

Supporting Information for

Catalytic Asymmetric Direct Mannich Reaction of Glycine Schiff Bases with α -Amido Sulfones as Precursors of Enolizable Aliphatic Imines

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1. Experimental Section

1.1. General methods

All the reactions were carried out in anhydrous solvents and under inert atmosphere. Melting points were measured in open-end capillary tubes. NMR spectra were recorded at 300 MHz (^1H), 75 MHz (^{13}C), at room temperature in CDCl_3 [calibrated at 7.28 ppm (^1H) and 77.0 ppm (^{13}C)] and acetone [calibrated at 2.05 (^1H) and 206.7. (^{13}C)] unless indicated. Mass spectra (MS) were determined at an ionizing voltage of 70 eV. The sodium and/or methoxy adduct of the molecular ion were detected in most of mass spectra due to the presence of Na^+ as the ionization source or MeOH as solvent. HPLC experiments were conducted using Daicel Chiralpak AD and IA columns. Flash column chromatography was performed using silica gel Merk-60 (230-400 mesh). Iminoesters **2a-d** were prepared according to reported literature procedures.¹ The racemic products were prepared under identical conditions at room temperature, but using 1,1'-Bis(diphenyl-phosphino)ferrocene (dppf), (10 mol%) instead of (*R*)-Fesulphos as the ligand.²

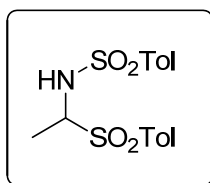
1.2. Synthesis of α -Amido sulfones

General procedure A³: To a solution of sulfonamide (1.0 equiv) and ToISO_2Na (1.2 equiv) in a 1:1 mixture of formic acid and H_2O (30 mL), cooled to 0 °C, was added the corresponding aliphatic aldehyde (1.0 equiv). The solution was warmed up to room temperature and stirred for 24 h, whereupon a white solid precipitated. The white powder was successively washed with water and pentane, and then air-dried to give the α -amido sulfone.

General procedure B⁴: To a solution of *tert*-Butyl carbamate (1.0 equiv) and ToISO_2Na (2.0 equiv) in a 1:2 mixture of MeOH/ H_2O (20 mL), cooled to 0 °C, was successively added the corresponding aliphatic aldehyde (1.5 equiv) and formic acid (0.41 mL). The solution was warmed up to room temperature and stirred for 24 h, whereupon a white solid precipitated. The white powder was successively washed with water, diethyl ether and pentane, to give the corresponding α -amido sulfone.

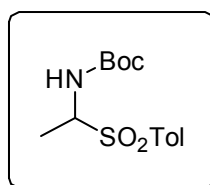
1. (a) S. Cabrera, R. Gómez Arrayás, J. C. Carretero, *J. Am. Chem. Soc.* **2005**, *127*, 16394; (b) T. Llamas, R. Gómez Arrayás, J. C. Carretero, *Org. Lett.* **2006**, *8*, 1795; (c) D. G. Brenner, K. M. Cavolowsky, K. L. Shepard, *J. Het. Chem.* **1995**, *22*, 805; (d) M. J. O'Donnell, R. L. Polt. *J. Org. Chem.* **1982**, *47*, 2663.
2. 1,1'-Bis(diphenyl-phosphino)ferrocene (dppf) typically provides lower yields and much poorer *syn*-diastereoselectivities than the (*R*)-Fesulphos ligand.
3. F. Chemla, V. Hebbe, J-F. Normandt, *Synthesis*, **2000**, *1*, 75.
4. H. Zhang, S. Syed, Carlos F. Barbas III, *Org. Lett.* **2010**, *12*, 708.

4-Methyl-*N*-(1-tosylethyl)benzenesulfonamide (1a). Following the general procedure



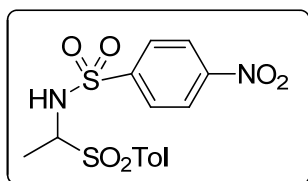
A, the reaction of acetaldehyde (0.56 mL, 10.0 mmol) with *p*-toluenesulfonamide (1.71 g, 10.0 mmol) and TolSO₂Na (1.97 g, 12.0 mmol), afforded **1a** as a white solid; yield: 3.18 g (90%); m.p: 114-116 °C. ¹H NMR (300 MHz, CDCl₃), δ (ppm): 7.77 (d, *J* = 8.1 Hz, 2H); 7.58 (d, *J* = 8.1 Hz, 2H); 7.33 (d, *J* = 7.9 Hz, 2H); 7.23 (d, *J* = 7.9 Hz, 2H); 5.78 (d, *J* = 9.8 Hz, 1H); 4.47-4.45 (m, 1H); 2.48 (s, 3H); 2.44 (s, 3H); 1.49 (d, *J* = 6.8 Hz, 3H). ¹³C-NMR (75 MHz, CDCl₃), δ (ppm): 145.4; 143.4; 137.3; 132.3; 129.7; 129.6; 126.8; 69.4; 21.8; 21.6; 14.3. HRMS (ESI⁺) (M⁺-*p*TolSO₂+H): calculated C₉H₁₂NO₂S: 198.0590; Found: 198.0576. (M⁺-*p*TolSO₂+Na+MeO⁻): calculated C₁₀H₁₁NNaO₃S: 252.0670; Found: 252.0656. Elemental analysis: calculated C₁₆H₁₉NO₄S₂: C, 54.37; H, 5.42; N, 3.96; S, 18.14. Found: C, 54.48; H, 5.37; N, 3.92; S, 18.08.

***tert*-Butyl-(1-tosylethyl)carbamate (1b).** Following procedure B, *tert*-butyl carbamate



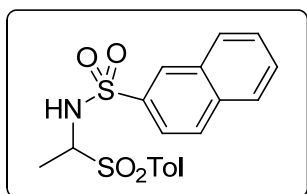
(0.69 g, 5.94 mmol) and TolSO₂Na (2.17 g, 11.88 mmol) reacted with acetaldehyde (0.50 mL, 8.91 mmol) to afford **1b** as a white solid; yield: 1.41 g (80%); m.p: 110-111 °C. ¹H-NMR (300 MHz, CDCl₃), δ (ppm): 7.83 (d, *J* = 8.1 Hz, 2H); 7.37 (d, *J* = 7.7 Hz, 2H); 5.14-4.89 (m, 2H); 2.46 (s, 3H); 1.64 (d, *J* = 6.6 Hz, 3H); 1.26 (s, 9H). ¹³C-NMR (75 MHz, CDCl₃), δ (ppm): 153.6; 144.8; 133.6; 129.6; 129.4; 80.4; 66.9; 27.9; 21.5; 12.8. HRMS (ESI⁺) (M+Na⁺): calculated C₁₄H₂₁NNaO₄S: 322.1083 Found: 322.1089. (2M+Na⁺): calculated C₂₈H₄₂N₂NaO₈S₂: 621.2280; Found: 621.2276.

4-Nitro-*N*-(1-tosylethyl)benzenesulfonamide (1c). Following the general procedure A,



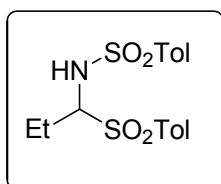
the reaction of acetaldehyde (0.22 mL, 3.87 mmol) with 4-nitrobenzenesulfonamide (0.52 g, 2.58 mmol) and TolSO₂Na (0.93 g, 5.17 mmol), afforded **1c** as a white solid; yield: 0.70 g (71%); m.p: 135-137 °C. ¹H-NMR (300 MHz, Acetone), δ (ppm): 8.36 (d, *J* = 8.9 Hz, 2H); 8.01 (d, *J* = 8.8 Hz, 2H); 7.82 (d, *J* = 9.4 Hz, 1H); 7.68 (d, *J* = 8.2, 2H); 7.36 (d, *J* = 7.9 Hz, 2H); 4.85 (dd, *J* = 10.0 Hz, *J* = 6.8 Hz, 1H); 2.42 (s, 3H); 1.46 (d, *J* = 6.6 Hz, 3H). ¹³C-NMR (75 MHz, Acetone), δ (ppm): 150.9; 147.6; 146.0; 134.2; 130.5; 130.4; 129.0; 125.2; 70.3; 21.5; 14.9. HRMS (ESI⁺) (M+Na⁺): calculated C₁₅H₁₆N₂NaO₆S₂: 407.0342; Found: 407.0332. (2M+Na⁺): calculated C₃₀H₃₂N₄Na₂O₁₂S₄: 791.0747; Found: 791.0822.

***N*-(1-Tosylethyl)naphthalene-2-sulfonamide (1d).** Following the general procedure A,



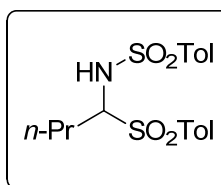
the reaction of acetaldehyde (0.20 mL, 3.62 mmol) with naphthalene-2-sulfonamide (0.50 g, 2.41 mmol) and TolSO₂Na (0.86 g, 4.82 mmol) afforded **1d** as a white solid; yield: 0.63 g (67%); m.p: 118-119 °C. ¹H-NMR (300 MHz, CDCl₃), δ (ppm): 8.46-8.39 (m, 1H); 8.11-8.03 (m, 2H); 7.99-7.93 (m, 1H); 7.78-7.59 (m, 2H); 7.50-7.40 (m, 3H); 6.90 (d, *J* = 8.1 Hz, 2H); 5.44-5.25 (m, 1H); 4.67-4.49 (m, 1H); 2.33 (s, 3H); 1.56 (d, *J* = 6.8 Hz, 3H). ¹³C-NMR (75 MHz, CDCl₃), δ (ppm): 144.8; 134.6; 134.4; 134.1; 132.1; 129.2; 129.0; 128.9; 128.6; 127.7; 127.0; 124.2; 124.0; 69.4; 21.7; 14.9. HRMS (ESI⁺) (2M+Na⁺): calculated C₁₉H₁₉NNaO₄S₂: 412.0647; Found: 412.0648. (2M+Na⁺): calculated C₃₈H₃₈N₂NaO₈S₄: 801.1409; Found: 801.1448.

4-Methyl-*N*-(1-tosylpropyl)benzenesulfonamide (10): Following the general



procedure A, the reaction of propionaldehyde (0.73 mL, 10.0 mmol) with *p*-toluenesulfonamide (1.71 g, 10.0 mmol) and TolSO₂Na (1.97 g, 12.0 mmol) afforded **10** as a white solid; yield 2.84 g (77%); m.p: 118–120 °C. ¹H-NMR (300 MHz, CDCl₃), δ (ppm): 7.73 (d, *J* = 8.3 Hz, 2H); 7.58 (d, *J* = 8.5 Hz, 2H); 7.31 (d, *J* = 8.5 Hz, 2H); 7.23 (d, *J* = 7.9 Hz, 2H); 5.33 (d, *J* = 9.7 Hz, 1H), 4.43 (dt, *J* = 4.0 Hz, *J* = 10.0, 1H); 2.48 (s, 3H); 2.45 (s, 3H); 2.37-2.25 (m, 1H); 1.76-1.74 (m, 1H); 0.91 (t, *J* = 7.4 Hz, 3H). ¹³C-NMR (75 MHz, CDCl₃), δ (ppm): 145.2; 143.6; 137.9; 132.9; 129.7; 129.6; 129.6; 126.7; 75.0; 21.9; 21.8; 21.6; 9.8. HRMS (ESI⁺) (M⁺-*p*TolSO₂+H): calculated C₁₀H₁₄NO₂S: 212.0747. Found: 212.0742. (M⁺-*p*TolSO₂+Na+MeO⁻): calculated C₁₁H₁₇NNaO₃S: 266.0827; Found: 266.0837.

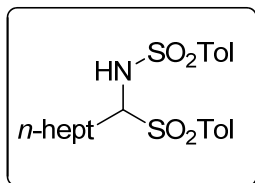
4-Methyl-*N*-(1-tosylbutyl)benzenesulfonamide (11). Following the general procedure



A, the reaction of butyraldehyde (0.90 mL, 10.0 mmol) with *p*-toluenesulfonamide (1.71 g, 10.0 mmol) and TolSO₂Na (1.97 g, 12.0 mmol) afforded **11** as a white solid; yield: 2.58 g (67%); m.p: 119–120 °C. ¹H-NMR (300 MHz, CDCl₃), δ (ppm): 7.70 (d, *J* = 8.3 Hz, 2H); 7.57 (d, *J* = 8.3 Hz, 2H); 7.30 (d, *J* = 8.1 Hz, 2H); 7.23 (d, *J* = 8.1 Hz, 2H); 5.35 (d, *J* = 10.4 Hz, 1H), 4.61 (dt, *J* = 10.2 Hz, *J* = 3.6, 1H); 2.47 (s, 3H); 2.45 (s, 3H); 2.16-2.13 (m, 1H); 1.69-1.67 (m, 1H); 1.41-1.39 (m, 1H); 1.27-1.25 (m, 1H); 0.86 (t, *J* = 7.2 Hz, 3H). ¹³C-NMR (75 MHz, CDCl₃), δ (ppm): 145.3; 143.6; 137.9; 132.8; 129.7; 129.6; 126.8; 126.5; 73.7; 30.4; 21.8; 21.6; 18.5; 13.5. HRMS

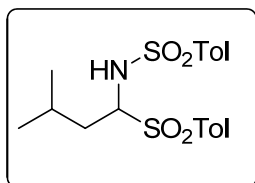
(ESI⁺) (M⁺-pTolSO₂+H): C₁₁H₁₆NO₂S: 226.0902. Found: 226.0895. (M⁺-pTolSO₂+Na+MeO⁻): calculated C₁₂H₁₉NNaO₃S: 280.0983; Found: 280.0983.

4-Methyl-N-(1-tosyloctyl)benzenesulfonamide (12). Following the general procedure



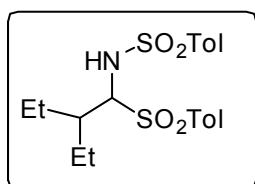
A, the reaction of octanal (1.5 mL, 9.59 mmol) with *p*-toluenesulfonamide (1.67 g, 9.59 mmol) and TolSO₂Na (2.09 g, 11.51 mmol) afforded **12** as a white solid; yield: 3.30 g (76%); m.p: 112–113 °C. ¹H-NMR (300 MHz, CDCl₃), δ (ppm): 7.76 (d, *J* = 8.3 Hz, 2H); 7.60 (d, *J* = 8.3 Hz, 2H); 7.35 (d, *J* = 8.1 Hz, 2H); 7.23 (d, *J* = 8.3 Hz, 2H); 5.51 (d, *J* = 9.8 Hz, 1H); 4.57 (dt, *J* = 10.2 Hz, *J* = 3.6 Hz, 1H); 2.48 (s, 3H); 2.44 (s, 3H); 2.17-2.14 (m, 1H); 1.69-1.66 (m, 1H); 1.40-1.00 (m, 10 H); 0.89 (t, *J* = 6.8 Hz, 3H). ¹³C-NMR (75 MHz, CDCl₃), δ (ppm): 145.3; 143.6; 137.9; 132.8; 129.7; 129.6; 126.8; 73.8; 31.5; 28.9; 28.8; 28.2; 25.1; 22.6; 21.8; 21.5; 14.0. HRMS (ESI⁺) (M⁺-pTolSO₂+H): calculated C₁₅H₂₄NO₂S: 282.1522; Found: 282.1520. (M⁺-pTolSO₂+Na+MeO⁻): calculated C₁₆H₂₇NNaO₃S: 336.1616; Found: 336.1620.

4-Methyl-N-(3-methyl-1-tosylbutyl)benzenesulfonamide (13). Following the general



procedure A, the reaction of 3-methyl-butyr aldehyde (1.10 mL, 10.0 mmol) with *p*-toluenesulfonamide (1.71 g, 10.0 mmol) and TolSO₂Na (1.97 g, 12.0 mmol) afforded **13** as a white solid; yield: 3.40 g (84%). m.p: 122–123 °C; ¹H-NMR (300 MHz, CDCl₃), δ (ppm): 7.58 (d, *J* = 8.3 Hz, 2H); 7.47 (d, *J* = 8.3 Hz, 2H); 7.21 (d, *J* = 7.9 Hz, 2H); 7.14 (d, *J* = 7.9 Hz, 2H); 4.84 (d, *J* = 9.4 Hz, 1H); 4.61 (dt, *J* = 10.5 Hz, *J* = 3.7 Hz, 1H); 2.37 (s, 3H); 2.35 (s, 3H); 1.90-1.87 (m, 1H); 1.53-1.51 (m, 2H); 0.82 (d, *J* = 6.4 Hz, 3H); 0.77 (d, *J* = 6.4 Hz, 3H). ¹³C-NMR (75 MHz, CDCl₃), δ (ppm): 145.3; 143.6; 138.0; 132.74; 129.7; 129.7; 129.5; 126.8; 72.6; 37.4; 24.1; 23.3; 21.8; 21.6; 21.1. HRMS (ESI⁺) (M⁺-pTolSO₂+H): calculated C₁₂H₁₈NO₂S: 240.1058. Found: 240.1056. (M⁺-pTolSO₂+Na+MeO⁻): calculated C₁₃H₂₁NNaO₃S: 294.1140; Found: 294.1126. Elemental analysis: calculated C₁₉H₂₅NO₄S₂: C, 57.69; H, 6.37; N, 3.54; S, 16.21. Found: C, 57.64; H, 6.31; N, 3.49; S, 16.24.

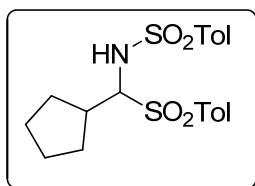
N-(2-Ethyl-1-tosylbutyl)-4-methylbenzenesulfonamide (14). Following the general



procedure A, the reaction of 2-ethylbutanal (1.0 mL, 8.83 mmol) with *p*-toluenesulfonamide (1.51 g, 8.83 mmol) and TolSO₂Na (1.89 g, 10.61 mmol) afforded **14** as a white solid; yield: 1.10 g (31%); m.p: 56-57 °C. ¹H-NMR (300 MHz, CDCl₃), δ (ppm): 7.61 (d, *J* = 8.3 Hz, 2H); 7.44 (d, *J* = 8.3 Hz, 2H); 7.24-7.16 (m, 2H); 7.11 (d, *J* = 8.1 Hz, 2H); 5.14 (d, *J* = 10.6 Hz, 1H); 4.60 (dd, *J* = 10.6 Hz, *J* = 1.9 Hz, 1H); 2.37 (s, 3H);

2.34 (s, 3H); 2.03-1.92 (m, 1H); 1.82-1.68 (m, 1H); 1.51-1.37 (m, 1H); 1.11-0.93 (m, 1H); 0.92-0.83 (t, $J = 7.2$ Hz, 1H); 0.83-0.74 (t, $J = 6.8$ Hz, 1H). ^{13}C -NMR (75 MHz, CDCl_3), δ (ppm): 145.0; 143.6; 138.1; 134.3; 129.7; 129.5; 129.2; 126.6; 74.2; 41.5; 22.8; 22.0; 21.7; 21.6; 11.9; 11.7. HRMS (ESI^+) (M^+ - $p\text{TolSO}_2+\text{H}$): calculated $\text{C}_{13}\text{H}_{20}\text{NO}_2\text{S}$: 254.1215. Found: 254.1210. (M^+ - $p\text{TolSO}_2+\text{Na}+\text{MeO}^-$): calculated $\text{C}_{14}\text{H}_{23}\text{NNaO}_3\text{S}$: 308.1290 Found: 308.1283.

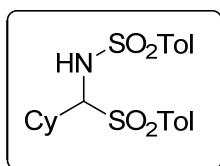
***N*-[Cyclopentyl(tosyl)methyl]-4-methylbenzenesulfonamide (15).** Following the



general procedure A, the reaction of cyclopentanecarboxaldehyde (0.50 mL, 4.54 mmol) with *p*-toluenesulfonamide (0.79 g, 4.54 mmol) and ToISO_2Na (1.0 g, 5.45 mmol) afforded **15** as a white solid; yield: 1.48 g (80%); m.p: 111–112 °C. ^1H -NMR (300 MHz, CDCl_3), δ (ppm): 7.69 (d, $J = 8.3$ Hz, 2H); 7.52(d, $J = 8.1$ Hz,

2H); 7.27 (d, $J = 7.9$ Hz, 2H); 7.21 (d, $J = 8.1$ Hz, 2H); 5.19 (d, $J = 10.6$ Hz, 1H); 4.73 (dd, $J = 10.3$ Hz, $J = 5.1$ Hz, 1H); 2.67-2.64 (m, 1H); 2.47 (s, 3H); 2.45 (s, 3H); 1.89-1.85 (m, 2H), 1.57-1.54 (m, 4H), 1.30-1.26 (m, 2H). ^{13}C -NMR (75 MHz, CDCl_3), δ (ppm): 145.0; 143.5; 138.1; 133.8; 129.7; 129.5; 129.4; 126.7; 38.9; 30.2; 27.9; 24.9; 24.7; 21.8; 21.5. HRMS (ESI^+) (M^+ - $p\text{TolSO}_2+\text{H}$): calculated $\text{C}_{13}\text{H}_{18}\text{NO}_2\text{S}$: 252.1052. Found: 252.1058. (M^+ - $p\text{TolSO}_2+\text{Na}+\text{MeO}^-$): calculated $\text{C}_{14}\text{H}_{21}\text{NNaO}_3\text{S}$: 306.1140. Found: 306.1140. Elemental analysis: calculated $\text{C}_{20}\text{H}_{25}\text{NO}_4\text{S}_2$: C, 58.94; H, 6.18; N, 3.44; S, 15.74. Found: C, 58.56; H, 6.11; N, 3.38; S, 15.50.

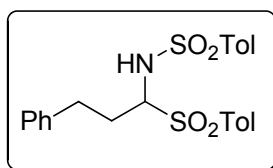
***N*-[Cyclohexyl(tosyl)methyl]-4-methylbenzenesulfonamide (16).** Following the



general procedure A, the reaction of cyclohexanecarboxaldehyde (0.93 mL, 10.0 mmol) with *p*-toluenesulfonamide (1.71 g, 10.0 mmol) and ToISO_2Na (1.97 g, 12.0 mmol) afforded **16** as a white solid; yield: 3.01 g (71%); m.p: 101–103 °C. ^1H -NMR (300 MHz, CDCl_3), δ (ppm): 7.69 (d, $J = 8.3$ Hz, 2H); 7.48 (d, $J = 8.3$ Hz, 2H); 7.25 (d, $J = 8.1$ Hz,

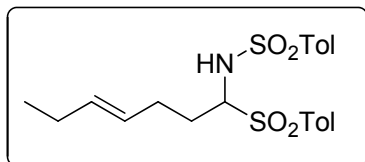
2H); 7.20 (d, $J = 7.9$ Hz, 2H); 5.28 (d, $J = 10.6$ Hz, 1H); 4.50 (dd, $J = 10.7$ Hz, $J = 2.8$ Hz, 1H); 2.47 (s, 3H); 2.45 (s, 3H); 2.43-2.41 (m, 1H); 2.06-2.03 (m, 1H); 1.76-1.72 (m, 4H); 1.23-1.19 (m, 2H); 1.07-1.03 (m, 3H). ^{13}C -NMR (75 MHz, CDCl_3), δ (ppm): 145.0; 143.4; 138.2; 134.2; 129.7; 129.5; 129.3; 126.7; 37.4; 31.0; 27.2; 26.2; 25.7; 25.6; 21.8; 21.6. HRMS (ESI^+) (M^+ - $p\text{TolSO}_2+\text{H}$): calculated $\text{C}_{14}\text{H}_{20}\text{NO}_2\text{S}$: 266.1215. Found: 266.1210. (M^+ - $p\text{TolSO}_2+\text{Na}+\text{MeO}^-$): calculated $\text{C}_{15}\text{H}_{23}\text{NNaO}_3\text{S}$: 320.1296; Found: 320.1278.

