Supporting Information

Stereodivergent Mannich reaction of bis(trimethylsilyl)ketenes with *N*-tert-butanesulfinyl imines by Lewis acid or Lewis base activation, a one pot protocol to obtain chiral β-amino acids.

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General remarks

The synthesis of sulfinyl imines[1] and bistrimethylsilylketenes[2] were done following reported procedures. The THF was distilled from sodium benzophenone ketyl and DCM from P_2O_5. ^{1}H and ^{13}C NMR were recorded at 300 or 400 MHz and 75 or 100 MHz respectively. Chemical shifts (δ) were reported in ppm and coupling constants are in Hertz. Mass spectra were obtained by DART and TOF mass spectrometer.

General procedure for the one-pot Mannich reaction.

In a 4 mL vial it were added the corresponding sulfinyl imine (0.48 mmol, 1 equiv.) and 26 mg (0.048 mmol, 0.1 equiv.) of TBAT. It was purged with N_2 and the solids were dissolved in: Method A 1.6 mL of DCM and to the solution added 0.2 mL (1.4 mmol, 3 equiv.) of $BF_3{\cdot}OEt_2$. Method B 1.6 mL of anhydrous THF. The reaction mixture was cooled with a ice-water and the corresponding bistrimethylsilylketene acetal (0.96 mmol, 2 equiv.) was added. After the addition, the reaction was warmed in a water bath at 20 °C and kept for 24 h. with stirring.

An aliquot of the reaction was taken to obtain the d.r. of the reaction and poured into a 1:1 mixture AcOEt/HCl 0.2 M, the aqueous layer was washed with AcOEt twice and the combined organic layers dried with Na_2SO_4 (anh.) and concentrated. The residue was dissolved in $CDCl_3$ and analyzed by ^{1}H NMR.

It was added to the reaction mixture 0.36 mL of MeOH and 0.24 mL (0.096 mmol, 2 equiv) of HCl 4M in dioxane and stirred for 24 h at room temperature. The next day was observed a solid and added AcOEt to induce more precipitation. The suspension was transferred to eppendorf tubes, centrifuged for 2 min. The liquid was removed with a Pasteur pipette and the solid was suspended again in AcOEt. It was put inside an ultrasonic bath (2 min.), centrifuged (2 min.) and again removed again the liquid. This washing of the solid was repeated twice. The solid that corresponds to the aminoacid hydrochloride was dried under high vacuum and weighed to obtain the yield showed in Tables 3, 4 and Figure 4.

The ESI contains the physical and spectroscopic data of the compounds obtained by Method B (only TBAT). The enantiomer obtained by method A have the same data only with opposite sign of optical rotation and lower magnitude because a lower diastereoselectivity in the Mannich reaction

(*S*)-3-Amino-2, 2-dimethyl-3-phenylpropanoic acid hydrochloride (**5a**).

White solid, $[\alpha]_D^{25}$ -29.3 (*c* 1, NaOH 1M). Lit.[3] $[\alpha]_D^{25}$ -31.6 (*c* 1.1, HCl 1M). ^{1}H NMR (300 MHz, D_2O): δ = 7.54-7.35 (m, 5H), 4.30 (s, 1H), 1.29 (s, 3H), 1.01 (s, 3H). ^{13}C NMR (75 MHz, D_2O): δ = 183.5, 135.3, 129.2, 129.0, 128.0, 62.0, 45.4, 24.9, 22.1. HRMS (DART/TOF): $[M+H]^+$ Calcd. for $C_{11}H_{16}NO_2$ 194.1181; found 194.1183.

(*S*)-3-Amino-2,2-dimethyl-3-(4-nitrophenyl)propanoic acid hydrochloride (**5b**).

Yellow solid, $[\alpha]_D^{25}$ -27 (*c* 0.2, NaOH 1M). ^{1}H NMR (300 MHz, D_2O): δ = 8.30 (s, 2H), 7.64 (s, 2H), 4.72 (s, 1H), 1.33 (s, 3H), 1.20 (s, 3H). ^{13}C NMR (75 MHz, D_2O): δ = 178.9, 148.2, 140.7, 129.4, 124.2, 60.4, 45.2, 23.3, 20.9. HRMS (DART/TOF): $[M+H]^+$ Calcd for $C_{11}H_{15}N_2O_4$ 239.1031; found 239.1028.

(*S*)-3-Amino-3-(4-(methoxycarbonyl)phenyl)-2,2-dimethylpropanoic acid hydrochloride (**5c**).

White solid, $[\alpha]_D^{25}$ -19.2 (*c* 0.26 in NaOH 1M). ^{1}H NMR (300 MHz, D_2O): δ = 8.04 (s, 2H), 7.51 (s, 2H), 4.64 (s, 1H), 3.91 (s, 3H), 1.32 (s, 3H), 1.19 (s, 3H). ^{13}C NMR (75 MHz, D_2O): δ = 178.8, 168.5, 138.7, 130.4, 129.8, 128.2, 60.6, 52.7, 45, 23.1, 20.7. HRMS (DART/TOF): $[M+H]^+$ Calcd for $C_{13}H_{18}NO_4$ 252.1235; found 252.1244.

(*S*)-3-Amino-2,2-dimethyl-3-(4-(trifluoromethyl)phenyl)propanoic acid hydrochloride (**5d**).

White solid, $[\alpha]_D^{25}$ -14.8 (*c* 0.31, NaOH 1M). ^{1}H NMR (300 MHz, D_2O): δ = 7.79 (d, *J* = 7.5 Hz, 2H), 7.56 (d, *J* = 7.5 Hz, 2H), 4.65 (s, 1H), 1.32 (s, 3H), 1.19 (s, 3H). ^{13}C NMR (100 MHz, D_2O): δ = 178.8, 137.5, 130.8 (q, *J* = 32.5 Hz), 128.5, 125.9 (q, *J* = 3.4 Hz), 123.8 (q, *J* = 271.9 Hz), 60.6, 45, 23.2, 20.7. HRMS (DART/TOF): $[M+H]^+$ Calcd for $C_{12}H_{15}F_3NO_2$ 262.1054; found 262.1048.

(*S*)-3-Amino-3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dimethylpropanoic acid hydrochloride (**5e**).

White solid, $[\alpha]_D^{25}$ -45.2 (*c* 0.25, NaOH 1M). ^{1}H NMR (300 MHz, D_2O): δ = 8.24 (s, 1H), 8.05 (s, 2H), 1.38 (s, 3H), 1.24 (s, 3H). ^{13}C NMR (100 MHz, D_2O): δ = 178.7, 135.8, 131.6 (q, *J* = 33.6 Hz), 128.70 – 128.46 (m), 123.9 (m), 123 (q, 202.7 Hz), 60.25, 45.12, 23.07, 20.52. HRMS (DART/TOF): $[M+H]^+$ Calcd for $C_{13}H_{14}F_6NO_2$ 330.0928; found 330.0917.

(S)-3-Amino-2,2-dimethyl-3-(p-tolyl)propanoic acid hydrochloride (**5f**).

White solid, $[\alpha]_D^{25}$ -3 (*c* 0.36, NaOH 1M). ^{1}H NMR (300 MHz, D_2O): δ = 7.28 (s, 4H), 4.49 (s, 1H), 2.34 (s, 3H), 1.31 (s, 3H), 1.17 (s, 3H). ^{13}C NMR (75 MHz, D_2O): δ = 179.6, 140, 130.7, 129.6, 128.0, 61.1, 45.3, 23.4, 21.0, 20.3. HRMS (DART/TOF): $[M+H]^+$ Calcd for $C_{12}H_{18}NO_2$ 208.1337; found 208.1337.

(S)-3-Amino-3-(4-methoxyphenyl)-2,2-dimethylpropanoic acid hydrochloride (**5g**).

White solid, $[\alpha]_D^{25}$ +16.0 (*c* 0.4, NaOH 1M). ^{1}H NMR (300 MHz, D_2O): δ = 7.22 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.6 Hz, 2H), 4.39 (s, 1H), 3.71 (s, 3H), 1.19 (s, 3H), 1.06 (s, 3H). ^{13}C NMR (75 MHz, Deuterium Oxide) δ 179, 159.5, 129.4, 126, 114.3, 60.6, 55.4, 45.2, 23.2, 20.8. HRMS (DART/TOF): $M+H]^+$ Calcd for $C_{12}H_{18}NO_3$ 224.1286; found 224.1292.

(R)-3-Amino-2,2-dimethyl-3-(thiophen-2-yl)propanoic acid hydrochloride (**5h**).

White solid, $[\alpha]_D^{25}$ +29.5 (*c* 0.2, NaOH 1M). ^{1}H NMR (300 MHz, D_2O): δ = 7.52 (d, *J* = 5.1 Hz, 1H), 7.23 (d, *J* = 3.6 Hz, 1H), 7.11 (t, *J* = 4.3 Hz, 1H), 4.87 (s, 1H), 1.37 (s, 3H), 1.23 (s, 3H). ^{13}C NMR (100 MHz, D_2O): δ = 179, 134.7, 129.4, 127.7, 127.3, 57.1, 45.2, 23.1, 21. HRMS (DART/TOF): $[M+H]^+$ Calcd for $C_9H_{14}NO_2S$ 200.0745; found 200.0743.

(S)-3-Amino-2,2-dimethyl-3-(naphthalen-1-yl)propanoic acid hydrochloride (**5i**).

White solid, ^{1}H NMR (300 MHz, D_2O): δ = 8.34 – 8.16 (m, 1H), 8.03 (s, 1H), 7.81 – 7.40 (m, 2H), 5.55 (s, 1H), 1.36 (s, 1H), 1.16 (s, 7H). ^{13}C NMR (75 MHz, D_2O): δ = 179.9, 133.6, 131.4, 130.6, 130.2, 129.3, 127.4, 126.7, 125.5, 124.7, 122.9, 54.7, 46.3, 24.1, 20.7. HRMS (DART/TOF): $[M+H]^+$ Calcd for $C_{15}H_{18}NO_2$ 244.1337; found 244.1327.

(S)-1-(1-Amino-1-phenylmethyl)cyclobutane-1-carboxylic acid hydrochloride (**6a**).

White solid, $[\alpha]_D^{25}$ +10.9 (*c* 0.11, NaOH 1M). ^{1}H NMR (300 MHz, D_2O): δ = 7.44 – 7.37 (m, 3H), 7.37 – 7.31 (m, 2H), 4.60 (s, 1H), 2.34 – 2.17 (m, 3H), 1.96 – 1.82 (m, 3H). ^{13}C NMR (75 MHz, D_2O): δ = 182.4, 134.3, 129.2, 129.1, 127.3, 60.1, 50.9, 30.2, 27, 14.8. HRMS (DART/TOF): $[M+H]^+$ Calcd for $C_{12}H_{16}NO_2$ 206.1181; found 206.1183.

(S)-1-(1-Amino-1-phenylmethyl)cyclopentane-1-carboxylic acid hydrochloride (**6b**).

White solid, $[\alpha]_D^{25}$ -10.9 (*c* 0.11, NaOH 1M). ^{1}H NMR (400 MHz, D_2O): δ 7.45 – 7.38 (m, 3H), 7.38 – 7.31 (m, 2H), 4.48 (s, 1H), 2.23 – 2.11 (m, 1H), 1.93 – 1.76 (m, 2H), 1.74 – 1.49 (m, 5H). ^{13}C NMR (100 MHz, D_2O): δ

= 178.7, 134.2, 129.5, 129.1, 127.3, 60.7, 57.3, 35.8, 32.9, 24.0, 23.7. HRMS (DART/TOF): $[M+H]^+$ Calcd for $C_{13}H_{18}NO_2$ 220.1337; found 220.1337.

(*S*)-1-(1-Amino-1-phenylmethyl)cyclohexane-1-carboxylic acid (**6c**).

White solid, $[\alpha]_D^{25}$ -12.3 (*c* 0.26, NaOH 1M). ^1H NMR (300 MHz, D_2O): δ = 7.39 (s, 3H), 7.28 (s, 2H), 4.24 (s, 1H), 1.61 – 1.04 (m, 10H). ^{13}C NMR (75 MHz, D_2O): δ = 181.2, 134.6, 129.2, 128.8, 127.6, 60.9, 50.1, 33.8, 31.2, 25.2, 22.8, 22.2. HRMS (DART/TOF): $[M+H]^+$ Calcd for $C_{14}H_{20}NO_2$ 234.1494; found 234.1490.

