

Palladium-Catalyzed α -Arylation of Sultams With Aryl and Heteroaryl Iodides

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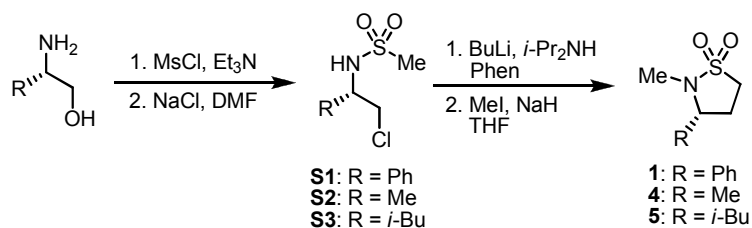
SUPPORTING INFORMATION

A. General Methods

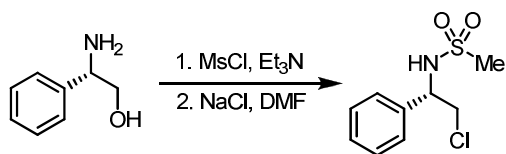
Reaction mixtures were analyzed on a Water Acquity UPLC-MS system using Formic acid/MeCN mobile phases and an Acquity UPLC[®] C18 column (1.7 μ m, 2.1x30 mm). ¹H and ¹³C NMR spectra were recorded in CDCl₃ solutions using a Bruker AV-400 spectrometer (400 MHz for ¹H, 101 MHz for ¹³C). The internal standard is TMS (0.00 ppm) for the resonance of protons and residual chloroform (77.0 ppm) for the resonance of carbons. High resolution mass spectra were obtained on a Thermo Q-Exactive system using positive EI mode. Flash column chromatography purification was performed using a CombiFlashRf Teledyne ISCO instrument with SiliCycle SiliaFlash[®] or RediSep[®]R_f cartridges. Preparative HPLC purification was performed on a Waters preparative HPLC system using Formic acid/MeCN mobile phases and a Gemini-XN C18 column (10 μ m, 100x30 mm). Diastereomers were separated on a PIC-100 SFC system using CO₂/MeOH + 0.1% NH₄OH mobile phases and a Chiralpak AD column (5 μ m, 21.2 x 150 mm). 2,2,6,6-Tetramethylpiperdylzinc chloride lithium chloride complex was used from Rockwood Lithium and titrated using the method of Knochel *et al.*¹ Unless otherwise specified, all reagents and solvents were used as is from commercial sources.

¹ Krasovskiy, A.; Knochel, P. *Synthesis* **2006**, 890.

B. Synthesis of Sultam Intermediates

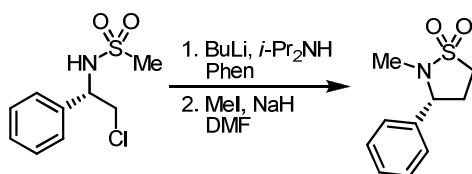


(*S*)-*N*-(2-Chloro-1-phenylethyl)methanesulfonamide (S1)



A three neck round bottomed flask was charged with (*S*)-2-phenylglycinol (66 g, 467 mmol), THF (1550 mL), and triethylamine (99.17 g, 980 mmol, 2.1 equiv) and the resulting mixture was cooled to -10 °C. Methanesulfonyl chloride (114.6 g, 980 mmol, 2.1 equiv) was added and the reaction was warmed to room temperature. Upon complete consumption of the starting material (monitored by HPLC), MTBE (1400 mL) was added and the resulting mixture was filtered and concentrated to dryness under reduced pressure. The resulting oil was dissolved in DMF (1000 mL), and solid NaCl (38.14 g, 653 mmol, 1.4 equiv) was added and the reaction was heated to 100 °C for 18h. The reaction mixture was cooled, diluted with saturated sodium chloride (1000 mL) and water (500 mL), and extracted with EtOAc (1000 mL). Concentration of the organic layer followed by silica gel column chromatography afforded 97.4 g (89%) of the desired product as a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 7.43 – 7.35 (m, 5H), 5.04 – 5.03 (m, 1H), 4.84 – 4.79 (m, 1H), 3.90 – 3.73 (m, 2H), 2.78 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 137.72, 129.13, 128.91, 126.91, 58.59, 48.40, 42.06. Matches literature values.²

(*R*)-2-Methyl-3-phenylisothiazolidine 1,1-dioxide (1)

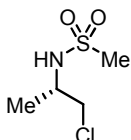


A three neck round bottomed flask was charged with (*S*)-*N*-(2-chloro-1-phenylethyl)methanesulfonamide (40 g, 171 mmol), THF (800 mL), and diisopropylamine (6.02 mL, 43 mmol, 0.25 equiv) and phenanthroline (77 mg, 0.43 mmol, 0.0025 equiv). The reaction was cooled to -50 °C, *n*-BuLi (150 mL of a 2.5 M solution in hexanes) was added and the reaction was warmed to 0 °C. The reaction was quenched with 2M HCl until pH reached *ca.* 5. Saturated aqueous sodium chloride (500 mL) was added, and the resulting mixture was extracted with EtOAc (800 mL) and concentrated to dryness under reduced pressure. The resulting oil was dissolved in *N,N*-dimethylformamide (800 mL), and iodomethane (16 mL, 256 mmol, 1.5 equiv) was added. The reaction was cooled to 0 °C, sodium hydride

² Lee, J.; Zhong, Y. L.; Reamer, R. A.; Askin, D. *Org. Lett.* **2003**, 5, 4175.

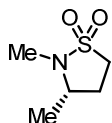
(9.81 g of a 60% w/w in mineral oil, 256 mmol, 1.5 equiv) was added, and the reaction was warmed to room temperature. The reaction was quenched with aqueous sodium chloride (200 mL) and extracted with EtOAc (800 mL). Concentration of the organic layer followed by silica gel column chromatography afforded 29.7 g (83%) of the desired product as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.42 – 7.33 (m, 5H), 4.13 (dd, J = 12 Hz, 8.0 Hz, 1H), 3.42 – 3.35 (m, 1H), 3.24 – 3.17 (m, 1H), 2.67 – 2.60 (m, 1H), 2.52 (s, 3H), 2.32 – 2.22 (m, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 139.24, 129.16, 128.71, 126.83, 76.70, 46.32, 29.15, 28.80; HRMS calcd for $\text{C}_9\text{H}_{12}\text{ClNO}_2\text{S}$ $[\text{M}+\text{H}]^+$ 212.0740, found 212.0744.

(S)-N-(1-Chloropropan-2-yl)methanesulfonamide (S2)



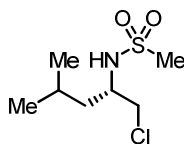
Prepared using the same method as **S1**. Yield: 79%. ^1H NMR (400 MHz, CDCl_3) δ 4.49 (s, 1H), 3.91 – 3.82 (m, 1H), 3.72 – 3.54 (m, 2H), 3.02 (s, 3H), 1.36 (d, J = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 50.88, 48.33, 31.76, 21.32; HRMS calcd for $\text{C}_4\text{H}_{10}\text{ClNO}_2\text{S}$ $[\text{M}+\text{H}]^+$ 172.0194, found 172.0194.

(S)-2,3-Dimethylisothiazolidine 1,1-dioxide (4)



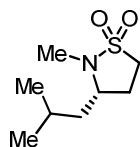
Prepared using the same method as **1**. Yield: 29%. ^1H NMR (400 MHz, CDCl_3) δ 3.28 – 3.17 (m, 1H), 3.12 – 3.03 (m, 1H), 2.64 (d, J = 5.6), 2.45 – 2.36 (m, 1H), 2.01 – 1.90 (m, 1H), 1.28 – 1.26 (m, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 55.30, 45.94, 28.24, 27.26, 19.44; HRMS calcd for $\text{C}_5\text{H}_{11}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$ 150.0583, found 150.0581.

(S)-N-(1-Chloro-4-methylpentan-2-yl)methanesulfonamide (S3)



Prepared using the same method as **S1**. Yield: 72%. ^1H NMR (400 MHz, CDCl_3) δ 4.59 (d, J = 8.8 Hz, 1H), 3.83 – 3.71 (m, 2H), 3.64 – 3.56 (m, 1H), 3.03 (s, 3H), 1.80 – 1.67 (m, 1H), 1.56 – 1.40 (m, 2H), 0.97 (d, J = 2.6 Hz, 3H), 0.95 (d, J = 2.3 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 52.76, 49.02, 42.40, 42.21, 24.50, 22.72, 22.14; HRMS calcd for $\text{C}_7\text{H}_{16}\text{ClNO}_2\text{S}$ $[\text{M}+\text{H}]^+$ 214.0663, found 214.0659.

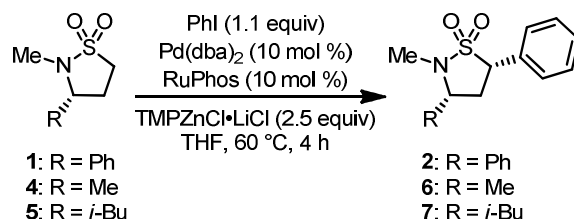
(S)-3-Isobutyl-2-methylisothiazolidine 1,1-dioxide (5)



Prepared using the same method as **1**. Yield: 36%. ^1H NMR (400 MHz, CDCl_3) δ 3.26 – 3.18 (m, 1H), 3.18 – 3.11 (m, 1H), 3.10 – 3.01 (m, 1H), 2.66 (s, 3H), 2.49 – 2.38 (m, 1H), 2.04 – 1.91 (m, 1H), 1.77 – 1.65 (m, 1H), 1.64 – 1.54 (m, 1H), 1.41 – 1.32 (m, 1H), 0.98 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.5 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 58.21, 45.69, 42.75, 29.17, 25.41, 24.26, 23.84, 21.80; HRMS calcd for $\text{C}_8\text{H}_{17}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$ 192.1053, found 192.1044.

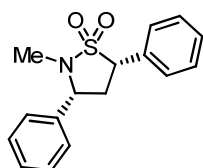
C. α -Arylation of Sultams

General Procedure 1 for the arylation of sultams **1**, **4** and **5**.