4-Methyl-*N*-(3-phenyl-1-tosylpropyl)benzenesulfonamide (17). Following the



general procedure A, the reaction of hydrocinnamaldehyde (1.46 mL, 10.0 mmol) with *p*-toluenesulfonamide (1.71 g, 10.0 mmol) and TolSO₂Na (1.97 g, 12.0 mmol) afforded **17** as a white solid; yield: 3.91 g (88%); m.p: 127–129 °C. ¹H-NMR (300 MHz, CDCl₃), δ (ppm): 7.60 (d, *J* = 8.3 Hz, 2H); 7.46 (d, *J* = 8.5 Hz, 2H); 7.23–7.15 (m, 7H); 6.96 (d, *J* = 6.7 Hz, 2H); 5.33 (s, 1H), 4.50 (dt, *J* = 10.3 Hz, *J* = 4.1 Hz, 1H); 2.68–2.39 (m, 3H); 2.36 (s, 3H); 2.33 (s, 3H); 2.01–1.81 (m, 1H). ¹³C-NMR (75 MHz, CDCl₃), δ (ppm): 145.4.; 143.8; 139.8; 137.8; 132.7; 129.8; 129.7; 128.6; 128.4; 126.8; 126.4; 73.2; 31.3; 30.3; 21.8; 21.6. HRMS (ESI⁺) (M⁺-pTolSO₂+H): calculated C₁₆H₁₈NO₂S: 288.1058. Found: 288.1047. (M⁺-pTolSO₂+Na+MeO⁻): calculated C₁₇H₂₁NNaO₃S: 342.1140; Found: 342.1134.

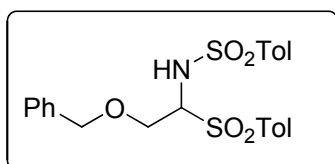
(*E*)-4-Methyl-*N*-(1-tosylhept-4-enyl)benzenesulfonamide (18). Following the general



procedure A, the reaction of *trans*-4-hepten-1-al (1.50 mL, 11.37 mmol) with *p*-toluenesulfonamide (1.97 g, 11.37 mmol) and TolSO₂Na (2.48 g, 13.64 mmol) afforded **18** as a white solid; yield: 1.48 g (30%); m.p:

103–105 °C. ¹H-NMR (300 MHz, CDCl₃), δ (ppm): 7.73 (d, *J* = 8.1 Hz, 2H); 7.60 (d, *J* = 8.3 Hz, 2H); 7.33 (d, *J* = 8.1 Hz, 2H); 7.25 (d, *J* = 8.1 Hz, 2H); 5.42–5.39 (m, 1H); 5.23–5.20 (m, 2H); 4.58 (dt, *J* = 9.6 Hz, *J* = 4.1 Hz, 1H); 2.49 (s, 3H); 2.45 (s, 3H); 2.30–2.17 (m, 1H); 2.15–1.59 (m, 4H); 1.58–1.56 (m, 1H); 0.94 (t, *J* = 7.3 Hz, 3H). ¹³C-NMR (75 MHz, CDCl₃), δ (ppm): 145.3; 143.7; 137.9; 133.8; 132.8; 129.8; 129.7; 129.6; 126.8; 126.1; 73.4; 28.7; 23.0; 21.8; 21.5; 20.5; 14.1. HRMS (ESI⁺) (M⁺-pTolSO₂+H): calculated C₁₄H₂₀NO₂S: 266.1215. Found: 266.1215. (M⁺-pTolSO₂+Na+MeO⁻): calculated C₁₅H₂₃NNaO₃S: 320.1296; Found: 320.1275.

***N*-[2-(Benzyloxy)-1-tosylethyl]-4-methylbenzenesulfonamide (19).** Following the

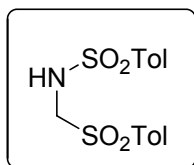


general procedure A, the reaction of 2-(benzyloxy)acetaldehyde (0.40 mL, 2.85 mmol) with *p*-toluenesulfonamide (0.48 g, 2.85 mmol) and TolSO₂Na (0.56 g, 3.42 mmol) afforded **19** as a white solid; yield:

0.91 g (70%); m.p: 118–120 °C. ¹H-NMR (300 MHz, CDCl₃), δ (ppm): 7.71–7.66 (m, 2H); 7.65–7.59 (m, 2H); 7.38–7.32 (m, 3H); 7.28–7.23 (m, 3H); 7.23–7.17 (m, 3H); 5.52 (d, *J* = 10.2 Hz, 1H); 4.71–4.63 (m, 1H); 4.96 (dt, *J* = 11.8 Hz, *J* = 7.7 Hz, 2H); 4.12 (dd, *J* = 10.8 Hz, *J* = 3.1 Hz, 1H); 3.64 (dd, *J* = 10.7 Hz, *J* = 4.3 Hz, 1H); 2.47 (s, 3H); 2.45 (s, 3H). ¹³C-NMR (75 MHz, CDCl₃), δ (ppm): 145.3; 143.9; 137.3; 136.6; 133.3; 129.7;

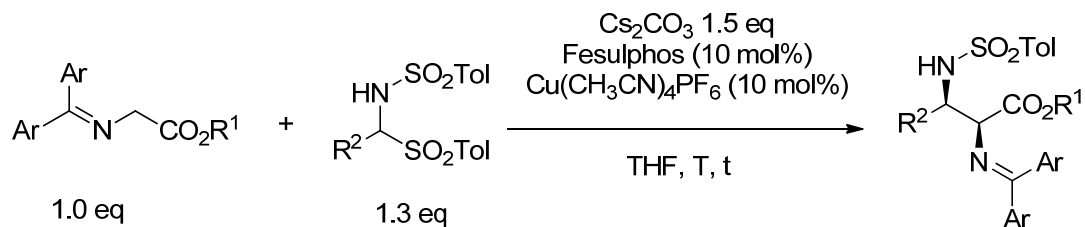
129.6; 129.6; 128.4; 128.0; 127.8; 127.0; 73.7; 72.7; 65.9; 21.7; 21.6. HRMS (ESI⁺) (M⁺-pTolSO₂+H): calculated C₁₆H₁₈NO₃S: 304.1007. Found: 304.1015. (M⁺-pTolSO₂+Na+MeO⁻): calculated C₁₇H₂₁NNaO₄S: 358.1083. Found: 358.1102.

4-Methyl-N-(tosylmethyl)benzenesulfonamide (30). Following the general procedure



A, the reaction of formaldehyde (0.74 mL, 37% w/w aq. solution, 10.0 mmol) with *p*-toluenesulfonamide (1.71 g, 10.0 mmol) and TolSO₂Na (1.97 g, 12.0 mmol) afforded **30** as a white solid; yield: 2.91 g (86%); m.p: 161–162 °C. ¹H-NMR (300 MHz, CDCl₃), δ (ppm): 7.77 (d, *J* = 8.3 Hz, 2H); 7.62 (d, *J* = 8.3 Hz, 2H); 7.37 (d, *J* = 7.9 Hz, 2H); 7.32 (d, *J* = 7.9 Hz, 2H); 5.34 (t, *J* = 7.4 Hz, 1H), 4.37 (d, *J* = 7.1 Hz, 2H); 2.50 (s, 3H); 2.47 (s, 3H). ¹³C-NMR (75 MHz, CDCl₃), δ (ppm): 145.7; 144.2; 136.8; 133.0; 130.0; 129.8; 129.1; 126.8; 63.5; 21.8; 21.6. HRMS (ESI⁺) (M⁺-pTolSO₂+H): calculated C₈H₁₀NO₂S: 184.0426; Found: 184.0433. (M⁺-pTolSO₂+Na+MeO⁻): calculated C₉H₁₃NNaO₃S: 238.0514; Found: 238.0501. Elemental analysis: calculated C₁₅H₁₇NO₄S₂: C, 53.08; H, 5.05; N, 4.13; S, 18.89. Found: C, 53.32; H, 5.05; N, 4.06; S, 18.64.

1.3. General procedure for the asymmetric Mannich reaction

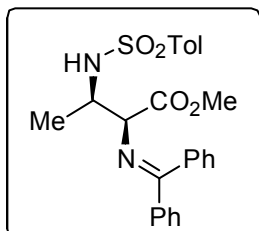


To a solution of (*R*)-Fesulphos (6.87 mg, 10 mol %) and Cu(CH₃CN)₄PF₆ (5.59 mg, 10 mol %) in THF (2 mL), under inert atmosphere and the optimum temperature (indicated in each entry), were successively added the corresponding glycine derivative (0,15 mmol), Cs₂CO₃ (0.22 mmol) and the aliphatic α -amido sulfone (0.19 mmol). The reaction mixture was stirred upon consumption of the starting material (TLC monitoring) and filtered through Celite. After evaporation of the solvent, the crude product was analyzed by ¹H NMR spectroscopy to determine the diastereomeric ratio and then purified by column chromatography on silica gel (the eluent is indicated for each case).

Products **6** and **20-29**, were isolated as inseparable mixtures of *syn/anti* diastereomers, which were analyzed by chiral HPLC to determine enantioselectivity, as well as diastereoselectivity.

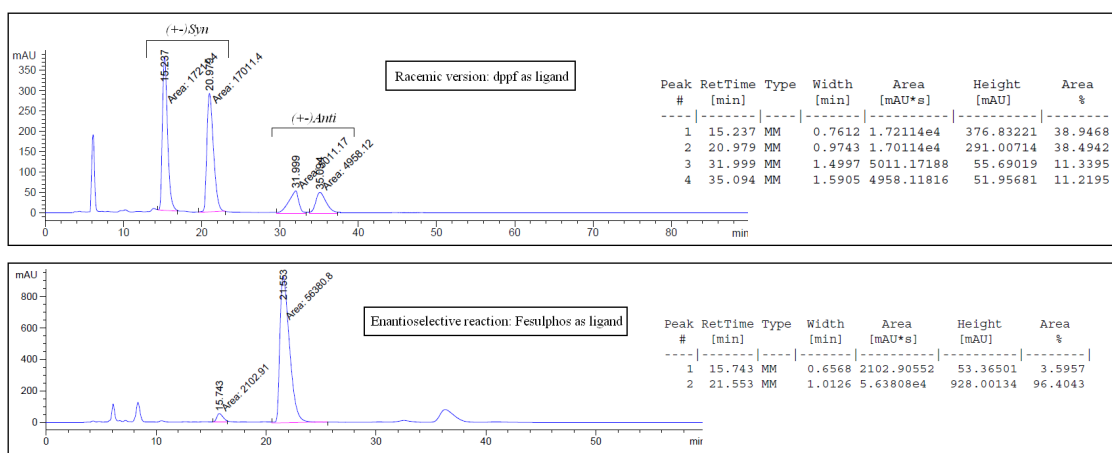
Racemic Mannich reaction: In spite of the high diastereo and enantioselectivities achieved with the Fesulphos ligand, very poor *syn/anti* mixtures were obtained following the general procedure using a combination of dppf [1,1'-Bis-(diphenylphosphino)-ferrocene] and Cu(CH₃CN)₄PF₆ as the catalyst.

(2*S*,3*R*)-Methyl-2-(diphenylmethyleneamino)-3-(4-methylphenylsulfonamido)-

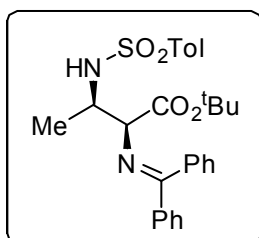


butanoate (3). Following the general procedure, the reaction of methyl 2-[(diphenylmethylene)amino]acetate (**2a**) (38.0 mg, 0.15 mmol) with 4-methyl-*N*-(1-tosylethyl)benzenesulfonamide (**1a**) (69.0 mg, 0.19 mmol) in THF (2 mL) at rt for 5 h, afforded, after flash chromatography (*n*-hexane-EtOAc 6:1), *syn*-**3** as a yellow oil; yield: 35.1 mg (52%, *syn/anti* = 88:12). ¹H-NMR (300 MHz, CDCl₃), δ (ppm): 7.68 (d, *J* = 8.3 Hz, 2H); 7.57-7.53 (m, 2H); 7.39-7.32 (m, 4H); 7.30-7.24 (m, 2H); 7.22-7.16 (m, 2H); 7.03-6.91 (m, 2H); 5.56 (d, *J* = 9.0 Hz, 1H); 3.96-3.87 (m, 1H); 3.86 (d, *J* = 3.0 Hz, 1H); 3.31 (s, 3H); 2.34 (s, 3H); 1.06 (d, *J* = 6.0 Hz, 3H).

ee = 93 %; [α]_D²⁵: -14 (*c* = 1.0; CHCl₃). HPLC: Daicel Chiralpak IA, *i*-PrOH/hexane 10/90, flow rate 1.0 mL/min (λ = 254.4 nm), τ_{syn}: 15.7 min (2*R*,3*S*) and 21.5 min (2*S*,3*R*).



(2*S*,3*R*)-*tert*-Butyl-2-(diphenylmethyleneamino)-3-(4-methylphenylsulfonamido)-

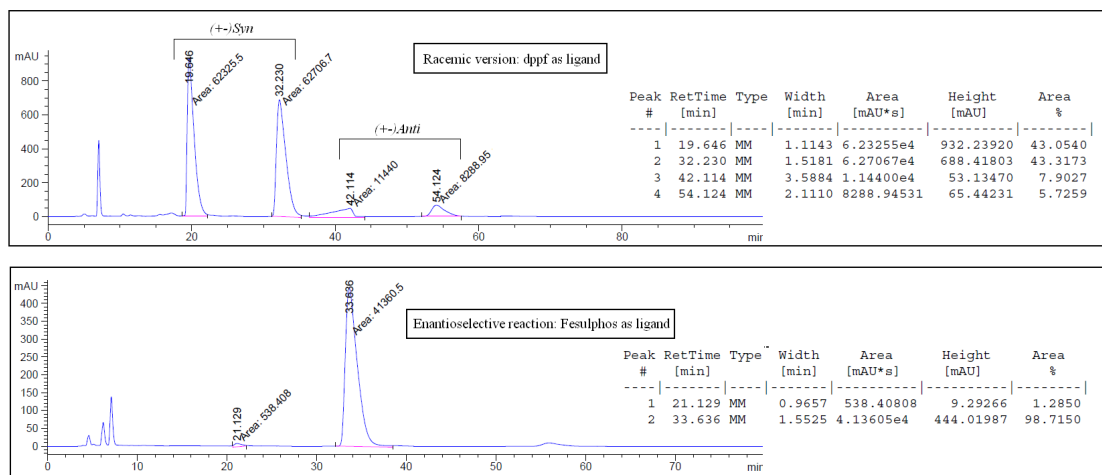


butanoate (4). Following the general procedure, the reaction of methyl *tert*-butyl 2-(diphenylmethyleneamino)acetate (**2b**) (44.3 mg, 0.15 mmol) with **1a** (68.9 mg, 0.19 mmol) in THF (2 mL) at -20°C for 17 h, afforded, after flash chromatography (*n*-hexane-EtOAc 6:1), *syn*-**4** as a yellow oil; yield: 29.5 mg (40%, *syn/anti*

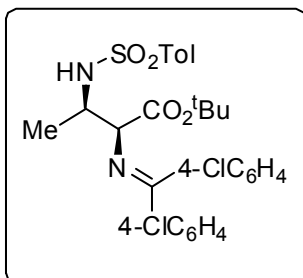
= 96:4). ¹H-NMR (300 MHz, CDCl₃), δ (ppm): 7.69 (d, *J* = 8.1 Hz, 2H); 7.58-7.52 (m, 2H); 7.36-7.32 (m, 4H); 7.31-7.26 (m, 2H); 7.20-7.14 (m, 2H); 7.04-6.96 (m, 2H); 5.51 (d, *J* = 9.2 Hz, 1H); 3.99-3.87 (m, 1H); 3.75 (d, *J* = 2.2 Hz, 1H); 2.33 (s, 3H); 1.27 (s,

9H); 0.98 (d, $J = 6.6$ Hz, 3H). ^{13}C -NMR (75 MHz, CDCl_3), δ (ppm): 172.3; 168.9; 142.8; 139.2; 138.9; 136.2; 130.7; 129.5; 128.8; 128.8; 128.6; 128.1; 127.4; 126.9; 82.0; 69.3; 52.1; 27.8; 21.5; 19.6.

$ee = 97\%$; $[\alpha]_D^{25}$: -17 ($c = 1.0$; CHCl_3). HPLC: Daicel Chiralpak IA, i -PrOH/hexane 4/96, flow rate 1.0 mL/min ($\lambda = 254.4$ nm), τ_{syn} : 21.1 min ($2R,3S$) and 33.6 min ($2S,3R$).



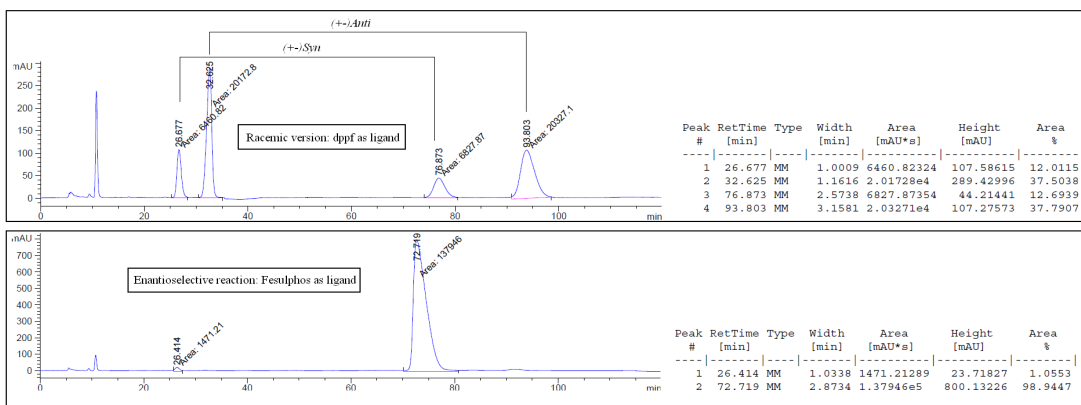
(2*S*,3*R*)-*tert*-Butyl-2-[[bis(4-chlorophenyl)methylene]amino]-3-(4-methylphenyl-



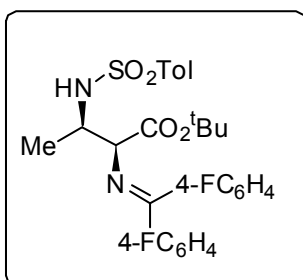
sulfonamido)butanoate (5). Following the general procedure, the reaction of *tert*-butyl 2-[bis(4-chlorophenyl)methyleneamino]acetate (**2c**) (54.6 mg, 0.15 mmol) with **1a** (68.9 mg, 0.19 mmol) in THF (2 mL), at -20 °C for 17 h, afforded, after flash chromatography (n -hexane-EtOAc 6:1), *syn*-**5** as a light yellow solid; yield: 52.2 mg (62%, *syn/anti* = >98:<2); m.p: 197-200 °C. ^1H -NMR (300

MHz, CDCl_3), δ (ppm): 7.68 (d, $J = 8.3$ Hz, 2H); 7.46 (d, $J = 8.5$ Hz, 2H); 7.33 (d, $J = 8.4$ Hz, 2H); 7.23 (d, $J = 8.6$ Hz, 2H); 7.18 (m, 2H); 6.94 (d, $J = 8.4$ Hz, 2H); 5.40 (d, $J = 3.0$ Hz, 1H); 3.97-3.83 (m, 1H); 3.70 (d, $J = 1.0$ Hz, 1H); 2.33 (s, 3H); 1.28 (s, 9H); 0.97 (d, $J = 6.7$ Hz, 3H). ^{13}C -NMR (75 MHz, CDCl_3), δ (ppm): 169.0; 167.4; 142.0; 138.0; 136.2; 136.0; 134.2; 133.0; 129.0; 128.5; 128.1; 127.8; 127.4; 125.9; 81.4; 68.5; 51.0; 26.8; 20.5; 18.3.

$ee = 98\%$; $[\alpha]_D^{25}$: -17 ($c = 0.6$; CHCl_3). HPLC: Daicel Chiralpak AD, i -PrOH/hexane 5/95, flow rate 0.7 mL/min ($\lambda = 254.4$ nm), τ_{syn} : 26.7 min ($2R,3S$) and 72.7 min ($2S,3R$).



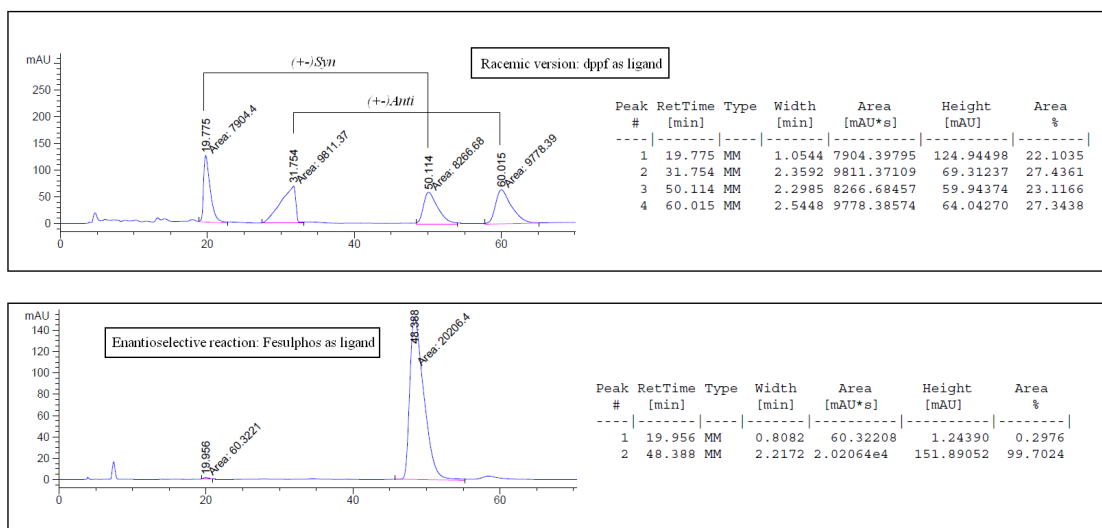
(2*S*,3*R*)-*tert*-Butyl-2-[bis(4-fluorophenyl)methyleneamino]-3-(4-methylphenyl-



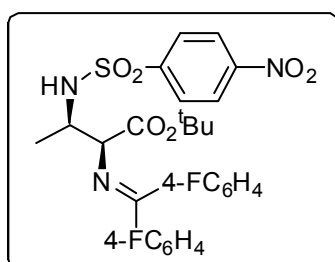
sulfonamido)butanoate (6). Following the general procedure, the reaction of *tert*-butyl 2-[bis(4-fluorophenyl)methyleneamino]acetate (**2d**) (49.7 mg, 0.15 mmol) with **1a** (68.9 mg, 0.19 mmol) in THF (2 mL), at -20 °C for 17 h, afforded, after flash chromatography (*n*-hexane-EtOAc 6:1), *syn*-**6** as a light yellow solid; yield: 58.2 mg

(74%, *syn/anti* = >98:<2); m.p: 163–164 °C. $^1\text{H-NMR}$ (300 MHz, CDCl_3), δ (ppm): 7.67 (d, $J = 8.3$ Hz, 2H); 7.56-7.48 (m, 2H); 7.17 (d, $J = 7.7$ Hz, 2H); 7.06-6.90 (m, 6H); 5.42 (d, $J = 9.4$ Hz, 1H); 3.97-3.84 (m, 1H); 3.71 (d, $J = 3.0$ Hz, 1H); 2.33 (s, 3H); 1.28 (s, 9H); 0.97 (d, $J = 6.6$ Hz, 1H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3), δ (ppm): 170.2; 168.6; 164.5 (d, $^1J_{\text{C-F}} = 250.5$ Hz); 162.8 (d, $^1J_{\text{C-F}} = 247.5$ Hz); 143.0; 139.0; 135.05 (d, $^4J_{\text{C-F}} = 3.0$ Hz); 131.7 (d, $^4J_{\text{C-F}} = 3.7$ Hz); 130.9 (d, $^3J_{\text{C-F}} = 8.2$ Hz); 129.5; 129.4 (d, $^3J_{\text{C-F}} = 8.2$ Hz); 126.9; 115.92 (d, $^2J_{\text{C-F}} = 21.3$ Hz); 115.2 (d, $^2J_{\text{C-F}} = 21.8$ Hz); 82.3; 69.4; 52.0; 27.8; 21.5; 19.4. $^{19}\text{F-NMR}$ (300 MHz, CDCl_3), δ (ppm): -111.3; -109.4; HRMS (ESI $^+$) ($\text{M}^+\text{+H}$): calculated $\text{C}_{28}\text{H}_{31}\text{N}_2\text{O}_4\text{F}_2\text{S}$: 529.1967 Found: 529.1952.