2. References

1. G. Liu, D. A. Cogan, T. D. Owens, T. P. Tang, J. A. Ellman, *J. Org. Chem.*, **1999**, *64*, 1278-1284.

2. C. Ainsworth, Y. N. Kuo, *J. Organomet. Chem.*, **1976**, *46*, 73-87.

3. V. H. Kunz, D. Schanzenbach, *Angew. Chem.* **1989**, 101, 1042-1043.

3. Spectra of the β-amino acids hydrochlorides 5 and 6

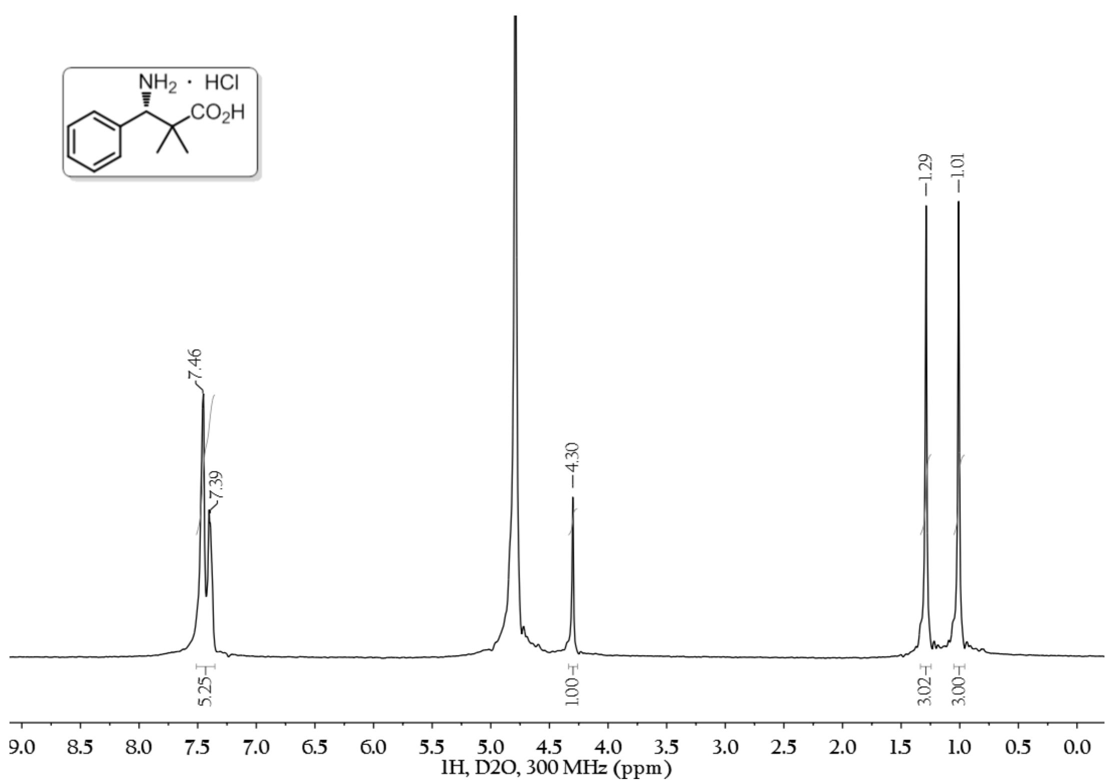

Figure S1. ^1H-NMR spectrum of **5a**

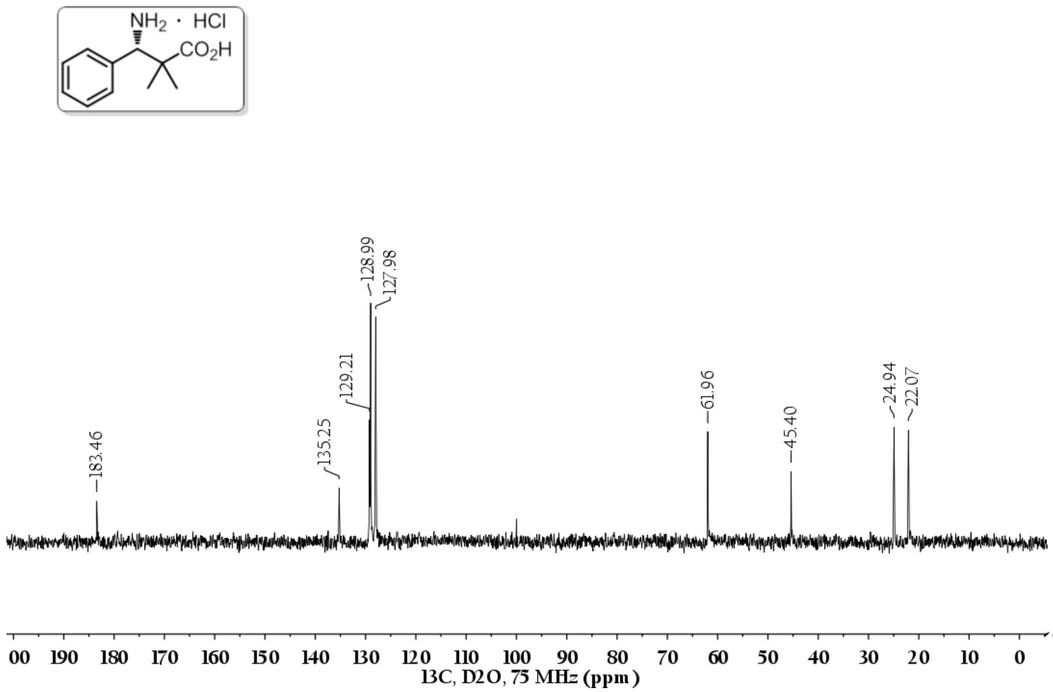

Figure S2. ^{13}C-NMR spectrum of **5a**

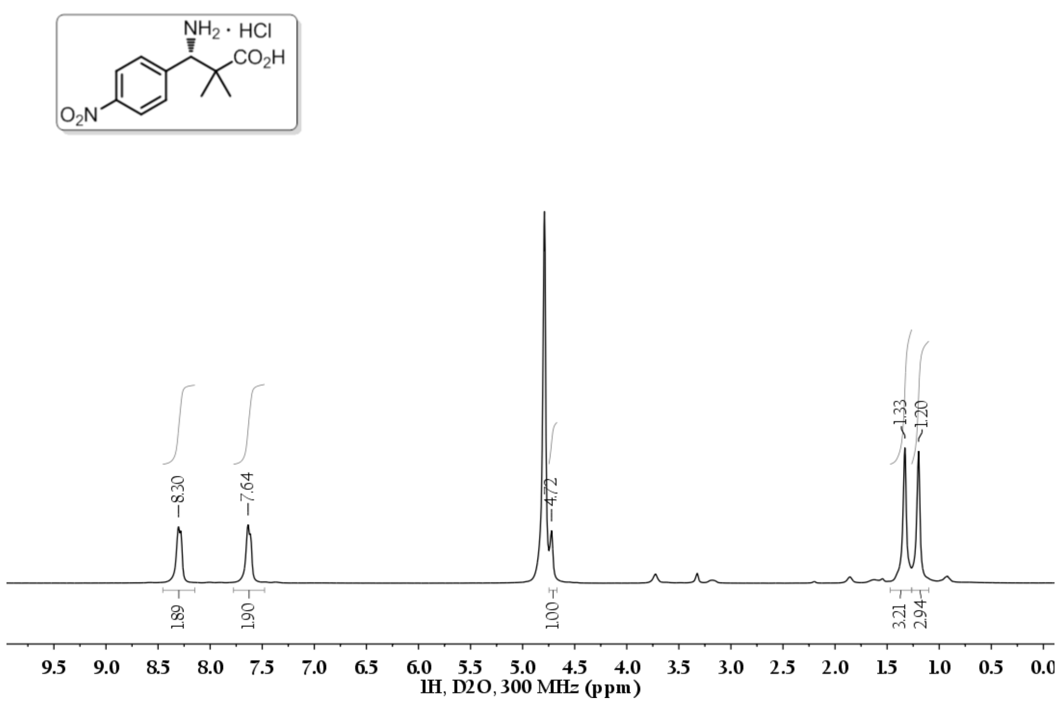

Figure S3. ^{1}H-NMR spectrum of **5b**

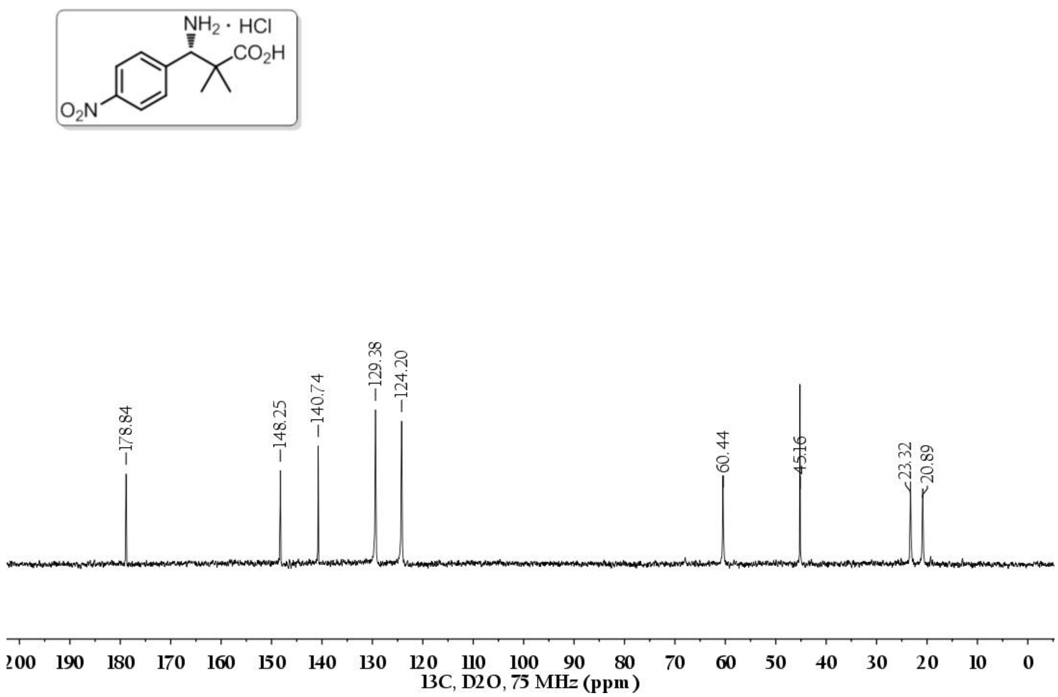

Figure S4. ^{13}C-NMR spectrum of **5b**

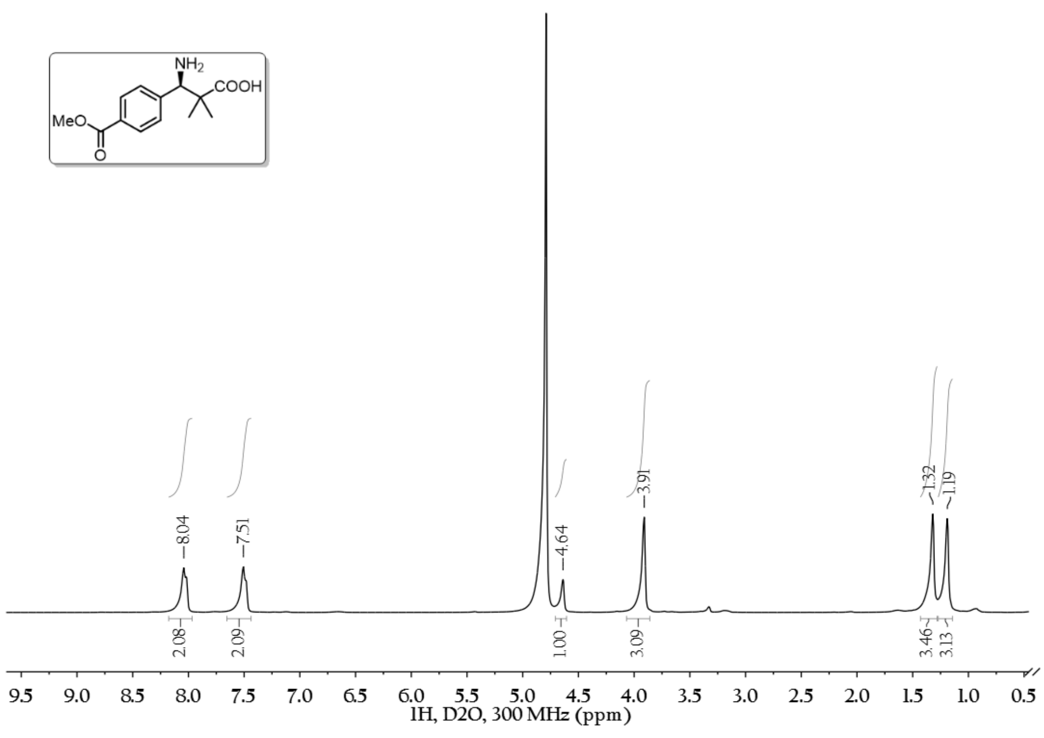

Figure S5. ^{1}H-NMR spectrum of **5c**

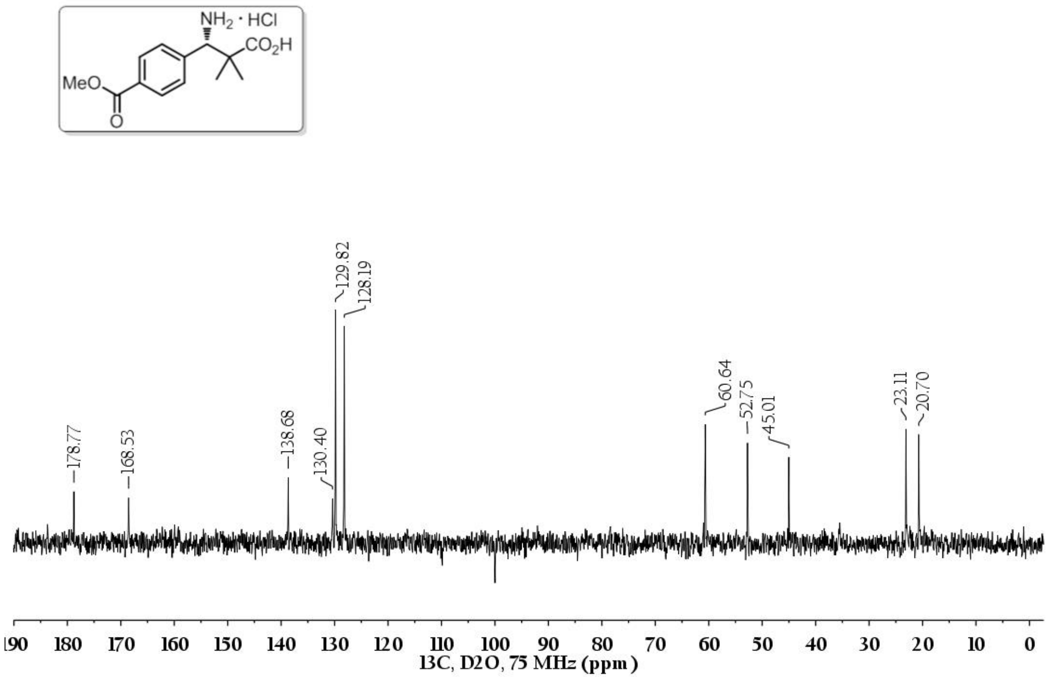

Figure S6. ^{13}C-NMR spectrum of **5c**