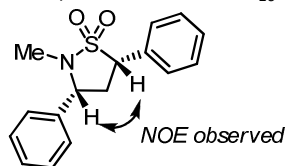


A vial containing sultam **1**, **4** or **5** (1.0 mmol), $\text{Pd}(\text{dba})_2$ (61 mg, 0.1 mmol, 0.1 equiv), and 2-dicyclohexylphosphino-2',6'-di-*i*-propoxy-1,1'-biphenyl (43 mg, 0.1 mmol, 0.1 equiv) was evacuated and purged with nitrogen three times. To the vial was added degassed THF (3 mL – degassed by sparging with nitrogen), iodobenzene (226 mg, 1.1 mmol, 1.1 equiv), and to the resulting mixture was added a solution of 2,2,6,6-tetramethylpiperdylzinc chloride lithium chloride complex solution (3.8 mL of a 0.67 M solution in THF, 2.5 mmol, 2.5 equiv). The resulting mixture was heated to 60 °C for 4 h, quenched by adding the crude reaction mixture into a solution of saturated NH_4Cl in water, and extracted with EtOAc (3 X 3 mL). Concentration of the organic layer, followed by silica gel column chromatography afforded product **2** (89% yield, 9:1 *dr*), **6** (85% yield, 2.5:1 *dr*) or **7** (75% yield, 3:1 *dr*). Small amounts (~50 mg) of the mixtures of diastereomers were separated by supercritical fluid chromatography for characterization of the individual diastereomers.

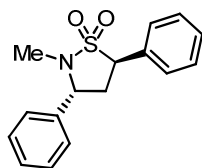
(3*R*,5*S*)-2-Methyl-3,5-diphenylisothiazolidine 1,1-dioxide (**2**)



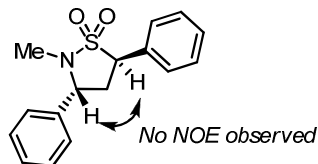
Prepared according to general procedure 1 (major isomer). ^1H NMR (400 MHz, CDCl_3) δ 7.51 – 7.34 (m, 10H), 4.41 (dd, J = 12.7, 7.1 Hz, 1H), 4.22 (dd, J = 10.4, 5.9 Hz, 1H), 2.91 – 2.80 (m, 1H), 2.65 (s, 3H), 2.63 – 2.50 (m, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 139.00, 130.89, 129.23, 129.17, 129.03, 128.96, 128.72, 126.86, 63.73, 63.01, 36.83, 30.75; HRMS calcd for $\text{C}_{16}\text{H}_{17}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$ 288.1053, found 288.1044.



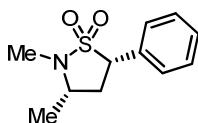
(3*R*,5*R*)-2-Methyl-3,5-diphenylisothiazolidine 1,1-dioxide (3)



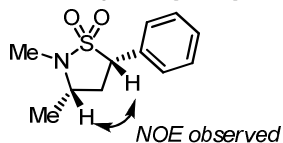
Prepared according to general procedure 1 (minor isomer). ^1H NMR (400 MHz, CDCl_3) δ 7.52 – 7.34 (m, 10H), 4.58 (dd, J = 10.3, 8.6 Hz, 1H), 4.31 (dd, J = 8.6, 4.6 Hz, 1H), 3.09 – 2.98 (m, 1H), 2.66 (s, 3H), 2.59 – 2.49 (m, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 140.10, 130.20, 129.29, 129.25, 129.15, 128.96, 128.51, 126.52, 60.86, 59.96, 35.06, 28.60; HRMS calcd for $\text{C}_{16}\text{H}_{17}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$ 288.1053, found 288.1043.



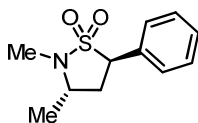
(3*S*,5*S*)-2,3-Dimethyl-5-phenylisothiazolidine 1,1-dioxide (*cis*-6)



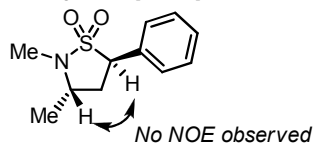
Prepared according to general procedure 1 (major isomer). ^1H NMR (400 MHz, CDCl_3) δ 7.47 – 7.34 (m, 5H), 4.26 (dd, J = 12.0, 7.5 Hz, 1H), 3.33 – 3.21 (m, 1H), 2.76 (s, 3H), 2.73 – 2.64 (m, 1H), 2.32 – 2.18 (m, 1H), 1.37 (d, J = 6.2 Hz, 4H); ^{13}C NMR (101 MHz, CDCl_3) δ 131.47, 129.08, 129.02, 128.89, 63.21, 54.02, 35.27, 30.04, 19.63; HRMS calcd for $\text{C}_{11}\text{H}_{15}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$ 226.0896, found 226.0899.



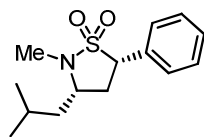
(3*S*,5*R*)-2,3-Dimethyl-5-phenylisothiazolidine 1,1-dioxide (*trans*-6)



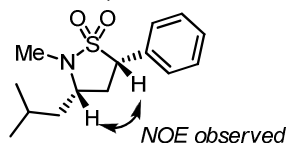
Prepared according to general procedure 1 (minor isomer). ^1H NMR (400 MHz, CDCl_3) δ 7.49 – 7.34 (m, 5H), 4.44 (dd, J = 9.8, 8.9 Hz, 1H), 3.44 – 3.32 (m, 1H), 2.82 – 2.74 (m, 1H), 2.73 (s, 3H), 2.34 – 2.22 (m, 1H), 1.35 (d, J = 6.4 Hz, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ 130.74, 129.15, 129.12, 128.89, 60.01, 52.54, 33.41, 28.14, 19.83; HRMS calcd for $\text{C}_{11}\text{H}_{15}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$ 226.0896, found 226.0898.



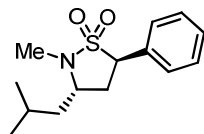
(3S,5S)-3-Isobutyl-2-methyl-5-phenylisothiazolidine 1,1-dioxide (*cis*-7)



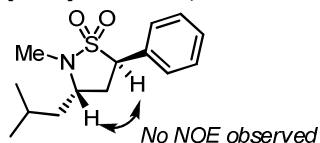
Prepared according to general procedure 1 (major isomer). ^1H NMR (400 MHz, CDCl_3) δ 7.47 – 7.34 (m, 5H), 4.20 (dd, J = 12.2, 7.4 Hz, 1H), 3.28 – 3.17 (m, 1H), 2.78 (s, 3H), 2.76 – 2.67 (m, 1H), 2.30 – 2.17 (m, 1H), 1.82 – 1.66 (m, 2H), 1.53 – 1.43 (m, 1H), 1.00 (d, J = 6.3 Hz, 3H), 0.95 (d, J = 6.2 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 131.37, 129.05, 128.99, 128.87, 62.81, 57.07, 43.33, 33.44, 31.58, 24.32, 23.78, 21.87; HRMS calcd for $\text{C}_{14}\text{H}_{21}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$ 268.1366, found 268.1365.



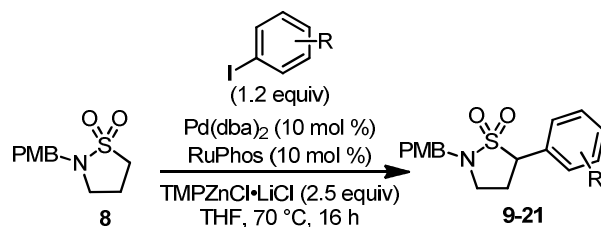
(3S,5R)-3-Isobutyl-2-methyl-5-phenylisothiazolidine 1,1-dioxide (*trans*-7)



Prepared according to general procedure 1 (minor isomer). ^1H NMR (400 MHz, CDCl_3) δ 7.50 – 7.35 (m, 5H), 4.42 (dd, J = 10.1, 8.5 Hz, 1H), 3.34 – 3.22 (m, 1H), 2.78 – 2.70 (m, 4H), 2.40 – 2.29 (m, 1H), 1.80 – 1.67 (m, 1H), 1.67 – 1.58 (m, 1H), 1.52 – 1.41 (m, 1H), 1.00 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 6.5 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 130.61, 129.16, 129.10, 128.89, 59.84, 55.57, 42.82, 31.43, 28.96, 24.54, 23.71, 21.93; HRMS calcd for $\text{C}_{14}\text{H}_{21}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$ 268.1366, found 268.1366.

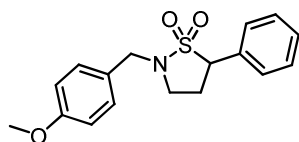


General Procedure 2 for the arylation of sultams 8.



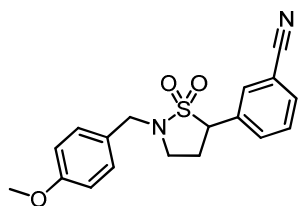
A vial containing *N*-(4-methoxybenzyl)-1,3-propanesultam (50 mg, 0.21 mmol), Pd(dba)₂ (12 mg, 0.021 mmol, 0.1 equiv), and 2-dicyclohexylphosphino-2',6'-di-*i*-propoxy-1,1'-biphenyl (10 mg, 0.021 mmol, 0.1 equiv) was evacuated and purged with nitrogen three times. To the vial was added degassed THF (1 mL – degassed by sparging with nitrogen), the aryl iodide (226 mg, 0.25 mmol, 1.2 equiv), and to the resulting mixture was added a solution of 2,2,6,6-tetramethylpiperdylzinc chloride lithium chloride complex solution (0.77 mL of a 0.67 M solution in THF, 0.52 mmol, 2.5 equiv). The resulting mixture was heated to 70 °C for 16 h, quenched by adding the crude reaction mixture into a solution of saturated NH₄Cl in water, and extracted with EtOAc (3 X 3 mL). Concentration of the organic layer, followed by preparative HPLC purification and lyophilization afforded products **9-21**.

2-(4-Methoxybenzyl)-5-phenylisothiazolidine 1,1-dioxide (**9**)

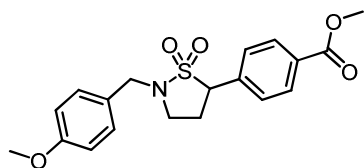


Prepared according to general procedure 2. Yield: 82%. ¹H NMR (400 MHz, CDCl₃) δ 7.47 – 7.36 (m, 5H), 7.33 – 7.26 (m, 2H), 6.93 – 6.86 (m, 2H), 4.38 – 4.30 (m, 1H), 4.27 (d, *J* = 14.1 Hz, 1H), 4.15 (d, *J* = 14.2 Hz, 1H), 3.81 (s, 3H), 3.26 – 3.17 (m, 1H), 3.17 – 3.08 (m, 1H), 2.63 – 2.52 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 159.38, 131.41, 130.01, 129.13, 129.01, 128.88, 127.40, 114.08, 62.46, 55.31, 48.18, 43.59, 25.50; HRMS calcd for C₁₇H₁₉NO₃S [M+Na]⁺ 340.0978, found 340.0969.