$ee = >99\%$; $[\alpha]_{\text{D}}^{25}$: -35 ($c = 1.0$; CHCl_3). HPLC: Daicel Chiralpak AD, *i*-PrOH/hexane 4/96, flow rate 1.0 mL/min ($\lambda = 254.4$ nm), τ_{syn} : 19.8 min (2*R*,3*S*) and 50.1 min (2*S*,3*R*).



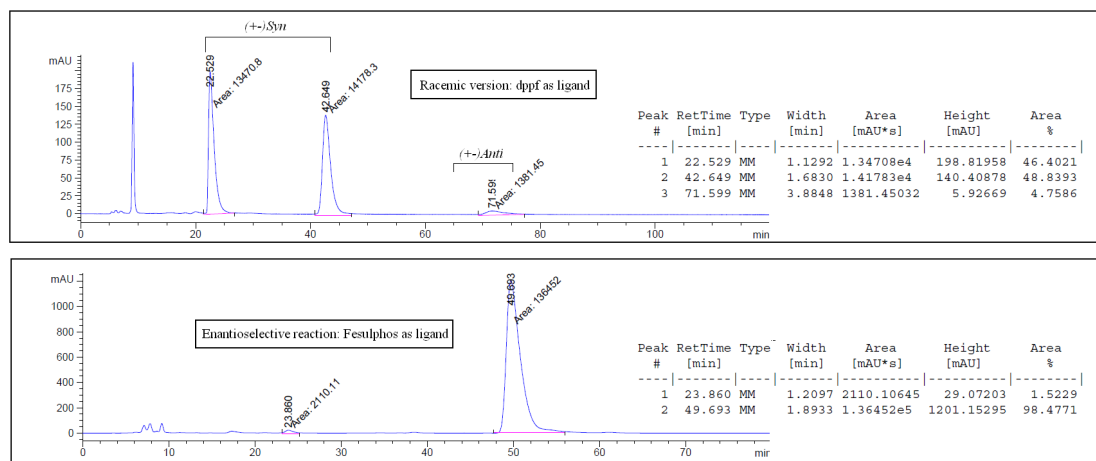
(2*S*,3*R*)-tert-Butyl-2-[[bis(4-fluorophenyl)methylene]amino]-3-(4-nitrophenyl-



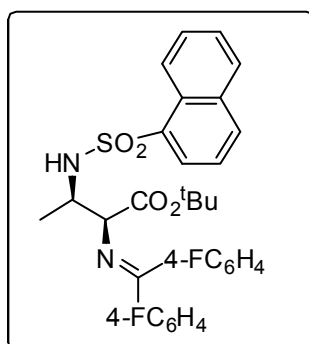
sulfonamido)butanoate (8). Following the general procedure, the reaction of *tert*-butyl 2-[bis(4-fluorophenyl)methyleneamino]acetate (**2d**) (49.7 mg, 0.15 mmol) with 4-nitro-*N*-(1-tosylethyl)benzenesulfonamide (**1c**) (75.0 mg, 0.19 mmol) in THF (2 mL) at $-20\text{ }^{\circ}\text{C}$ for 17 h, afforded, after flash chromatography (*n*-hexane-EtOAc

7:1), *syn*-**8** as a light yellow oil; yield: 26.7 mg (32%, *syn/anti* = >98:<2). $^1\text{H-NMR}$ (300 MHz, CDCl_3), δ (ppm): 8.27-8.21 (m, 2H); 8.06-7.97 (m, 2H); 7.56-7.47 (m, 2H); 7.11-6.91 (m, 6H); 5.73 (d, $J = 9.1$ Hz, 1H); 4.09-3.94 (m, 1H); 3.71 (d, $J = 2.6$ Hz, 1H); 1.25 (s, 9H); 1.03-0.99 (d, $J = 6.6$ Hz, 3H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3), δ (ppm): 170.8; 168.4; 164.6 (d, $^1J_{\text{C-F}} = 251.2$ Hz); 162.8 (d, $^1J_{\text{C-F}} = 246.7$ Hz); 149.8; 147.8; 134.84 (d, $^4J_{\text{C-F}} = 3.0$ Hz); 131.6 (d, $^4J_{\text{C-F}} = 3.7$ Hz); 130.9 (d, $^3J_{\text{C-F}} = 9.0$ Hz); 129.3 (d, $^3J_{\text{C-F}} = 8.3$ Hz); 128.1; 124.2; 116.0 (d, $^2J_{\text{C-F}} = 21.0$ Hz); 115.3 (d, $^2J_{\text{C-F}} = 21.7$ Hz); 82.5; 69.2; 52.3; 25.3; 19.9. $^{19}\text{F-NMR}$ (300 MHz, CDCl_3), δ (ppm): -110.9.; -109.0. HRMS (ESI $^+$) ($\text{M}^+\text{+H}$): calculated $\text{C}_{27}\text{H}_{28}\text{N}_3\text{O}_6\text{F}_2\text{S}$: 560.1687; Found: 560.1680; ($\text{M}^+\text{+2H-}^t\text{Bu}$): calculated $\text{C}_{23}\text{H}_{20}\text{N}_3\text{O}_6\text{F}_2\text{S}$: 504.1035; Found: 504.1030.

$ee = 97\%$; $[\alpha]_{\text{D}}^{25}$: -12 ($c = 0.3$; CHCl_3). HPLC: Daicel Chiralpak IA, *i*-PrOH/hexane 10/90, flow rate 0.7 mL/min ($\lambda = 254.4$ nm), τ_{syn} : 23.9 min (2*R*,3*S*), 49.4 (2*S*,3*R*).



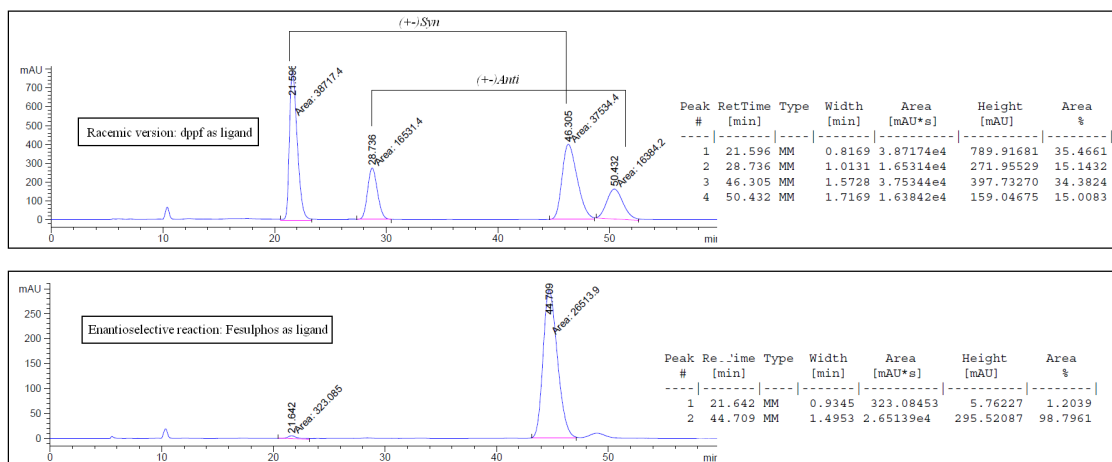
(2*S*,3*R*)-tert-Butyl-2-[[bis(4-fluorophenyl)methylene]amino]-3-(naphthalene-2-



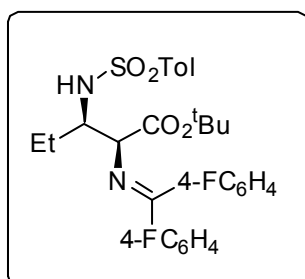
sulfonamido)butanoate (9). Following the general procedure, the reaction of *tert*-butyl 2-[bis(4-fluorophenyl)methyleneamino]acetate (**2d**) (49.7 mg, 0.15 mmol) with *N*-(1-tosylethyl)naphthalene-2-sulfonamide (**1d**) (75.9 mg, 0.19 mmol) in THF (2 mL) at $-20\text{ }^{\circ}\text{C}$ for 17 h, afforded, after flash chromatography (*n*-hexane-EtOAc 7:1), *syn*-**9** as a

colourless oil; yield: 45.5 mg (54%, *syn/anti* = >98:<2). ¹H-NMR (300 MHz, CDCl₃), δ (ppm): 8.56 (d, *J* = 8.5 Hz, 1H); 8.2 (dd, *J* = 7.3 Hz, *J* = 1.1 Hz, 1H); 7.96 (d, *J* = 8.3 Hz, 1H); 7.85 (d, *J* = 7.9 Hz, 1H); 7.65-7.56 (m, 1H); 7.55-7.50 (m, 1H); 7.49-7.38 (m, 3H); 7.03-6.85 (m, 6H); 5.74 (d, *J* = 9.2 Hz, 1H); 3.85-3.80 (m, 1H); 3.61 (d, *J* = 2.8 Hz, 1H); 1.20 (s, 9H); 0.84 (d, *J* = 6.8 Hz, 3H). ¹³C-NMR (75 MHz, CDCl₃), δ (ppm): 170.1; 168.53; 164.5 (d, ¹*J*_{C-F} = 250.5 Hz); 162.8 (d, ¹*J*_{C-F} = 247.5 Hz); 136.62; 135.05 (d, ⁴*J*_{C-F} = 3.0 Hz); 134.3; 133.9; 131.6 (d, ⁴*J*_{C-F} = 3.7 Hz); 130.8 (d, ³*J*_{C-F} = 8.2 Hz); 129.3 (d, ³*J*_{C-F} = 8.2 Hz); 129.0; 128.9; 128.2; 128.1; 126.7; 124.6; 124.2; 115.8 (d, ²*J*_{C-F} = 21.3 Hz); 115.1 (d, ²*J*_{C-F} = 21.3 Hz); 82.4; 69.3; 52.2; 27.8; 18.9. ¹⁹F-NMR (300 MHz, CDCl₃), δ (ppm): -111.3; -109.4. HRMS (ESI⁺) (M⁺+H): calculated C₃₁H₃₁N₂O₄F₂S: 565.1967; Found: 565.1986; (M⁺+2H-^tBu): calculated C₂₇H₂₃N₂O₄F₂S: 509.1341; Found: 509.1334.

ee = 97%; [α]_D²⁵: -30 (*c* = 1.0; CHCl₃). HPLC: Daicel Chiralpak AD, *i*-PrOH/hexane 5/95, flow rate 0.7 mL/min (λ = 254.4 nm), τ_{syn}: 21.6 min (2*R*,3*S*), 44.7 (2*S*,3*R*).



(2*S*,3*R*)-*tert*-Butyl-2-[[bis(4-fluorophenyl)methylene]amino]-3-(4-methylphenyl-

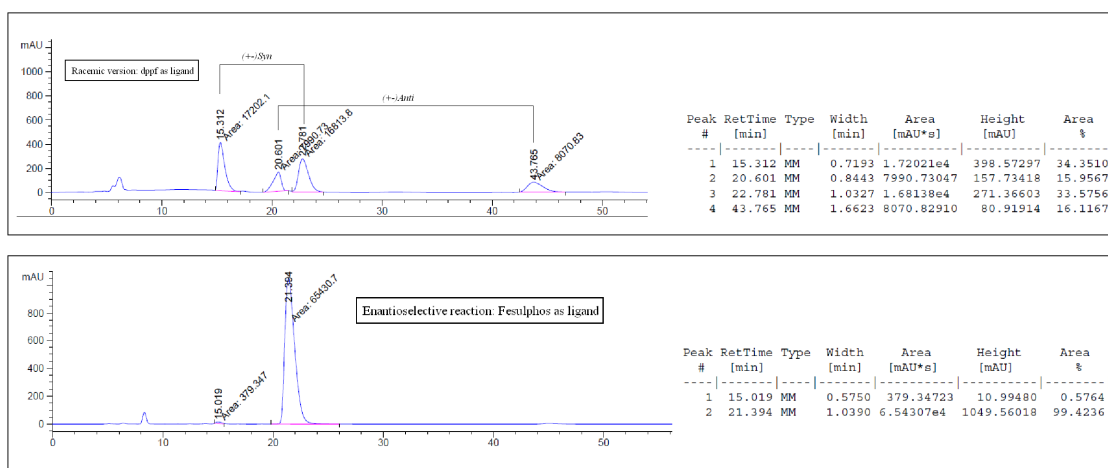


sulfonamido)pentanoate (20). Following the general procedure, the reaction of *tert*-butyl 2-[bis(4-fluorophenyl)methyleneamino]acetate (**2d**) (49.7 mg, 0.15 mmol) with 4-methyl-*N*-(1-tosylpropyl)benzenesulfonamide (**10**) (71.6 mg, 0.19 mmol) in THF (2 mL) at -20 °C for 23 h, afforded, after flash chromatography (*n*-hexane-EtOAc 7:1), *syn*-**20** as a

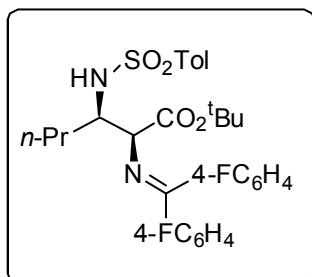
light yellow solid; yield: 72.9 mg (90%, *syn/anti* = 99:1); m.p: 151.0–152.3 °C. ¹H-NMR (300 MHz, CDCl₃), δ (ppm): 7.71-7.64 (m, 2H); 7.55-7.47 (m, 2H); 7.16 (d, *J* = 8.1 Hz, 2H); 7.07-6.90 (m, 6H); 5.50 (d, *J* = 9.4 Hz, 1H); 3.85-3.79 (m, 1H); 3.77-3.62 (m, 1H); 2.33 (s, 3H); 1.51-1.38 (m, 2H); 1.28 (s, 9H); 0.60 (t, *J* = 7.3 Hz, 3H). ¹³C-NMR (75 MHz, CDCl₃), δ (ppm): 170.0; 169.1; 164.5 (d, ¹*J*_{C-F} = 249.7 Hz); 162.8 (d,

$^1J_{C-F} = 247.5$ Hz); 142.9; 139.4; 135.1 (d, $^4J_{C-F} = 3.0$ Hz); 131.8 (d, $^4J_{C-F} = 3.7$ Hz); 130.8 (d, $^3J_{C-F} = 9.0$ Hz); 129.5; 129.4 (d, $^3J_{C-F} = 8.2$ Hz); 126.8; 115.7 (d, $^2J_{C-F} = 21.3$ Hz); 115.2 (d, $^2J_{C-F} = 21.3$ Hz); 82.3; 66.7; 57.9; 27.9; 26.1; 21.4; 10.3. ^{19}F -NMR (300 MHz, CDCl_3), δ (ppm): -111.2; -109.5. HRMS (ESI⁺) ($\text{M}^+ + \text{H}$): calculated $\text{C}_{29}\text{H}_{33}\text{N}_2\text{O}_4\text{F}_2\text{S}$: 543.2123; Found: 543.2111.

$ee = 99\%$; $[\alpha]_{\text{D}}^{25}$: -43 ($c = 1.0$; CHCl_3). HPLC: Daicel Chiralpak IA, *i*-PrOH/hexane 8/92, flow rate 0.8 mL/min ($\lambda = 254.4$ nm), τ_{syn} : 15.0 min (2*R*,3*S*) and 21.4 min (2*S*,3*R*).



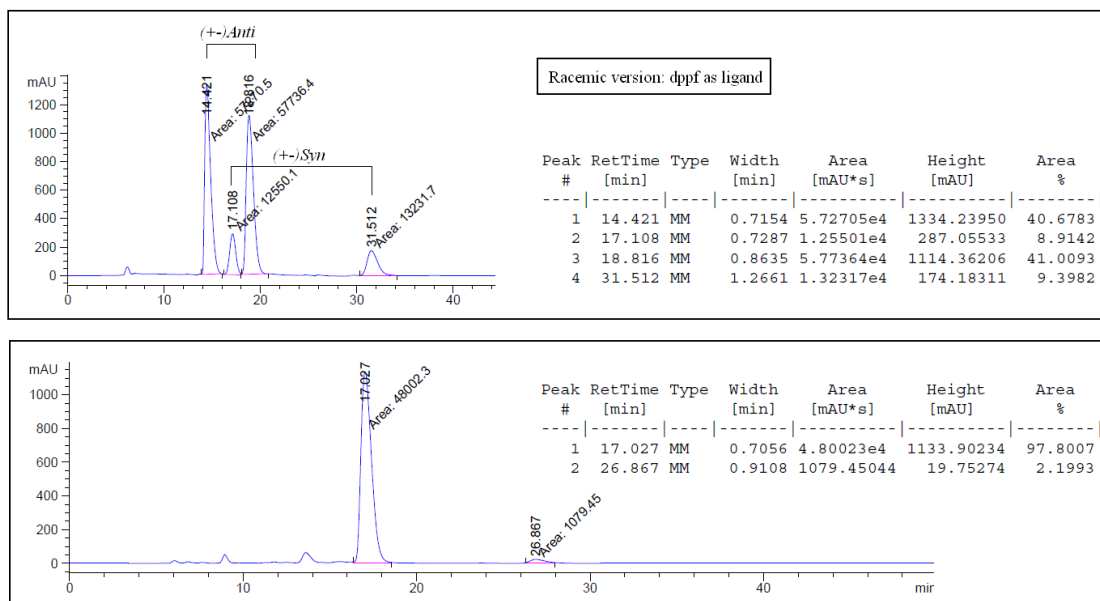
(2*S*,3*R*)-*tert*-Butyl-2-[[bis(4-fluorophenyl)methylene]amino]-3-(4-methylphenyl-



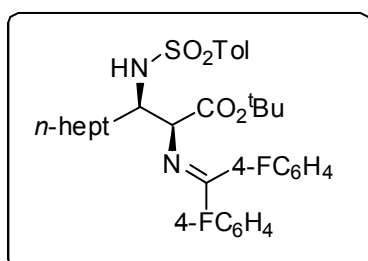
sulfonamido)-hexanoate (21). Following the general procedure, the reaction of *tert*-butyl 2-[bis(4-fluorophenyl)-methyleneamino]acetate (**2d**) (49.7 mg, 0.15 mmol) with 4-methyl-*N*-(1-tosylbutyl)benzenesulfonamide (**11**) (74.4 mg, 0.19 mmol) in THF (2 mL) at -20 °C for 23 h, afforded, after flash chromatography (*n*-hexane-EtOAc 7:1), *syn*-**21** as a colourless oil; yield: 73.4 mg (88 %, *syn/anti* = 96:4). ^1H -

NMR (300 MHz, CDCl_3), δ (ppm): 7.71-7.63 (m, 2H); 7.55-7.46 (m, 2H); 7.16 (d, $J = 7.9$ Hz, 2H); 7.07-6.91 (m, 6H); 5.44 (d, $J = 9.3$ Hz, 1H); 3.84-3.78 (m, 1H); 3.78-3.69 (m, 1H); 2.33 (s, 3H); 1.45-1.39 (m, 1H); 1.28 (s, 9H); 1.22-1.16 (m, 1H); 0.84-0.75 (m, 2H); 0.70 (t, $J = 7.2$ Hz, 3H). ^{13}C -NMR (75 MHz, CDCl_3), δ (ppm): 169.9; 169.1; 164.5 (d, $^1J_{C-F} = 249.7$ Hz); 162.8 (d, $^1J_{C-F} = 247.5$ Hz); 142.9; 139.3; 135.1 (d, $^4J_{C-F} = 3.0$ Hz); 131.8 (d, $^4J_{C-F} = 3.0$ Hz); 130.8 (d, $^3J_{C-F} = 8.2$ Hz); 129.4; 129.3 (d, $^3J_{C-F} = 8.2$ Hz); 126.7; 115.8 (d, $^2J_{C-F} = 21.3$ Hz); 115.2 (d, $^2J_{C-F} = 21.3$ Hz); 82.3; 67.1; 56.1; 35.1; 27.9; 21.4; 18.9; 13.7. ^{19}F -NMR (300 MHz, CDCl_3), δ (ppm): -111.2; -109.5. HRMS (ESI⁺) ($\text{M}^+ + \text{H}$): calculated $\text{C}_{30}\text{H}_{35}\text{N}_2\text{O}_4\text{F}_2\text{S}$: 557.2280; Found: 543.2278.

$ee = 96\%$; $[\alpha]_{\text{D}}^{25}$: -31 ($c = 1.0$; CHCl_3). HPLC: Daicel Chiralpak IA, *i*-PrOH/hexane 10/90, flow rate 0.7 mL/min ($\lambda = 254.4$ nm), τ_{syn} : 17.02 min (2*S*,3*R*), 26.9 min (2*R*,3*S*).



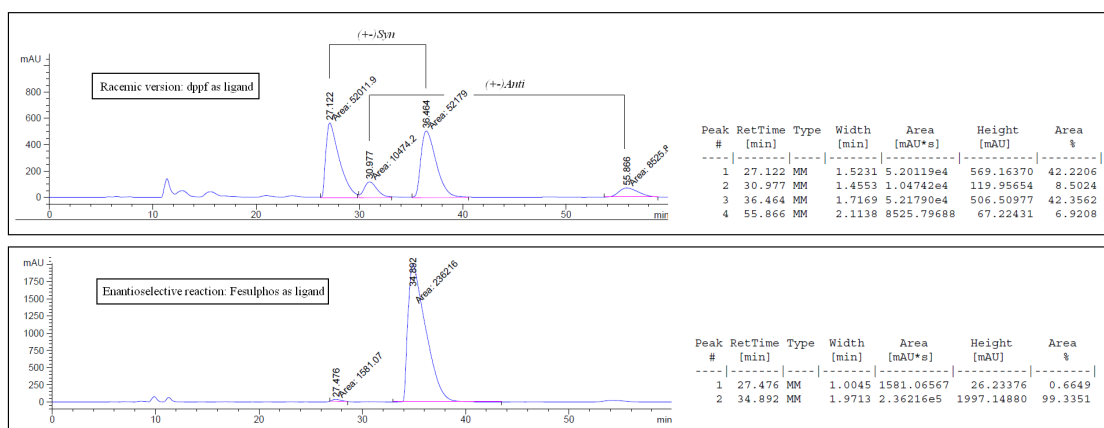
(2*S*,3*R*)-tert-Butyl-2-[[bis(4-fluorophenyl)methylene]amino]-3-(4-



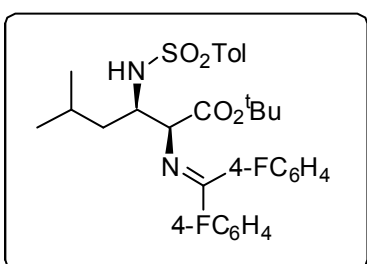
methylphenylsulfonamido)decanoate (22). Following the general procedure, the reaction of *tert*-butyl 2-[bis(4-fluorophenyl)methyleneamino]acetate (**2d**) (49.7 mg, 0.15 mmol) with 4-methyl-*N*-(1-tosyloctyl)benzenesulfonamide (**12**) (85.3 mg, 0.19 mmol) in THF (2 mL) at $-20\text{ }^{\circ}\text{C}$ for 24 h, afforded, after flash chromatography

(*n*-hexane-EtOAc 7:1), *syn*-**22** as a light yellow oil; yield: 73.5 mg (80%, *syn/anti* = 98:2). $^1\text{H-NMR}$ (300 MHz, CDCl_3), δ (ppm): 7.71-7.63 (m, 2H); 7.56- 7.48 (m, 2H); 7.16 (d, $J = 8.1$ Hz, 2H); 7.06-6.89 (m, 6H); 5.48 (d, $J = 9.6$ Hz, 1H); 3.81 (d, $J = 2.6$ Hz, 1H); 3.78-3.68 (m, 1H); 2.33 (s, 3H); 1.49-1.31 (m, 2H); 1.29 (s, 9H); 1.23-1.12 (m, 2H); 1.11-0.98 (m, 7H); 0.91-0.83 (m, 1H); 0.78 (t, $J = 6.9$ Hz, 3H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3), δ (ppm): 169.9; 169.1; 164.5 (d, $^1J_{\text{C-F}} = 250.5$ Hz); 162.8 (d, $^1J_{\text{C-F}} = 247.5$ Hz); 142.9; 139.3; 134.1 (d, $^4J_{\text{C-F}} = 3.0$ Hz); 131.8 (d, $^4J_{\text{C-F}} = 3.7$ Hz); 130.9 (d, $^3J_{\text{C-F}} = 9.0$ Hz); 129.4; 129.4 (d, $^3J_{\text{C-F}} = 8.2$ Hz); 126.9; 115.8 (d, $^2J_{\text{C-F}} = 21.9$ Hz); 115.2 (d, $^2J_{\text{C-F}} = 21.3$ Hz); 82.3; 67.1; 56.5; 32.9; 31.6; 29.1; 29.0; 27.9; 25.7; 22.6; 21.4; 14.0. $^{19}\text{F-NMR}$ (300 MHz, CDCl_3), δ (ppm): -111.2; -109.5. HRMS (ESI $^+$) ($\text{M}^+\text{+H}$): calculated $\text{C}_{34}\text{H}_{43}\text{N}_2\text{O}_4\text{F}_2\text{S}$: 613.2906; Found: 613.2906.