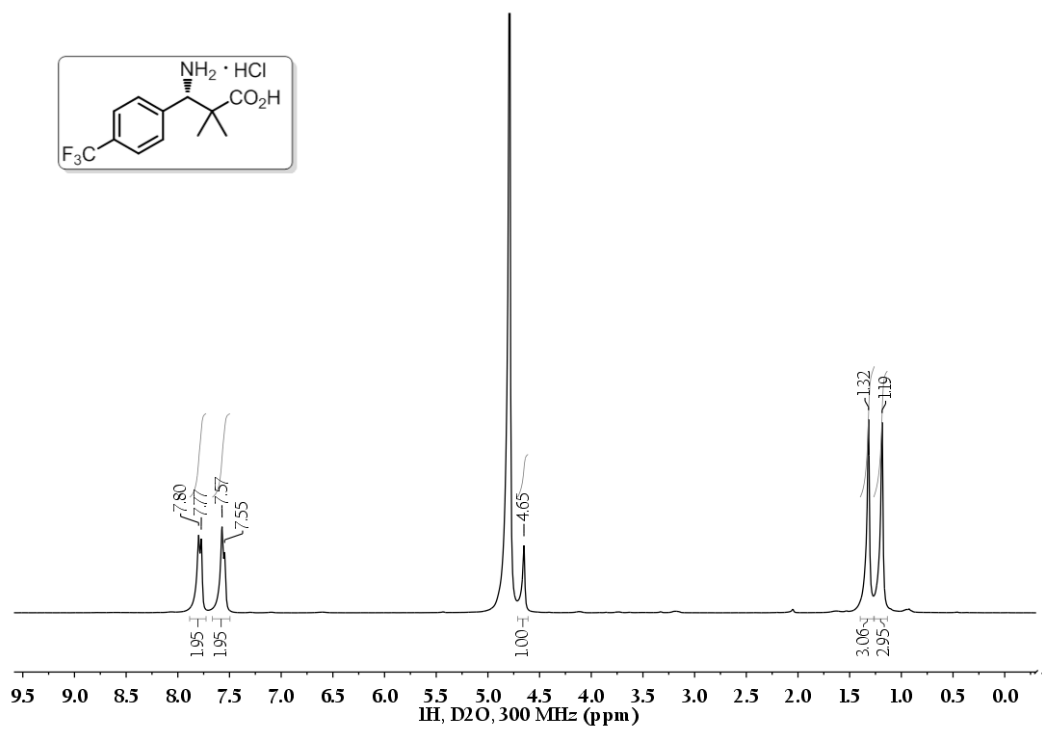

Figure S7. ^{1}H-NMR spectrum of **5d**

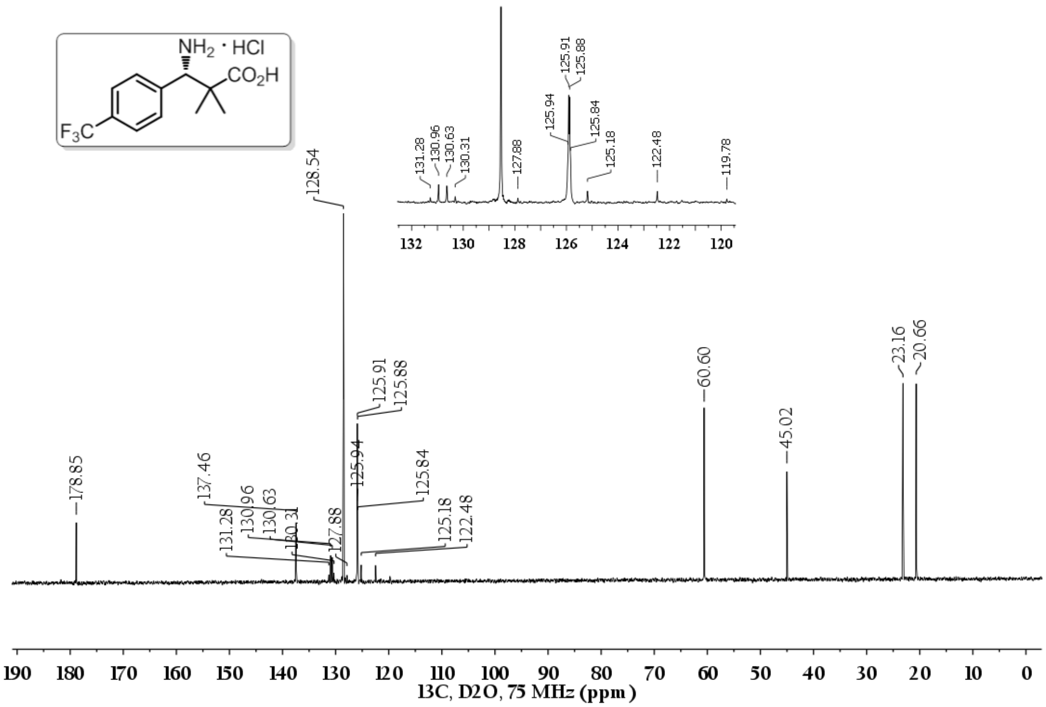

Figure S8. ^{13}C-NMR spectrum of **5d**

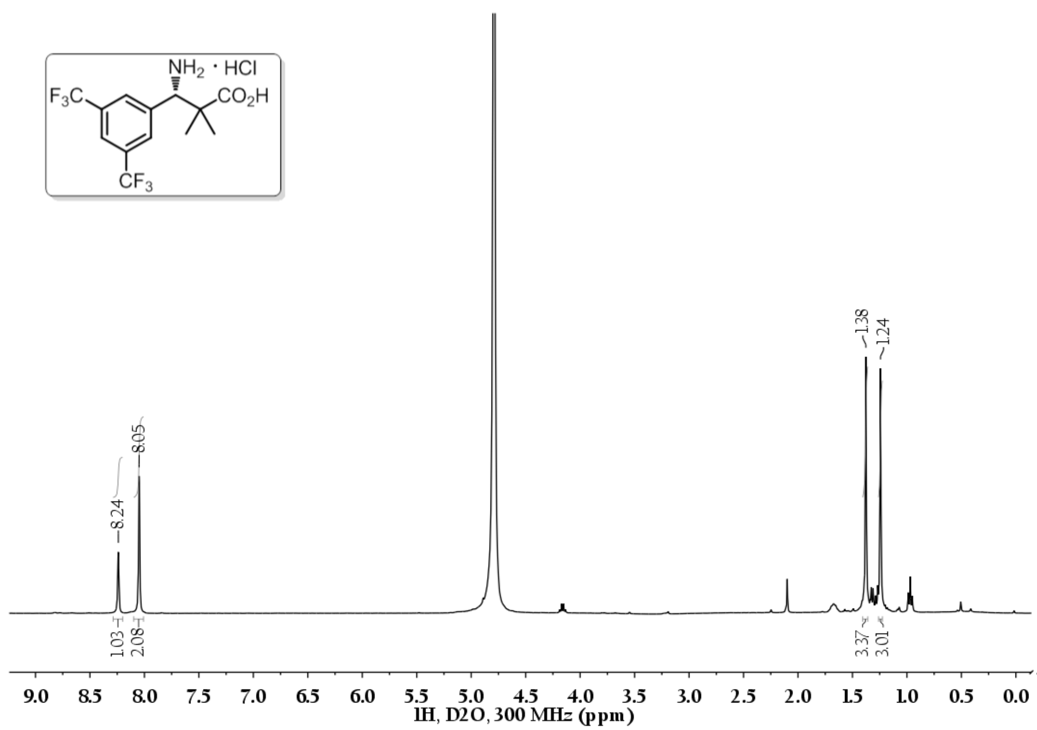

Figure S9. ^{1}H-NMR spectrum of **5e**

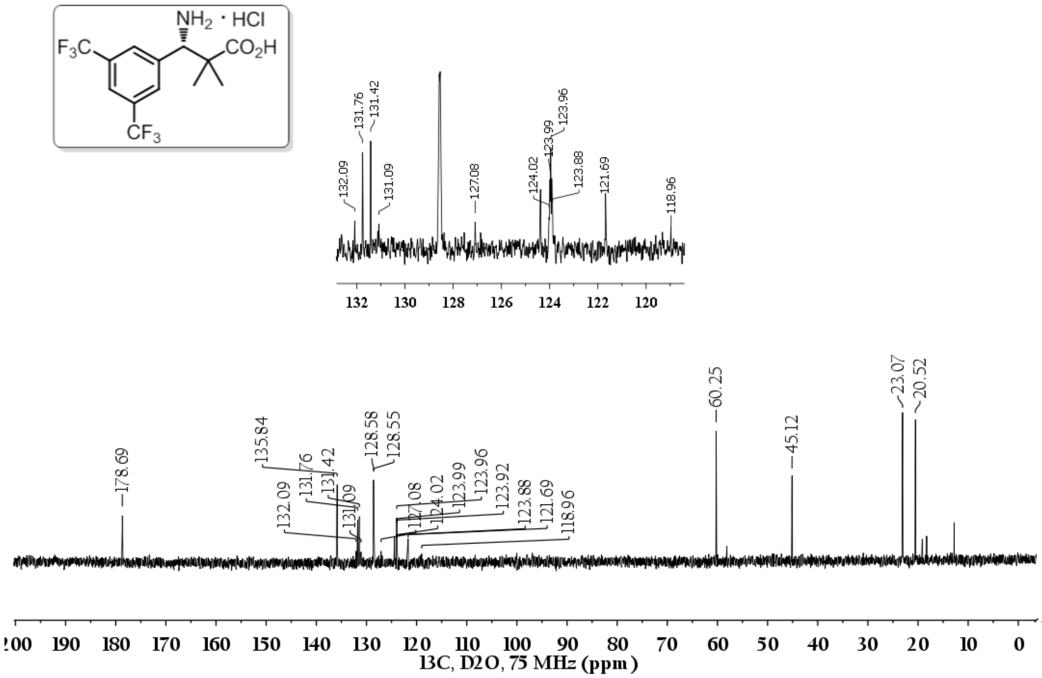

Figure S10. ^{13}C-NMR spectrum of **5e**

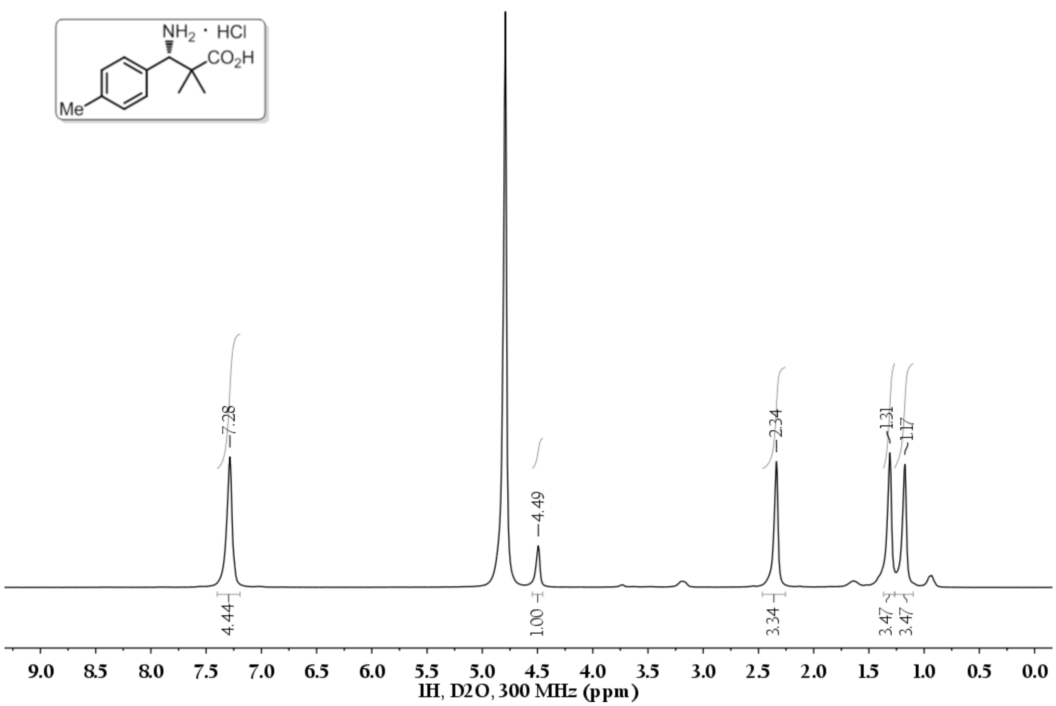

Figure S11. ^{1}H-NMR spectrum of **5f**

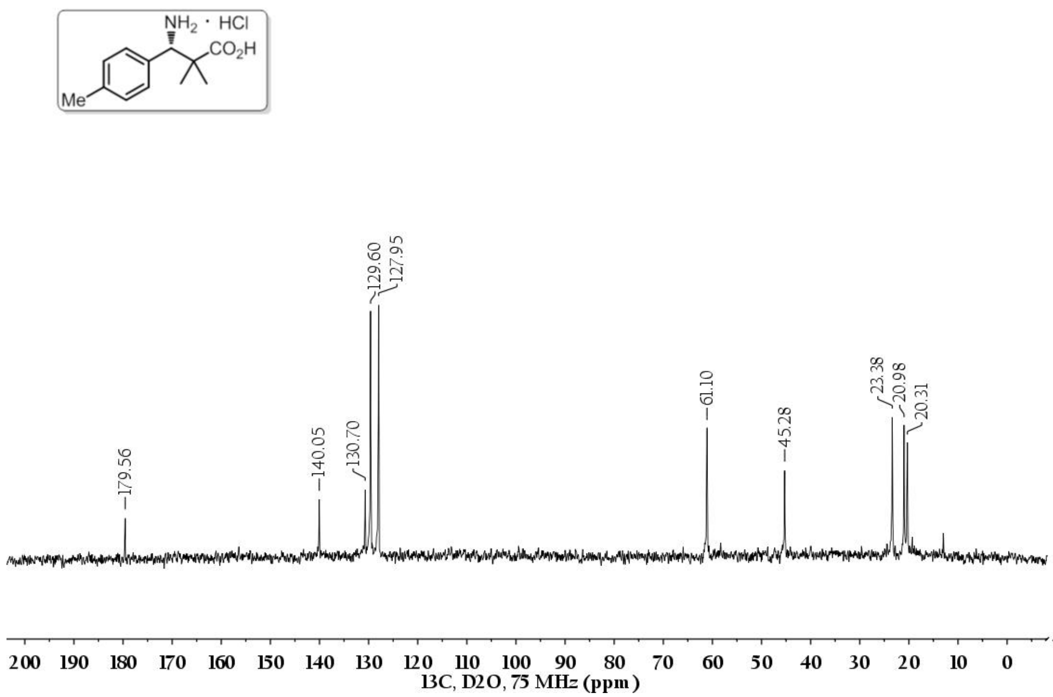

Figure S12. ^{13}C-NMR spectrum of **5f**

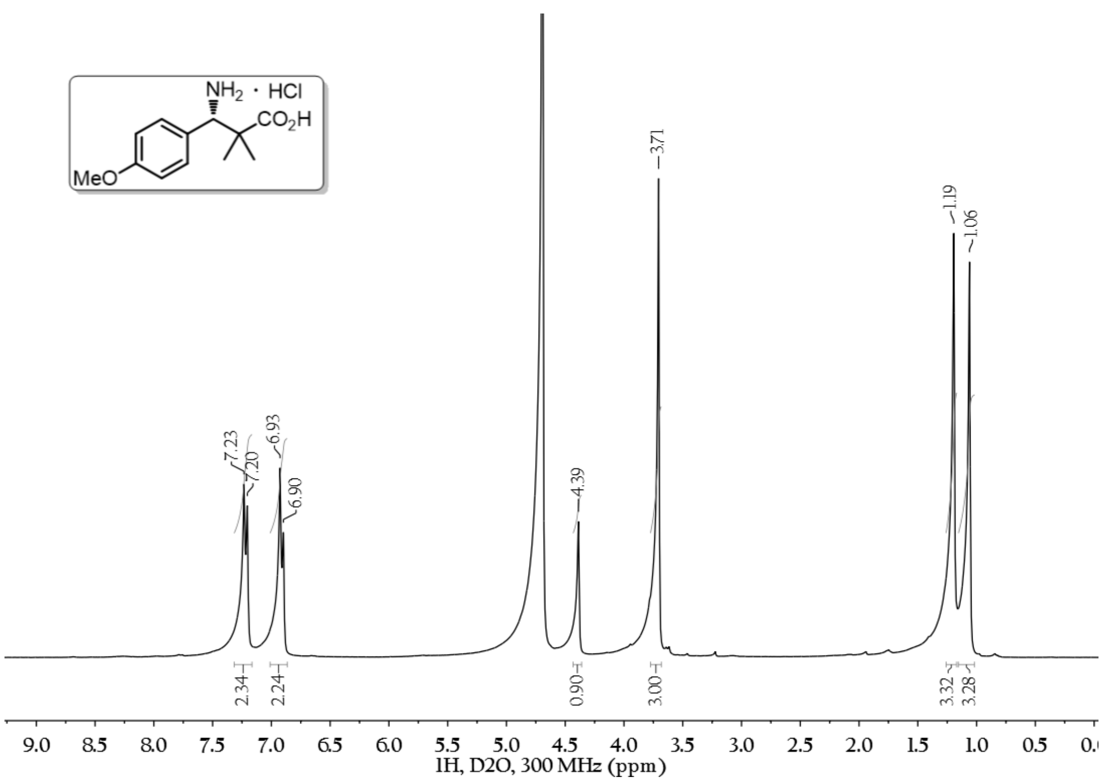

Figure S13. ^{1}H-NMR spectrum of **5g**

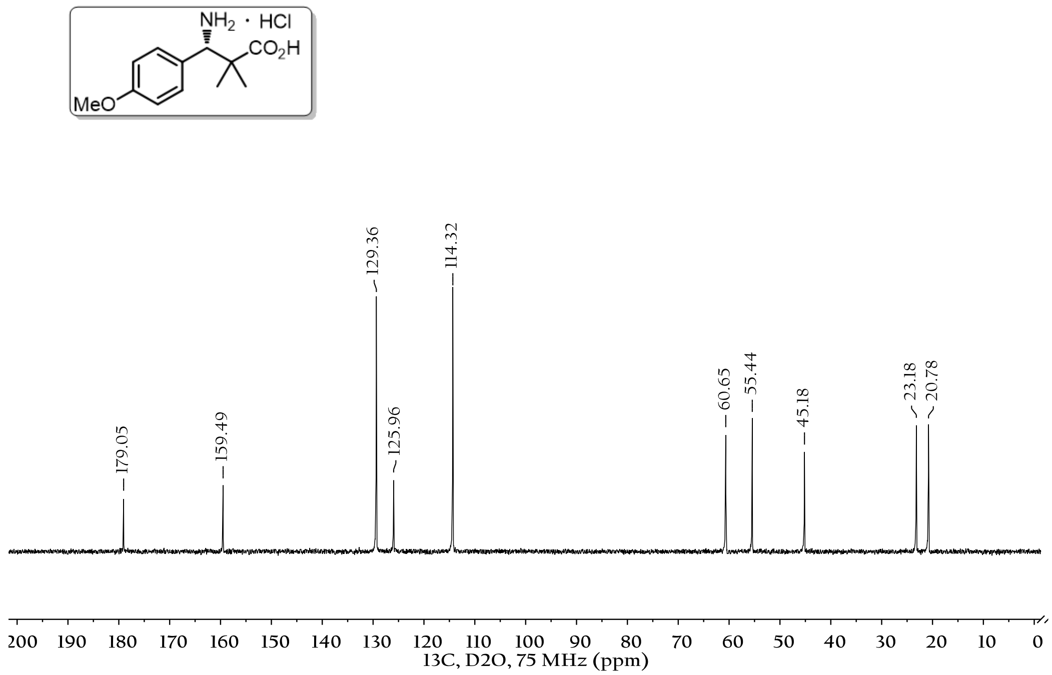

Figure S14. ^{13}C-NMR spectrum of **5g**

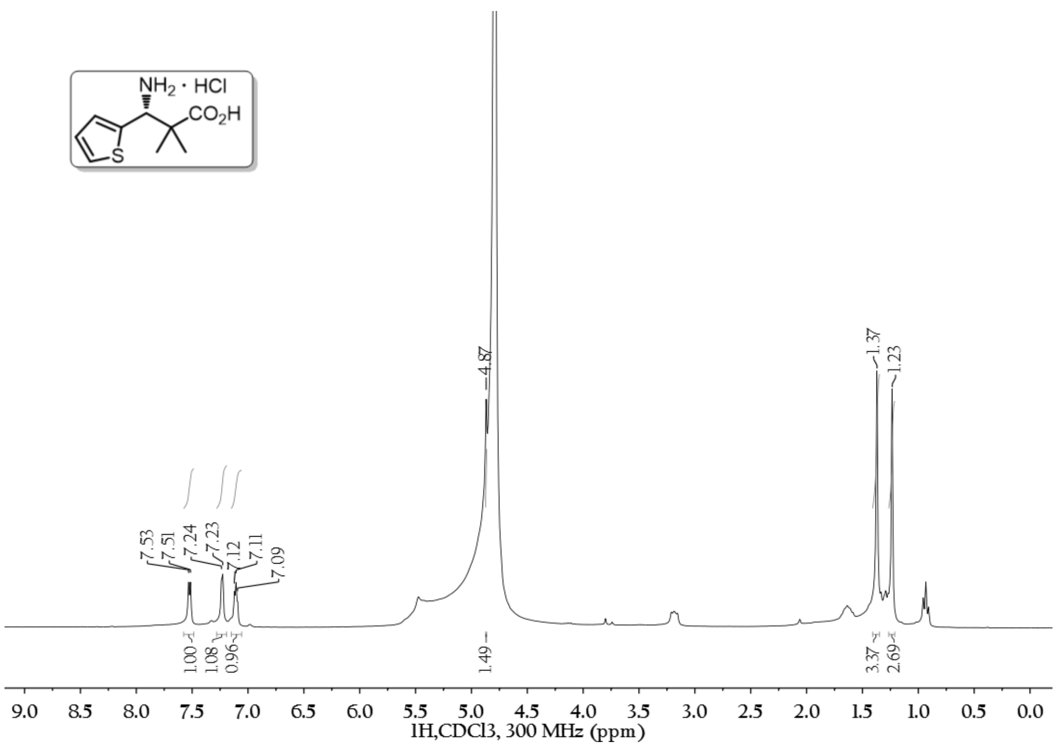

Figure S15. ^{1}H-NMR spectrum of **5h**

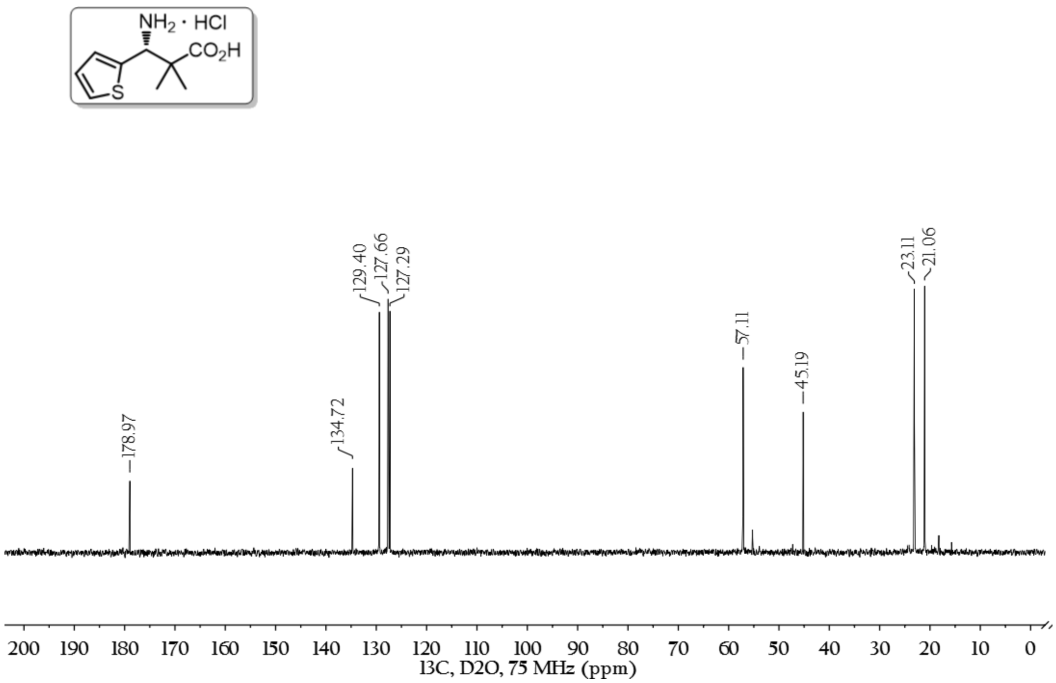

Figure S16. ^{13}C-NMR spectrum of **5h**