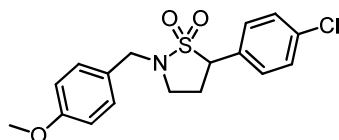
3-(2-(4-Methoxybenzyl)-1,1-dioxidoisothiazolidin-5-yl)benzonitrile (**10**)



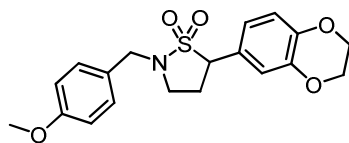
Prepared according to general procedure 2. Yield: 41%. ¹H NMR (400 MHz, CDCl₃) δ 7.74 – 7.66 (m, 3H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.32 – 7.24 (m, 2H), 6.95 – 6.87 (m, 2H), 4.39 – 4.25 (m, 2H), 4.15 (d, *J* = 14.1 Hz, 1H), 3.82 (s, 3H), 3.30 – 3.20 (m, 1H), 3.20 – 3.11 (m, 1H), 2.71 – 2.58 (m, 1H), 2.58 – 2.46 (m, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 159.53, 133.60, 133.51, 132.68, 132.45, 130.06, 129.75, 126.94, 118.16, 114.20, 113.28, 61.56, 55.34, 48.12, 43.27, 25.52; HRMS calcd C₁₈H₁₈N₂O₃S [M+Na]⁺ 365.0930, found 365.0914.

Methyl 4-(2-(4-methoxybenzyl)-1,1-dioxidoisothiazolidin-5-yl)benzoate (11)

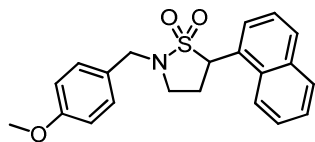
Prepared according to general procedure 2. Yield: 52%. ^1H NMR (400 MHz, CDCl_3) δ 8.10 – 8.04 (m, 2H), 7.55 – 7.49 (m, 2H), 7.32 – 7.26 (m, 2H), 6.94 – 6.87 (m, 2H), 4.38 (dd, J = 10.2, 8.2 Hz, 1H), 4.28 (d, J = 14.2 Hz, 1H), 4.15 (d, J = 14.2 Hz, 1H), 3.93 (s, 3H), 3.82 (s, 3H), 3.28 – 3.19 (m, 1H), 3.19 – 3.10 (m, 1H), 2.69 – 2.49 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 166.49, 159.45, 136.56, 130.83, 130.06, 130.05, 129.06, 127.19, 114.13, 62.17, 55.32, 52.26, 48.18, 43.50, 25.53; HRMS calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_5\text{S}$ $[\text{M}+\text{Na}]^+$ 398.1033, found 398.1023.

5-(4-Chlorophenyl)-2-(4-methoxybenzyl)isothiazolidine 1,1-dioxide (12)

Prepared according to general procedure 2. Yield: 50%. ^1H NMR (400 MHz, CDCl_3) δ 7.38 (s, 4H), 7.31 – 7.26 (m, 2H), 6.92 – 6.87 (m, 2H), 4.34 – 4.23 (m, 2H), 4.14 (d, J = 14.2 Hz, 1H), 3.81 (s, 3H), 3.24 – 3.17 (m, 1H), 3.17 – 3.07 (m, 1H), 2.65 – 2.46 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 159.44, 135.26, 130.32, 130.03, 130.03, 129.13, 127.23, 114.13, 61.78, 55.33, 48.17, 43.46, 25.56; HRMS calcd for $\text{C}_{17}\text{H}_{18}\text{ClNO}_3\text{S}$ $[\text{M}+\text{Na}]^+$ 374.0588, found 374.0584.

5-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-2-(4-methoxybenzyl)isothiazolidine 1,1-dioxide (13)

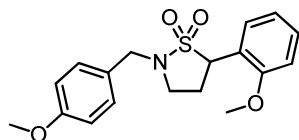
Prepared according to general procedure 2. Yield: 87%. ^1H NMR (400 MHz, CDCl_3) δ 7.33 – 7.24 (m, 2H), 6.95 (d, J = 2.0 Hz, 1H), 6.93 – 6.85 (m, 4H), 4.27 – 4.20 (m, 6H), 4.14 (d, J = 14.3 Hz, 1H), 3.81 (s, 3H), 3.21 – 3.12 (m, 1H), 3.12 – 3.03 (m, 1H), 2.58 – 2.43 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 159.35, 144.40, 143.73, 130.00, 127.45, 124.21, 122.06, 117.87, 117.64, 114.06, 64.38, 64.26, 61.94, 55.30, 48.18, 43.50, 25.42; HRMS calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_5\text{S}$ $[\text{M}+\text{Na}]^+$ 398.1033, found 398.1023.

2-(4-Methoxybenzyl)-5-(naphthalen-1-yl)isothiazolidine 1,1-dioxide (14)

Prepared according to general procedure 2. Yield: 65%. ^1H NMR (400 MHz, CDCl_3) δ 8.26 (d, J = 8.6 Hz, 1H), 7.93 – 7.86 (m, 2H), 7.66 – 7.58 (m, 2H), 7.56 – 7.48 (m, 2H), 7.34 – 7.28 (m, 2H), 6.94 – 6.87 (m, 2H), 5.25 (dd, J = 9.7, 7.8 Hz, 1H), 4.33 (d, J = 14.1 Hz, 1H), 4.15 (d, J = 14.2 Hz, 1H), 3.76 (s, 3H), 3.36 – 3.29 (m, 1H), 3.28 – 3.20 (m, 1H), 2.89 – 2.76 (m, 1H), 2.71 – 2.61 (m, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 159.40, 133.89, 132.46, 130.07, 129.71, 129.01,

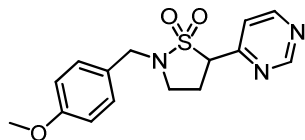
127.56, 127.45, 127.11, 126.11, 126.05, 125.25, 123.06, 114.09, 57.89, 55.32, 48.36, 44.01, 25.68; HRMS calcd for $C_{21}H_{21}NO_3S [M+Na]^+$ 390.1134, found 390.1125.

2-(4-Methoxybenzyl)-5-(2-methoxyphenyl)isothiazolidine 1,1-dioxide (15)



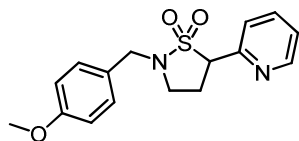
Prepared according to general procedure 2. Yield: 74%. 1H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, $J = 7.7, 1.6$ Hz, 1H), 7.37 – 7.31 (m, 1H), 7.31 – 7.26 (m, 2H), 7.04 – 6.97 (m, 1H), 6.94 (d, $J = 8.3$ Hz, 1H), 6.91 – 6.85 (m, 2H), 5.01 (t, $J = 8.8$ Hz, 1H), 4.29 (d, $J = 14.1$ Hz, 1H), 4.06 (d, $J = 14.1$ Hz, 1H), 3.88 (s, 3H), 3.81 (s, 3H), 3.25 – 3.15 (m, 1H), 3.15 – 3.06 (m, 1H), 2.62 – 2.42 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.31, 158.02, 130.04, 129.99, 128.59, 127.65, 120.83, 120.68, 114.02, 110.95, 55.89, 55.30, 55.06, 48.11, 43.82, 25.43; HRMS calcd for $C_{18}H_{21}NO_4S [M+Na]^+$ 370.1083, found 370.1088.

2-(4-Methoxybenzyl)-5-(pyrimidin-4-yl)isothiazolidine 1,1-dioxide (16)



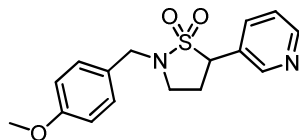
Prepared according to general procedure 2. Yield: 73%. 1H NMR (400 MHz, $CDCl_3$) δ 9.23 (d, $J = 1.1$ Hz, 1H), 8.79 (d, $J = 5.1$ Hz, 1H), 7.54 (dd, $J = 5.2, 1.5$ Hz, 1H), 7.25 – 7.21 (m, 2H), 6.91 – 6.85 (m, 2H), 4.52 – 4.44 (m, 1H), 4.24 – 4.17 (m, 2H), 3.81 (s, 3H), 3.43 – 3.31 (m, 1H), 3.25 – 3.15 (m, 1H), 3.01 – 2.88 (m, 1H), 2.71 – 2.57 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.34, 159.44, 158.95, 157.40, 129.91, 127.13, 121.84, 114.09, 62.63, 55.31, 48.40, 43.91, 22.99; HRMS calcd for $C_{15}H_{17}N_3O_3S [M+H]^+$ 320.1063, found 320.1061.

2-(4-Methoxybenzyl)-5-(pyridin-2-yl)isothiazolidine 1,1-dioxide (17)



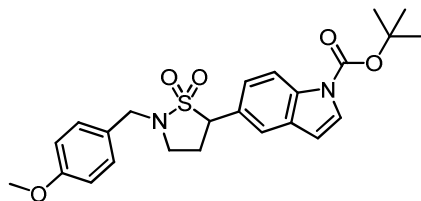
Prepared according to general procedure 2. Yield: 46%. 1H NMR (400 MHz, $CDCl_3$) δ 8.67 – 8.60 (m, 1H), 7.78 – 7.70 (m, 1H), 7.53 – 7.47 (m, 1H), 7.32 – 7.24 (m, 3H), 6.92 – 6.83 (m, 2H), 4.55 (t, $J = 8.0$ Hz, 1H), 4.19 (s, 2H), 3.80 (s, 3H), 3.38 – 3.28 (m, 1H), 3.23 – 3.12 (m, 1H), 3.04 – 2.92 (m, 1H), 2.69 – 2.54 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.31, 151.65, 149.78, 136.79, 129.91, 127.56, 124.61, 123.66, 114.01, 63.53, 55.31, 48.43, 44.15, 23.56; HRMS calcd for $C_{16}H_{18}N_2O_3S [M+H]^+$ 319.1111, found 319.1113.