$ee = 99\%$; $[\alpha]_{\text{D}}^{25}$: -30 ($c = 1.0$; CHCl_3). HPLC: Daicel Chiralpak IA, *i*-PrOH/hexane 3/97, flow rate 0.7 mL/min ($\lambda = 254.4$ nm), τ_{syn} : 27.5 min (2*R*,3*S*) and 34.9 min (2*S*,3*R*).



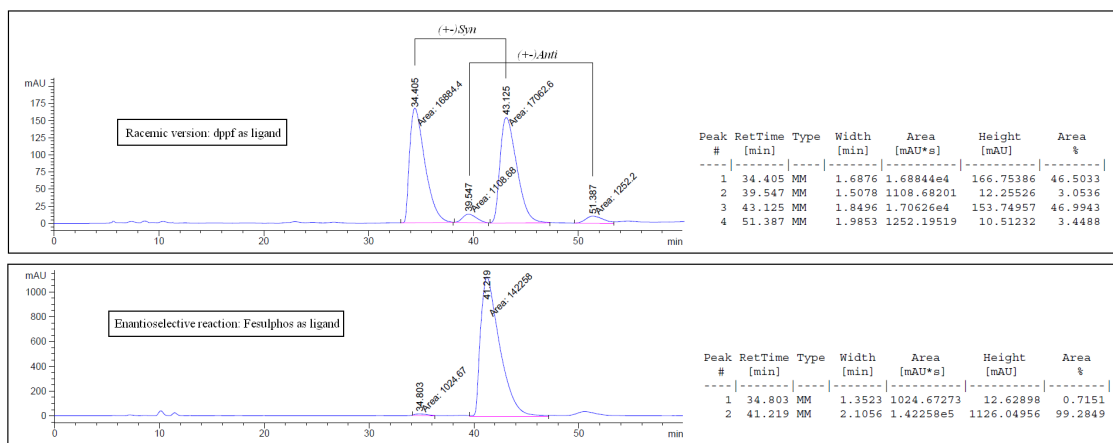
(2*S*,3*R*)-tert-Butyl-2-[[bis(4-fluorophenyl)methylene]amino]-5-methyl-3-(4-



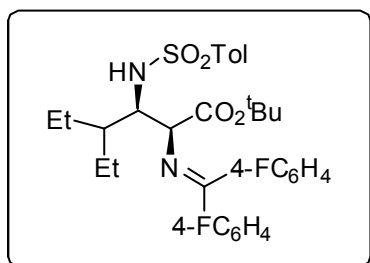
methylphenylsulfonamido) hexanoate (23**)**. Following the general procedure, the reaction of *tert*-butyl 2-[bis(4-fluorophenyl)methyleneamino]acetate (**2d**) (49.7 mg, 0.15 mmol) with 4-methyl-*N*-(3-methyl-1-tosylbutyl)-benzenesulfonamide (**13**) (77.1 mg, 0.19 mmol) in THF (2 mL) at $-20\text{ }^{\circ}\text{C}$ for 24 h, afforded, after flash

chromatography (*n*-hexane-EtOAc 7:1), *syn*-**23** as a light yellow solid; yield: 70.2 mg (80%, *syn/anti* = 96:4); m.p: 114.3–115.1 $^{\circ}\text{C}$. $^1\text{H-NMR}$ (300 MHz, CDCl_3), δ (ppm): 7.70–7.62 (m, 2H); 7.56–7.47 (m, 2H); 7.16 (d, $J = 8.1$ Hz, 2H); 7.06–6.89 (m, 6H); 5.42 (d, $J = 9.4$ Hz, 1H); 3.83–3.78 (m, 1H); 3.78–3.73 (m, 1H); 2.33 (s, 3H); 1.29 (s, 9H); 1.25–1.17 (m, 2H); 0.82–0.77 (m, 1H); 0.73 (d, $J = 6.2$ Hz, 3H); 0.67 (d, $J = 6.2$ Hz, 3H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3), δ (ppm): 169.9; 169.1; 164.5 (d, $^1J_{\text{C-F}} = 250.5$ Hz); 162.8 (d, $^1J_{\text{C-F}} = 247.5$ Hz); 142.9; 139.2; 135.1 (d, $^4J_{\text{C-F}} = 3.0$ Hz); 131.8 (d, $^4J_{\text{C-F}} = 3.7$ Hz); 130.8 (d, $^3J_{\text{C-F}} = 8.2$ Hz); 129.4; 129.3 (d, $^3J_{\text{C-F}} = 8.2$ Hz); 126.9; 115.8 (d, $^2J_{\text{C-F}} = 21.3$ Hz); 115.2 (d, $^2J_{\text{C-F}} = 21.9$ Hz); 82.3; 67.1; 54.6; 41.9; 27.9; 24.4; 22.5; 22.3; 21.4. $^{19}\text{F-NMR}$ (300 MHz, CDCl_3), δ (ppm): -111.2; -109.5. HRMS (ESI $^+$) ($\text{M}^+ + \text{H}$): calculated $\text{C}_{31}\text{H}_{37}\text{N}_2\text{O}_4\text{F}_2\text{S}$: 571.2436; Found: 571.2457.

$ee = 99\%$; $[\alpha]_{\text{D}}^{25}$: -33 ($c = 1.0$; CHCl_3). HPLC: Daicel Chiralpak IA, *i*-PrOH/hexane 3/97, flow rate 0.7 mL/min ($\lambda = 254.4$ nm), τ_{syn} : 34.8 min (2*R*,3*S*) and 41.2 min (2*S*,3*R*).



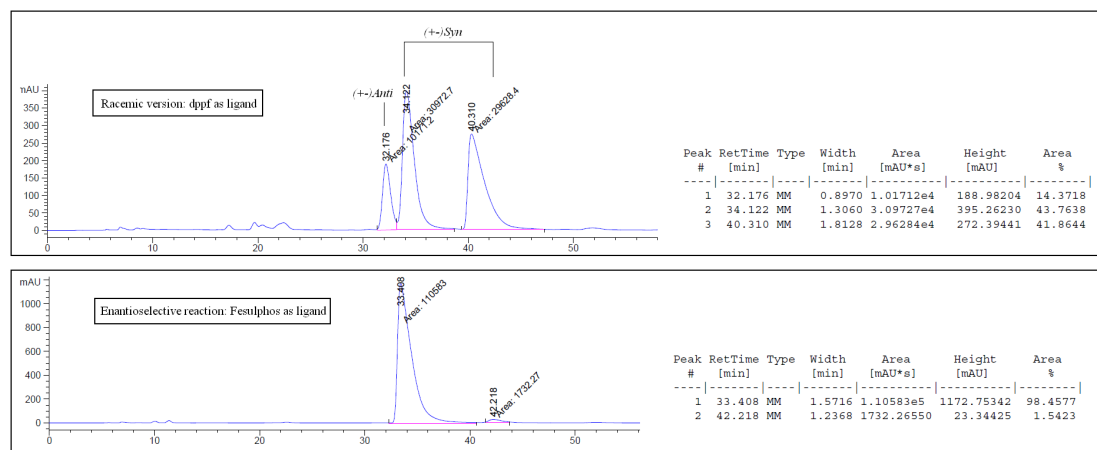
(2*S*,3*R*)-*tert*-Butyl-2-[[bis(4-fluorophenyl)methylene]amino]-4-ethyl-3-(4-



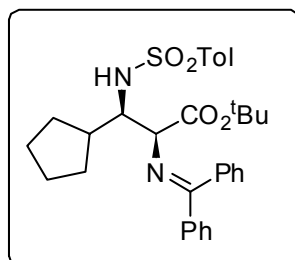
methylphenylsulfonamido) hexanoate (24). Following the general procedure, the reaction of *tert*-butyl 2-[bis(4-fluorophenyl)methyleneamino]acetate (**2d**) (49.7 mg, 0.15 mmol) with *N*-(2-ethyl-1-tosylbutyl)-4-methylbenzenesulfonamide (**14**) (79.9 mg, 0.19 mmol) in THF (2 mL) at rt for 18 h, afforded, after flash

chromatography (*n*-hexane-EtOAc 7:1), *syn*-**24** as a light yellow oil; yield: 60.0 mg (70%, *syn/anti* = >99:<1). ¹H-NMR (300 MHz, CDCl₃), δ (ppm): 7.72 (d, *J* = 8.1 Hz, 2H); 7.57-7.44 (m, 2H); 7.21 (d, *J* = 7.9 Hz, 2H); 7.12-6.90 (m, 6H); 5.91 (d, *J* = 8.5 Hz, 1H); 4.11-3.98 (m, 1H); 3.86-3.75 (m, 1H); 3.09 (s, 3H); 1.42-1.29 (m, 1H); 1.26 (s, 9H); 1.23-1.04 (m, 2H); 0.92-0.76 (m, 2H); 0.72 (t, *J* = 7.0 Hz, 3H); 0.62 (t, *J* = 6.6 Hz, 3H). ¹³C-NMR (125 MHz, CDCl₃), δ (ppm): 169.9; 169.6; 164.5 (d, ¹*J*_{C-F} = 249.7 Hz); 162.8 (d, ¹*J*_{C-F} = 247.5 Hz); 142.7; 139.3; 135.0 (d, ⁴*J*_{C-F} = 3.0 Hz); 132.1 (d, ⁴*J*_{C-F} = 3.7 Hz); 130.9 (d, ³*J*_{C-F} = 9.0 Hz); 129.4; 129.1 (d, ³*J*_{C-F} = 7.5 Hz); 127.0; 116.2 (d, ²*J*_{C-F} = 21.7 Hz); 115.6 (d, ²*J*_{C-F} = 21.7 Hz); 82.2; 65.0; 56.8; 45.5; 27.7; 22.6; 22.1; 21.4; 11.9; 11.6. ¹⁹F-NMR (300 MHz, CDCl₃), δ (ppm): 111.1; -109.4. HRMS (ESI⁺) (M⁺+H): calculated C₃₂H₃₉N₂O₄F₂S: 585.2593; Found: 585.2567.

ee = 97%; [α]_D²⁵: -44 (*c* = 1.0; CHCl₃). HPLC: Daicel Chiralpak IA, *i*-PrOH/hexane 3/97, flow rate 0.7 mL/min (λ = 254.4 nm), τ_{syn}: 33.4 min (2*S*,3*R*), 42.2 (2*R*,3*S*).



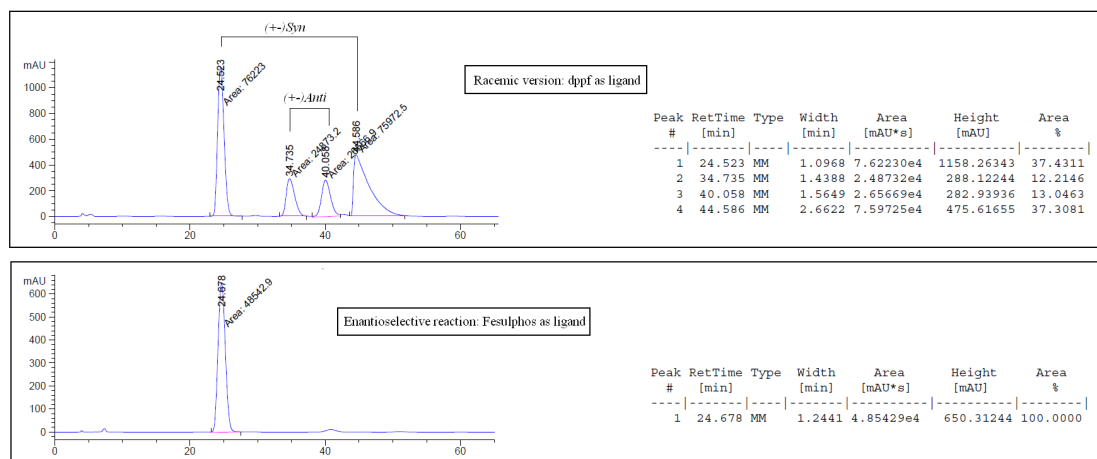
(2*S*,3*R*)-tert-Butyl-3-cyclopentyl-2-(diphenylmethyleamino)-3-(4-methylphenyl-sulfonamido)propanoate (25). Following the general



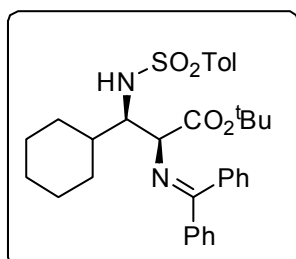
procedure, the reaction of *tert*-butyl 2-(diphenylmethyleamino)acetate (**2b**) (44.3 mg, 0.15 mmol) and *N*-[cyclopentyl-(tosyl)methyl]-4-methylbenzenesulfonamide (**15**) (79.5 mg, 0.19 mmol) in THF (2 mL) at $-20\text{ }^{\circ}\text{C}$ for 17 h, afforded, after flash chromatography (*n*-hexane-EtOAc 6:1), *syn*-**25** as a white

solid; yield: 68.2 mg (83%, *syn/anti* = >99:<1); m.p: 62–63 $^{\circ}\text{C}$. $^1\text{H-NMR}$ (300 MHz, CDCl_3), δ (ppm): 7.80 (d, $J = 8.3$ Hz, 2H); 7.68–7.59 (m, 2H); 7.48–7.40 (m, 4H); 7.40–7.34 (d, $J = 7.5$ Hz, 2H); 7.27–7.22 (m, 2H); 7.15–7.05 (m, 2H); 5.92 (d, $J = 8.8$ Hz, 1H); 3.98 (s, 1H); 4.05–3.90 (m, 1H); 2.41 (s, 3H); 1.98–1.80 (m, 1H); 1.60–1.45 (m, 3H); 1.45–1.35 (m, 2H); 1.39 (s, 9H); 1.24–1.01 (m, 2H); 0.95–0.86 (m, 1H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3), δ (ppm): 171.8; 169.3; 142.5; 139.9; 139.0; 130.7; 129.3; 128.9; 128.5; 128.1; 127.4; 126.9; 82.1; 67.9; 60.6; 44.6; 30.1; 29.5; 27.9; 25.11; 24.9; 21.5. HRMS (ESI $^+$) ($\text{M}^+ + \text{H}$): calculated $\text{C}_{32}\text{H}_{39}\text{N}_2\text{O}_4\text{S}$: 547.2625; Found: 547.2623

ee = >99 %; $[\alpha]_{\text{D}}^{25}$: -18 ($c = 0.5$; CHCl_3). HPLC: Daicel Chiralpak AD, *i*-PrOH/hexane 3/97, flow rate 1.0 mL/min ($\lambda = 254.4$ nm), τ_{syn} : 24.5 min (2*S*,3*R*), 44.6 min (2*R*,3*S*).



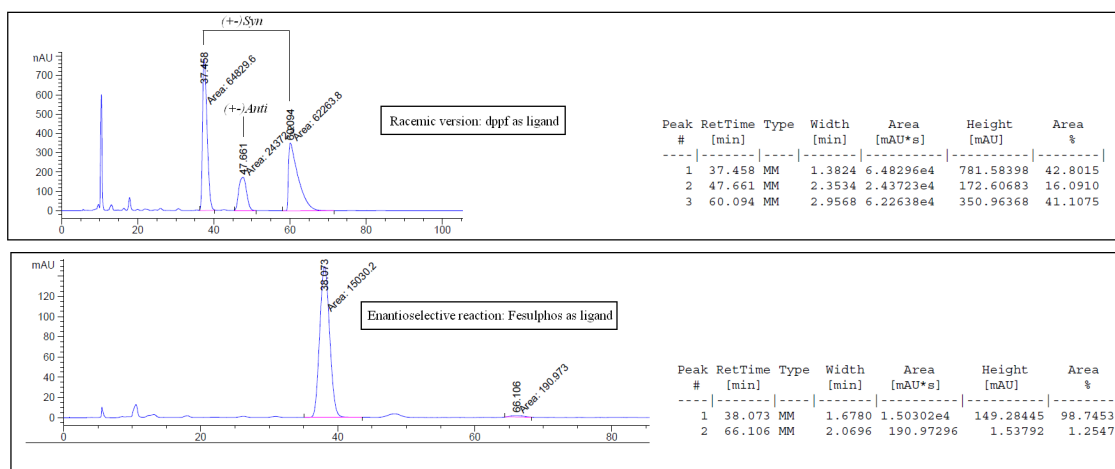
(2*S*,3*R*)-*tert*-Butyl-3-cyclohexyl-2-(diphenylmethyleneamino)-3-(4-methylphenyl-



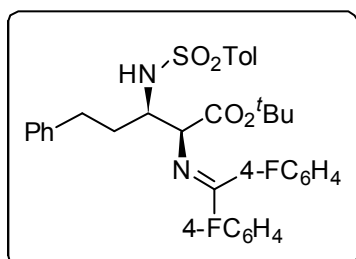
sulfonamido)-propanoate (26). Following the general procedure, the reaction of *tert*-butyl 2-(diphenylmethyleneamino)acetate (**2b**) (44.3 mg, 0.15 mmol) with *N*-[cyclohexyl(tosyl)methyl]-4-methylbenzenesulfonamide (**16**) (82.2 mg, 0.19 mmol) in THF (2 mL) at $-20\text{ }^{\circ}\text{C}$ for 17 h, afforded, after flash chromatography (*n*-hexane-EtOAc 6:1),

syn-**26b** as a white solid; yield: 67.3 mg (80%, *syn/anti* = 98:2); m.p: 58–60 $^{\circ}\text{C}$. ^1H -NMR (300 MHz, CDCl_3), δ (ppm): 7.70 (d, $J = 8.2$ Hz, 2H); 7.52 (d, $J = 8.5$ Hz, 2H); 7.39-7.25 (m, 4H); 7.36-7.18 (m, 2H); 7.18-7.11 (m, 2H); 7.05-6.90 (m, 2H); 5.90 (d, $J = 8.7$ Hz, 1H); 3.78 (dd, $J = 1.6$ Hz, $J = 6.72$ Hz, 1H); 2.30 (s, 3H); 1.60-1.42 (m, 5H); 1.24 (s, 9H); 1.10-0.61 (m, 6H). ^{13}C -NMR (75 MHz, CDCl_3), δ (ppm): 171.3; 169.6; 142.6; 139.6; 138.9; 136.6; 130.7; 129.3; 128.9; 128.5; 128.1; 127.2; 126.9; 81.9; 65.7; 60.6; 41.8; 29.7; 29.1; 27.8; 26.3; 26.3; 26.2; 21.4. HRMS (ESI $^+$) ($\text{M}^+\text{+H}$): calculated $\text{C}_{33}\text{H}_{41}\text{N}_2\text{O}_4\text{S}$: 561.2781. Found: 561.2783.

$ee = 97\%$; $[\alpha]_{\text{D}}^{25}$: -40 ($c = 1.0$; CHCl_3). HPLC: Daicel Chiralpak AD, *i*-PrOH/hexane 3/97, flow rate 0.7 mL/min ($\lambda = 254.4$ nm), τ_{syn} : 38.1 min (2*S*,3*R*) and 66.1 min (2*R*,3*S*).



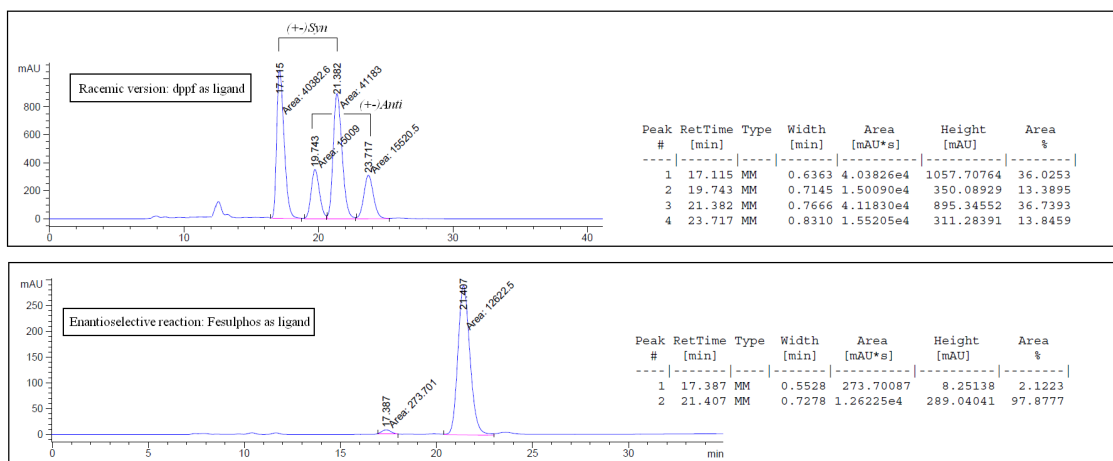
(2*S*,3*R*)-*tert*-Butyl-2-[[bis(4-fluorophenyl)methylene]amino]-3-(4-methylphenyl-



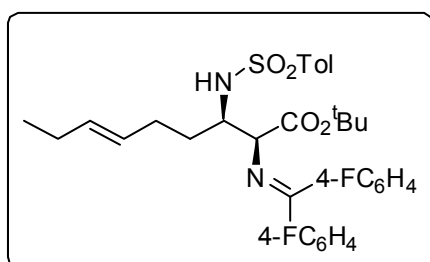
sulfonamido)-5-phenylpentanoate (27). Following the general procedure, the reaction of *tert*-butyl-2-[bis(4-fluorophenyl)methyleneamino]acetate (**2d**) (49.7 mg, 0.15 mmol) and 4-methyl-*N*-(3-phenyl-1-tosylpropyl)-benzenesulfonamide (**17**) (86.5 mg, 0.19 mmol) in THF (3 mL) at $-20\text{ }^{\circ}\text{C}$ for 18 h, afforded, after flash chromatography (*n*-hexane-EtOAc 7:1), *syn*-**27** as a light yellow solid; yield: 53.2 mg

(57%, *syn/anti* = 96:4); m.p: 55.4–56.0 °C. ¹H-NMR (300 MHz, CDCl₃), δ (ppm): 7.61 (d, *J* = 7.9 Hz, 2H); 7.53–7.44 (m, 2H); 7.21–7.12 (m, 4H); 7.11–6.85 (m, 9H); 5.54 (d, *J* = 9.4 Hz, 1H); 3.86 (d, *J* = 2.4 Hz, 1H); 3.75–3.68 (m, 1H); 2.44–2.33 (m, 1H); 2.33 (s, 3H); 2.30–2.22 (m, 1H); 1.90–1.75 (m, 1H); 1.74–1.60 (m, 1H); 1.28 (s, 9H). ¹³C-NMR (75 MHz, CDCl₃), δ (ppm): 170.1; 169.0; 164.6 (d, ¹*J*_{C-F} = 250.5 Hz); 162.8 (d, ¹*J*_{C-F} = 247.5 Hz); 143.0; 140.9; 139.0; 135.1 (d, ⁴*J*_{C-F} = 2.2 Hz); 131.7 (d, ⁴*J*_{C-F} = 3.7 Hz); 130.9 (d, ³*J*_{C-F} = 9.0 Hz); 129.5; 129.4 (d, ³*J*_{C-F} = 7.5 Hz); 128.4; 128.3; 126.9; 126.0; 116.0 (d, ²*J*_{C-F} = 21.3 Hz); 115.2 (d, ²*J*_{C-F} = 21.3 Hz); 82.4; 67.0; 55.9; 34.3; 32.0; 27.9; 21.4. ¹⁹F-NMR (300 MHz, CDCl₃), δ (ppm): -111.1; -109.4. HRMS (ESI⁺) (M⁺+H): calculated C₃₅H₃₇N₂O₄F₂S: 619.2436; Found: 619.2458.

ee = 96%; [α]_D²⁵: -37 (*c* = 1.0; CHCl₃). HPLC: Daicel Chiralpak AD, *i*-PrOH/hexane 15/85, flow rate 0.5 mL/min (λ = 254.4 nm), τ_{syn}: 17.4 min (2*R*,3*S*), 21.4 (2*S*,3*R*).