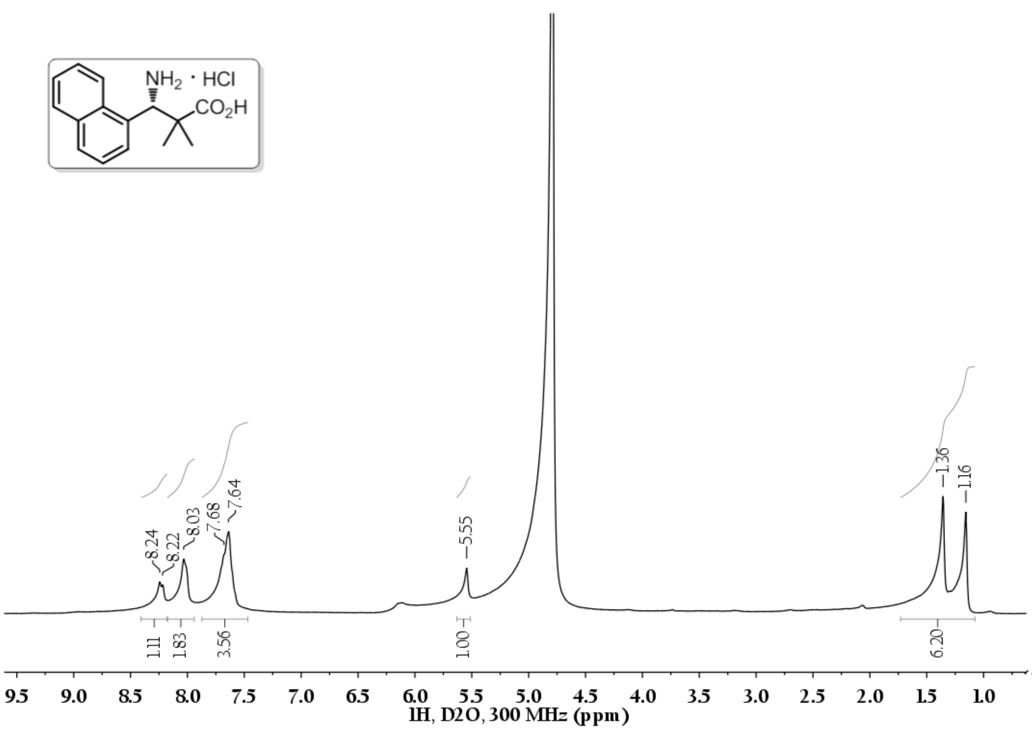

Figure S17. ^{1}H-NMR spectrum of **5i**

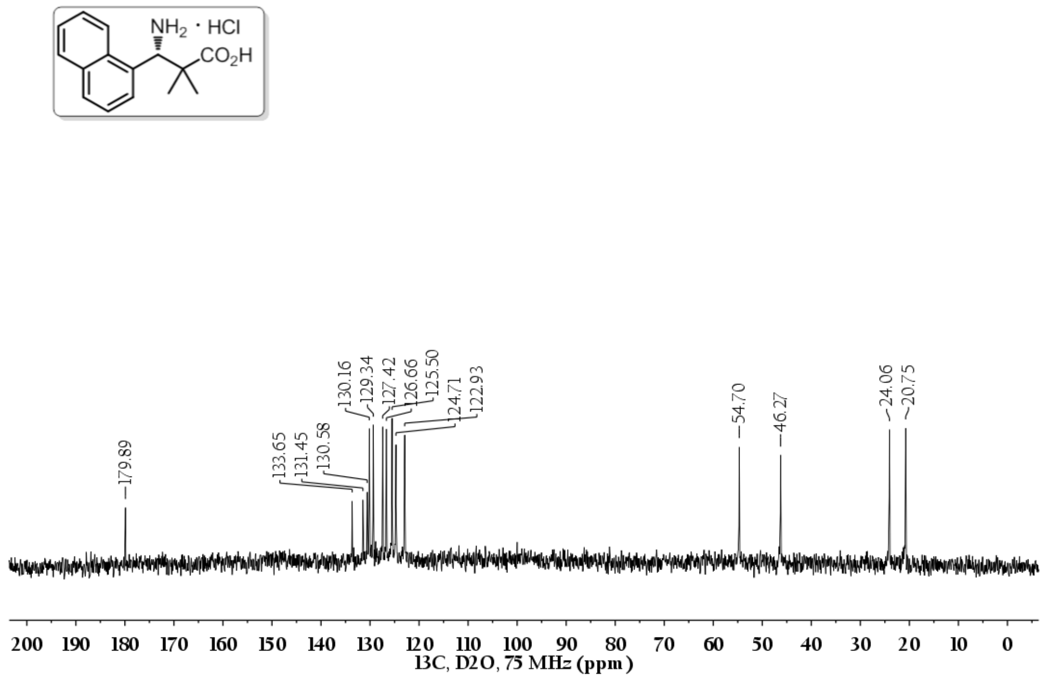

Figure S18. ^{13}C-NMR spectrum of **5i**

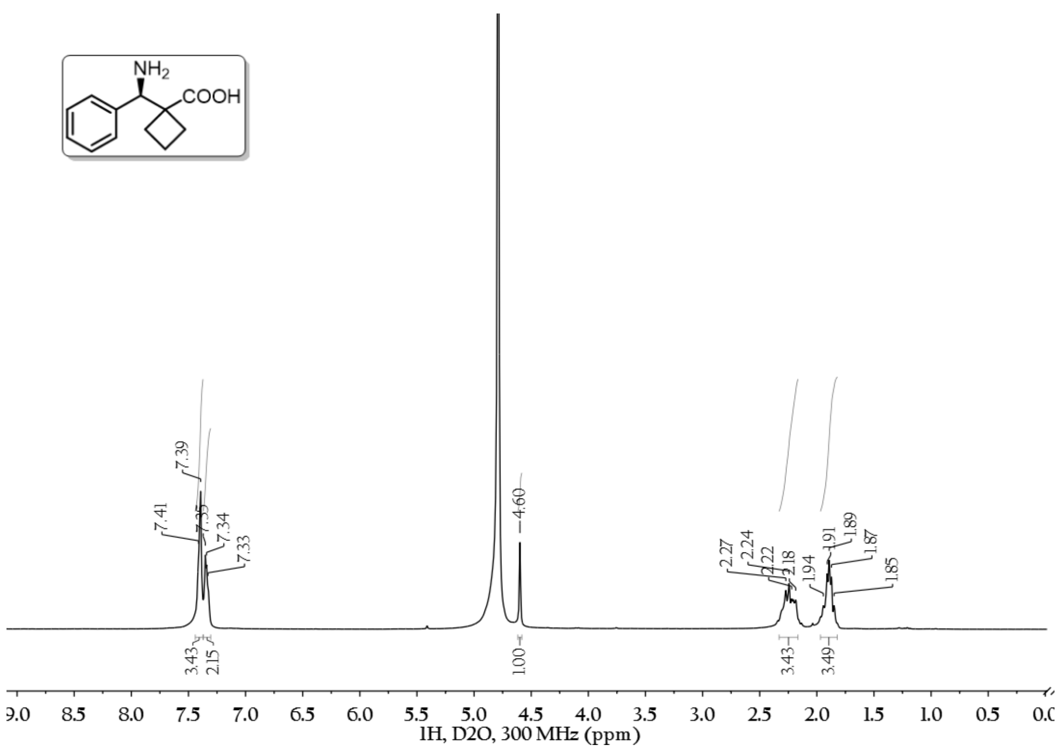

Figure S19. ^{1}H-NMR spectrum of **6a**

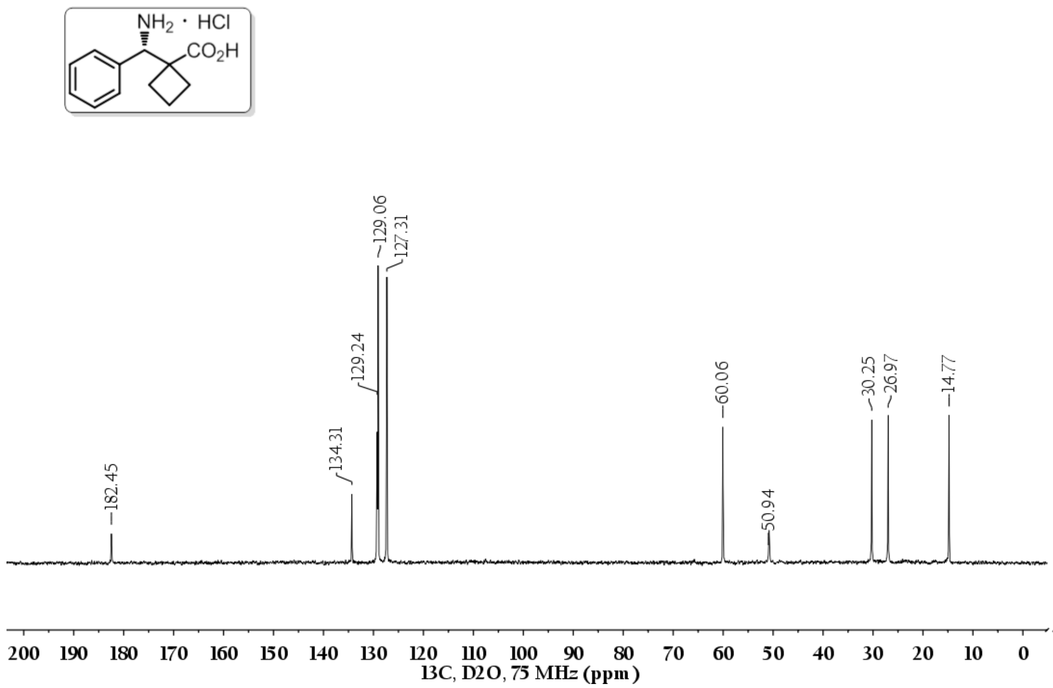

Figure S20. ^{13}C-NMR spectrum of **6a**

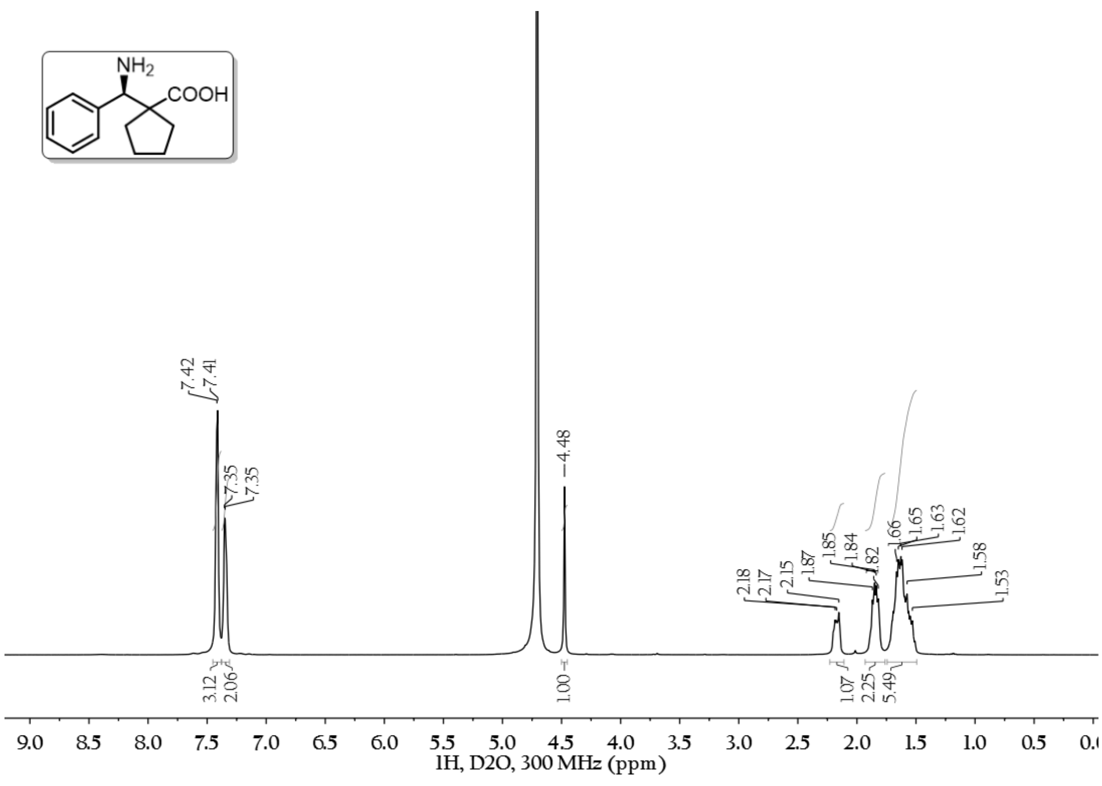

Figure S21. ^{1}H-NMR spectrum of **6b**

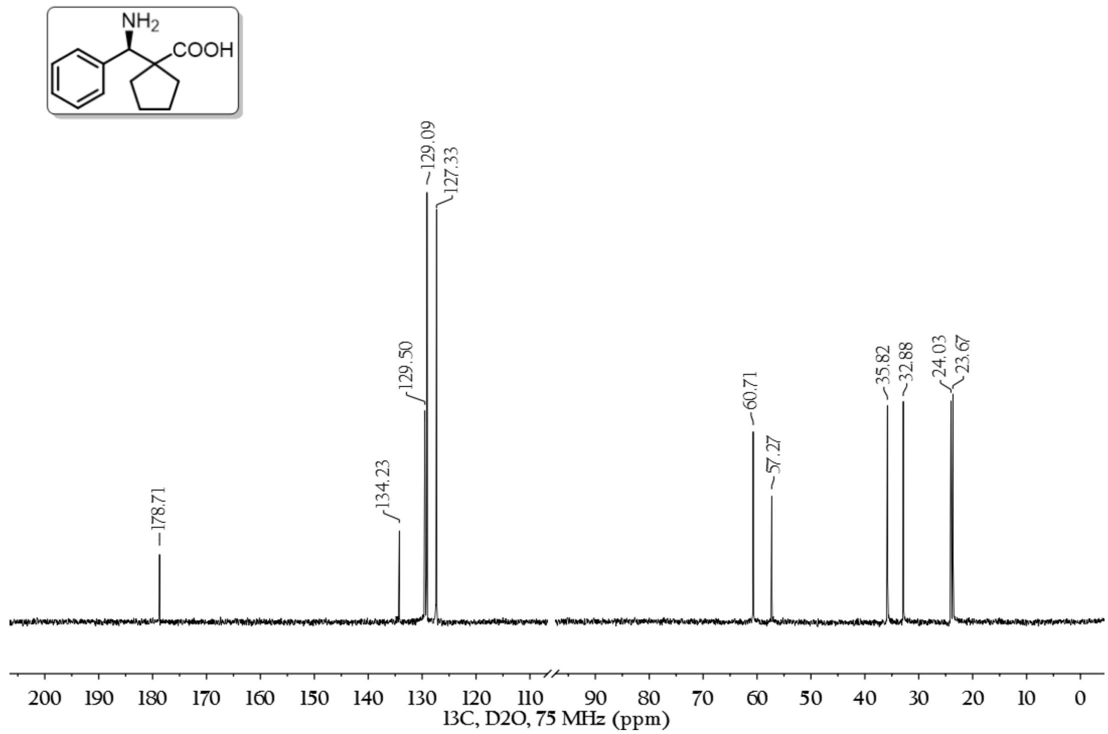

Figure S22. ^{13}C-NMR spectrum of **6b**

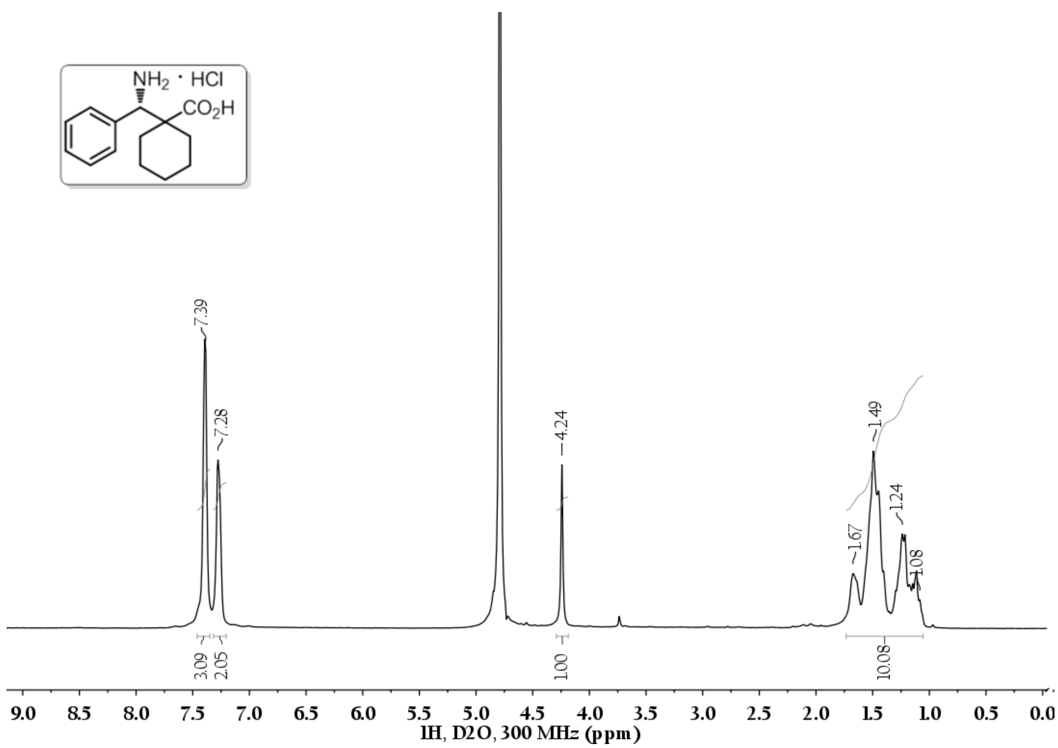

Figure S23. ^{1}H-NMR spectrum of **6c**

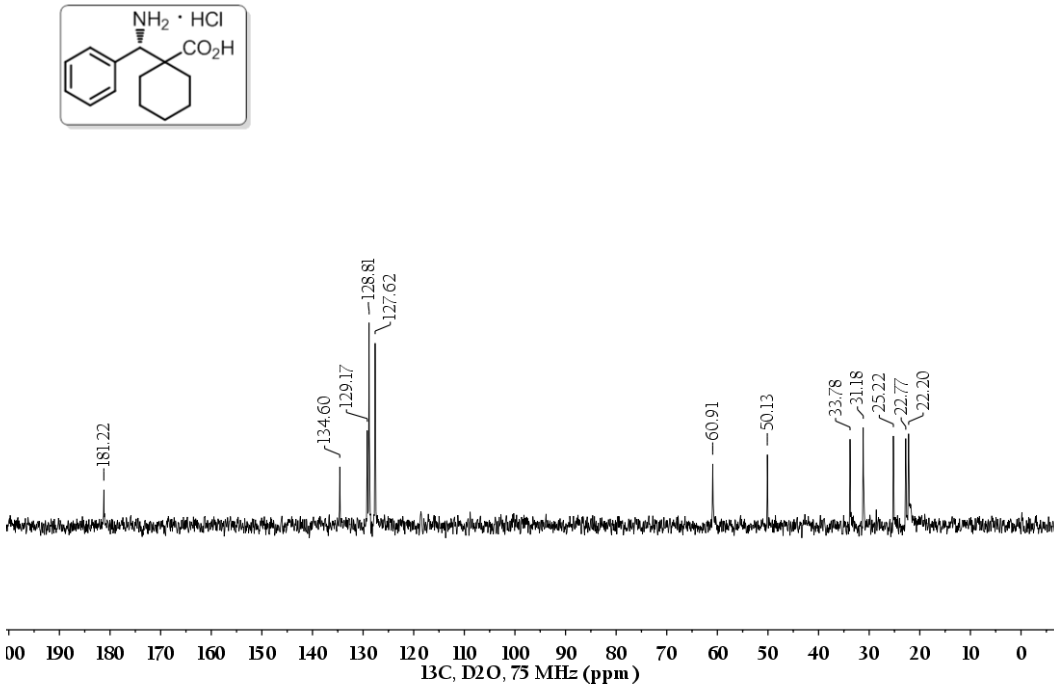

Figure S24. ^{13}C-NMR spectrum of **6c**

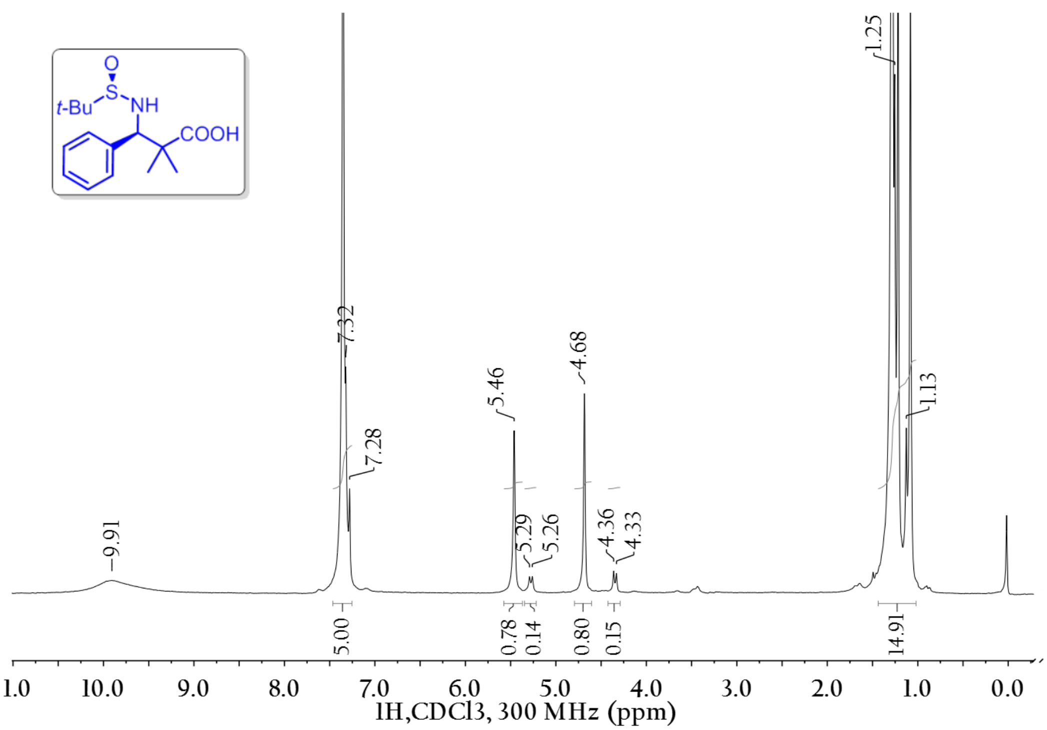

Figure S25. ^{1}H-NMR spectrum of **3a** recrystallized

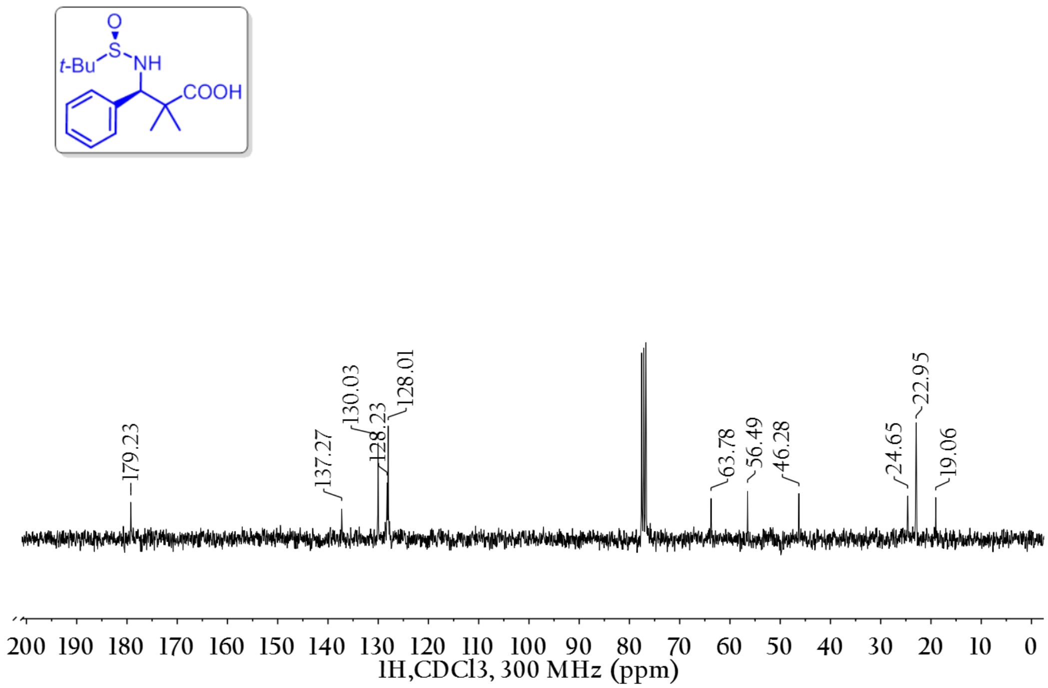

Figure S26. ^{13}C-NMR spectrum of **3a** recrystallized