2-(4-Methoxybenzyl)-5-(pyridin-3-yl)isothiazolidine 1,1-dioxide (18)



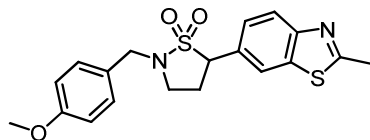
Prepared according to general procedure 2. Yield: 26%. ^1H NMR (400 MHz, CDCl_3) δ 8.68 – 8.60 (m, 2H), 7.83 (dt, J = 8.0, 2.0 Hz, 1H), 7.37 (dd, J = 7.9, 4.7 Hz, 1H), 7.32 – 7.27 (m, 2H), 6.93 – 6.87 (m, 2H), 4.36 – 4.26 (m, 2H), 4.17 (d, J = 14.2 Hz, 1H), 3.82 (s, 3H), 3.29 – 3.21 (m, 1H), 3.20 – 3.12 (m, 1H), 2.70 – 2.60 (m, 1H), 2.60 – 2.48 (m, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 159.50, 150.40, 150.19, 136.39, 130.04, 127.92, 127.06, 123.72, 114.17, 60.02, 55.33, 48.17, 43.45, 25.68; HRMS calcd for $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$ 319.1111, 319.1112.

Tert-butyl 5-(2-(4-methoxybenzyl)-1,1-dioxidoisothiazolidin-5-yl)-1H-indole-1-carboxylate (19)



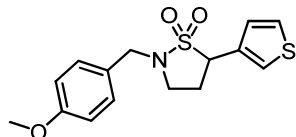
Prepared according to general procedure 2. Yield: 40%. ^1H NMR (400 MHz, CDCl_3) δ 8.17 (d, J = 8.7 Hz, 1H), 7.65 – 7.59 (m, 2H), 7.38 (dd, J = 8.7, 1.9 Hz, 1H), 7.33 – 7.26 (m, 2H), 6.93 – 6.86 (m, 2H), 6.57 (d, J = 3.8 Hz, 1H), 4.44 (t, J = 9.2 Hz, 1H), 4.29 (d, J = 14.2 Hz, 1H), 4.16 (d, J = 14.2 Hz, 1H), 3.82 (s, 3H), 3.28 – 3.18 (m, 1H), 3.18 – 3.09 (m, 1H), 2.69 – 2.57 (m, 2H), 1.67 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 159.38, 149.57, 135.50, 130.95, 130.05, 127.51, 126.80, 125.51, 124.90, 121.57, 115.60, 114.08, 107.25, 84.02, 62.63, 55.32, 48.19, 43.62, 28.18, 25.74; HRMS calcd for $\text{C}_{24}\text{H}_{28}\text{N}_2\text{O}_5\text{S}$ $[\text{M}+\text{Na}]^+$ 479.1611, found 479.1603.

2-(4-Methoxybenzyl)-5-(2-methylbenzo[d]thiazol-6-yl)isothiazolidine 1,1-dioxide (20)



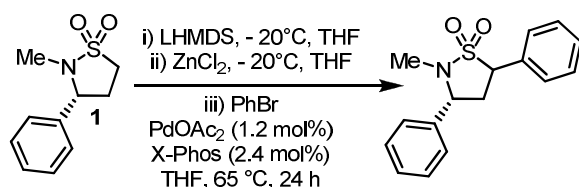
Prepared according to general procedure 2. Yield: 19%. ^1H NMR (400 MHz, CDCl_3) δ 7.97 (d, J = 8.5 Hz, 1H), 7.91 (d, J = 1.9 Hz, 1H), 7.51 (dd, J = 8.3, 2.0 Hz, 1H), 7.34 – 7.28 (m, 2H), 6.94 – 6.87 (m, 2H), 4.45 (dd, J = 10.1, 8.3 Hz, 1H), 4.30 (d, J = 14.2 Hz, 1H), 4.17 (d, J = 14.2 Hz, 1H), 3.85 – 3.80 (m, 3H), 3.29 – 3.21 (m, 1H), 3.21 – 3.11 (m, 1H), 2.85 (s, 3H), 2.72 – 2.55 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 168.37, 159.44, 153.89, 136.31, 130.07, 128.07, 127.28, 126.88, 122.67, 122.00, 114.13, 62.36, 55.32, 48.18, 43.47, 25.85, 20.23; HRMS calcd for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_3\text{S}_2$ $[\text{M}+\text{H}]^+$ 389.0988, found 389.0984.

2-(4-Methoxybenzyl)-5-(thiophen-3-yl)isothiazolidine 1,1-dioxide (21)



Prepared according to general procedure 2. Yield: 42%. ^1H NMR (400 MHz, Chloroform- d) δ 7.40 – 7.35 (m, 2H), 7.30 – 7.24 (m, 2H), 7.23 – 7.17 (m, 1H), 6.93 – 6.84 (m, 2H), 4.44 (dd, J = 10.4, 7.9 Hz, 1H), 4.24 (d, J = 14.2 Hz, 1H), 4.17 (d, J = 14.2 Hz, 1H), 3.81 (s, 3H), 3.23 – 3.06 (m, 2H), 2.69 – 2.45 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 159.39, 131.77, 130.00, 127.36, 127.25, 126.65, 125.11, 114.09, 58.05, 55.32, 48.18, 43.50, 25.84; HRMS calcd for $\text{C}_{15}\text{H}_{17}\text{NO}_3\text{S}_2$ $[\text{M}+\text{Na}]^+$ 346.0542, found 346.0552.

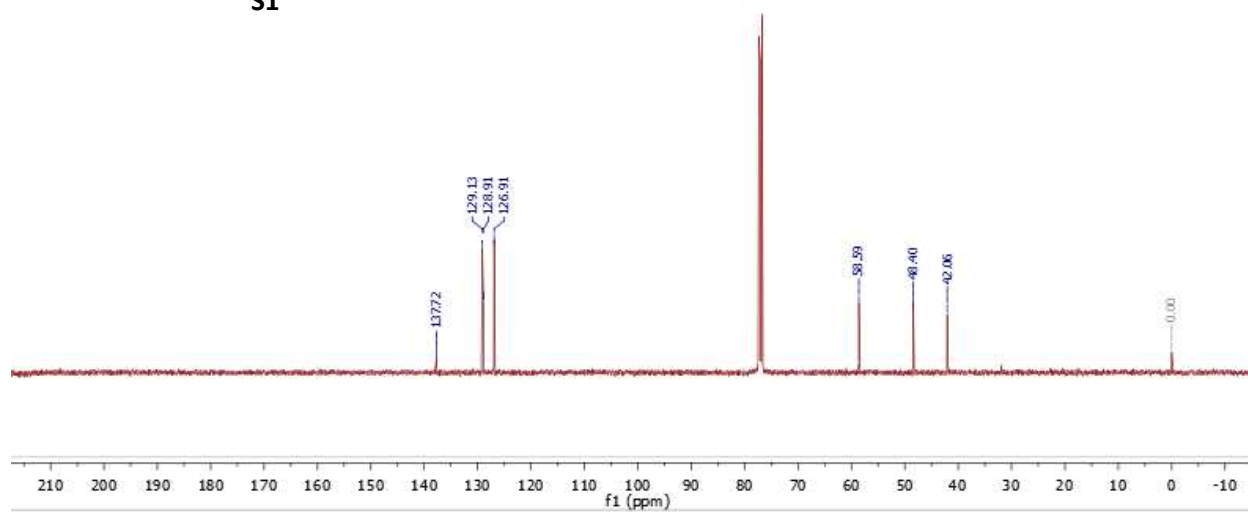
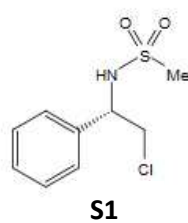
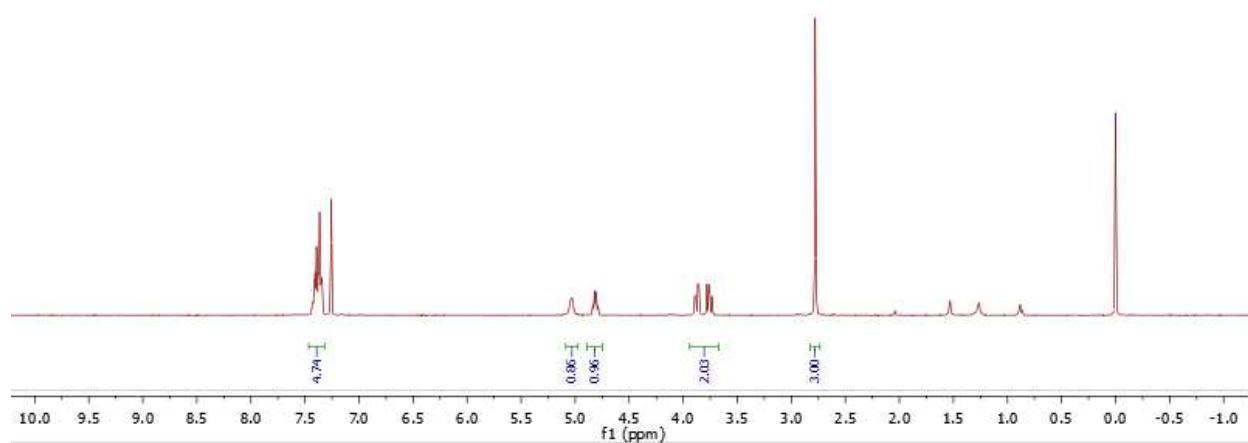
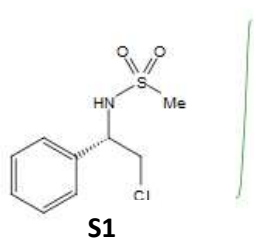
D. Arylation of sultam **1 using previously reported 3-step arylation process for acyclic sulfonamides³**