(2*S*,3*R*)-*tert*-Butyl-2-[[bis(4-fluorophenyl)methylene]amino]-3-(4-methylphenyl-sulfonamido)non-6-enoate (28).

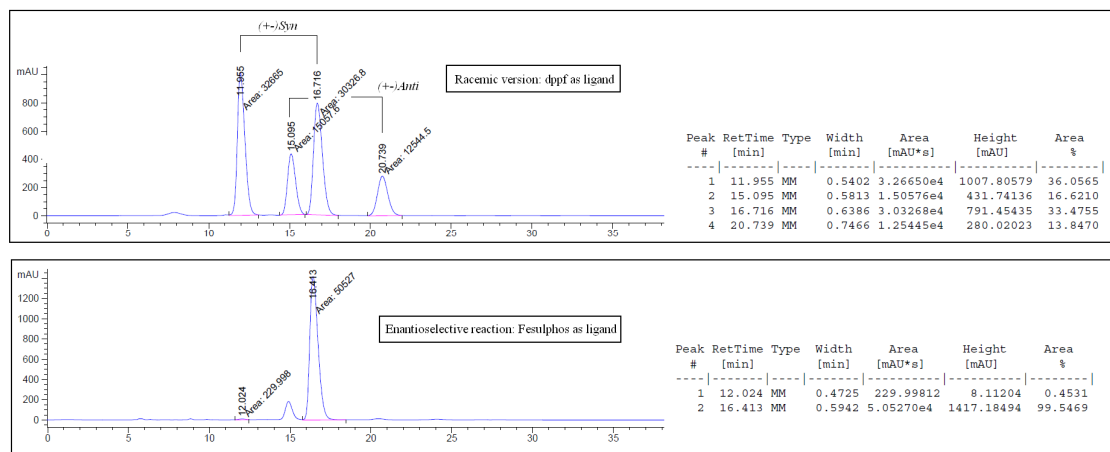


Following the general procedure, the reaction of *tert*-butyl 2-[[bis(4-fluorophenyl)methyleneamino]acetate (**2d**) (49.7 mg, 0.15 mmol) with 4-methyl-*N*-(1-tosylhept-4-enyl)benzenesulfonamide (**18**) (85.2 mg, 0.19 mmol) in THF (2 mL) at -20 °C for 20 h, afforded, after

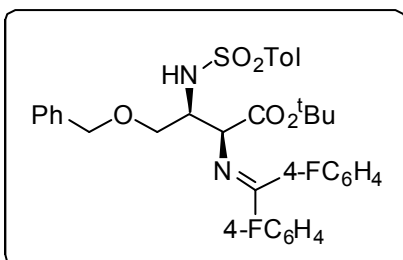
flash chromatography (*n*-hexane-EtOAc 7:1), *syn*-**28** as a colourless oil; yield: 70.4 mg (78%, *syn/anti* = 90:10). ¹H-NMR (300 MHz, CDCl₃), δ (ppm): 7.71–7.64 (m, 2H); 7.57–7.48 (m, 2H); 7.22–7.14 (m, 2H); 7.09–6.92 (m, 6H); 5.49 (d, *J* = 9.4 Hz, 1H); 5.28–5.15 (m, 1H); 5.13–4.98 (m, 1H); 3.82 (d, *J* = 2.6 Hz, 1H); 3.81–3.72 (m, 1H); 2.33 (s, 3H); 1.80–1.60 (m, 4H); 1.47–1.33 (m, 2H); 1.29 (s, 9H); 0.78 (t, *J* = 7.5 Hz, 3H). ¹³C-NMR (75 MHz, CDCl₃), δ (ppm): 170.0; 169.0; 164.5 (d, ¹*J*_{C-F} = 249.7 Hz); 162.9 (d, ¹*J*_{C-F} = 247.5 Hz); 142.9; 139.3; 135.1 (d, ⁴*J*_{C-F} = 3.0 Hz); 132.6; 131.8 (d, ⁴*J*_{C-F} =

3.7 Hz); 130.9 (d, $^3J_{C-F} = 9.0$ Hz); 129.5; 129.4 (d, $^3J_{C-F} = 9.0$ Hz); 127.2; 126.9; 115.8 (d, $^2J_{C-F} = 21.3$ Hz); 115.2 (d, $^2J_{C-F} = 21.3$ Hz); 82.3; 66.9; 56.0; 32.8; 27.9; 23.5; 21.4; 20.5; 14.2. ^{19}F -NMR (300 MHz, CDCl_3), δ (ppm): -111.2; -109.5. HRMS (ESI $^+$) ($\text{M}^+\text{+H}$): calculated $\text{C}_{33}\text{H}_{39}\text{N}_2\text{O}_4\text{F}_2\text{S}$: 597.2593; Found: 597.2601.

$ee = 99\%$; $[\alpha]_{\text{D}}^{25}$: -10 ($c = 0.3$; CHCl_3). HPLC: Daicel Chiralpak AD, *i*-PrOH/hexane 10/90, flow rate 0.7 mL/min ($\lambda = 254.4$ nm), τ_{syn} : 12.0 min (2*R*,3*S*), 16.4 (2*S*,3*R*).



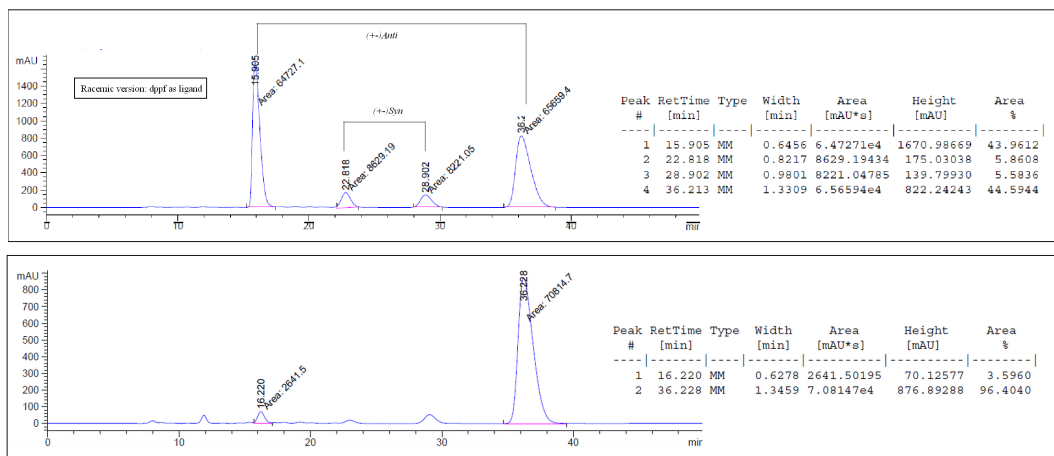
(2*S*,3*R*)-*tert*-Butyl-4-(benzyloxy)-2-[[bis(4-fluorophenyl)methylene]amino]-3-(4-methylphenylsulfonamido) butanoate (29).



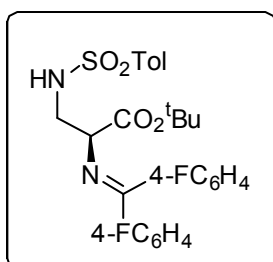
Following the general procedure, the reaction of *tert*-butyl 2-[bis(4-fluorophenyl)methyleneamino]acetate (**2d**) (49.7 mg, 0.15 mmol) and *N*-[2-(benzyloxy)-1-tosylethyl]-4-methylbenzenesulfonamide (**19**) (89.62 mg, 0.19 mmol) in THF (2 mL) at -20 °C for 19 h,

afforded, after flash chromatography (*n*-hexane-EtOAc 7:1), *syn*-**29** as a light yellow oil; yield: 46.7 mg (50%, *syn/anti* = 95:5). ^1H -NMR (300 MHz, CDCl_3), δ (ppm): 7.72-7.66 (m, 2H); 7.54-7.46 (m, 2H); 7.24-7.19 (m, 3H); 7.14 (d, $J = 8.1$ Hz, 2H); 7.08-7.02 (m, 2H); 6.98-6.84 (m, 6H); 5.59 (d, $J = 9.1$ Hz, 1H); 4.33-4.20 (m, 2H); 4.16-4.12 (m, 1H); 4.11-4.03 (m, 1H); 3.53-3.42 (m, 1H); 3.21 (t, $J = 9.1$ Hz, 1H); 2.31 (s, 3H); 1.21 (s, 9H). ^{13}C -NMR (75 MHz, CDCl_3), δ (ppm): 170.8; 168.8; 164.5 (d, $^1J_{C-F} = 249.7$ Hz); 162.7 (d, $^1J_{C-F} = 247.5$ Hz); 143.0; 138.9; 137.6; 135.1 (d, $^4J_{C-F} = 3.0$ Hz); 131.67 (d, $^4J_{C-F} = 3.7$ Hz); 130.9 (d, $^3J_{C-F} = 9.0$ Hz); 129.5 (d, $^3J_{C-F} = 7.5$ Hz); 129.5; 128.3; 127.7; 127.5; 126.9; 115.6 (d, $^2J_{C-F} = 21.3$ Hz); 115.1 (d, $^2J_{C-F} = 21.3$ Hz); 82.2; 73.1; 69.8; 64.7; 54.8; 27.7; 21.4. ^{19}F -NMR (300 MHz, CDCl_3), δ (ppm): -111.6; -109.5. HRMS (ESI $^+$) ($\text{M}^+\text{+H}$): calculated $\text{C}_{35}\text{H}_{37}\text{N}_2\text{O}_5\text{F}_2\text{S}$: 635.2385; Found: 635.2389.

$ee = 93\%$; $[\alpha]_{\text{D}}^{25}$: -30 ($c = 1.0$; CHCl_3). HPLC: Daicel Chiralpak AD, *i*-PrOH/hexane 15/85, flow rate 0.5 mL/min ($\lambda = 254.4$ nm), τ_{syn} : 16.2 min (2*R*,3*S*), 36.2 (2*S*,3*R*).

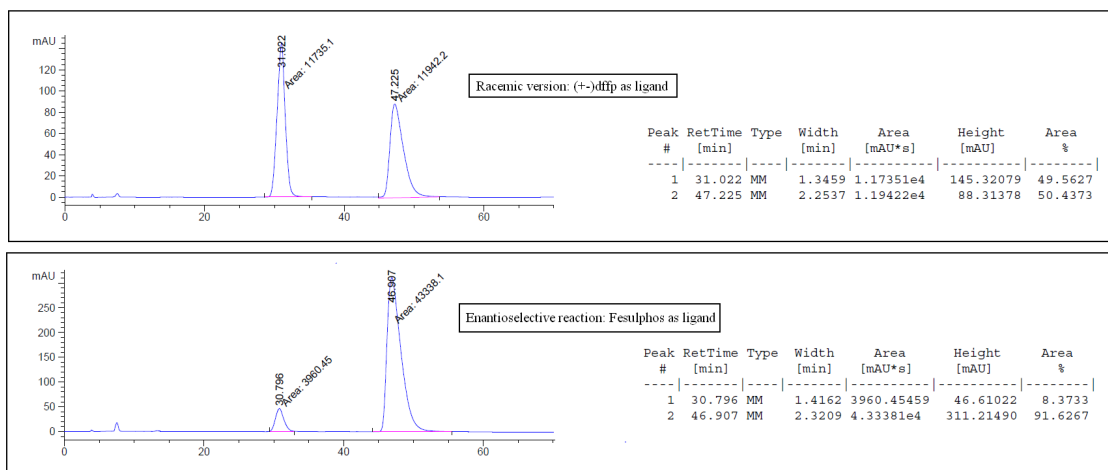


(2S)-tert-Butyl-2-[bis(4-fluorophenyl)Methyleneamino]-3-(4-methylphenyl-

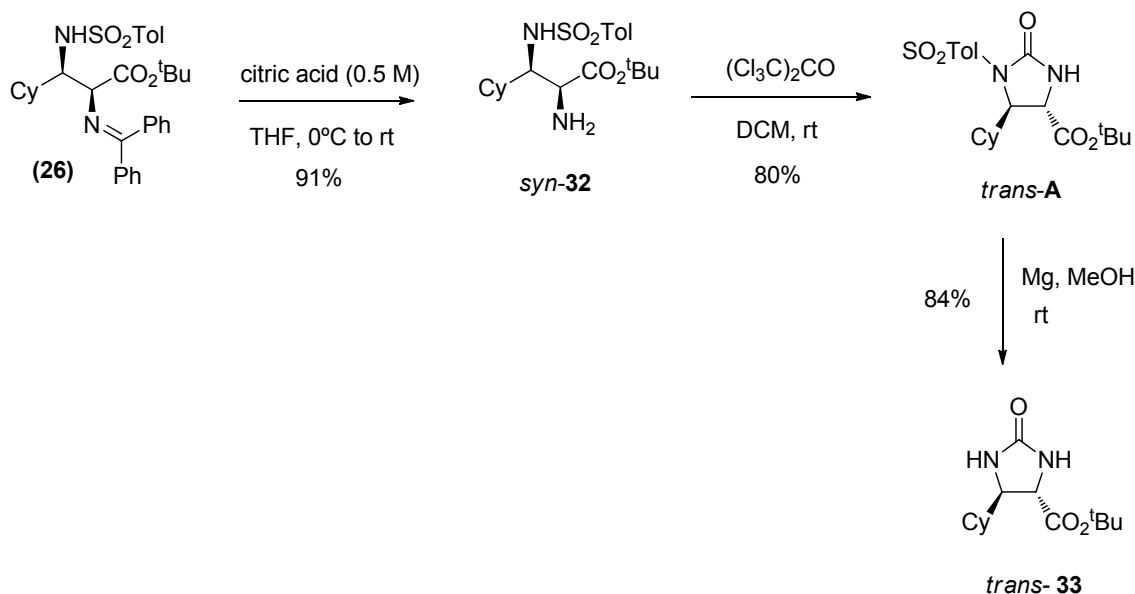


sulfonamido)propanoate (31). Following the general procedure, the reaction of *tert*-butyl 2-[bis(4-fluorophenyl)-methyleneamino]acetate (**2d**) (49.7 mg, 0.15 mmol) with 4-methyl-*N*-(tosylmethyl)benzenesulfonamide (**30**) (66.2 mg, 0.19 mmol) in THF (2 mL) at $-20\text{ }^{\circ}\text{C}$ for 12 h, afforded, after flash chromatography (*n*-hexane-EtOAc 6:1), *syn*-**31** as a light yellow solid; yield: 61.5 mg (80%); m.p: 59-60 $^{\circ}\text{C}$. $^1\text{H-NMR}$ (300 MHz, CDCl_3), δ (ppm): 7.61 (d, $J = 8.3$ Hz, 2H); 7.52-7.43 (m, 2H); 7.26 (d, $J = 7.4$ Hz, 2H); 7.05 (d, $J = 7.0$ Hz, 4H); 6.97-6.87 (m, 2H); 4.96 (t, $J = 6.4$ Hz, 1H); 3.98 (t, $J = 5.8$ Hz, 1H); 3.29 (t, $J = 6.2$ Hz, 2H); 2.33 (s, 3H); 1.31 (s, 9H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3), δ (ppm): 170.6; 168.8; 164.5 (d, $^1J_{\text{C-F}} = 250.5$ Hz); 162.9 (d, $^1J_{\text{C-F}} = 247.5$ Hz); 143.4; 137.1; 135.2 (d, $^4J_{\text{C-F}} = 3.0$ Hz); 131.4 (d, $^4J_{\text{C-F}} = 3.7$ Hz); 130.9 (d, $^3J_{\text{C-F}} = 8.2$ Hz); 129.7 (d, $^3J_{\text{C-F}} = 7.5$ Hz); 129.7; 127.0; 115.8 (d, $^2J_{\text{C-F}} = 21.7$ Hz); 115.2 (d, $^2J_{\text{C-F}} = 21.8$ Hz); 82.3; 64.8; 45.6; 27.9; 21.5. $^{19}\text{F-NMR}$ (300 MHz, CDCl_3), δ (ppm): -109.4; -111.3. HRMS (ESI $^+$) ($\text{M}^+ + \text{H}$): calculated $\text{C}_{27}\text{H}_{29}\text{N}_2\text{O}_4\text{F}_2\text{S}$: 515.1810 Found: 515.1804

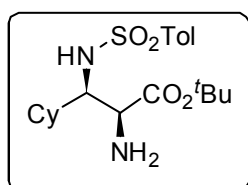
$ee = 83\%$; $[\alpha]_{\text{D}}^{25}$: -35 ($c = 1.0$; CHCl_3). HPLC: Daicel Chiralpak AD, *i*-PrOH/hexane 4/96, flow rate 1.0 mL/min ($\lambda = 254.4$ nm), τ : 30.8 min (*2R*) and 47.2 min (*2S*).



1.3. Selective *N*-deprotection of the Mannich adducts: conversion of **26** into the cyclic urea *trans*-**33**.⁵



(2*S*,3*R*)-*tert*-Butyl-2-amino-3-cyclohexyl-3-(4-methylphenylsulfonamido)-

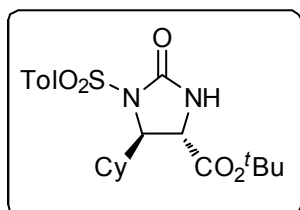


propanoate (*syn*-32**).** To a solution of *syn*-**26** (272.6 mg, 0.48 mmol) in THF (4 mL), cooled to 0 °C, was added a 0.5 M aq solution of citric acid (2.0 mL). The mixture was allowed to reach rt and stirred for 2 h before it was extracted with Et₂O (3 x 3 mL).

The combined organic phase was washed with water (3 x 3 mL), the aqueous phase was basified with saturated K₂CO₃ solution and it was then extracted with EtOAc (3 x 3 mL). The organic phase was washed with brine (4 mL), dried (Na₂SO₄) and concentrated to afford *syn*-**32** as a colourless oil; yield: 175.0 mg (91%). ¹H-NMR (300 MHz, CDCl₃), δ (ppm): 7.66 (d, *J* = 9.0 Hz, 2H); 7.18 (d, *J* = 9.0 Hz, 2H); 5.27 (s, 1H); 3.44-3.36 (m, 1H); 3.33 (d, *J* = 3.0 Hz, 1H); 2.34 (s, 3H); 1.65-1.42 (m, 7H); 1.36 (s, 9H); 1.10-0.61 (m, 6H). ¹³C-NMR (75 MHz, CDCl₃), δ (ppm): 172.8; 143.0; 138.7; 129.4; 127.0; 82.2; 60.2; 54.7; 41.4; 29.8; 28.8; 27.9; 26.2; 26.1; 21.5. HRMS (ESI⁺) (*M*⁺+*H*): calculated C₂₀H₃₃N₂O₄S: 397.2155; Found: 397.2152; (*M*⁺+2*H*-^tBu): calculated C₁₆H₂₅N₂O₄S: 341.1529; Found: 341.1525. [α]_D²⁵: + 51 (*c* = 0.8; CHCl₃).

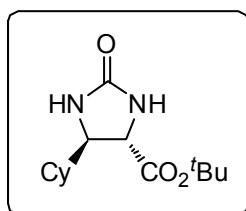
5. For *cis*- and *trans*- assignment on imidazolidinones derived from α,β -diamino acid derivatives, see: S. H. Lee, J. Yoon, S. H. Chung, Y. S. Lee, *Tetrahedron*, 2001, **57**, 2139.

(4*S*,5*R*)-tert-Butyl 5-cyclohexyl-2-oxo-1-tosylimidazolidine-4-carboxylate (*trans*-A).



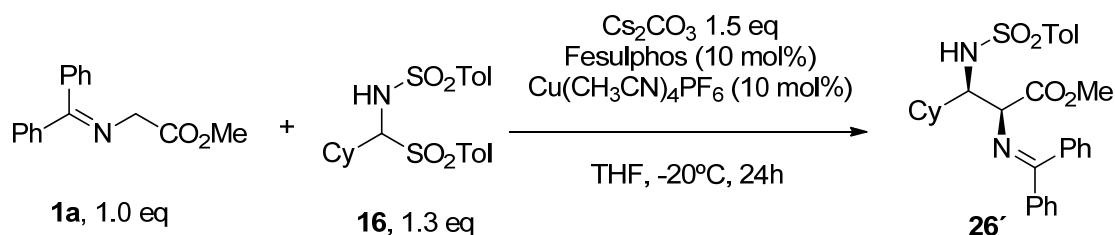
To a solution of *syn*-**32** (260.0 mg, 0.65 mmol) in dry CH₂Cl₂ (4 mL), under inert atmosphere and cooled to 0 °C, was added dropwise a solution of triphosgene (486.1 mg, 1.64 mmol). The reaction mixture was stirred at 0 °C for 1 h before it was allowed to reach rt and stirred for further 2 h at rt. The mixture was concentrated and the residue was purified by flash chromatography (*n*-hexane-EtOAc 2:1, stained with CAN) to afford *trans*-**A** as a light yellow solid; yield: 220.2 mg (80%); m.p: 73.1-75.0 °C. ¹H-NMR (300 MHz, CDCl₃), δ (ppm): 7.79 (d, *J* = 6.0 Hz, 2H); 7.21 (d, *J* = 6.0 Hz, 2H); 5.77 (s, 1H); 4.24-4.20 (m, 1H); 3.70 (d, *J* = 3.0 Hz, 1H); 2.34 (s, 3H); 1.49-1.43 (m, 6H); 1.33 (s, 9H); 1.10-0.70 (m, 5H). ¹³C-NMR (75 MHz, CDCl₃), δ (ppm): 169.7; 155.2; 144.6; 136.2; 129.4; 127.9; 83.14; 64.7; 53.0; 41.6; 28.4; 27.8; 26.2; 25.9; 25.5; 25.3; 21.6. HRMS (ESI⁺) (M⁺+H): calculated C₂₁H₃₁N₂O₅S: 423.1948; Found: 423.1939; (M⁺+Na): calculated C₂₁H₃₀N₂NaO₅S: 445.1767; Found: 445.1762. [α]_D²⁵: +44 (*c* = 0.7; CHCl₃).

(4*S*,5*R*)-tert-Butyl 5-cyclohexyl-2-oxoimidazolidine-4-carboxylate (*trans*-33).

