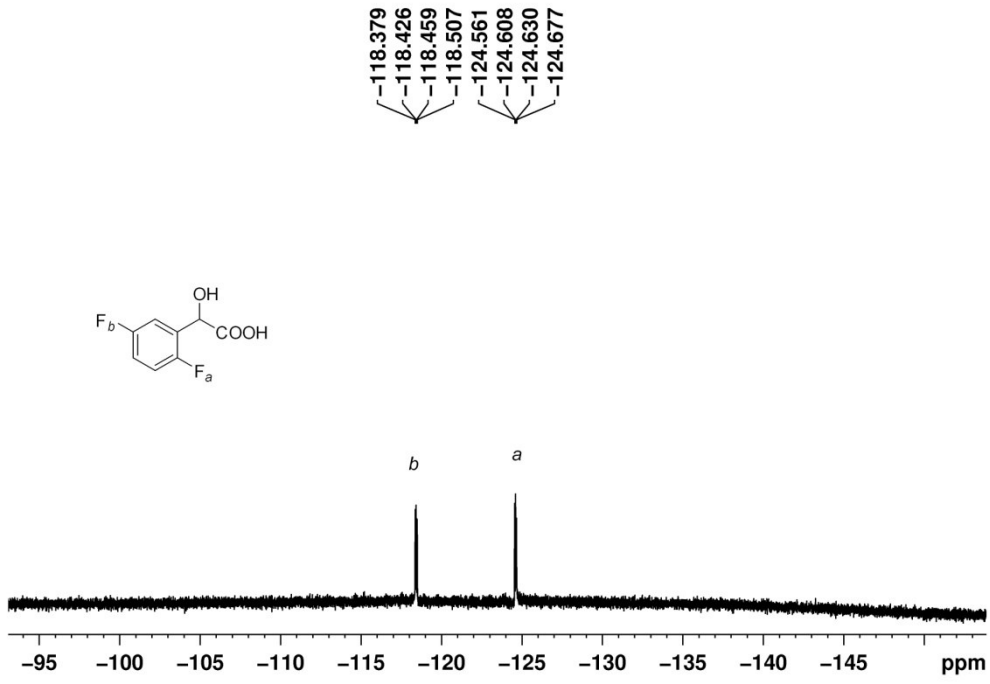


Figure S2f. ^{19}F NMR Spectra (376 MHz, $CDCl_3$) of (*S*)-aziridinyl diphenylmethanol 1 and (±)-2,5-difluoro-mandelic acid

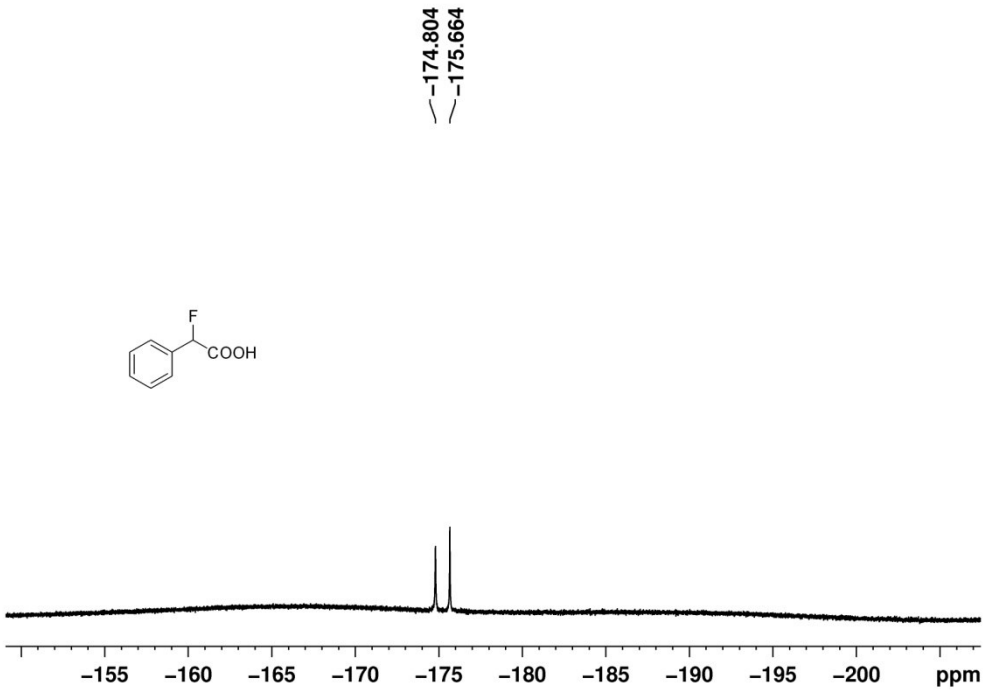


Figure S2g. ^{19}F NMR Spectra (376 MHz, $CDCl_3$) of (*S*)-aziridinyl diphenylmethanol 1 and (±)-α-fluoro-phenylacetic acid.

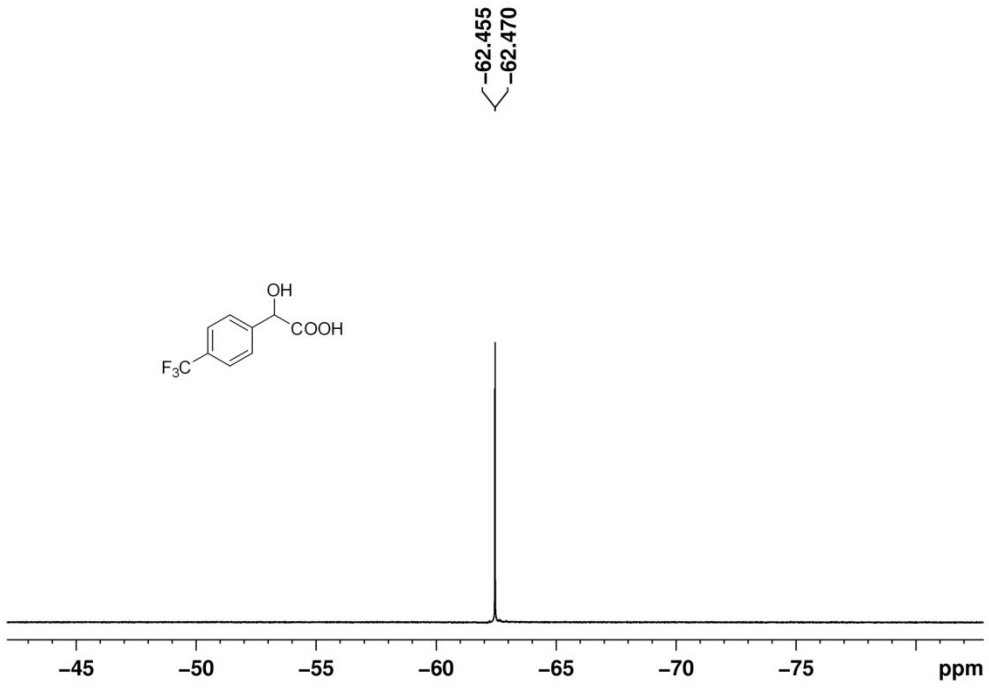


Figure S2h. ^{19}F NMR Spectra (376 MHz, $CDCl_3$) of (*S*)-aziridinyl diphenylmethanol 1 and (±)-4-trifluoromethyl-mandelic acid