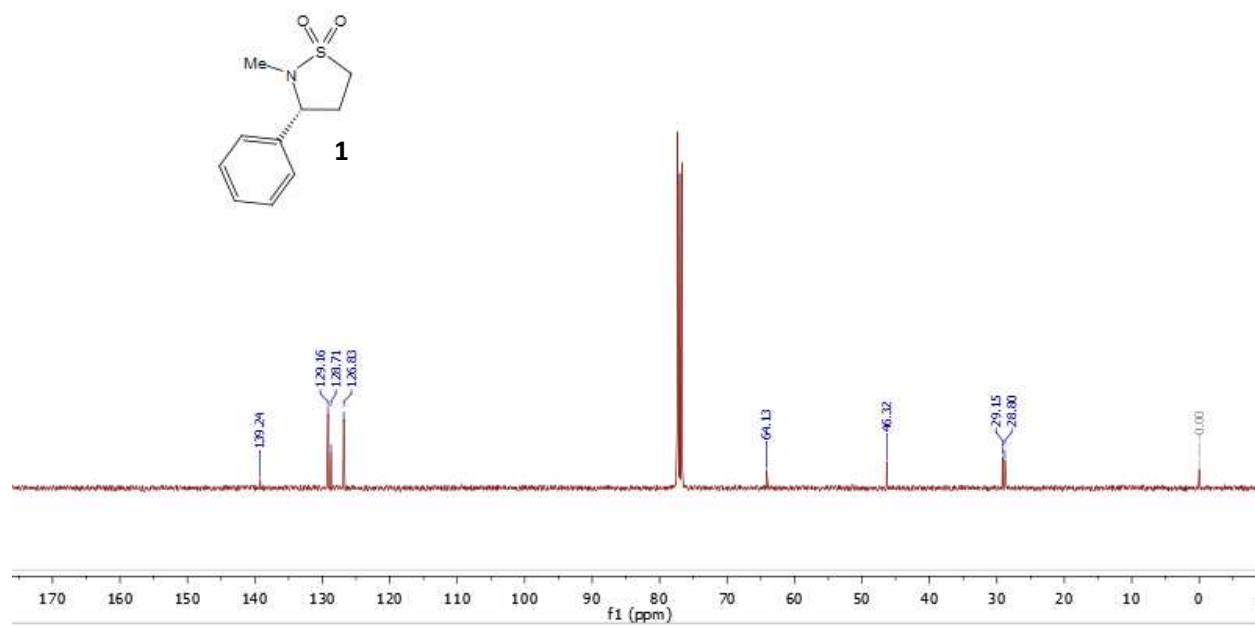
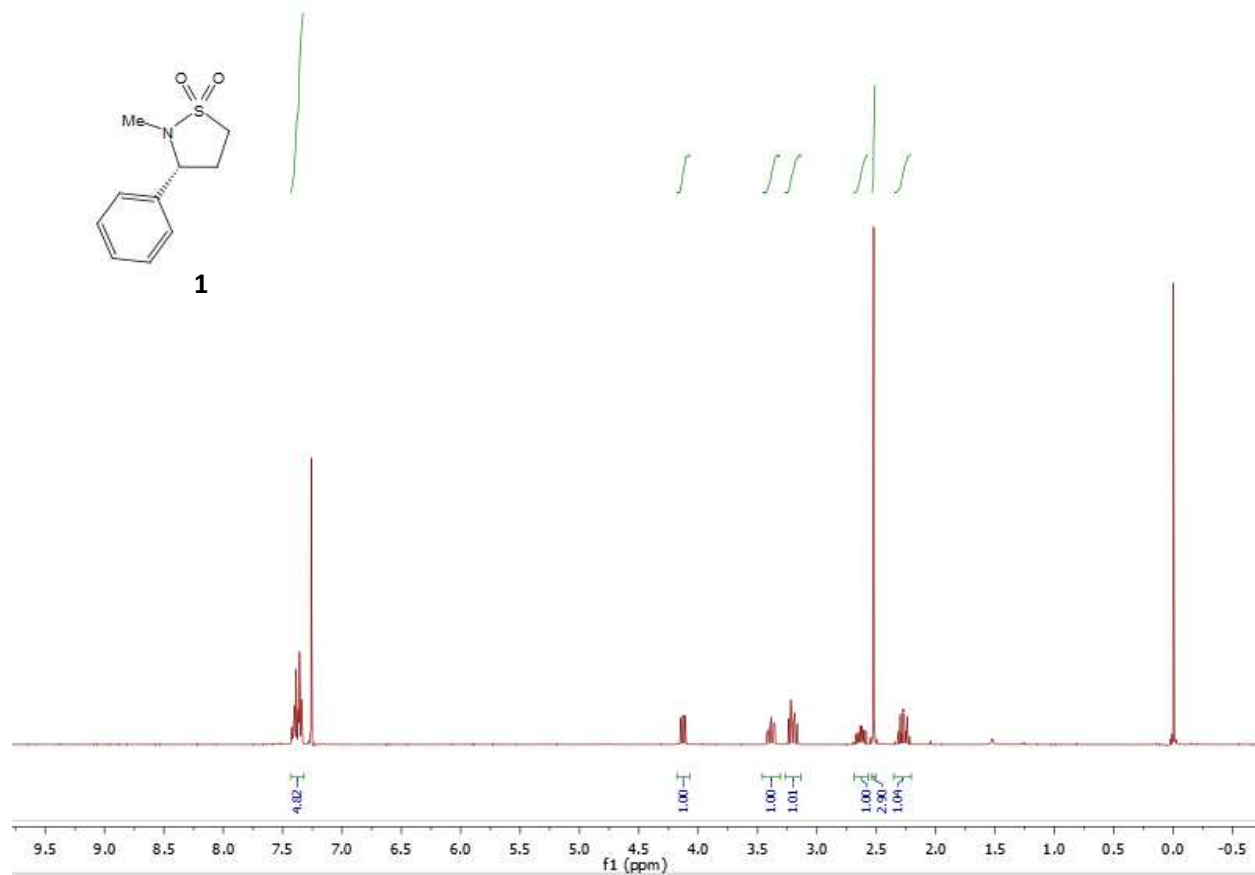


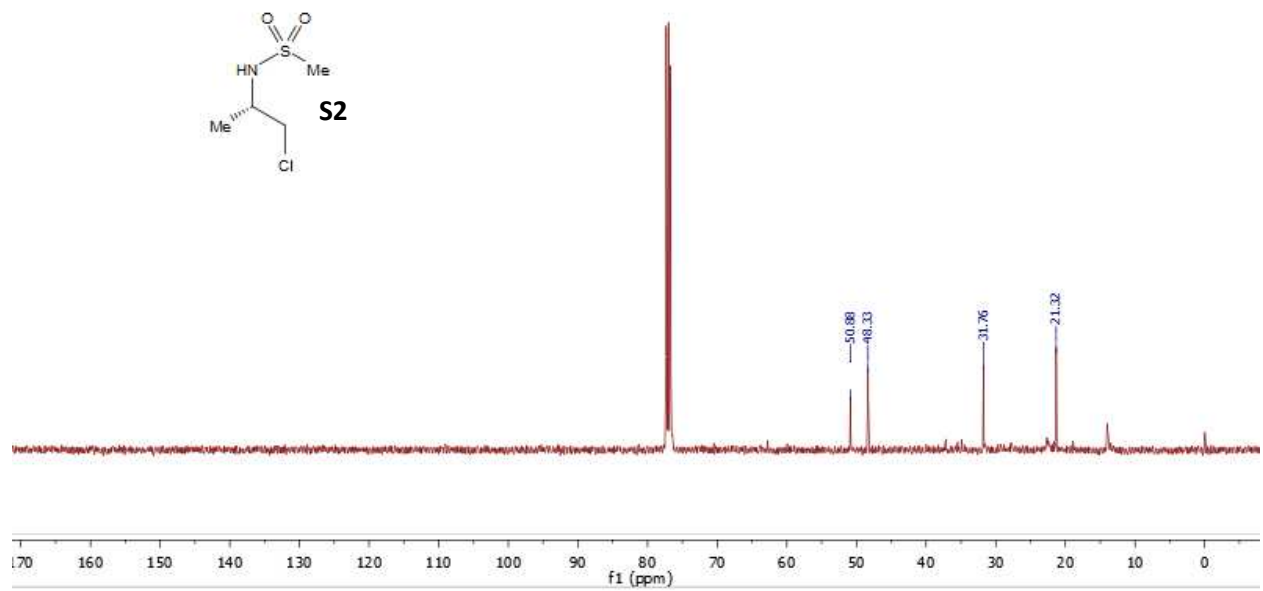
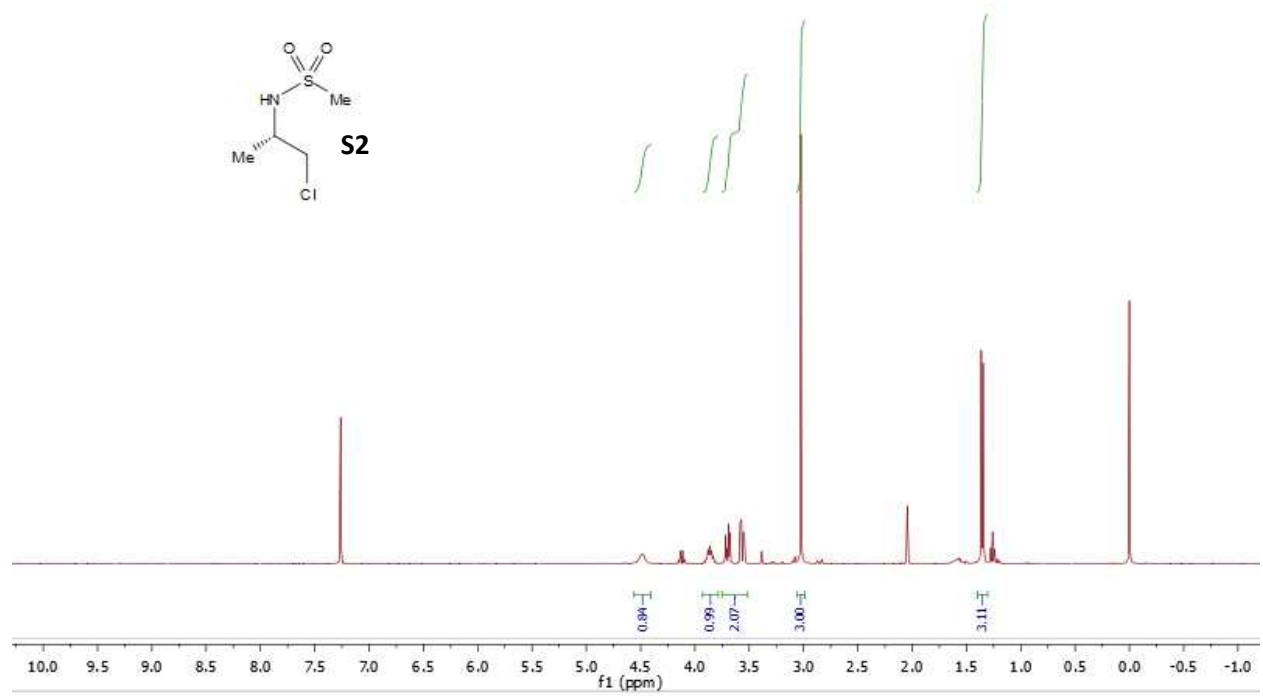
(3*R*)-2-Methyl-3,5-diphenylisothiazolidine 1,1-dioxide