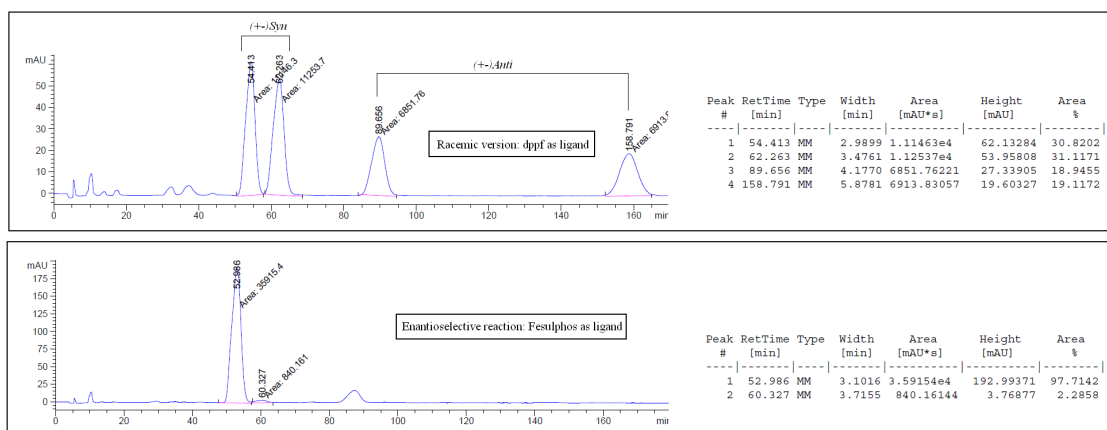


To a solution of *trans*-**A** (45.0 mg, 0.106 mmol) in MeOH (5 mL) were added Mg turnings (52.0 mg, 2.13 mmol) and the reaction mixture was stirred under sonication at rt for 1 h. After that time the Mg was dissolved and the reaction mixture was filtered through Celite. The filtrate was concentrated and it was dissolved in CH₂Cl₂ (2 mL), then successively washed with a saturated aq. solution of K₂CO₃ (3 x 2 mL) and brine. The organic phase was dried (Na₂SO₄) and concentrated to dryness. The residue was purified by flash chromatography (*n*-hexane-EtOAc 1:2, stained with ninhydrin) to afford *trans*-**33** as light brown solid; yield: 23.9 mg (84%); m.p: 156.1-157.8 °C. ¹H-NMR (300 MHz, CDCl₃), δ (ppm): 5.48 (s, 1H); 4.98 (s, 1H); 3.82 (d, *J* = 3.0 Hz, 1H); 3.56-3.49 (m, 1H); 1.76-1.55 (m, 6H); 1.41 (s, 9H); 1.22-1.06 (m, 5H). ¹³C-NMR (75 MHz, CDCl₃), δ (ppm): 169.9; 161.2; 81.5; 59.7; 56.6; 41.8; 27.6; 27.1; 26.9; 25.3; 24.8; 24.7. HRMS (ESI⁺) (M⁺+H): calculated C₁₄H₂₅N₂O₃: 269.1859; Found: 269.1870; (M⁺+Na): calculated C₁₄H₂₄N₂NaO₃: 291.1679; Found: 291.1668; (2M⁺+Na): calculated C₂₈H₄₈N₄NaO₆: 559.3472; Found: 559.3510. [α]_D²⁵: +38 (*c* = 1.0; CHCl₃).

2. Determination of the absolute and relative configuration of the Mannich products: preparation of compound 26'.



(2*S*,3*R*)-Methyl-3-cyclohexyl-2-(diphenylmethyleneamino)-3-(4-methylphenylsulfonamido)-propanoate (**26'**).⁶ Following the general procedure, the reaction of 2-[(diphenylmethylene)amino]acetate (**2a**) (38.0 mg, 0.15 mmol) (44.3 mg, 0.15 mmol) with *N*-[cyclohexyl(tosyl)methyl]-4-methylbenzenesulfonamide (**16**) (82.2 mg, 0.19 mmol) in THF (2 mL) at -20°C for 24 h, afforded, after flash chromatography (*n*-hexane-EtOAc 6:1), *syn*-**26'** as a yellow oil, yield: 50.5 mg (65%, *syn/anti* = 90:10). ¹H-NMR (300 MHz, CDCl_3), δ (ppm): 7.72-7.65 (d, $J = 8.2$ Hz, 2H); 7.57-7.51 (d, $J = 7.1$ Hz, 2H); 7.40-7.25 (m, 4H); 7.21-7.14 (m, 2H); 7.01-6.90 (m, 2H); 5.89 (d, $J = 9.0$ Hz, 1H); 4.05-3.98 (m, 1H); 3.68 (t, $J = 7.9$ Hz, 1H); 3.17 (s, 3H); 2.31 (s, 3H); 1.64-1.43 (m, 4H); 1.37-1.22 (m, 2H); 1.10-0.90 (m, 3H); 0.85-0.69 (m, 2H). HRMS (ESI⁺) (M^+H): calculated $\text{C}_{30}\text{H}_{35}\text{N}_2\text{O}_4\text{S}$: 519.2312. Found: 519.2323. $ee = 95\%$; $[\alpha]_D^{25}$: -38 ($c = 0.9$; CHCl_3). HPLC: Daicel Chiralpak AD, *i*-PrOH/hexane 3/97, flow rate 0.7 mL/min ($\lambda = 254.4$ nm), τ_{syn} : 52.9 min (2*S*,3*R*) and 60.3 min (2*R*,3*S*).

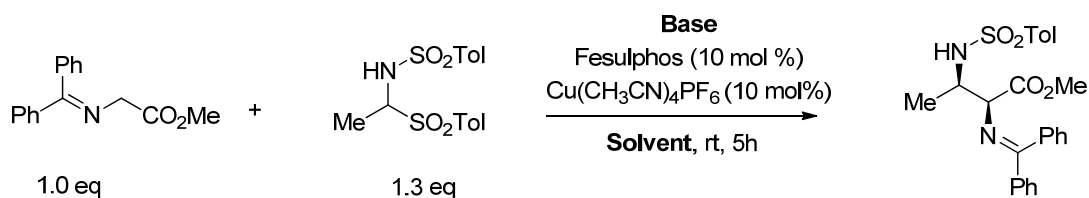


The absolute and relative configuration of the Mannich products was determined by preparation of the known compound **26'** (methyl ester derivative of product **26**) and comparison of the NMR data and optical rotation with those described in the literature⁶

6. L. Bernardi, A. S. Gothelf, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.*, 2003, 68, 2583. The configuration of all other products was assigned by analogy.

{ $[\alpha]_D^{25} = -39$ ($c = 1.088$, CDCl_3 for a 92% ee sample of **26'**)⁶. The configuration of all other product was assigned by analogy.

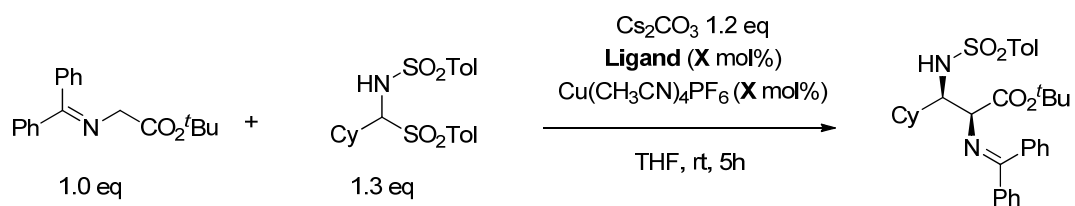
3. Base and solvent screening.



Entry	Base (1.2 eq)	Solvent	Conversion %	syn/anti	syn-ee %
1	Cs_2CO_3	THF	89	88:12	93*
2	Cs_2CO_3 (1.5)	DCM	8	-	-
3	Cs_2CO_3 (1.5)	Acetonitrile	53	79:21	-
4	Cs_2CO_3 (1.5)	Trifluorotoluene	53	87:13	93*
5	Cs_2CO_3 (1.5)	THF	95	88:12	90*
6	Diisopropylamine	THF	55	73:27	-
7	Triethylamine	THF	-	-	-
8	Diisopropylethylamine	THF	38	75:25	-
9	Tetraethylammonium bicarbonate	THF	74	66:34	-
10	K_3PO_4	THF	59	83:17	-
11	$(\text{NBu}_4)\text{PO}_4\text{H}_2$	THF	-	-	-

* The enantiomeric excesses were measured only when both, the conversion and diastereoselectivity were good.

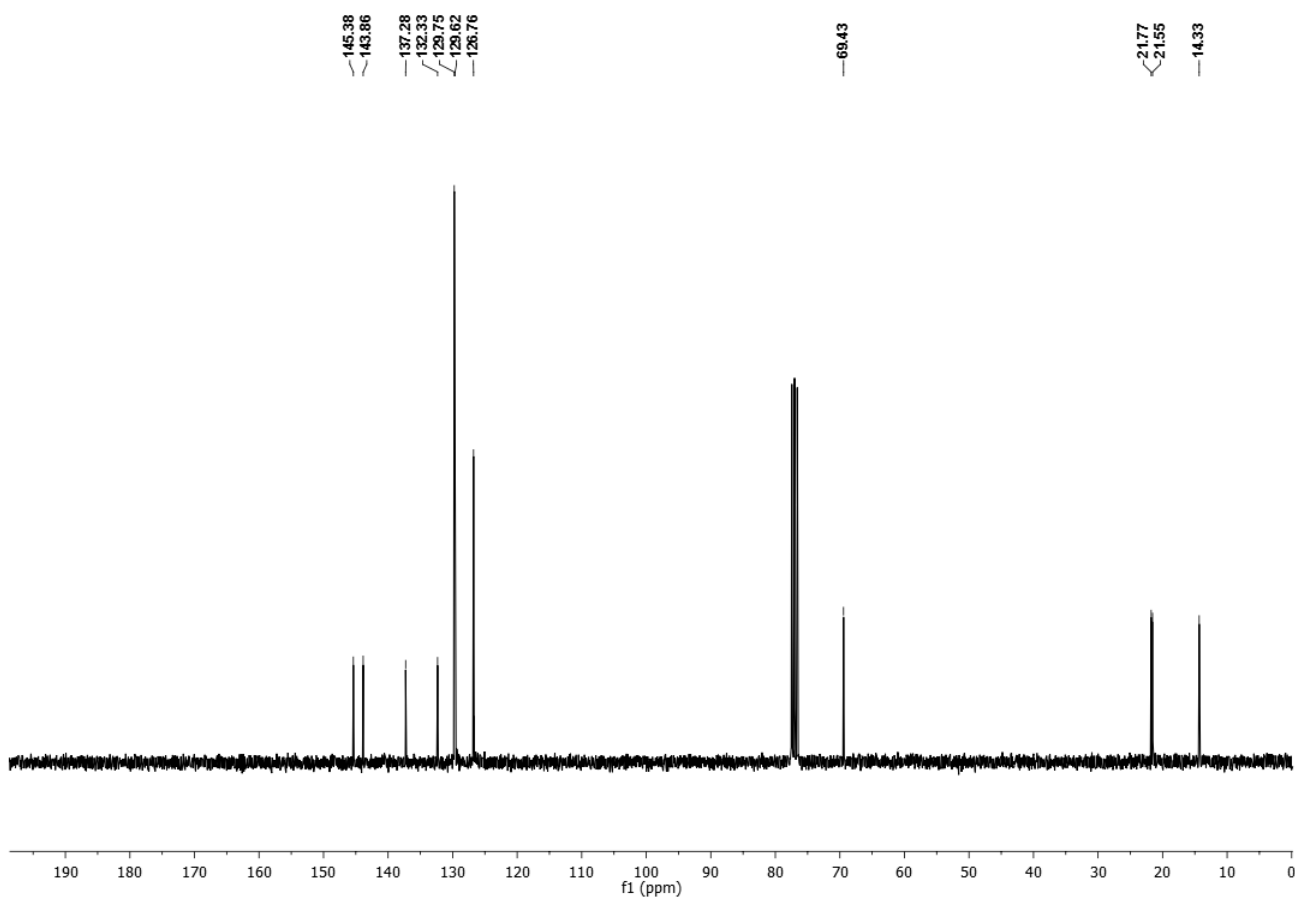
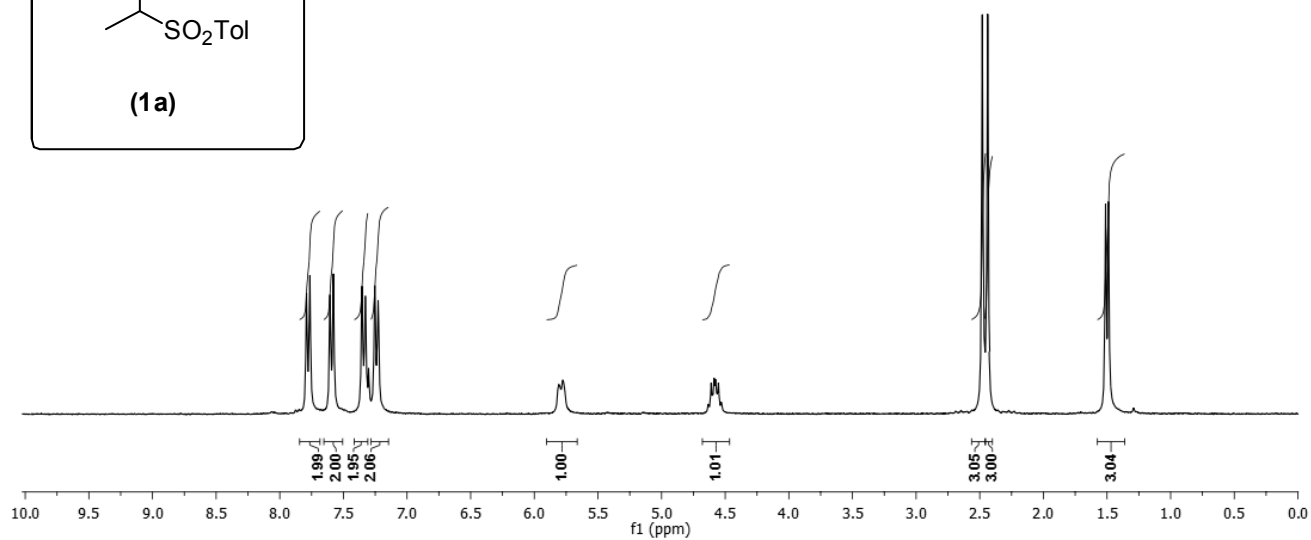
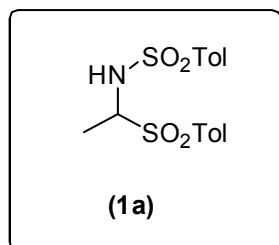
4. Chiral ligand screening.

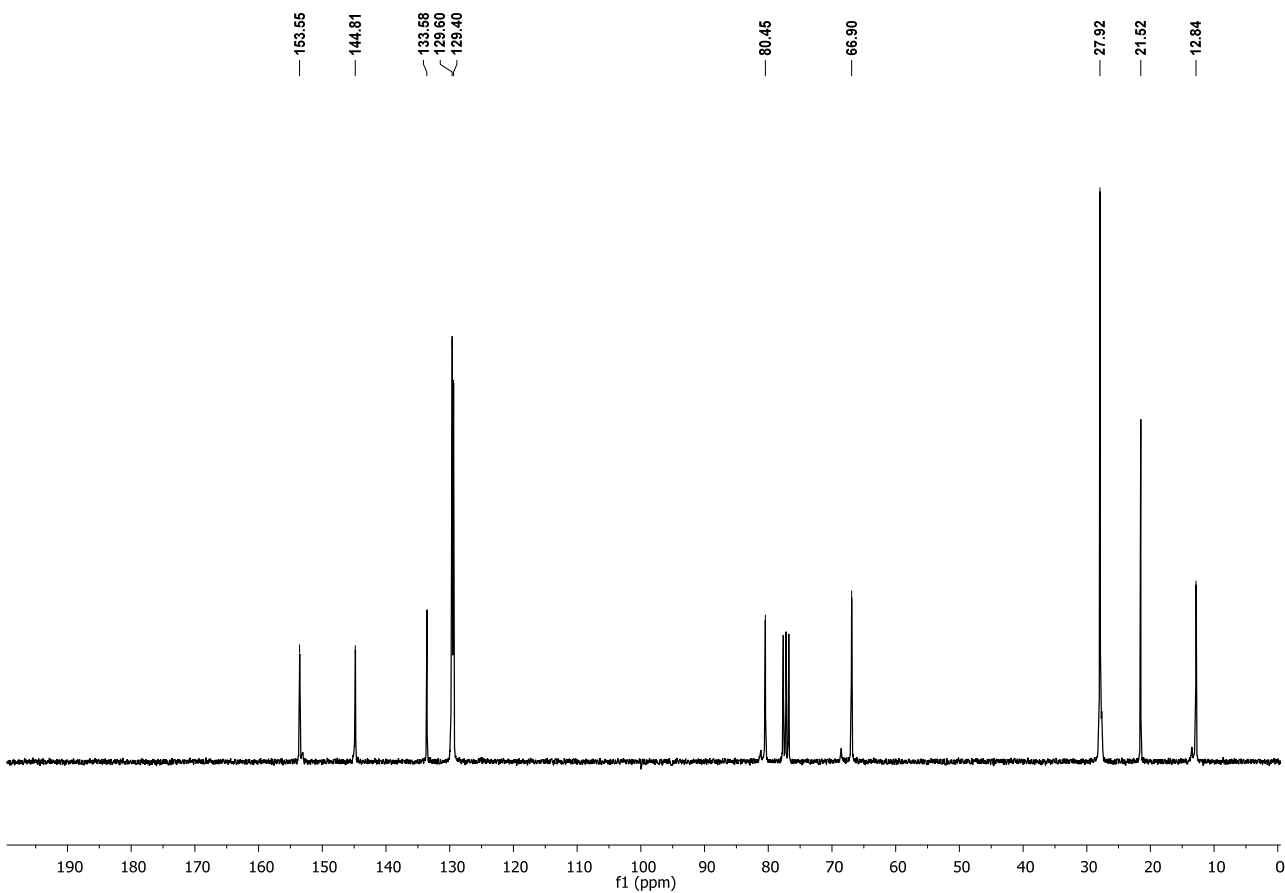
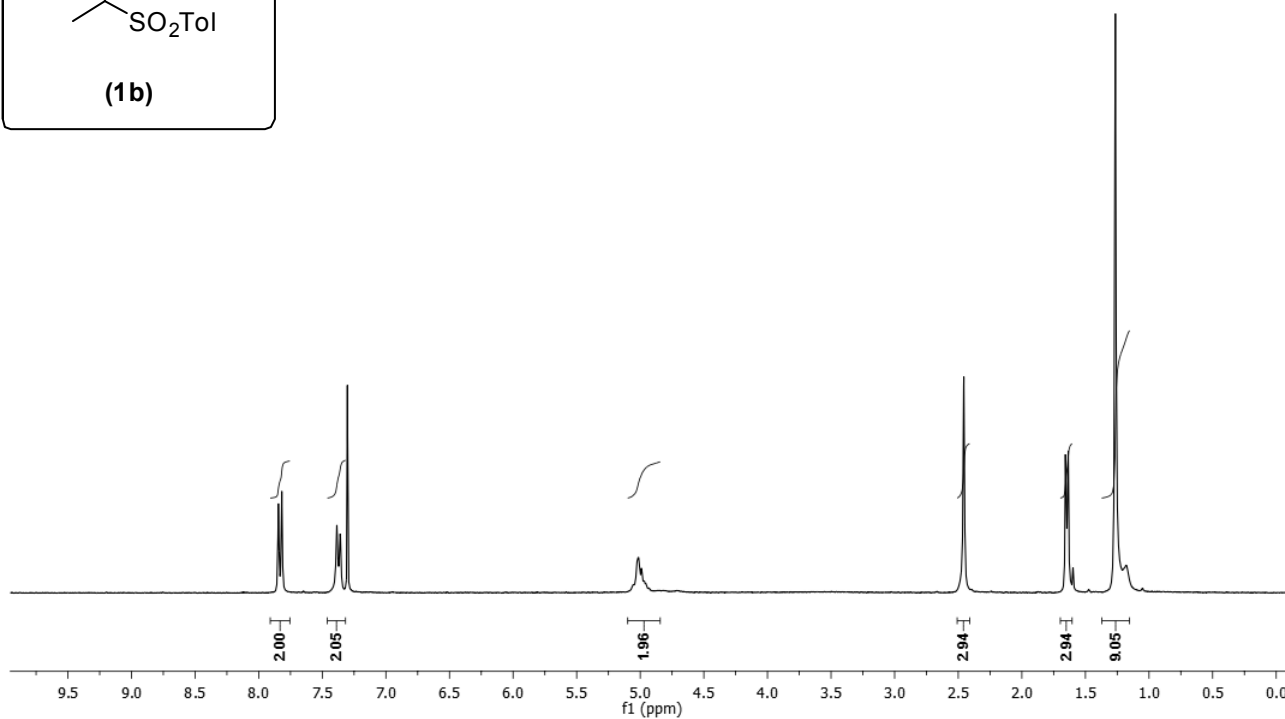
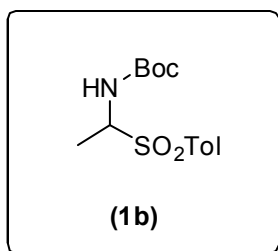


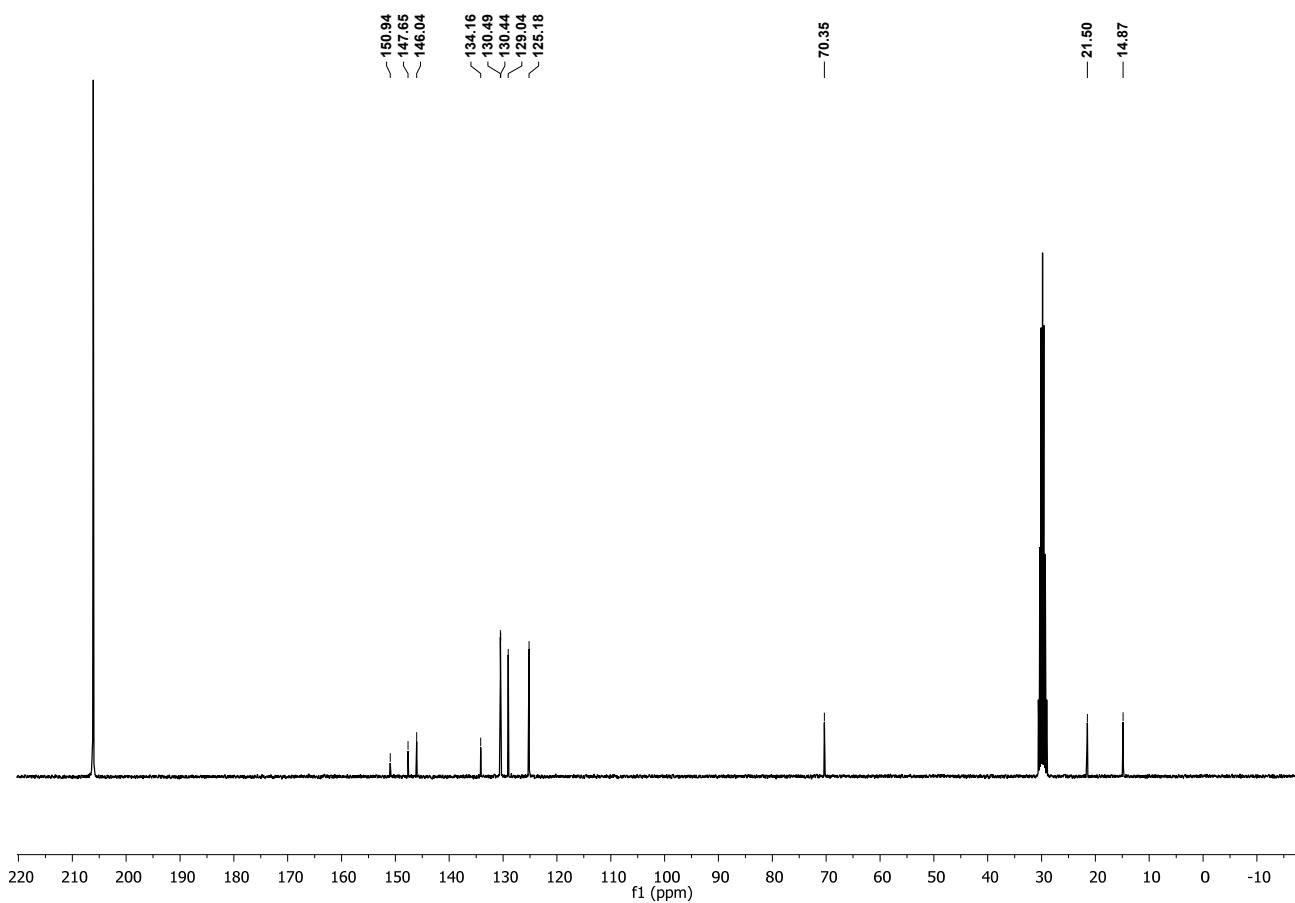
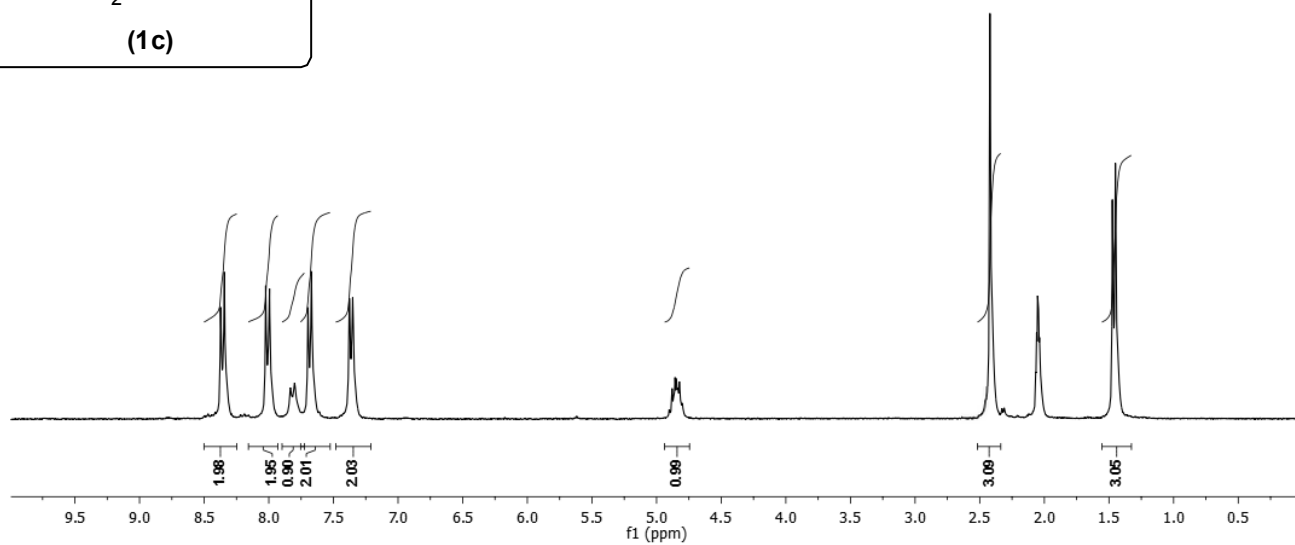
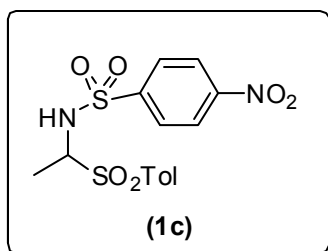
Entry	Ligand	% mmol	<i>syn/anti</i> ^a	Yield %	<i>syn-ee</i> %
1	Fesulphos	10	90:10	73	89
2	Fesulphos	5	87:13	52*	-
3	Fesulphos <i>p</i> -F	10	84:16	67	94
4	Fesulphos <i>p</i> -OMe	10	86:14	74	88
5	Mandyphos (<i>R,S</i>)	10	-	23	-
6	Josiphos (<i>R,S_p</i>)	10	92:8	54	93