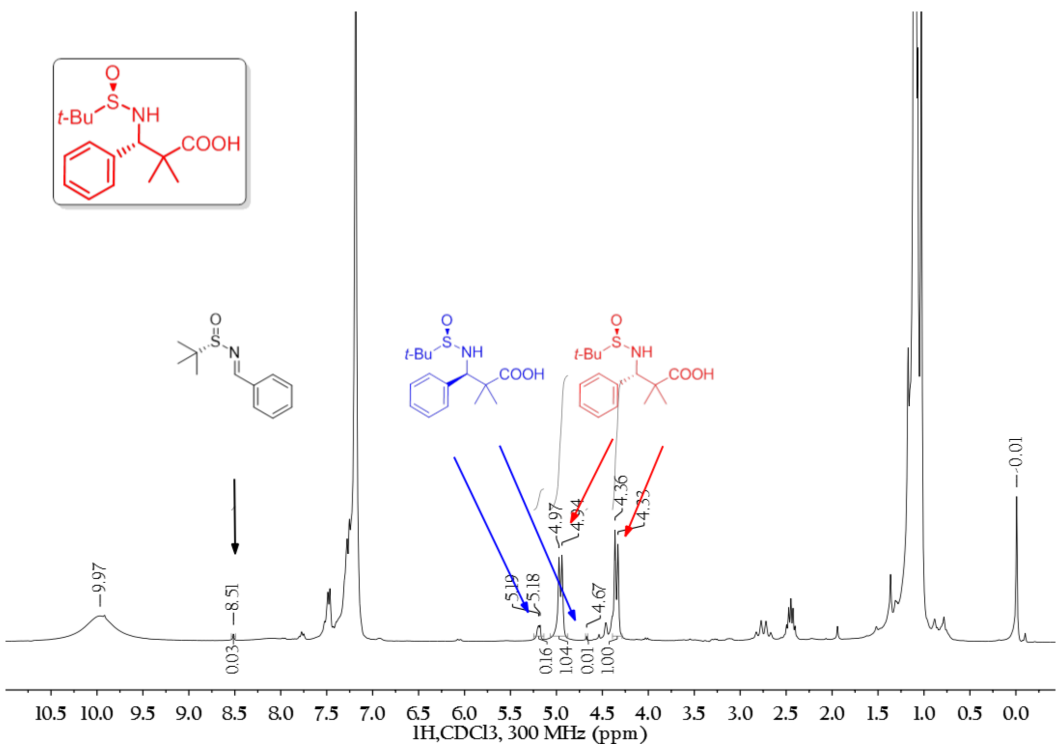

Figure S27. ^{1}H-NMR spectrum of **4a**

5. Spectra of the crude Mannich reaction of Tables 3 and 4

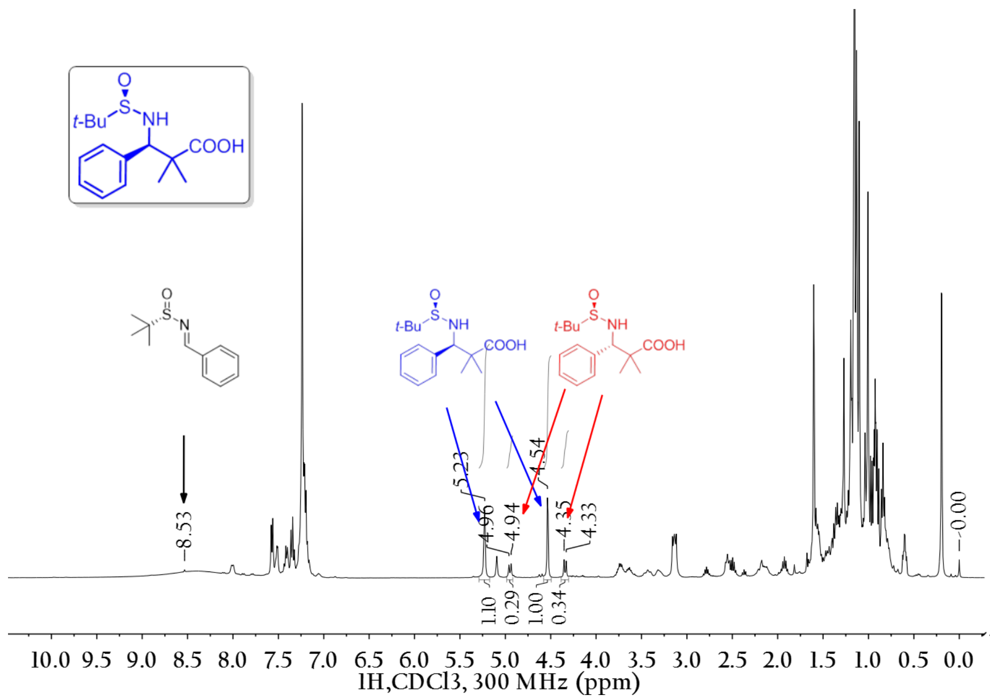

Figure S28. ^{1}H-NMR spectrum of the Mannich addition to obtain (*R*)-**5a** by method A (promoted by BF_3OEt_2) in Table 3.

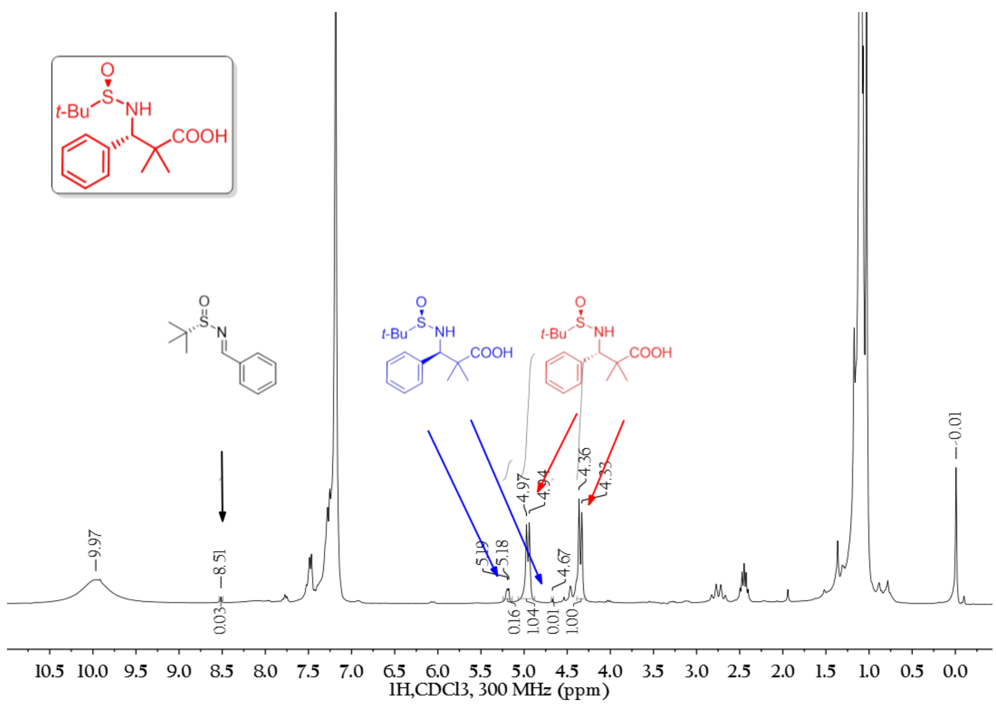

Figure S29. ^{1}H-NMR spectrum of the Mannich addition to obtain (*S*)-**5a** by method B (promoted by TBAT) in Table 4.

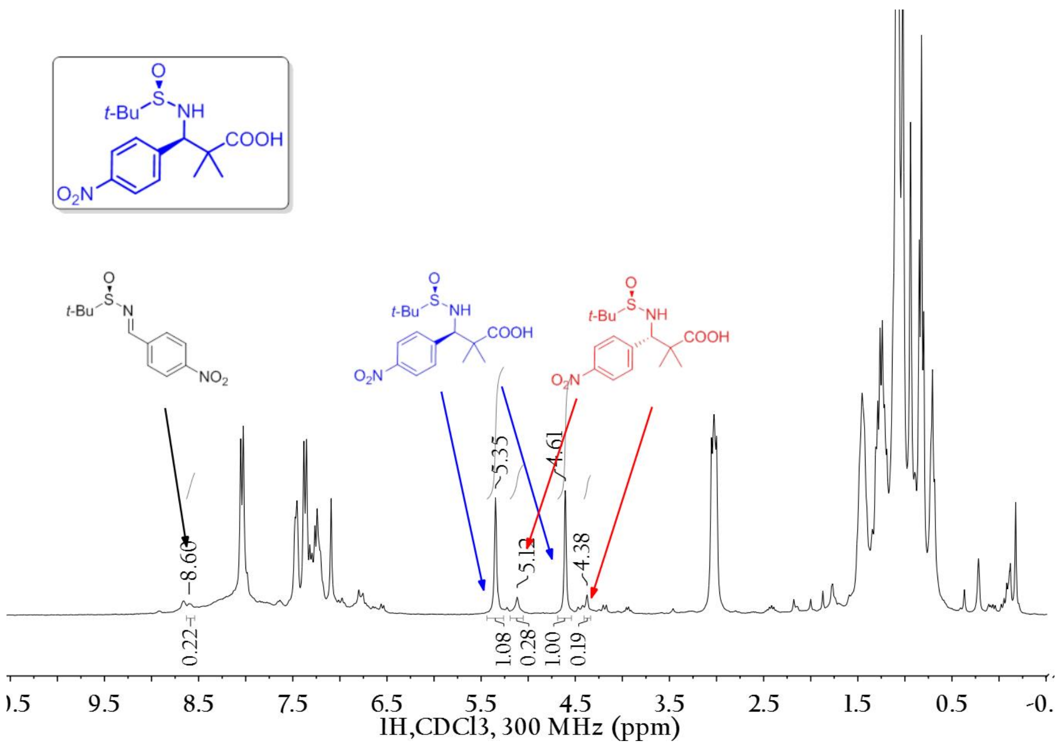

Figure S30. ^{1}H-NMR spectrum of the Mannich addition to obtain (*R*)-**5b** by method A (promoted by BF_3OEt_2) in Table 3.

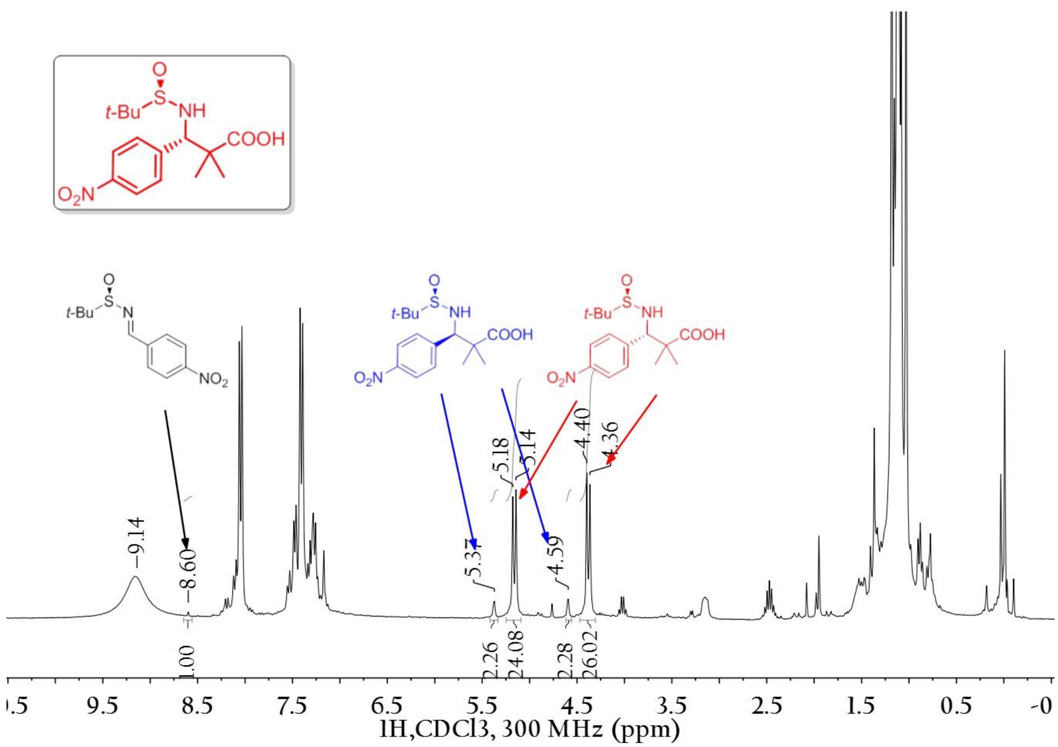

Figure S31. ^{1}H-NMR spectrum of the Mannich addition to obtain (*S*)-**5b** by method B (promoted by TBAT) in Table 4.