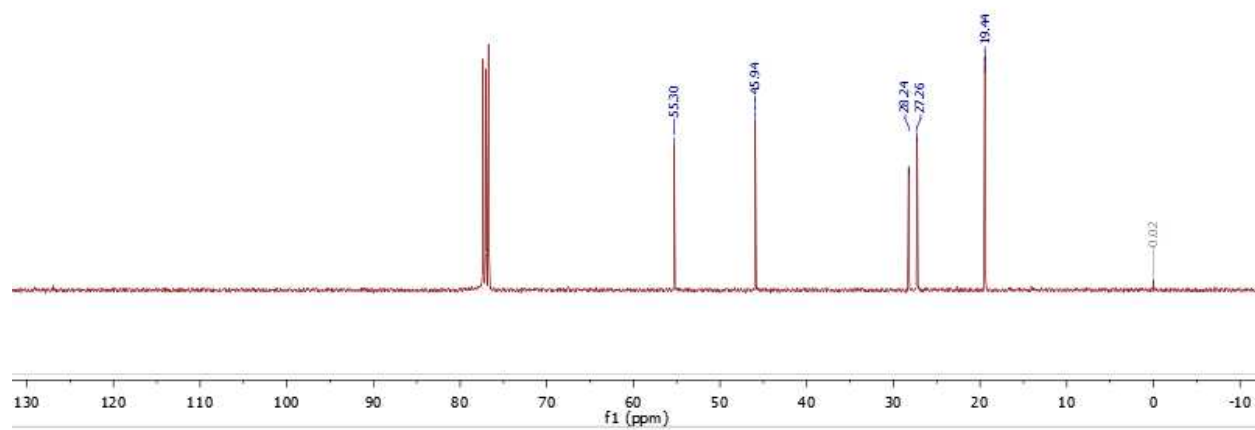
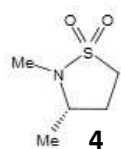
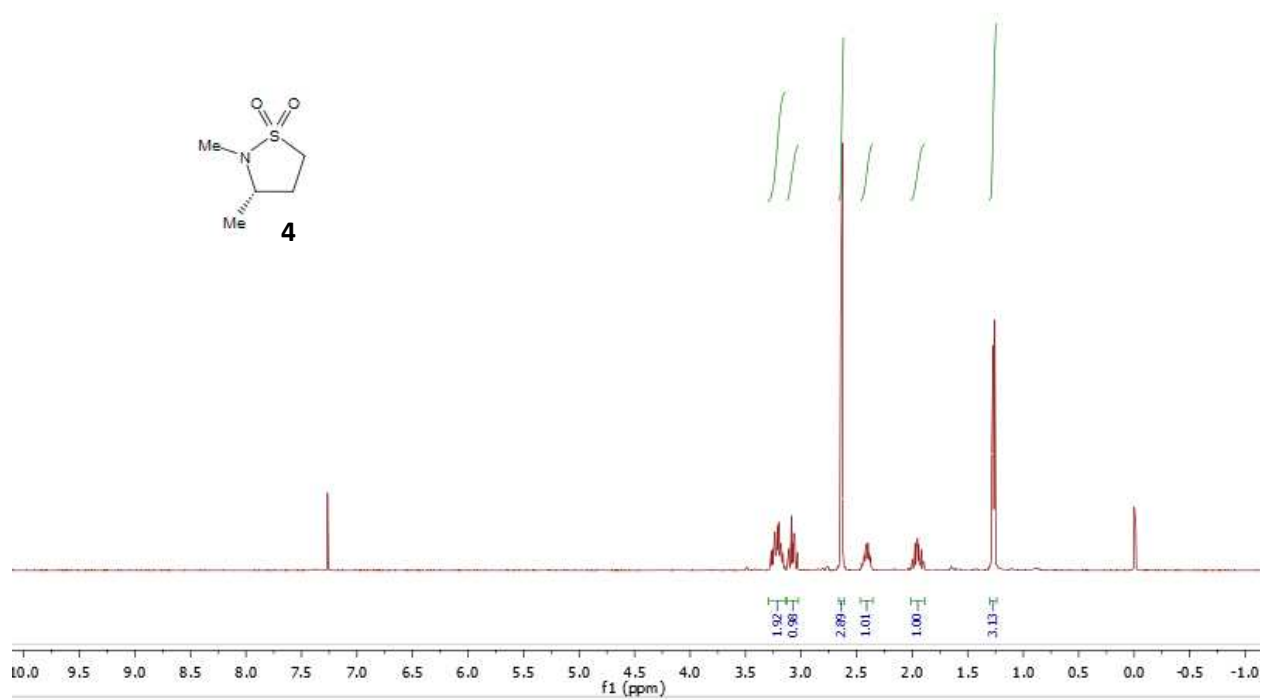
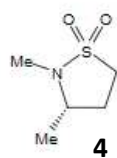
A vial containing (3*R*)-2-methyl-3-phenyl-1,2-thiazolidine 1,1-dioxide (90 mg, 0.42 mmol,) was purged with nitrogen. To the vial was added tetrahydrofuran (2 mL) at -20 °C, followed by lithium bis(trimethylsilyl)amide (0.45 mL of a 1.0 M solution in THF, 0.45 mmol, 1.05 equiv) and the reaction was stirred at that temperature for 60 minutes. ZnCl₂ (1.0 mL of a 0.5M solution in THF, 0.51 mmol, 1.2 equiv) was then added and the reaction was stirred at -20 °C for an additional 60 minutes. In a separate vial, palladium (II) acetate (9.0 mg, 0.042 mmol, 0.10 equiv) and 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (4.1 mg, 0.082 mmol, 0.20 equiv) were weighed out and the vial was purged with nitrogen. To the catalyst-containing vial was added the freshly prepared sultam-zinc solution using a syringe, followed by bromobenzene (80 mg, 0.51 mmol, 1.2 equiv) and the reaction was stirred at 65 °C for 24 hours. The reaction was then quenched by the addition of saturated NH₄Cl in water and extracted with EtOAc (3 X 5 mL). Concentration of the organic layer, followed by silica gel column chromatography afforded 22mg (18%) of product as a 1:1 mixture of *cis* and *trans* diastereomers.

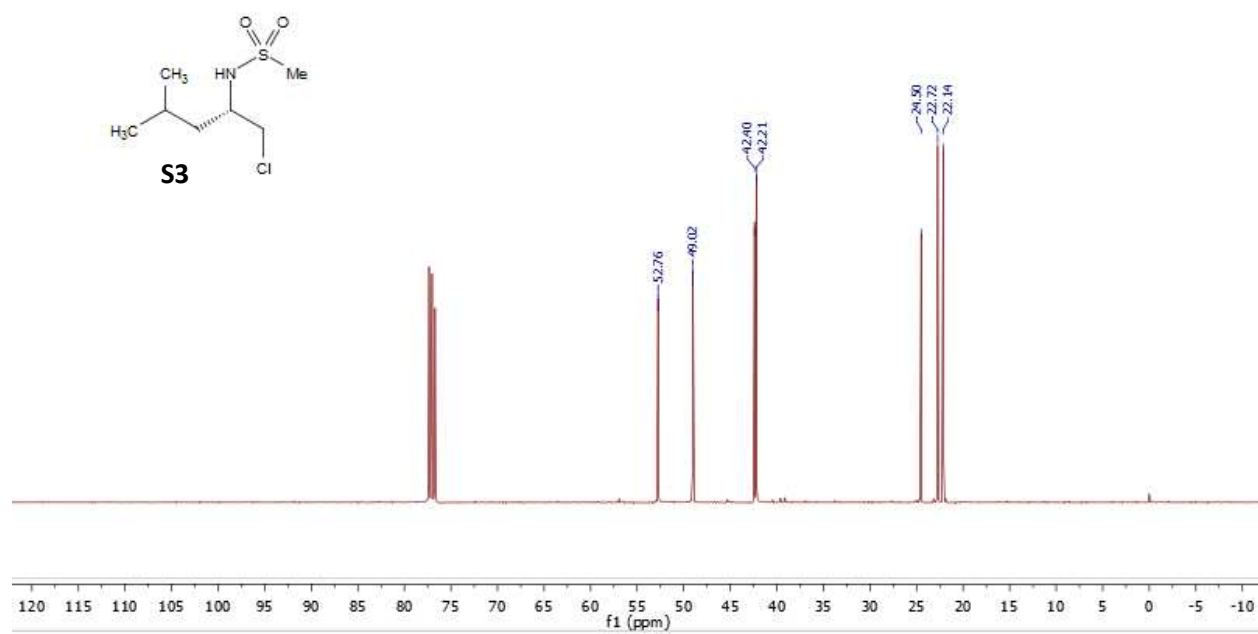
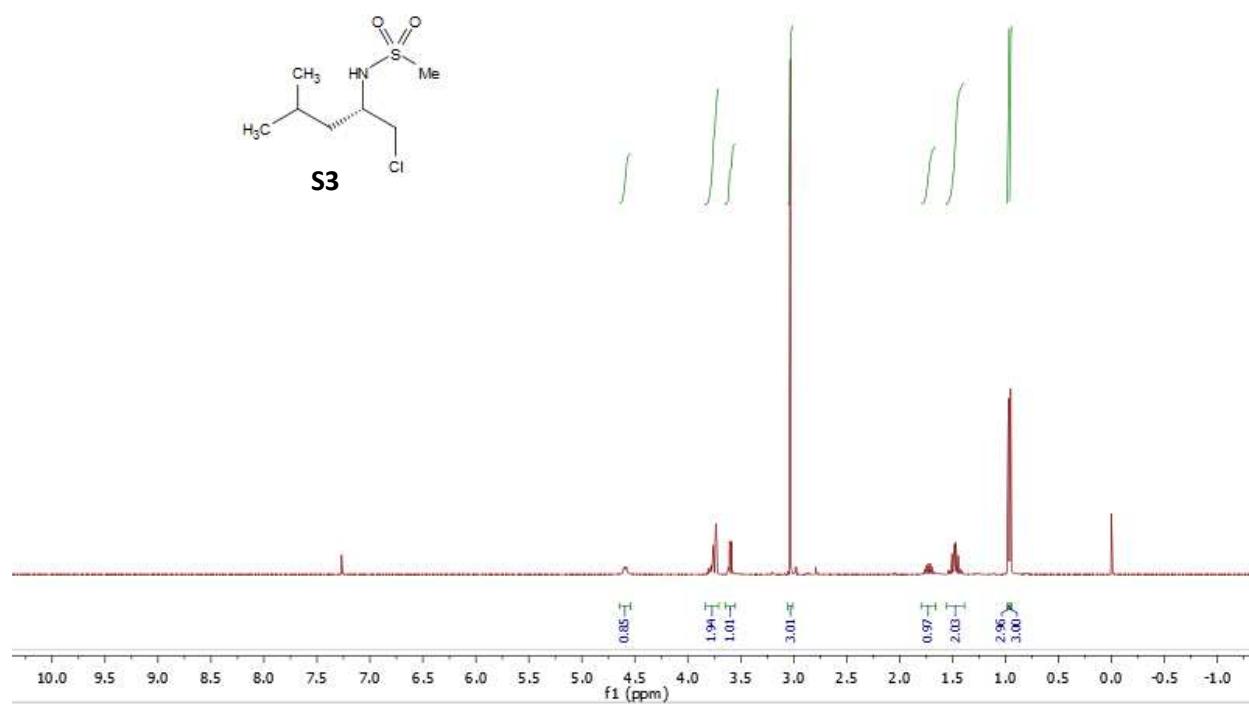
³ Zhou, G.; Ting, P.; Aslanian, R; Piwinski, J. *J. Org. Lett.* **2008**, *10*, 2517.