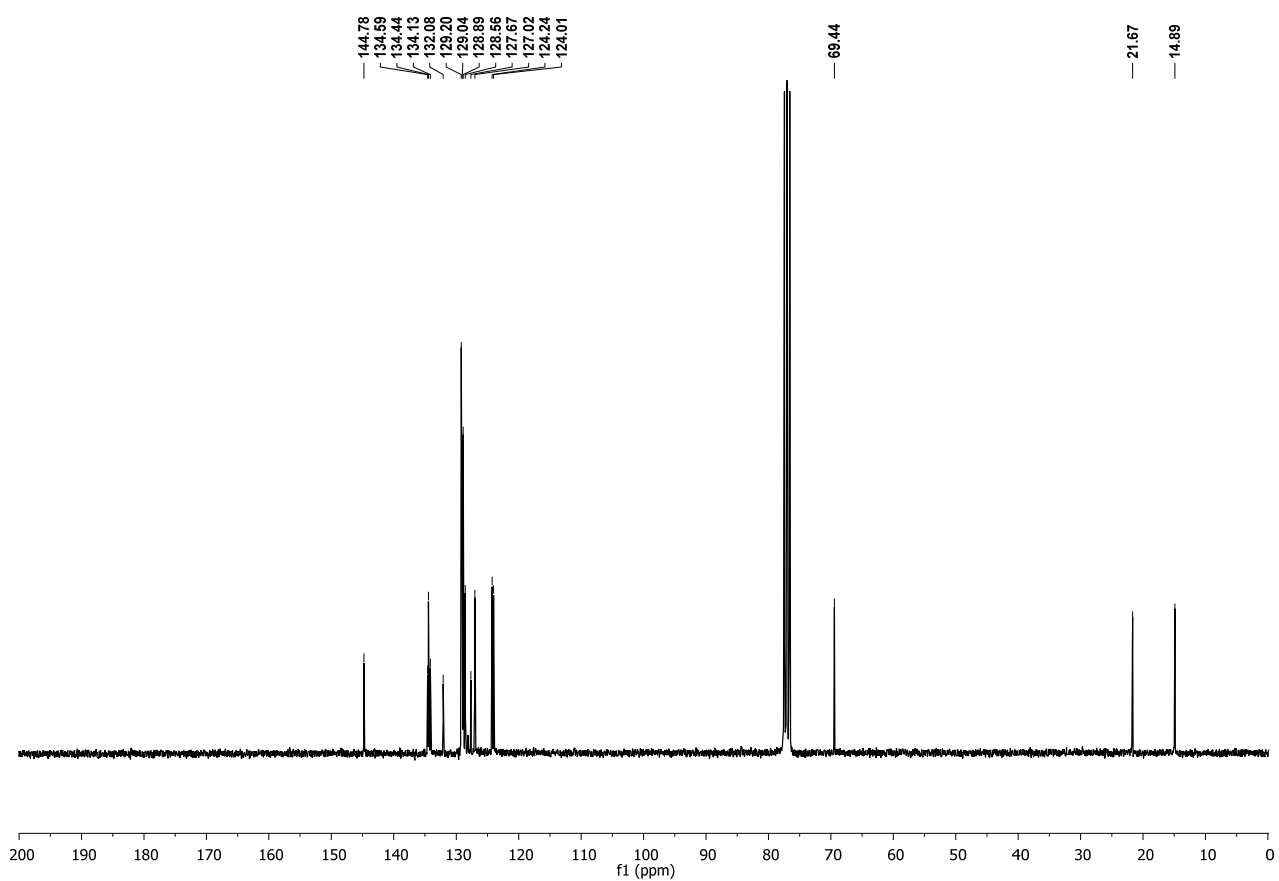
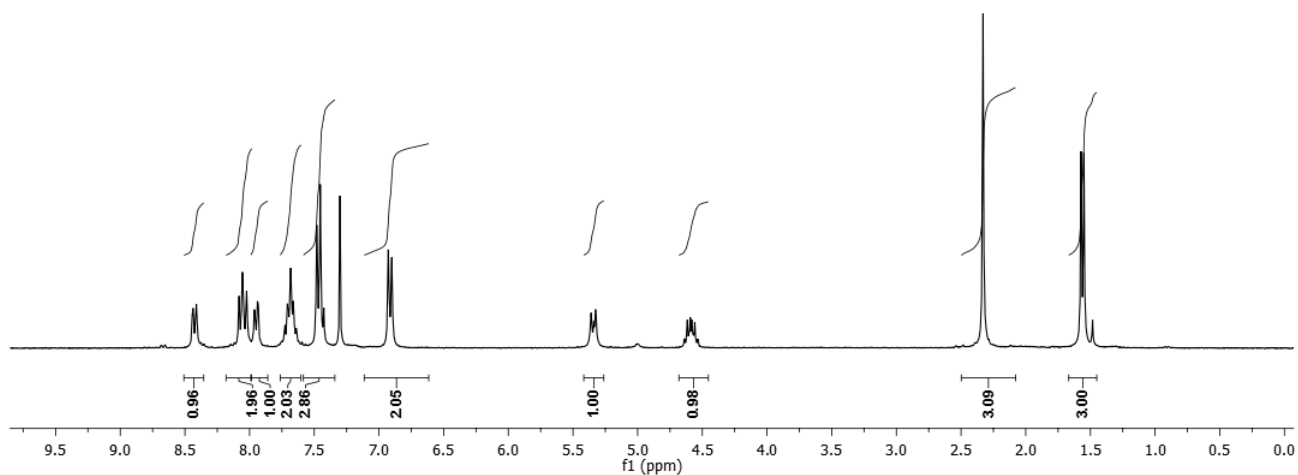
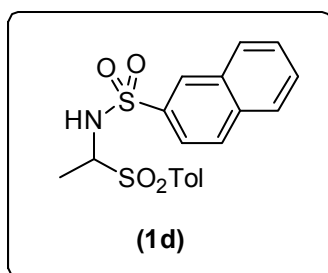
* Conversion value from the crude ¹H-NMR.

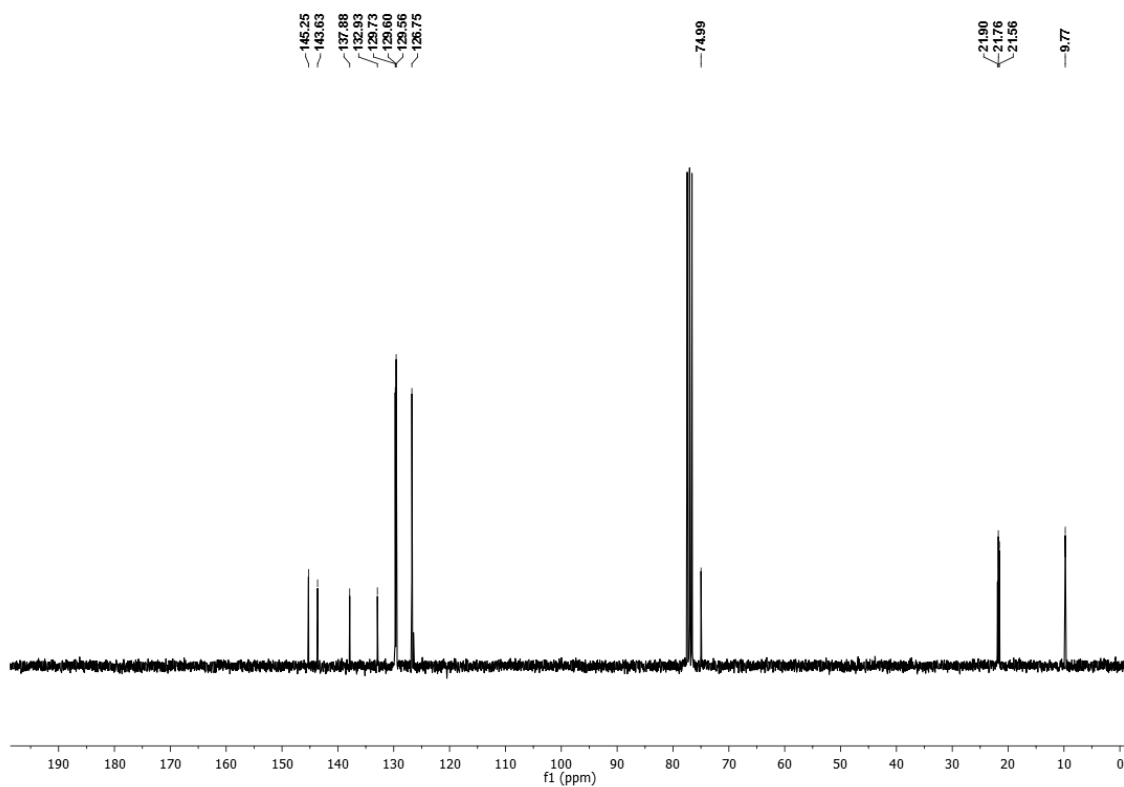
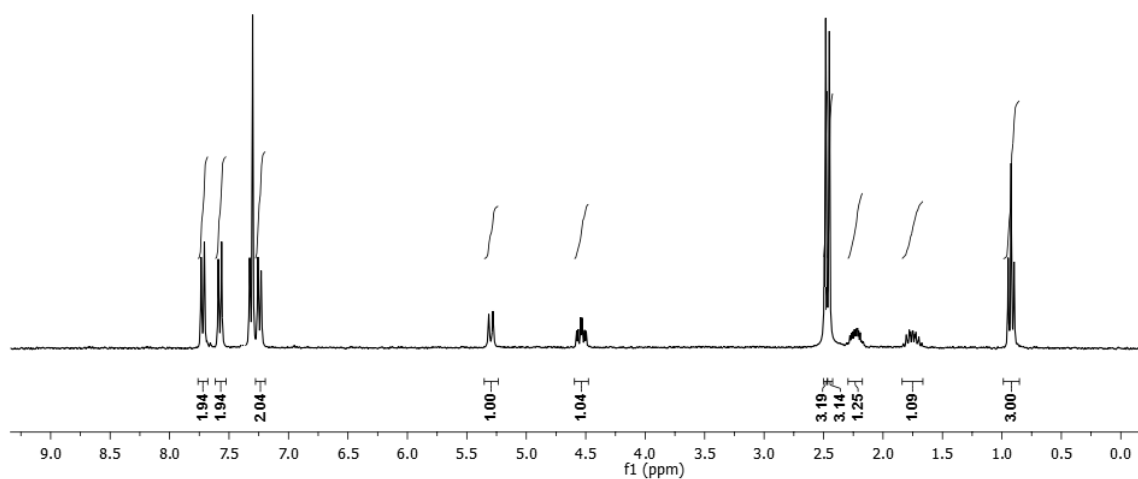
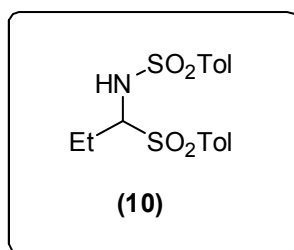
5. NMR spectra.

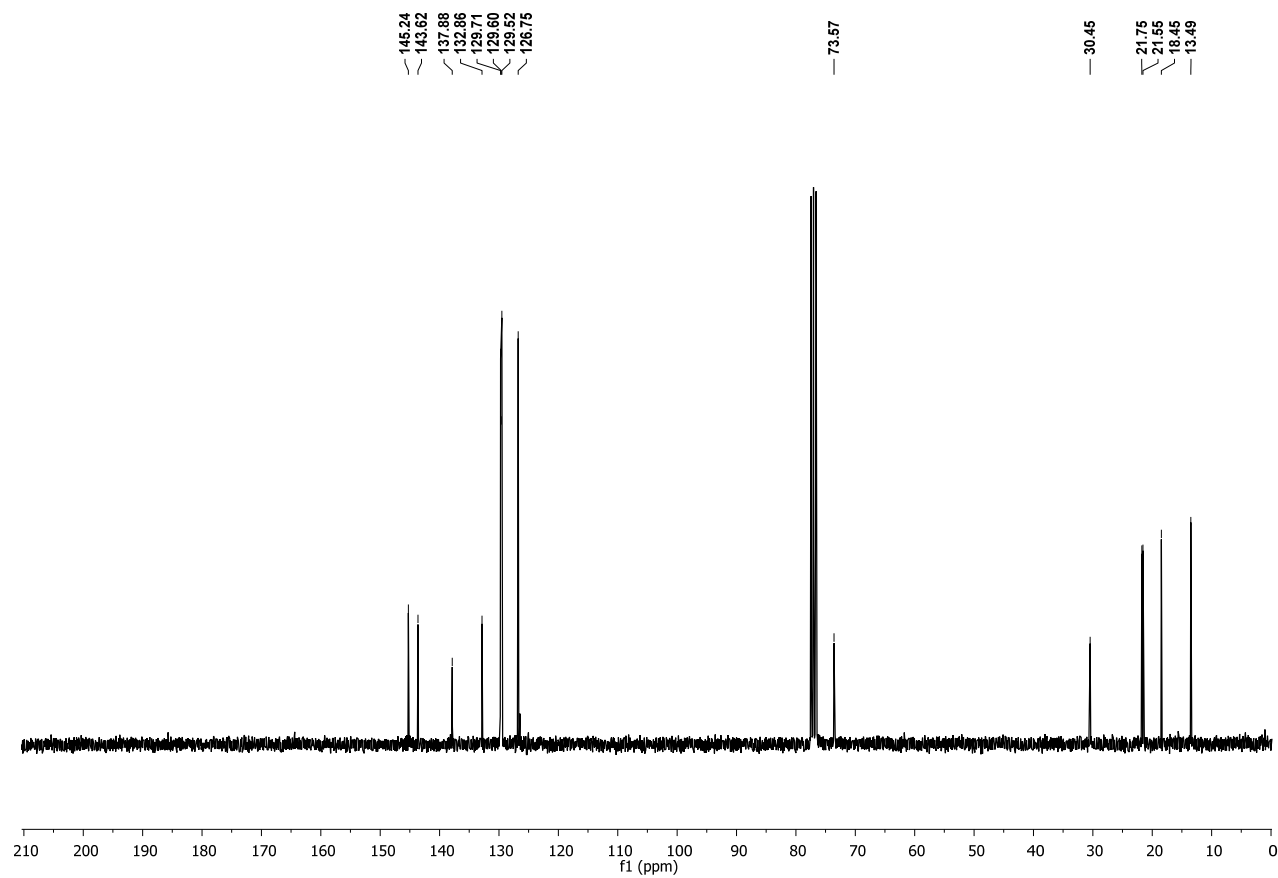
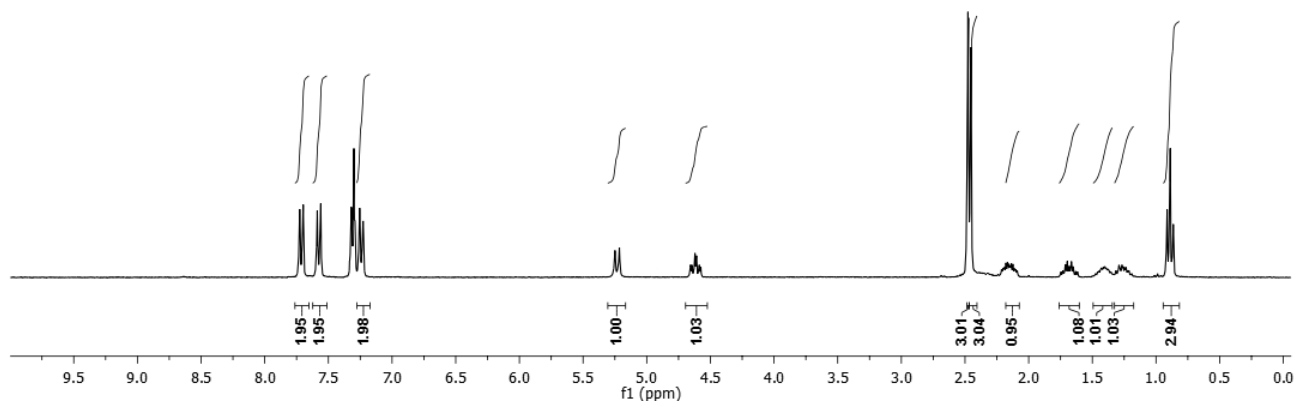
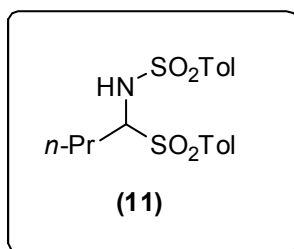


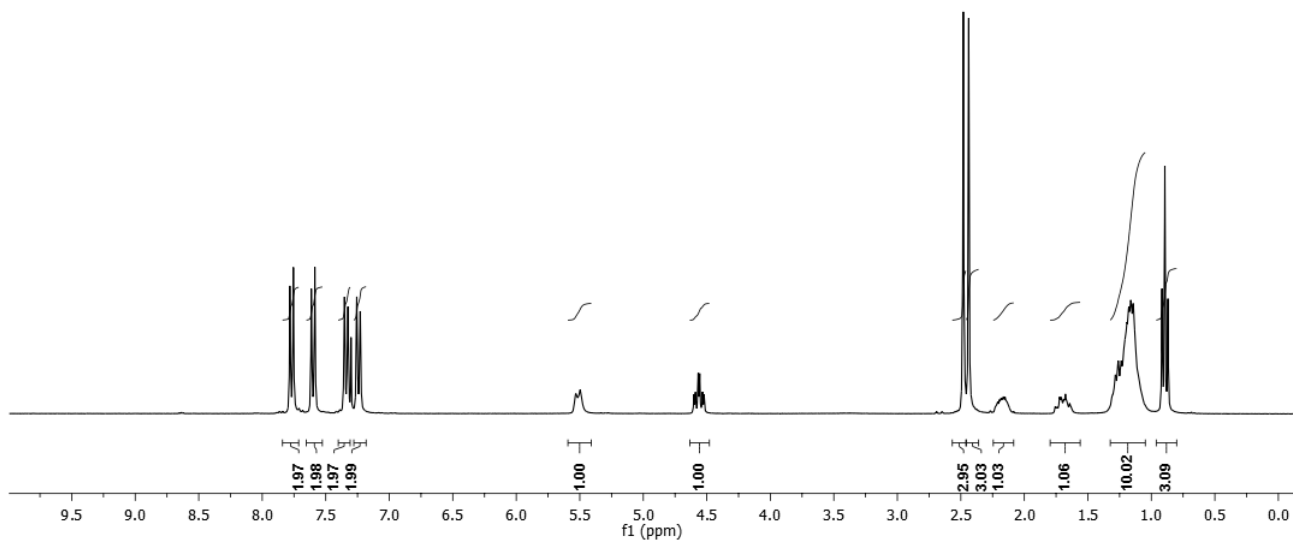
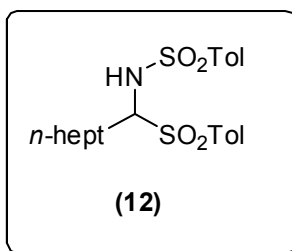








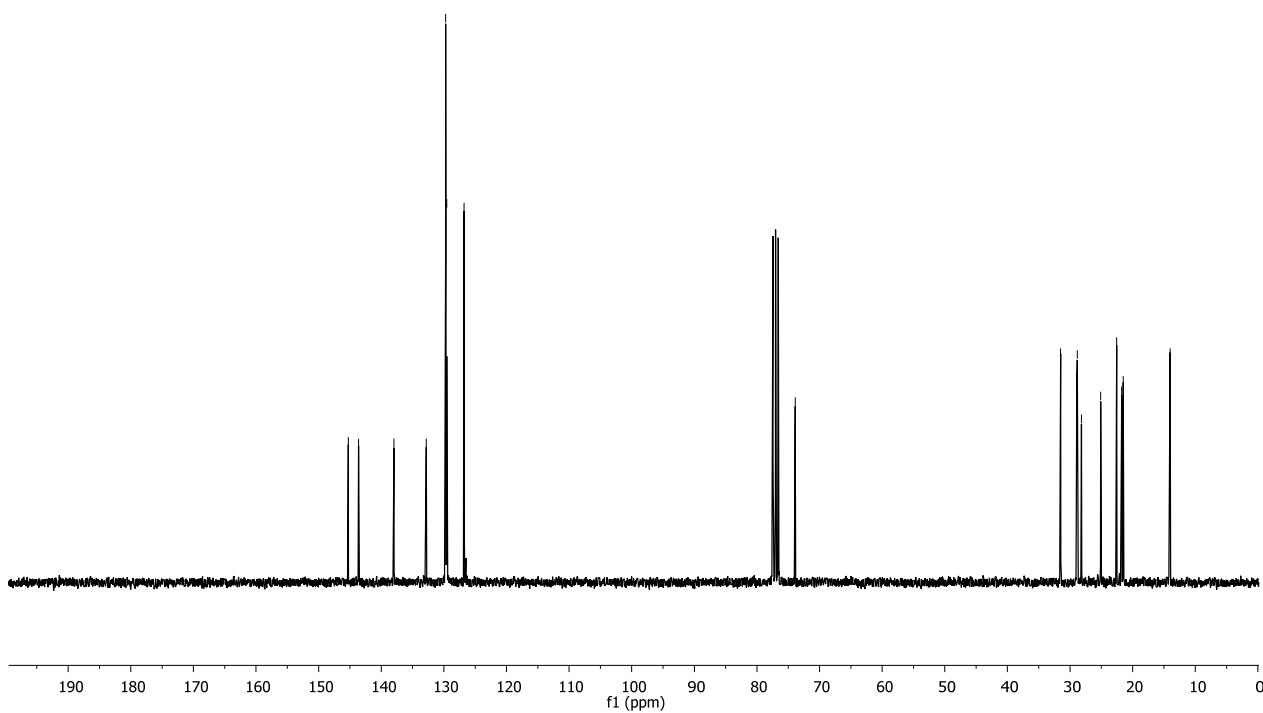


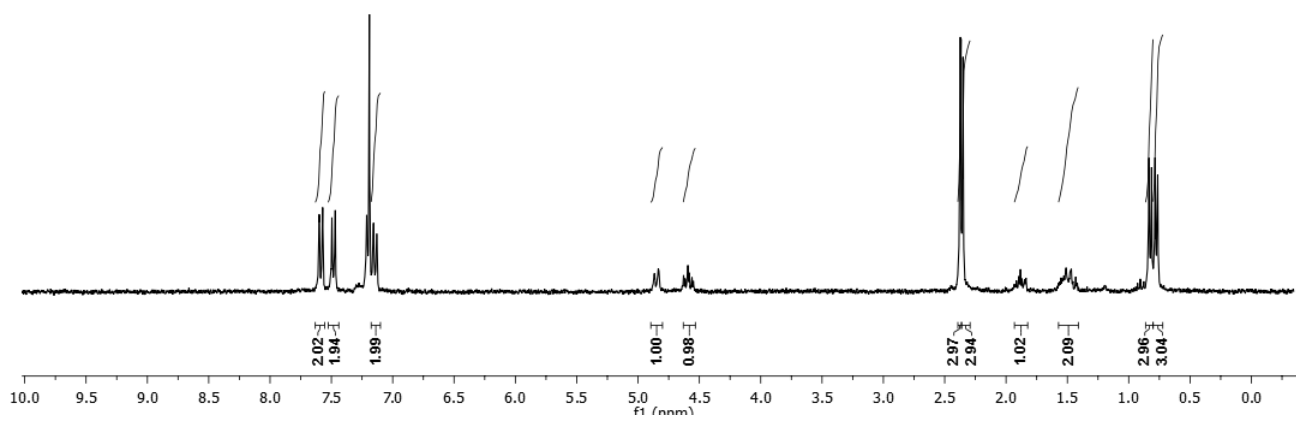
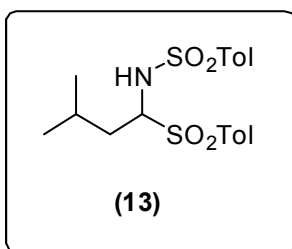