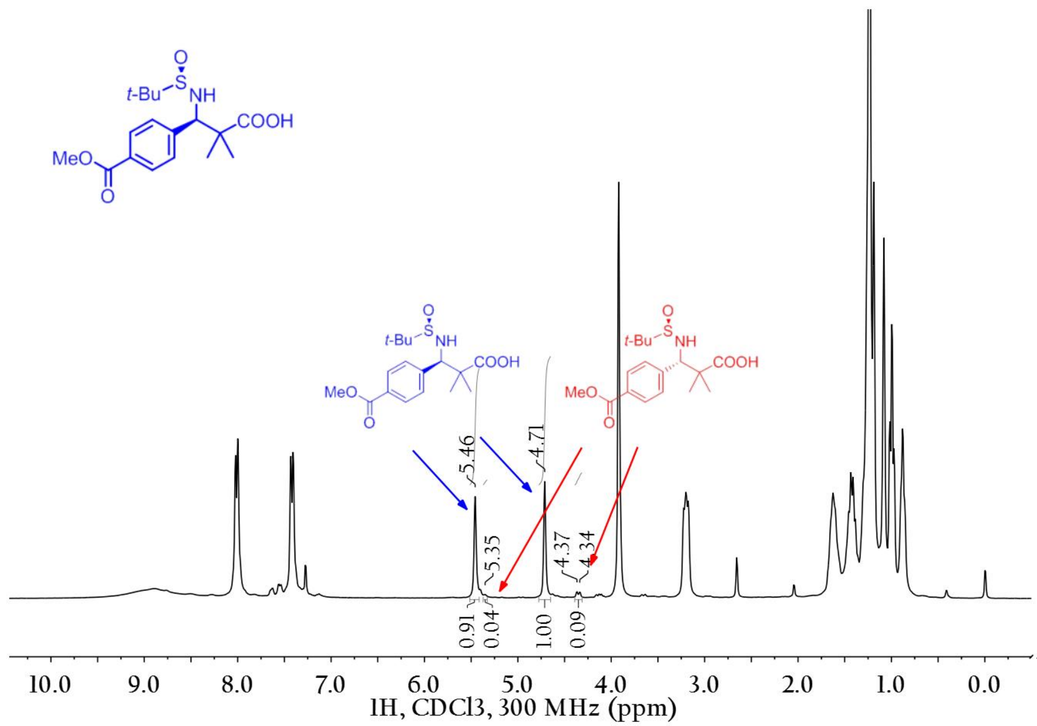

Figure S32. ^{1}H-NMR spectrum of the Mannich addition to obtain (*R*)-**5c** by method A (promoted by BF_3OEt_2) in Table 3.

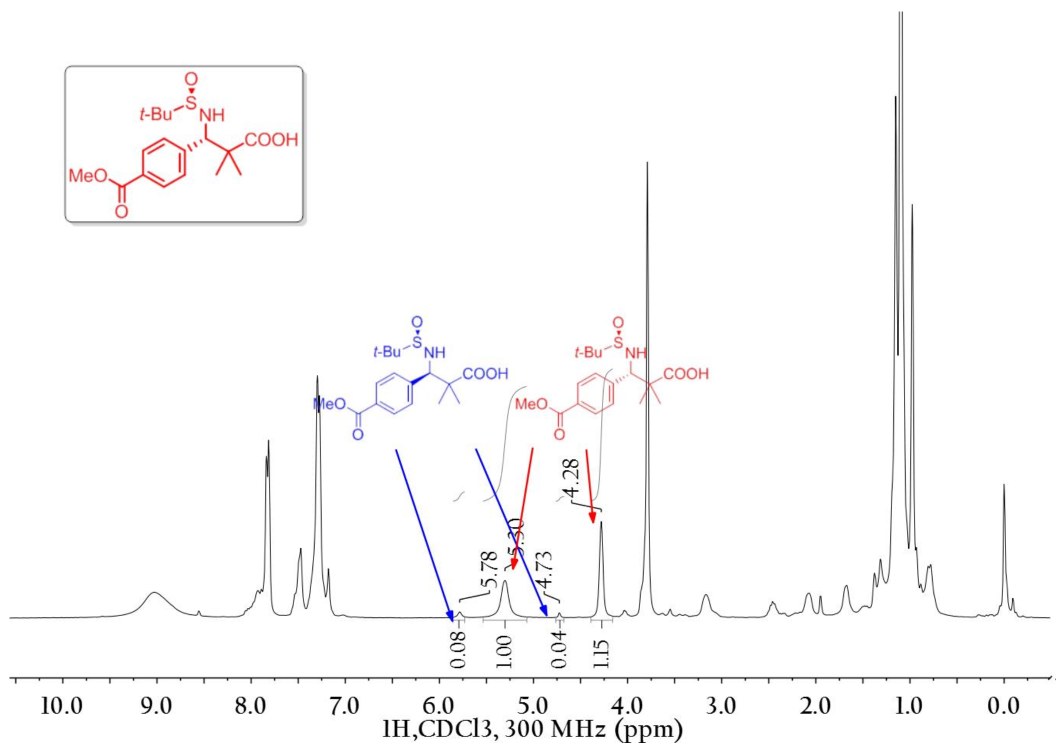

Figure S33. ^{1}H-NMR spectrum of the Mannich addition to obtain (*S*)-**5c** by method B (promoted by TBAT) in Table 4.

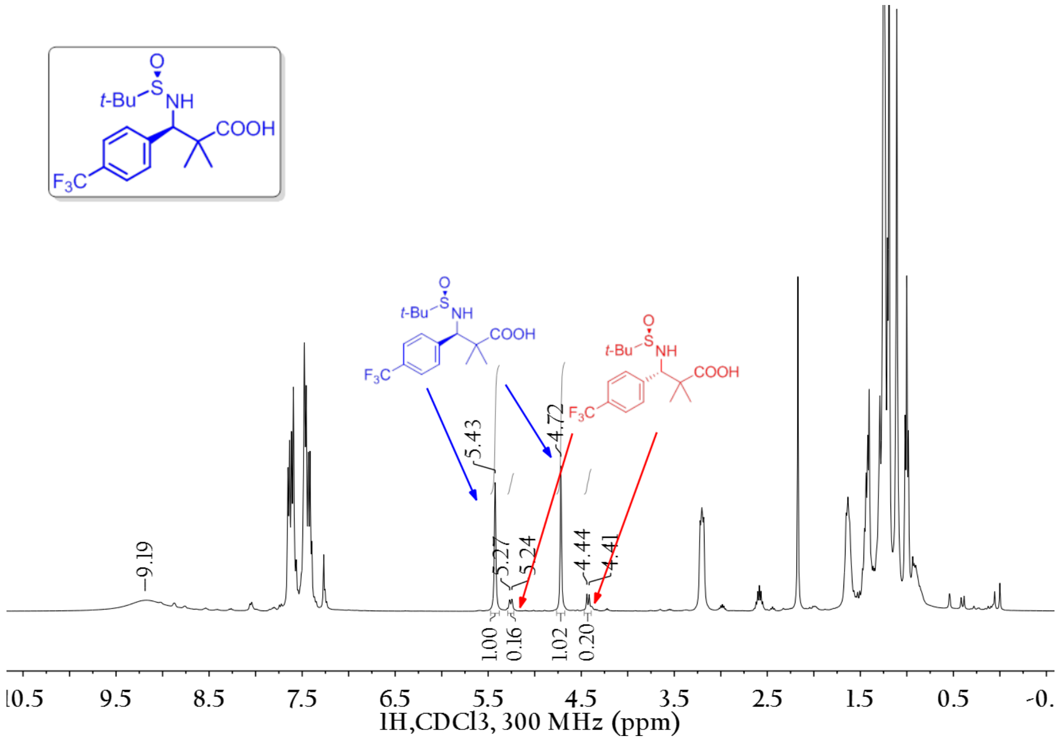

Figure S34. ^{1}H-NMR spectrum of the Mannich addition to obtain (*R*)-**5d** by method A (promoted by BF_3OEt_2) in Table 3.

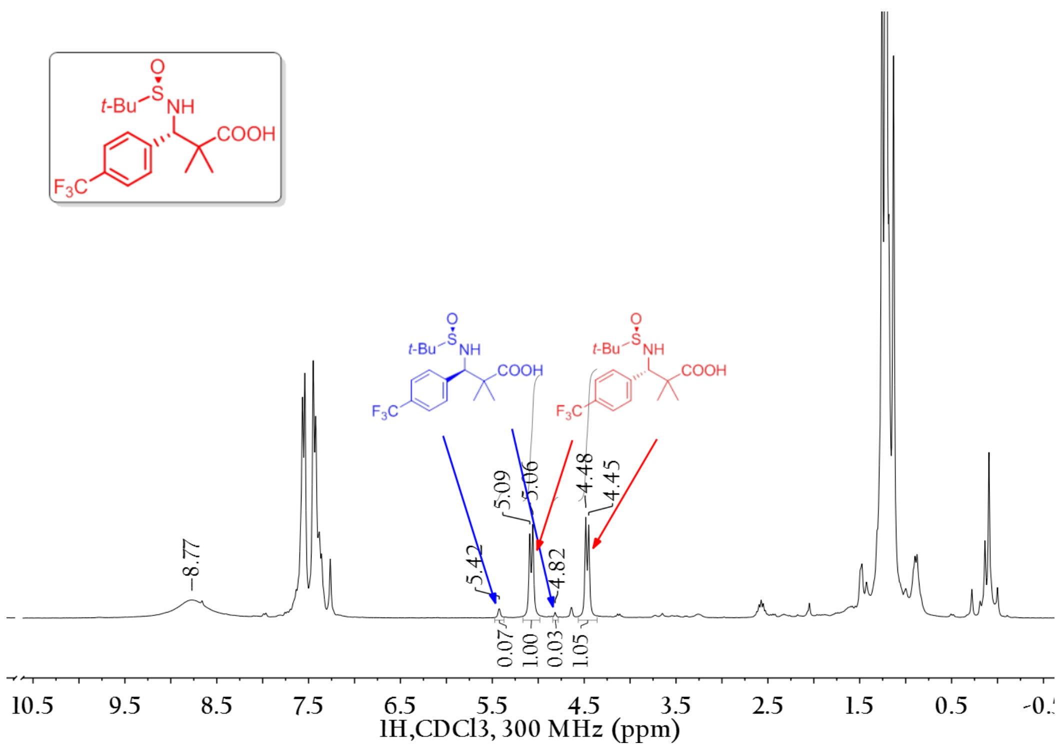

Figure S35. ^{1}H-NMR spectrum of the Mannich addition to obtain (*S*)-**5d** by method B (promoted by TBAT) in Table 4.

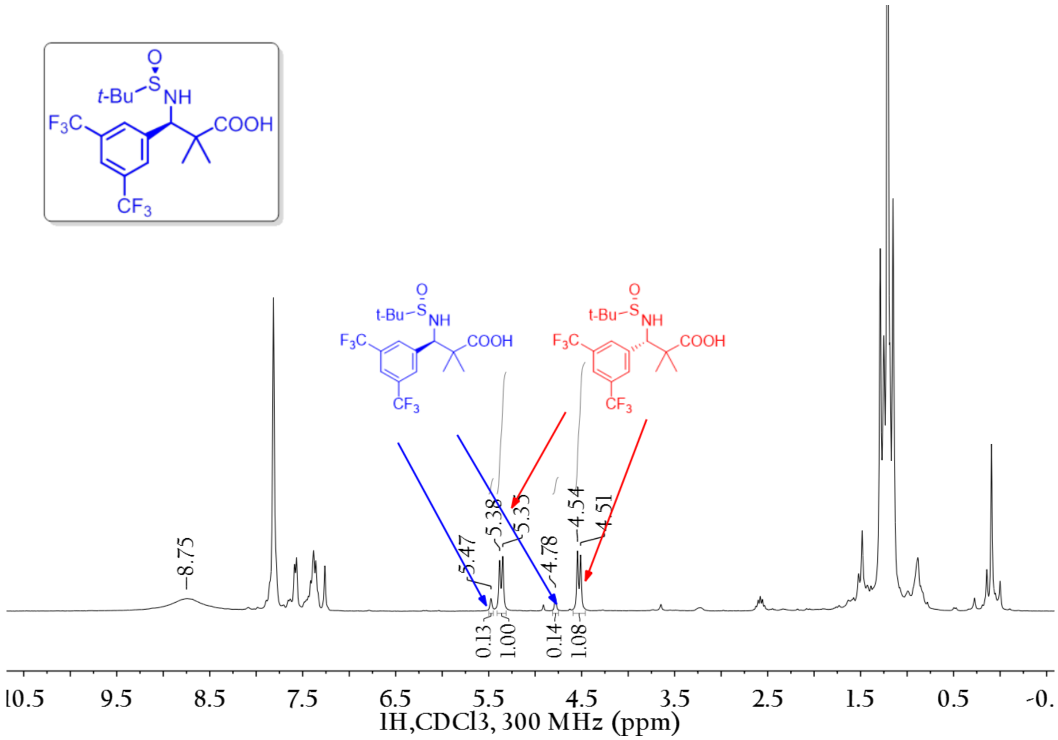

Figure S36. ^{1}H-NMR spectrum of the Mannich addition to obtain (*R*)-**5e** by method A (promoted by BF_3OEt_2) in Table 3.

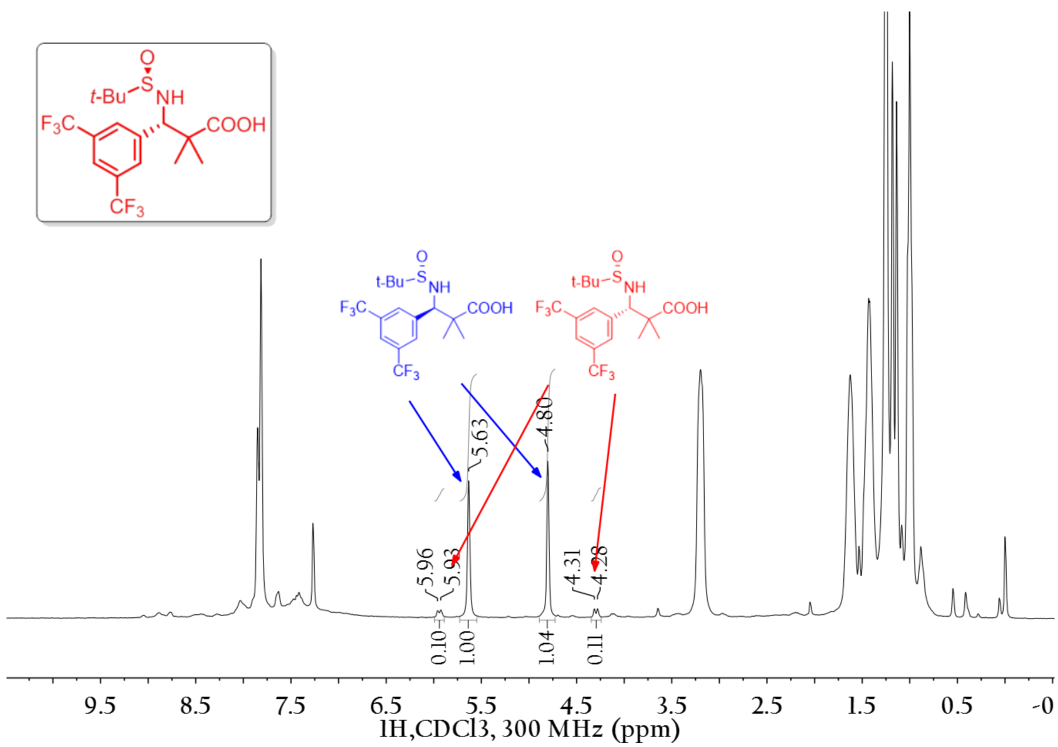

Figure S37. ^{1}H-NMR spectrum of the Mannich addition to obtain (*S*)-**5e** by method B (promoted by TBAT) in Table 4.