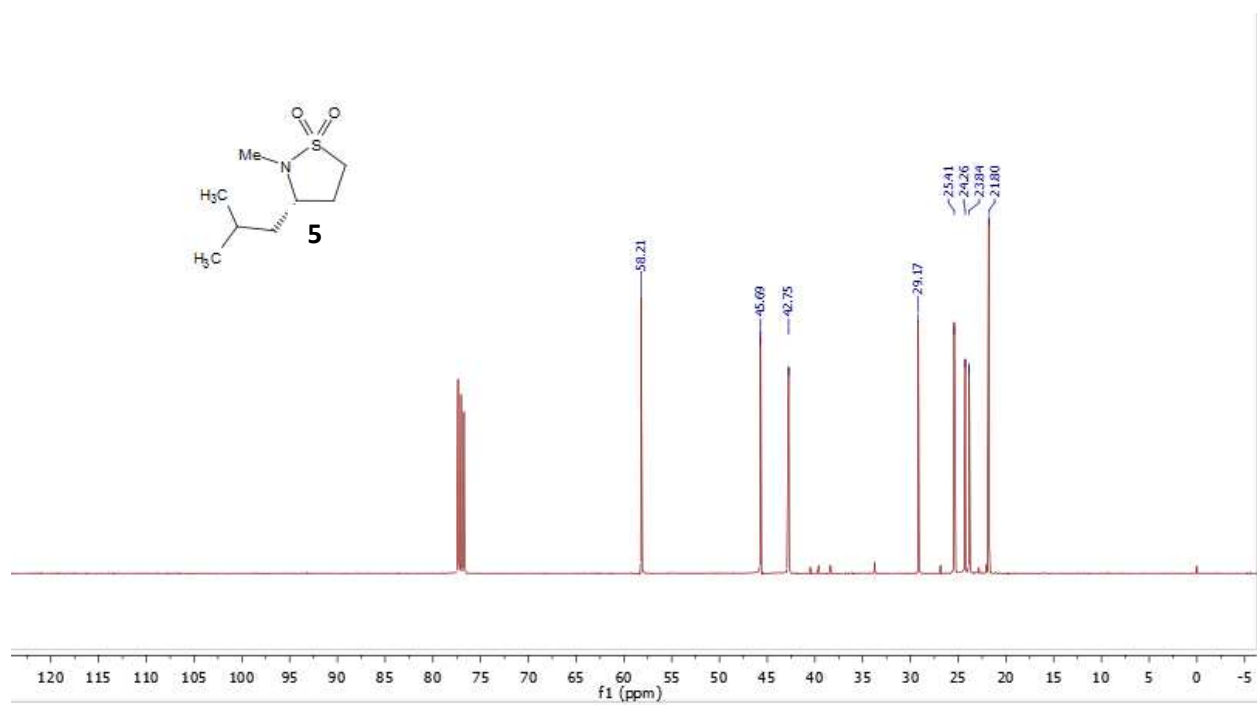
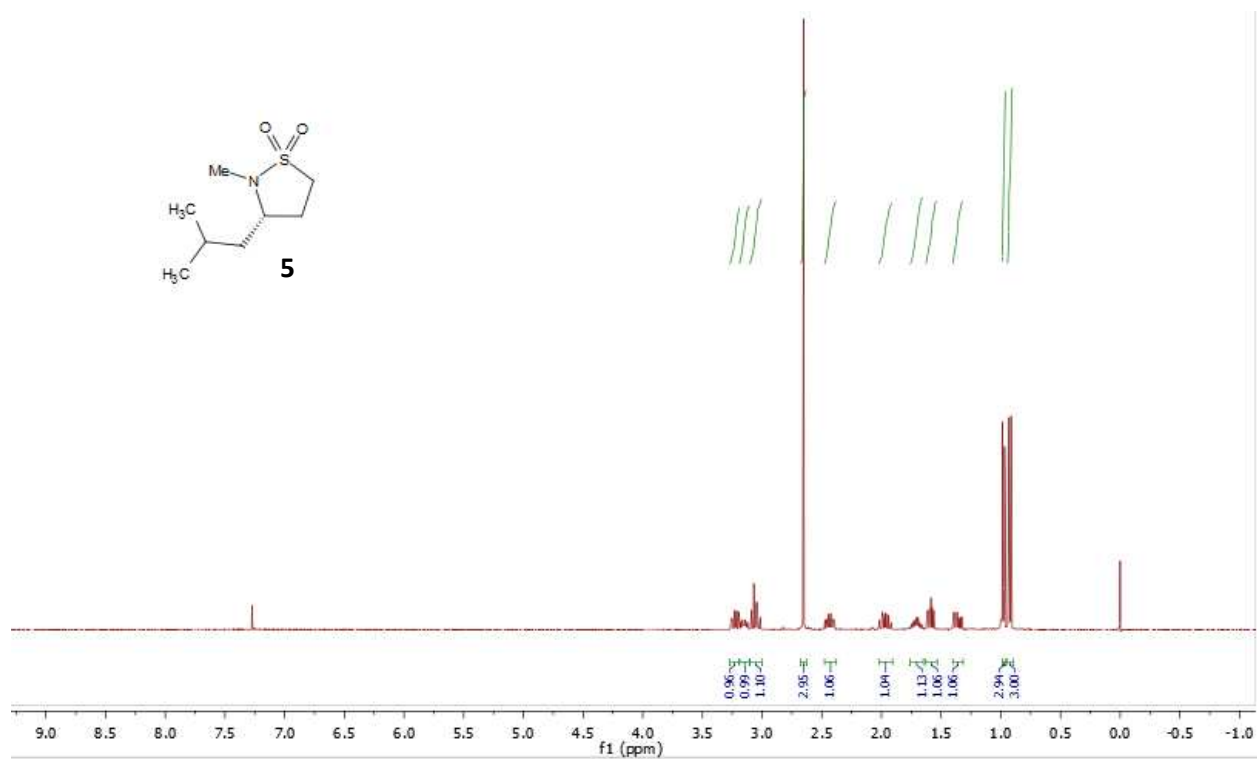