145.26
143.61
137.98
132.80
128.72
128.55
126.77

73.89

31.51
28.91
28.84
28.18
25.10
22.96
21.77
21.51
14.02



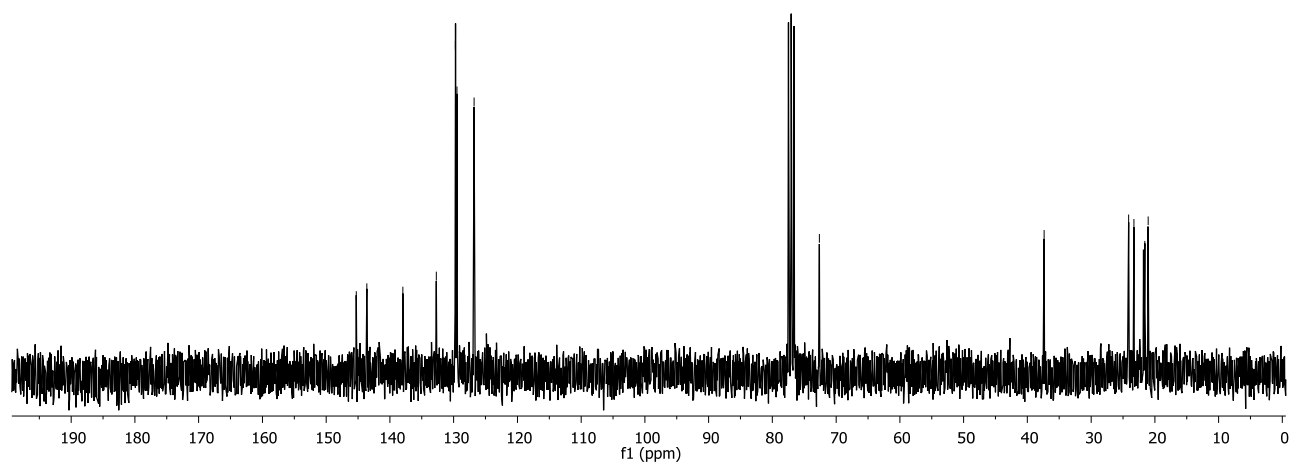


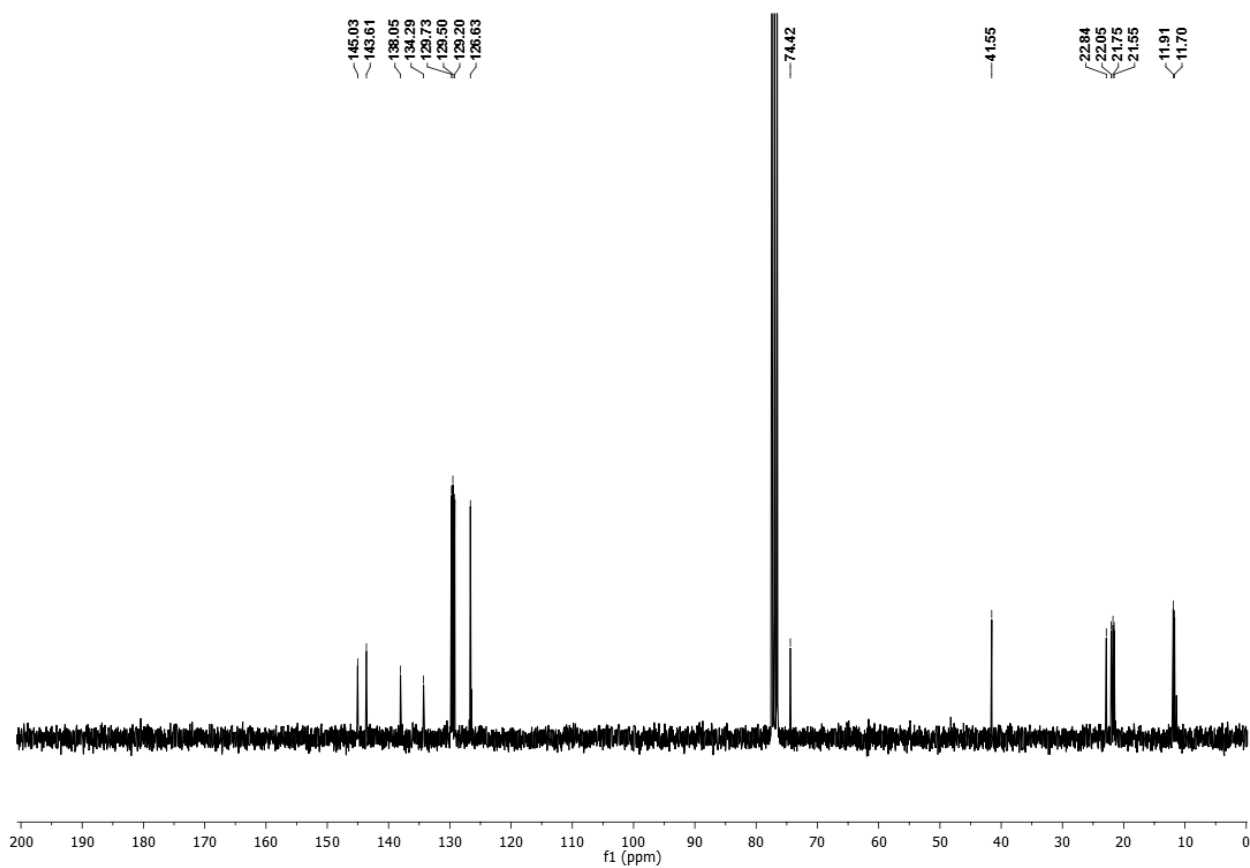
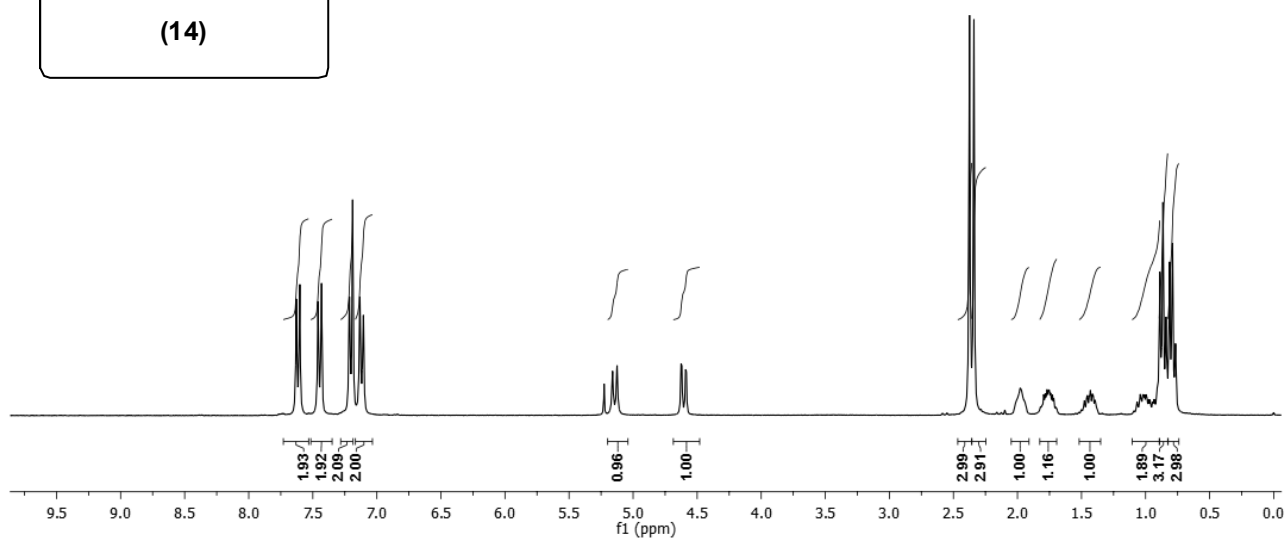
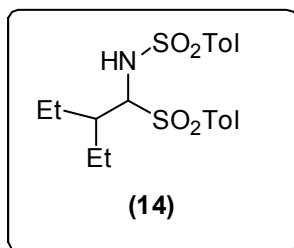
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143.82
137.97
132.72
129.74
128.71
128.48
126.79

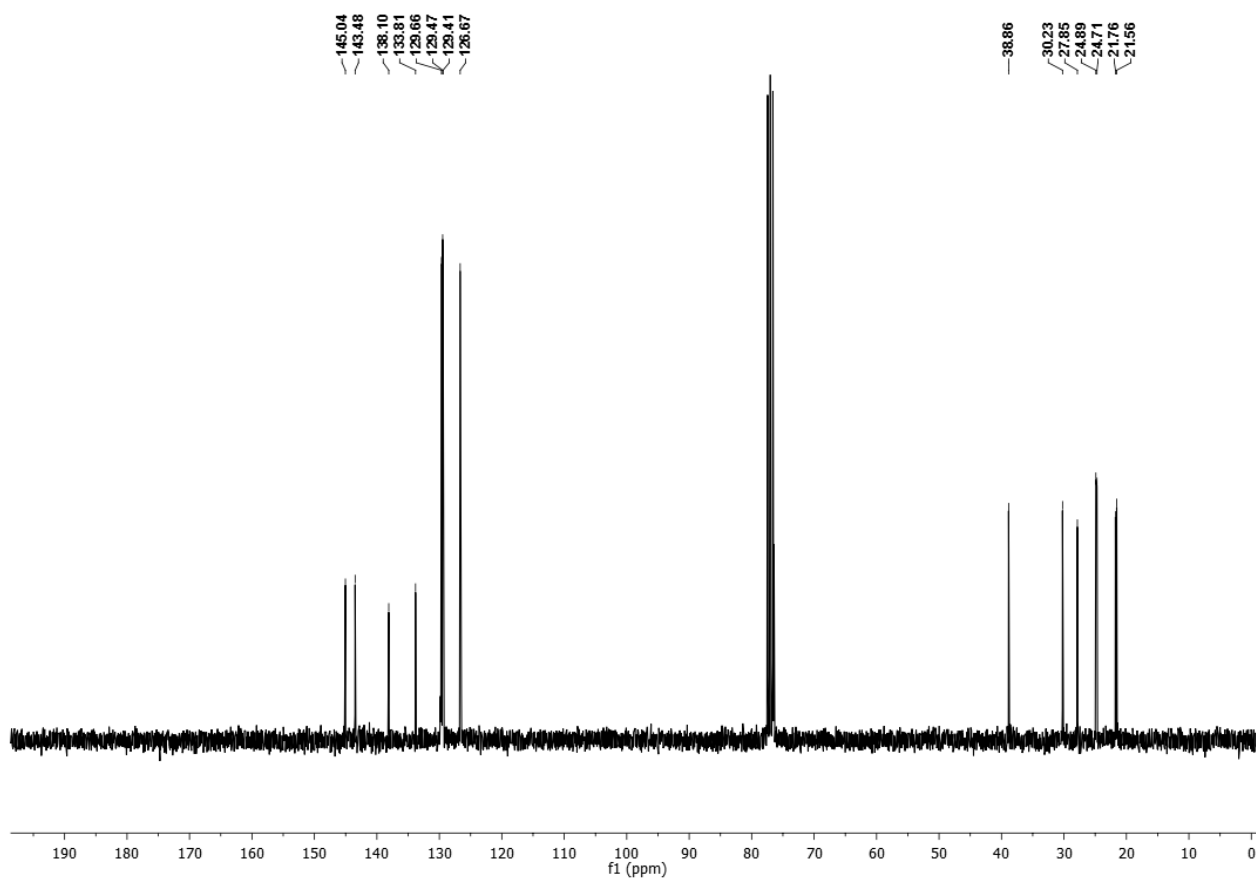
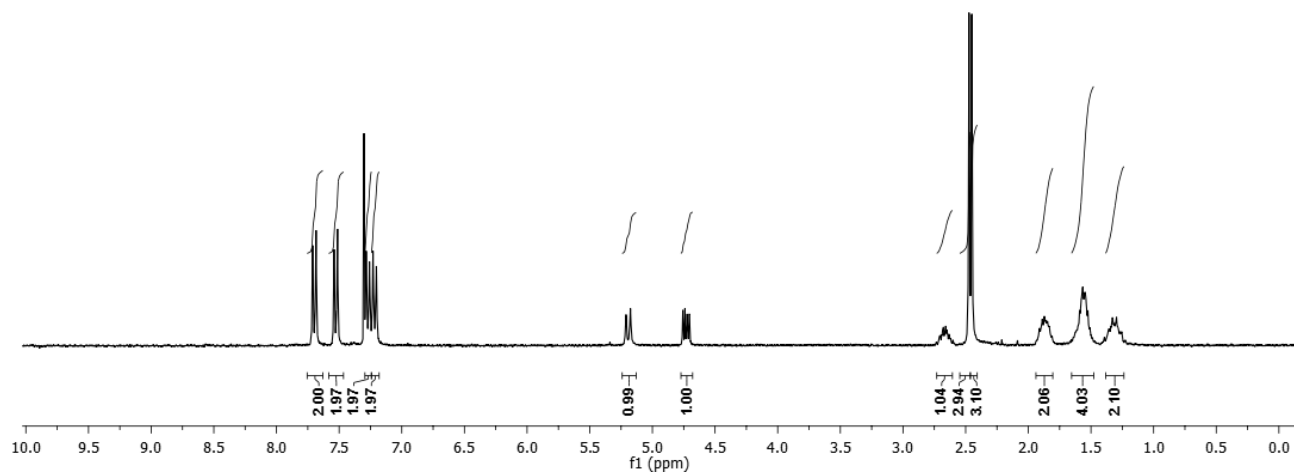
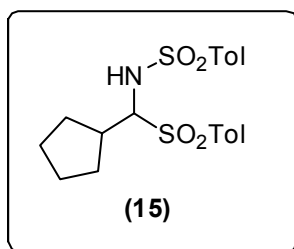
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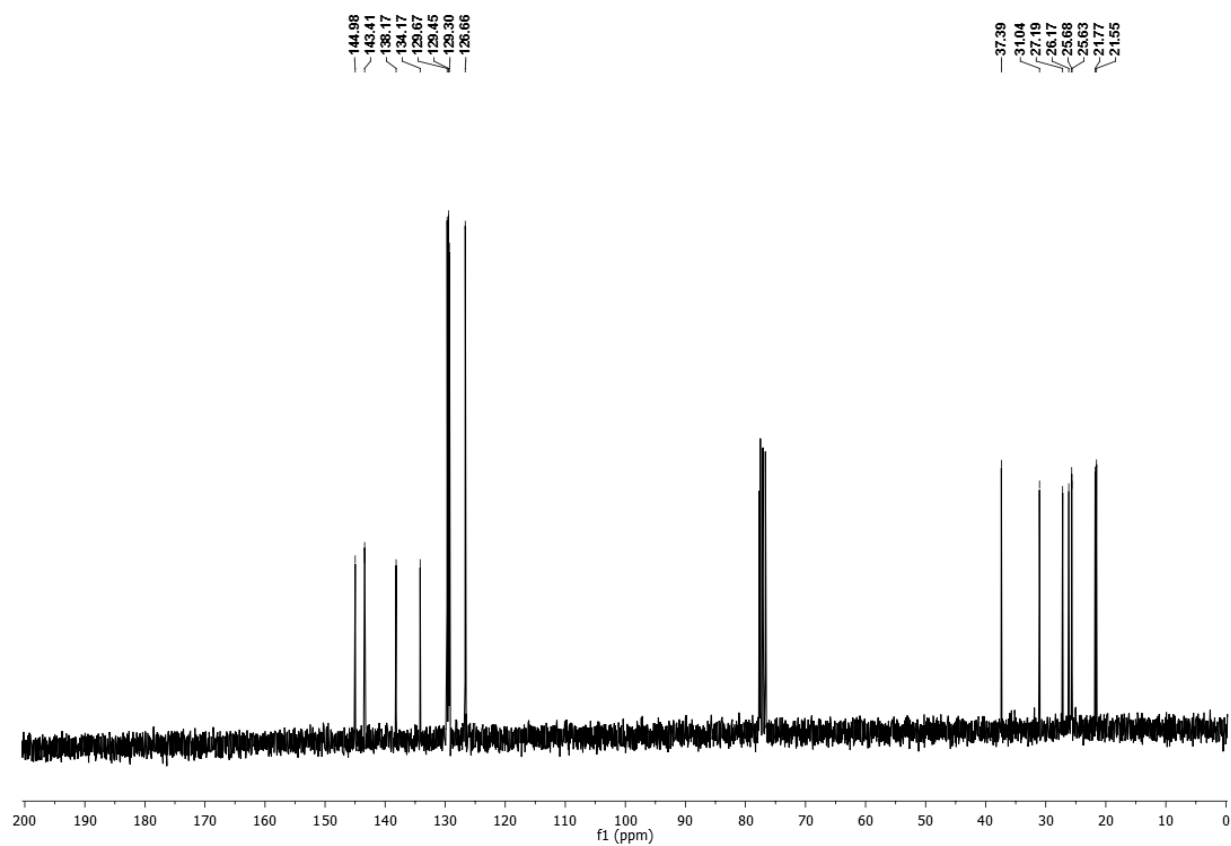
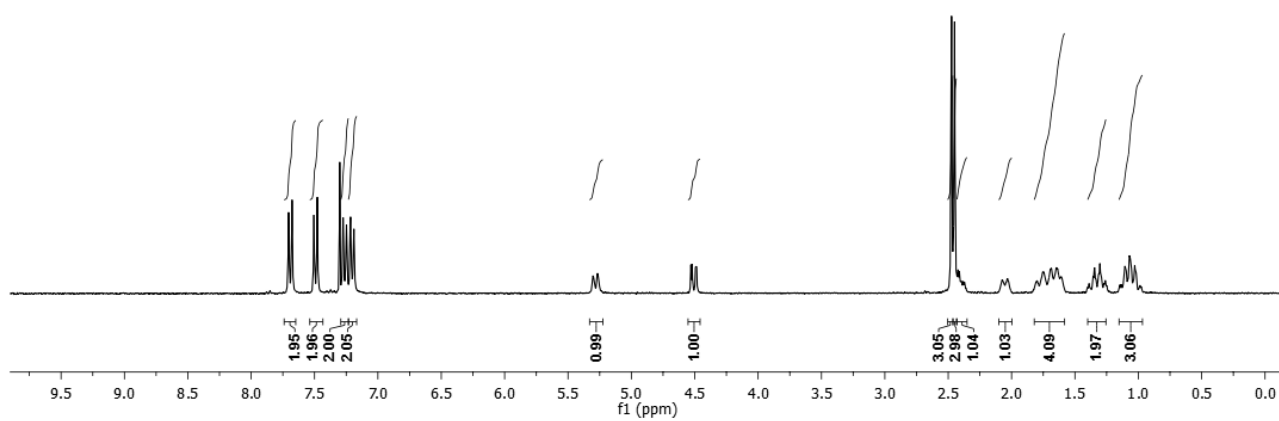
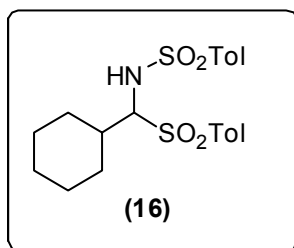
37.38

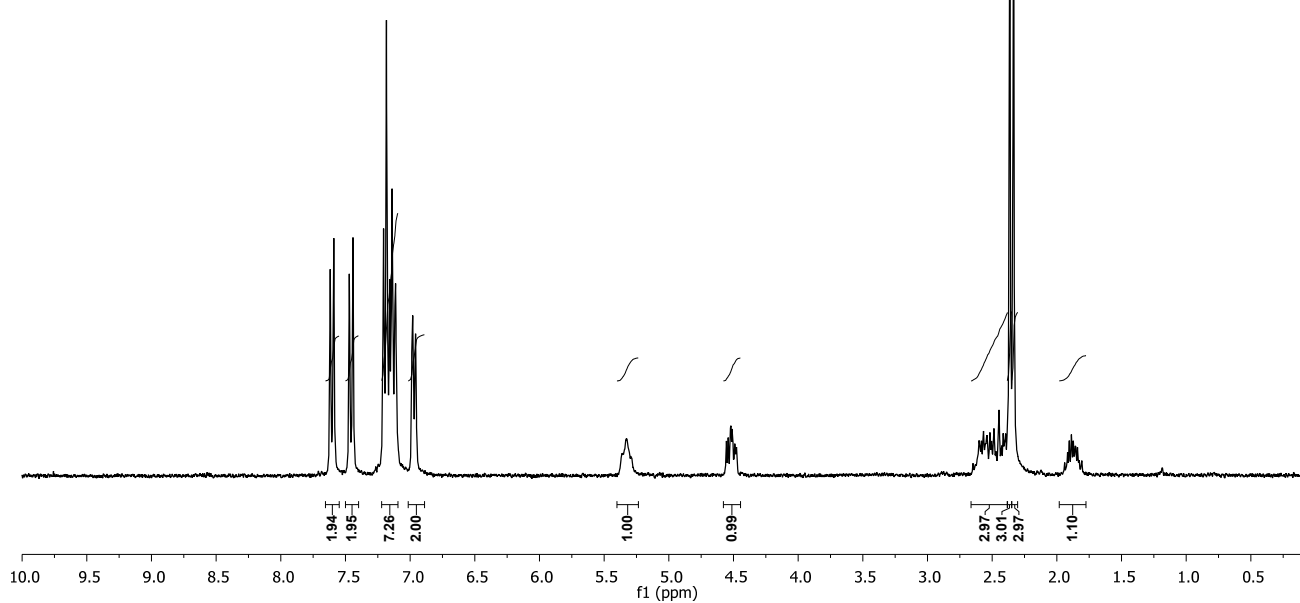
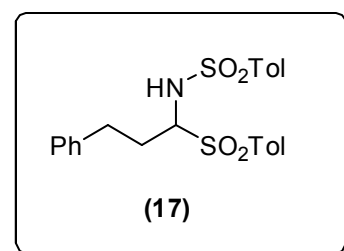
24.12
23.29
21.78
21.58
21.06











145.38
143.75
139.75
137.80
132.74
129.80
129.66
128.57
128.37
126.82
126.39

73.24

31.30
30.31
21.80
21.59