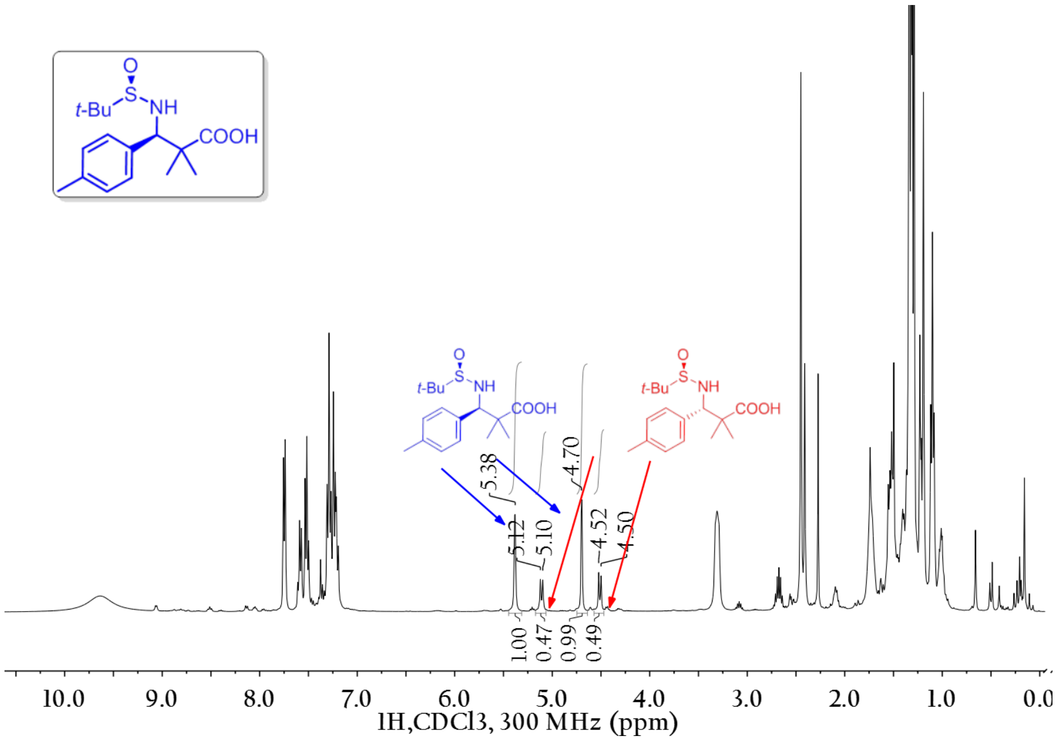

Figure S38. ^{1}H-NMR spectrum of the Mannich addition to obtain (*R*)-**5f** by method A (promoted by BF_3OEt_2) in Table 3.

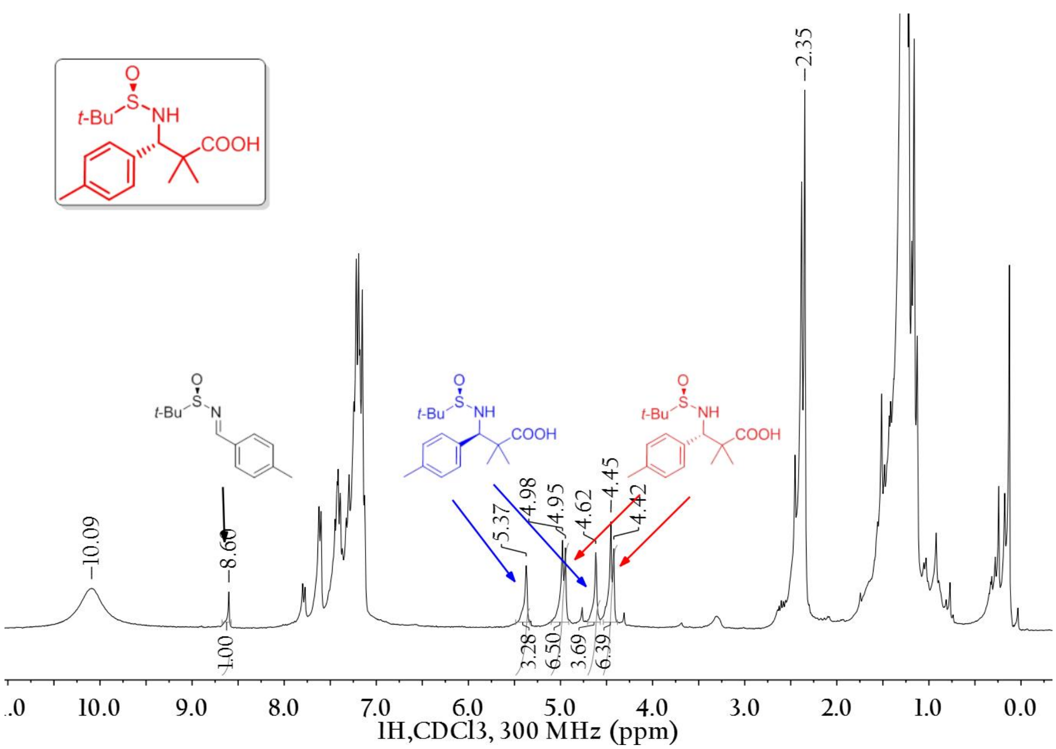

Figure S39. ^{1}H-NMR spectrum of the Mannich addition to obtain (*S*)-**5f** by method B (promoted by TBAT) in Table 4.

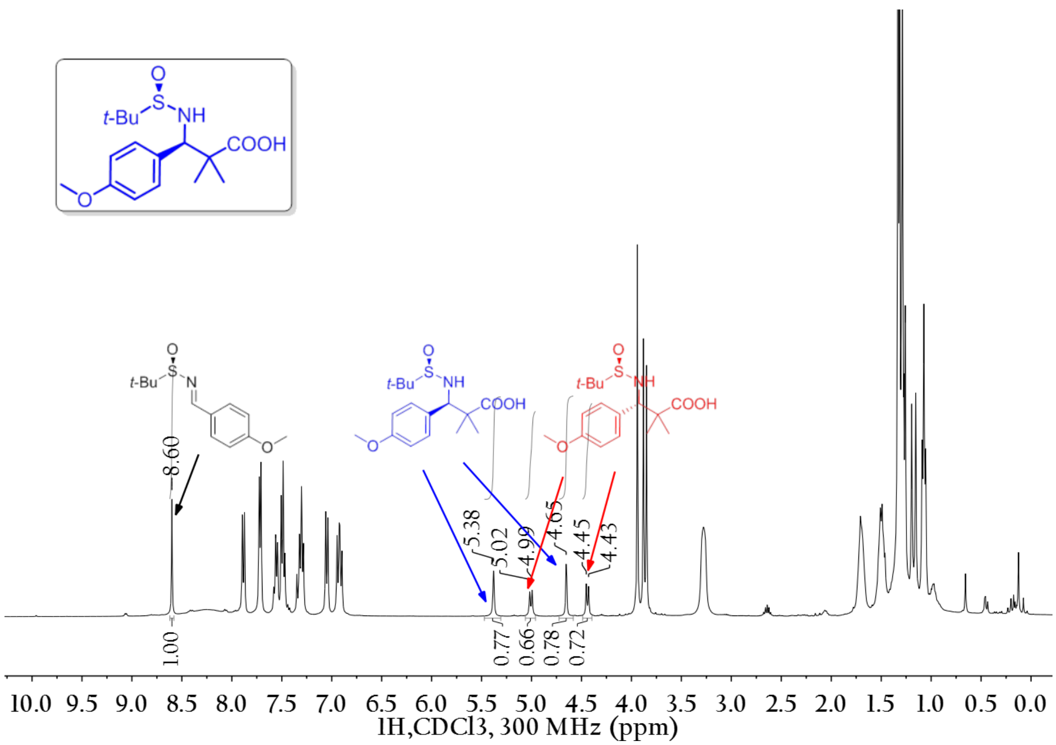

Figure S40. ^{1}H-NMR spectrum of the Mannich addition to obtain (*R*)-**5g** by method A (promoted by BF_3OEt_2) in Table 3.

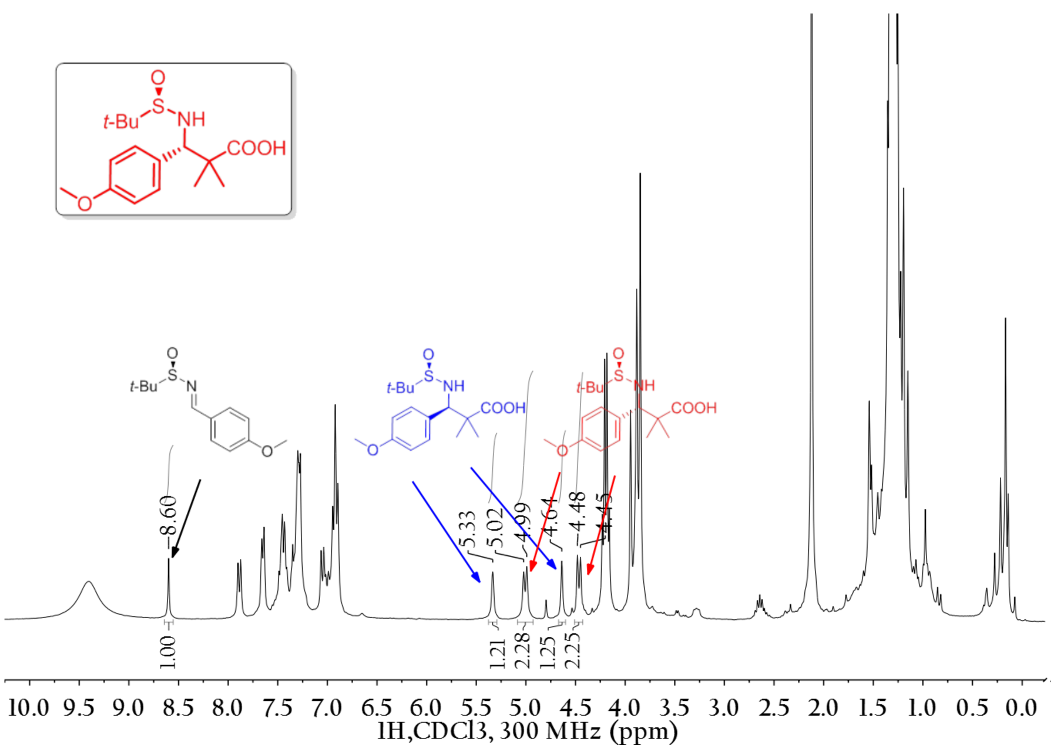

Figure S41. ^{1}H-NMR spectrum of the Mannich addition to obtain (*S*)-**5g** by method B (promoted by TBAT) in Table 4.

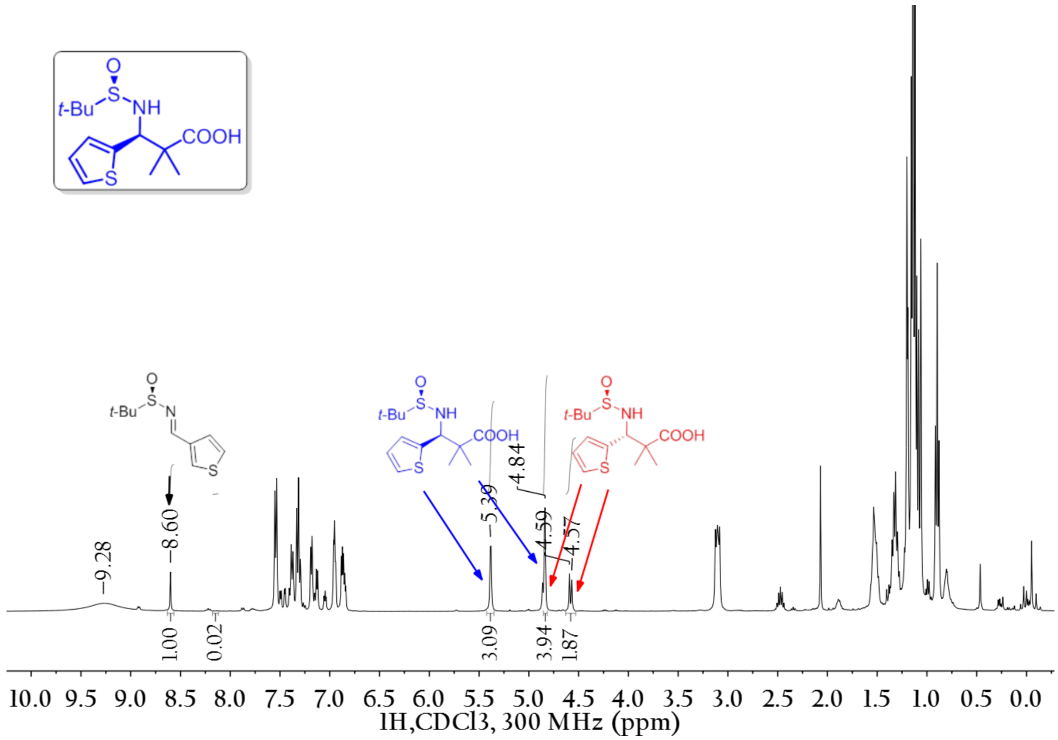

Figure S42. ^{1}H-NMR spectrum of the Mannich addition to obtain (*S*)-**5h** by method A (promoted by BF_3OEt_2) in Table 3.

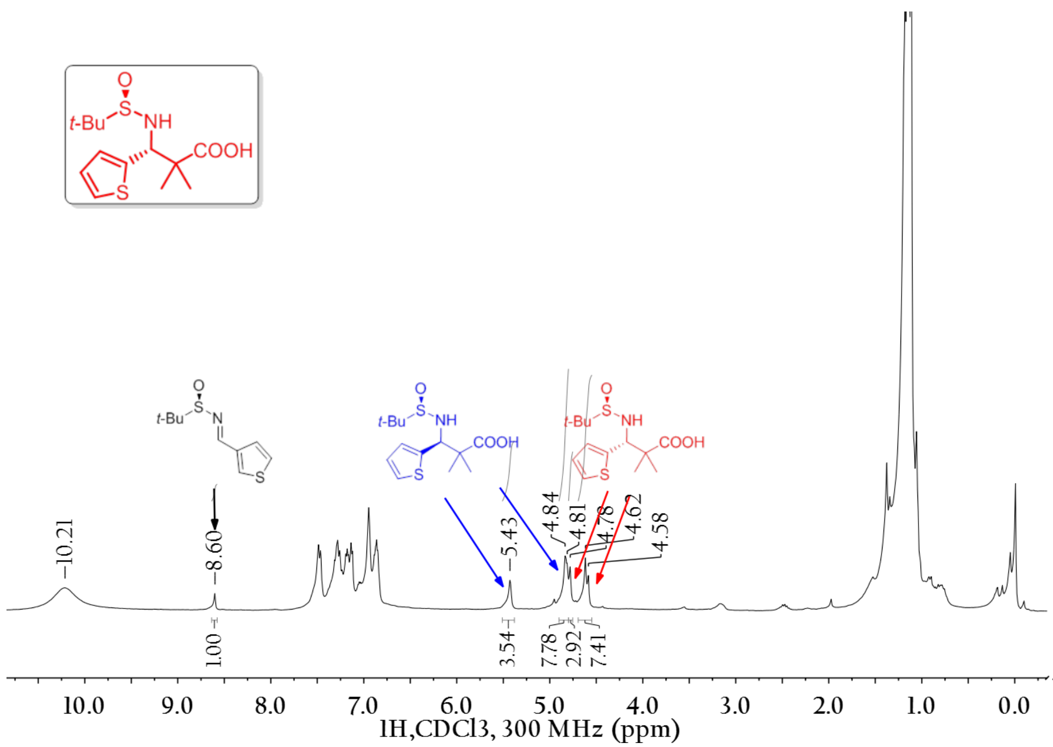

Figure S43. ^{1}H-NMR spectrum of the Mannich addition to obtain (*R*)-**5h** by method B (promoted by TBAT) in Table 4.

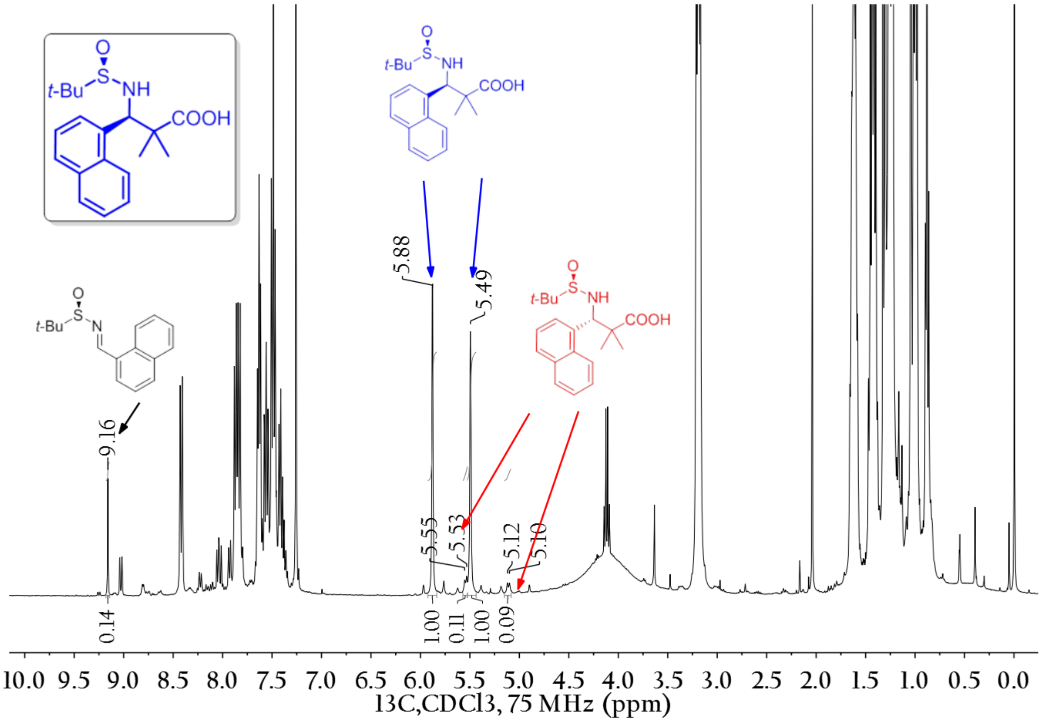

Figure S44. [1]H-NMR spectrum of the Mannich addition to obtain (*R*)-**5i** by method A (promoted by BF_3OEt_2) in Table 3.

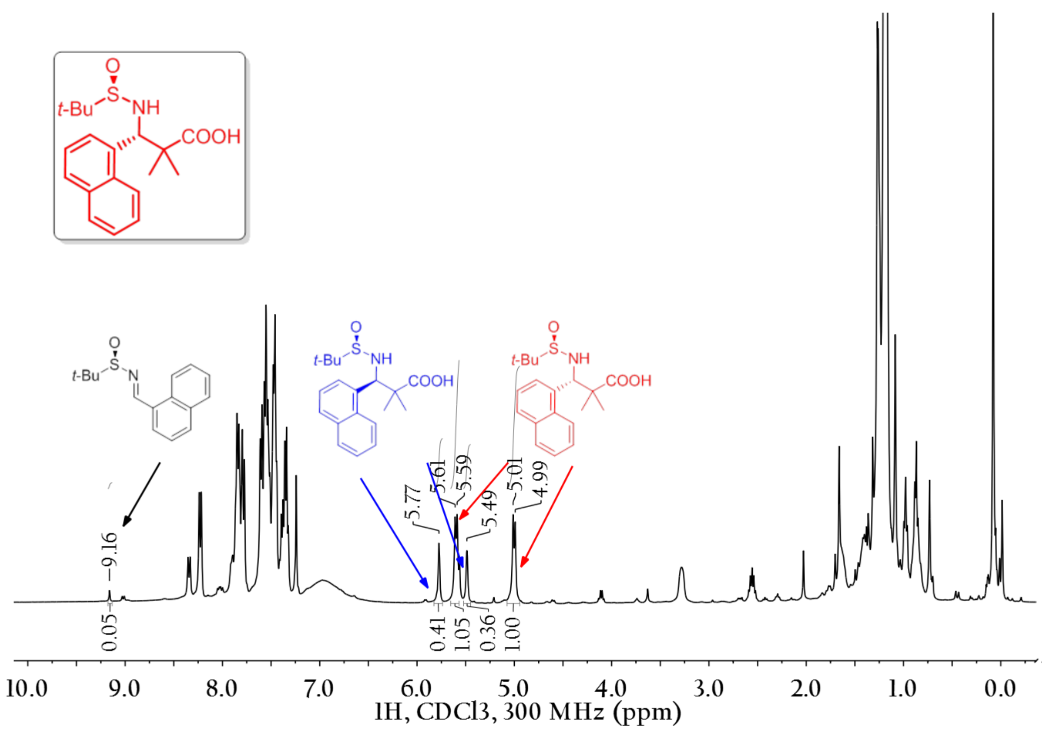

Figure S45. [1]H-NMR spectrum of the Mannich addition to obtain (*S*)-**5i** by method B (promoted by TBAT) in Table 4.

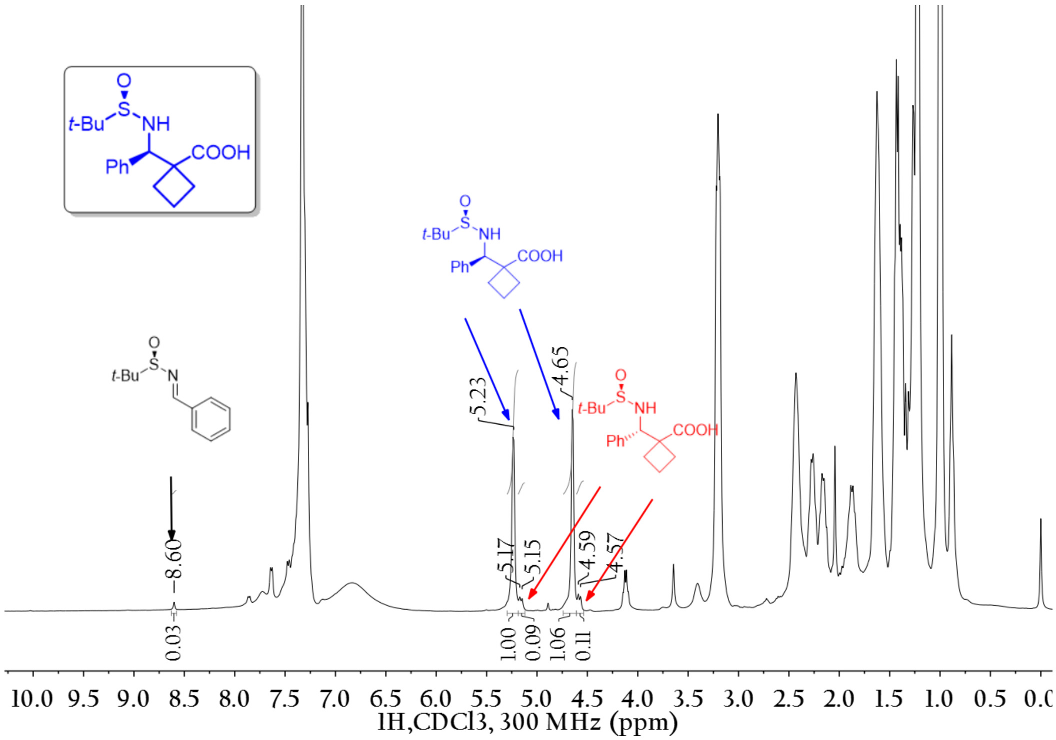

Figure S46. ^{1}H-NMR spectrum of the Mannich addition to obtain (*R*)-**6a** by method A (promoted by BF_3OEt_2) in Figure 4

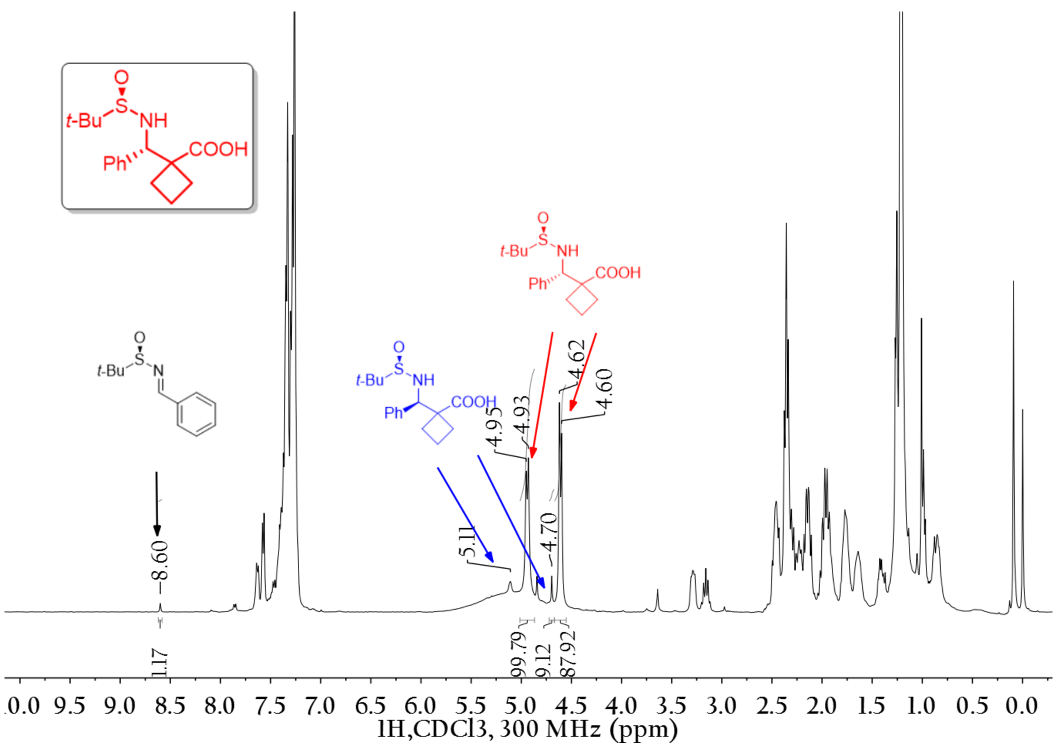

Figure S47. ^{1}H-NMR spectrum of the Mannich addition to obtain (*S*)-**6a** by method B (promoted by TBAT) in Figure 4.

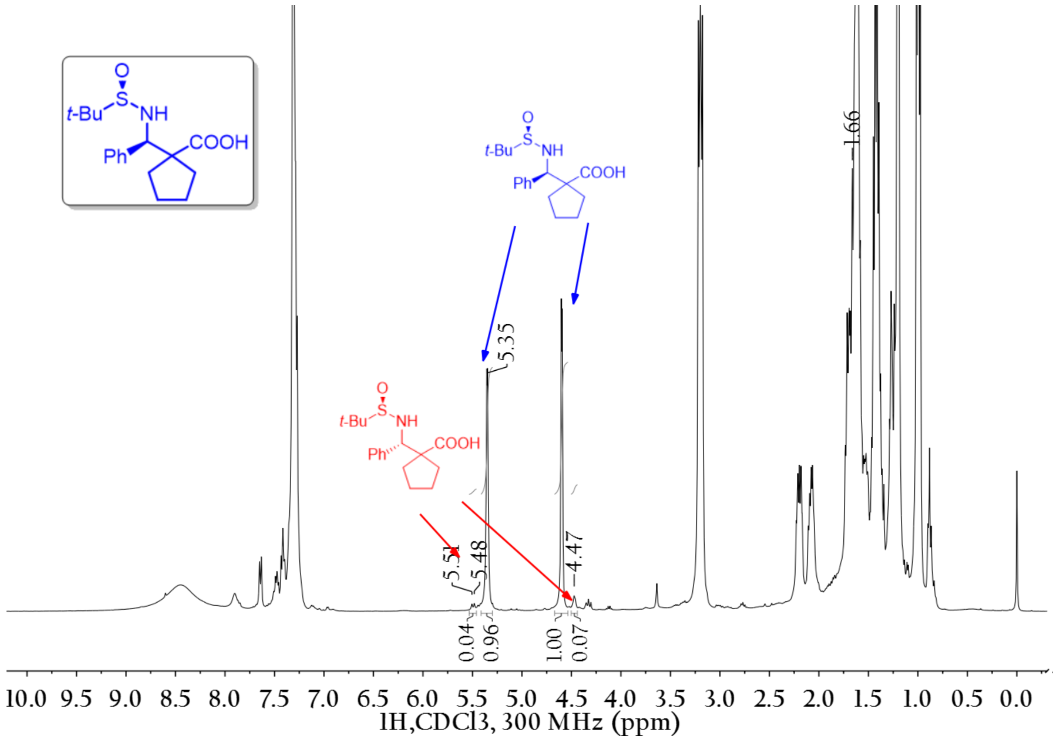

Figure S48. ^{1}H-NMR spectrum of the Mannich addition to obtain (*R*)-**6b** by method A (promoted by BF_3OEt_2) in Figure 4.

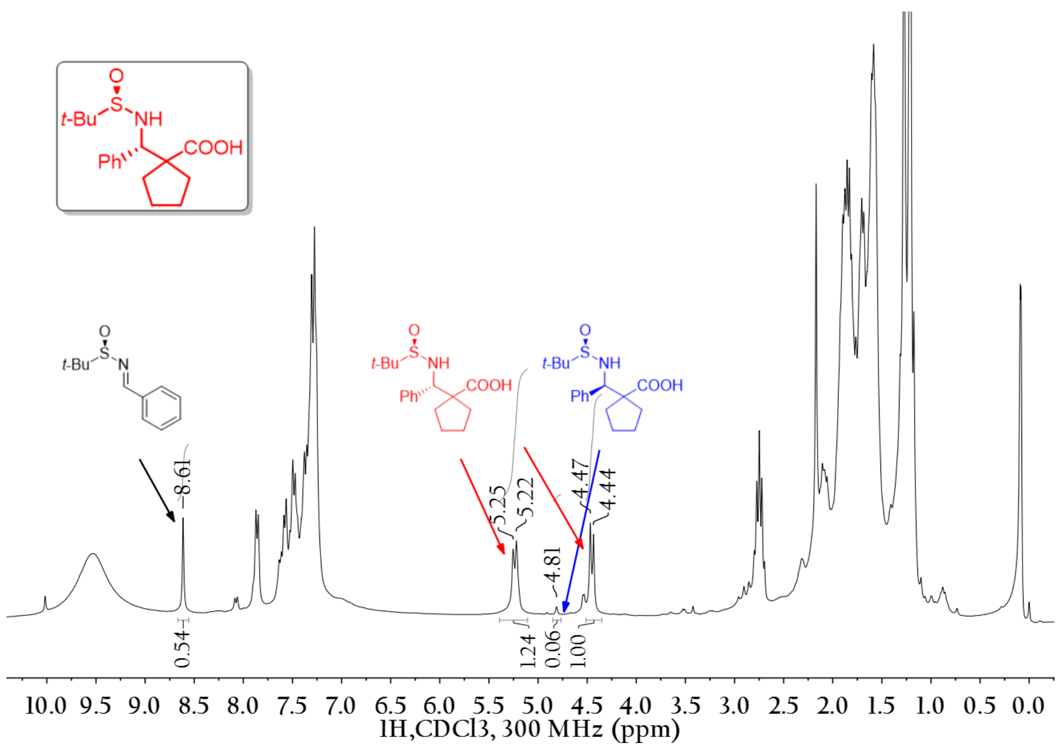

Figure S49. ^{1}H-NMR spectrum of the Mannich addition to obtain (*S*)-**6b** by method B (promoted by TBAT) in Figure 4.

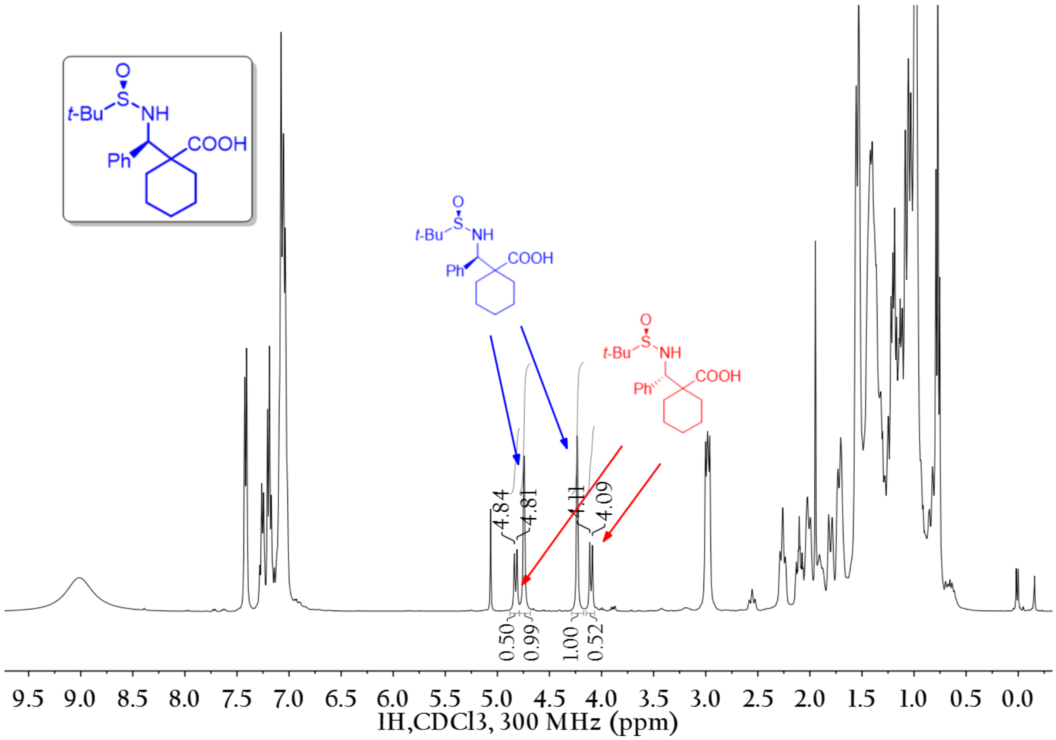

Figure S50. ^{1}H-NMR spectrum of the Mannich addition to obtain (*R*)-**6c** by method A (promoted by BF_3OEt_2) in Figure 4.

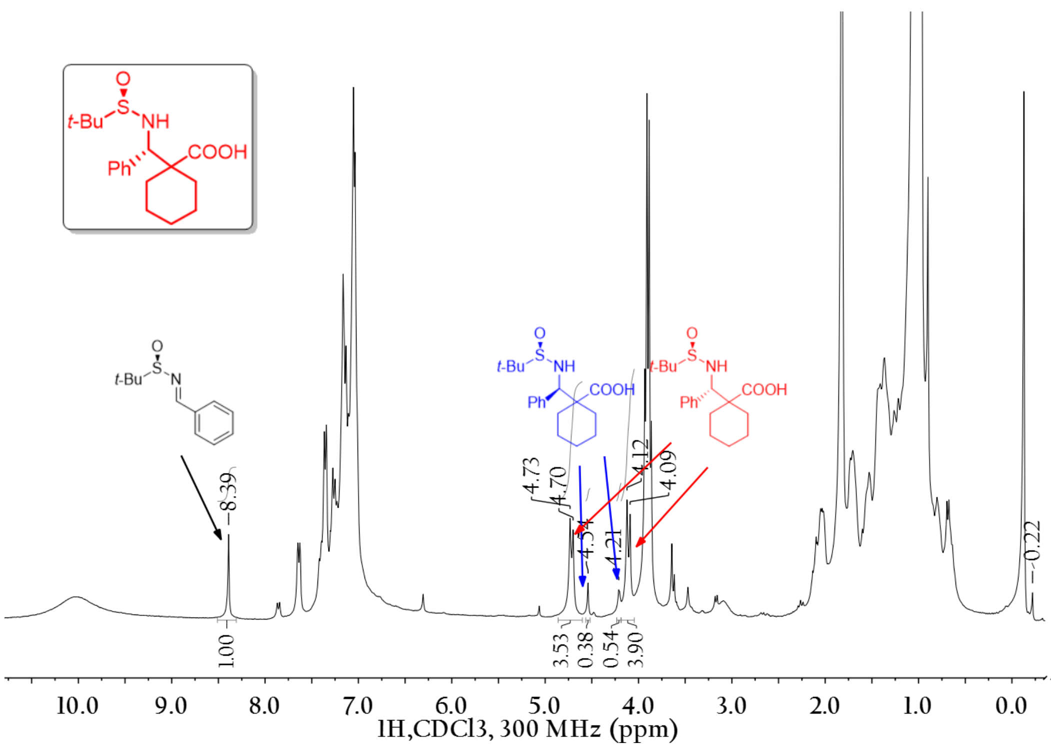

Figure S51. ^{1}H-NMR spectrum of the Mannich addition to obtain (S)-**6c** by method B (promoted by TBAT) in Figure 4.