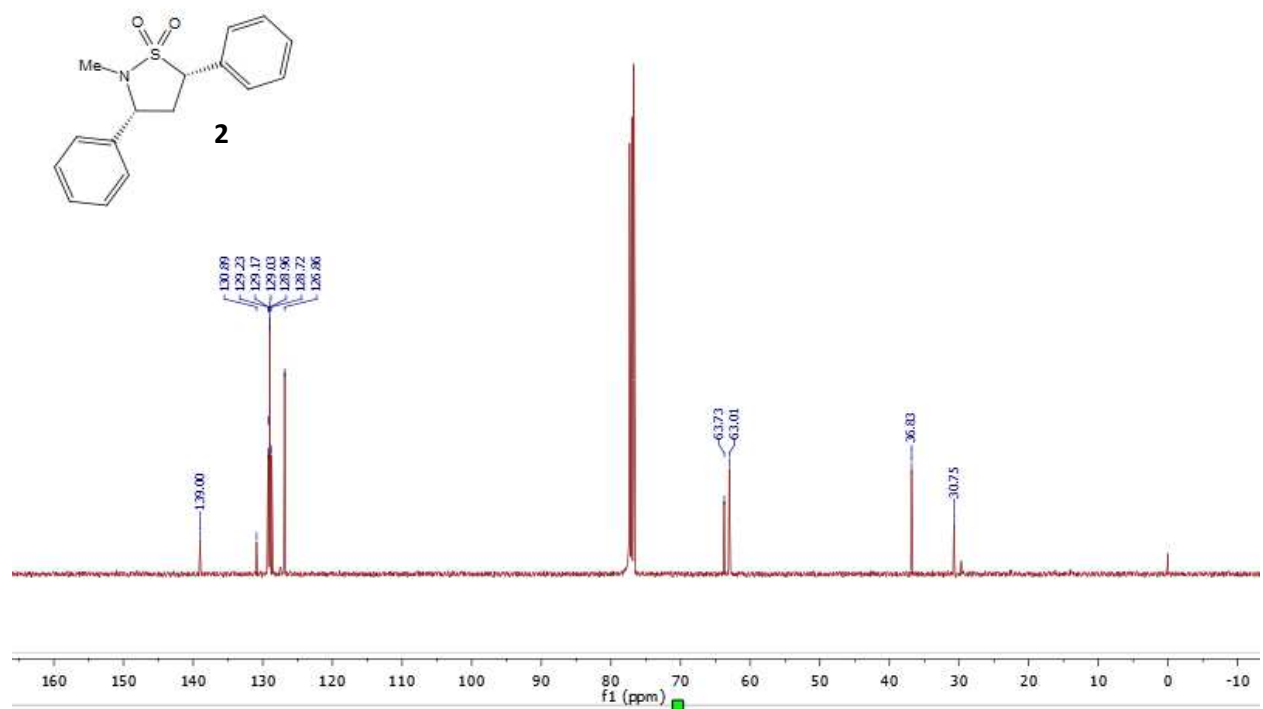
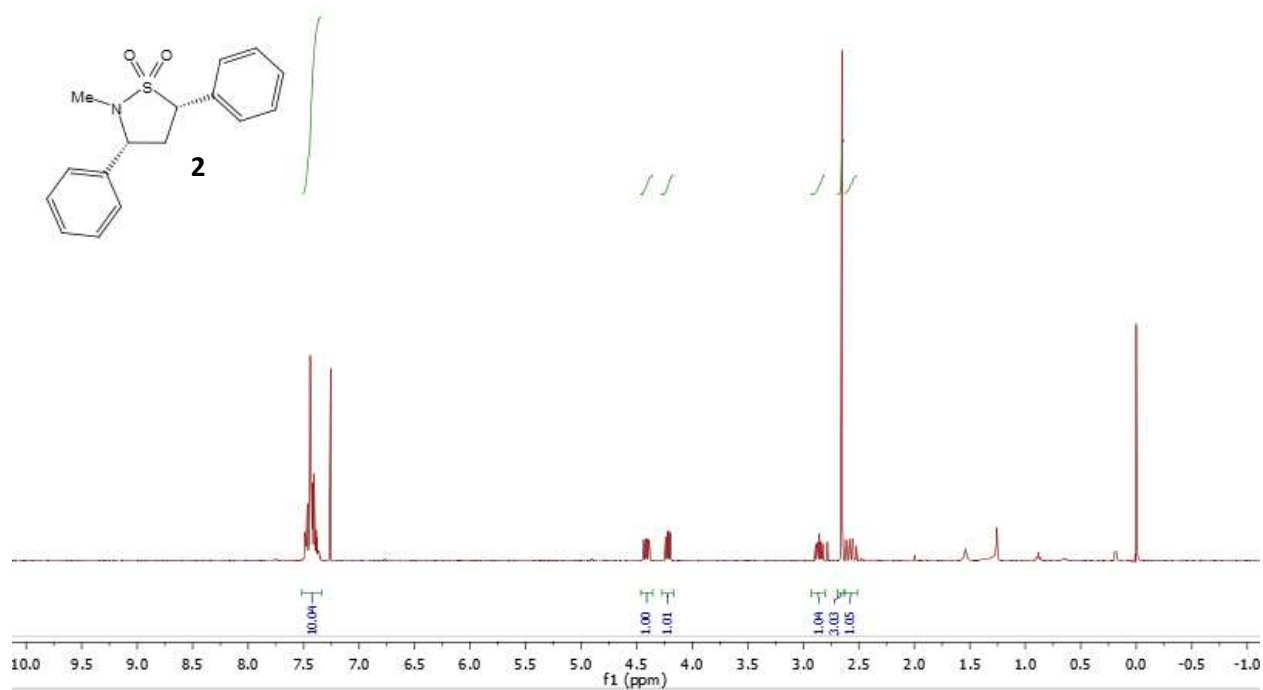


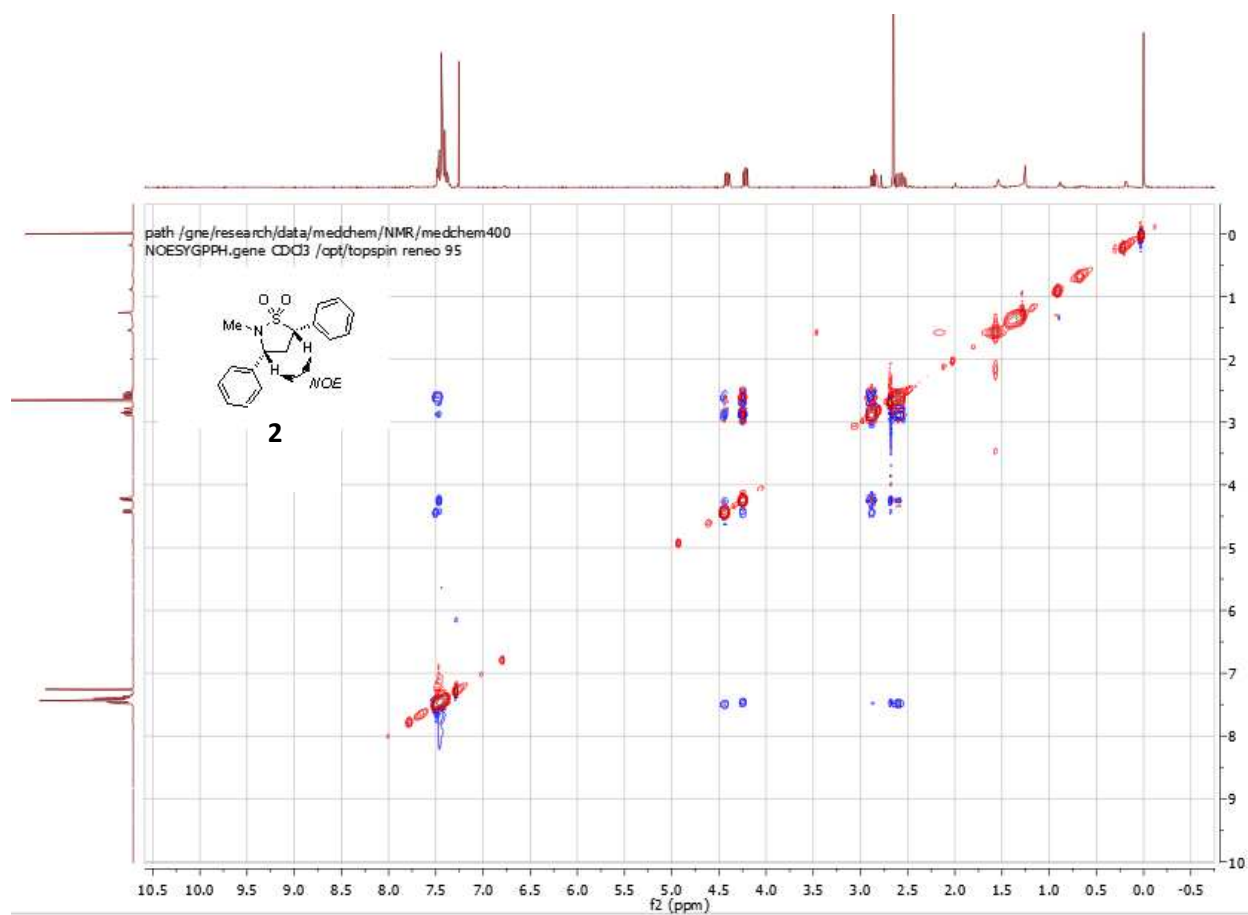


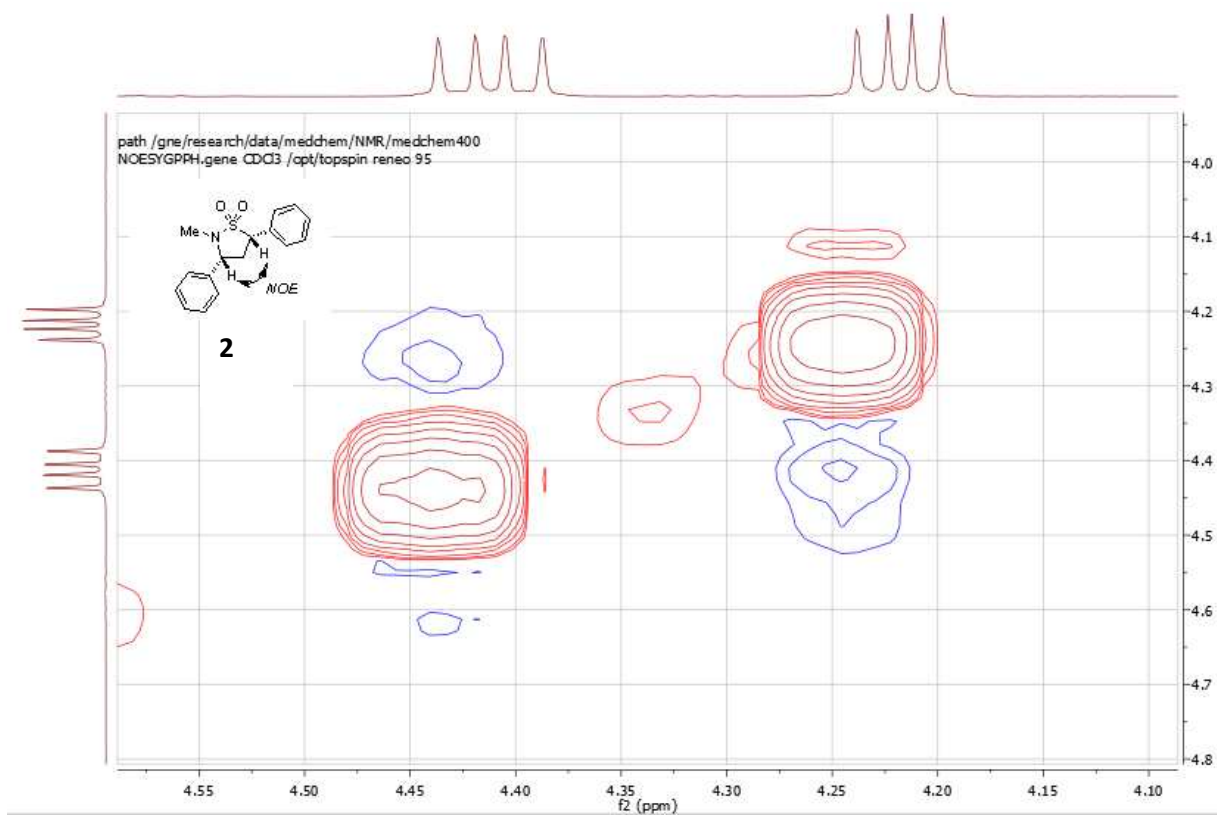


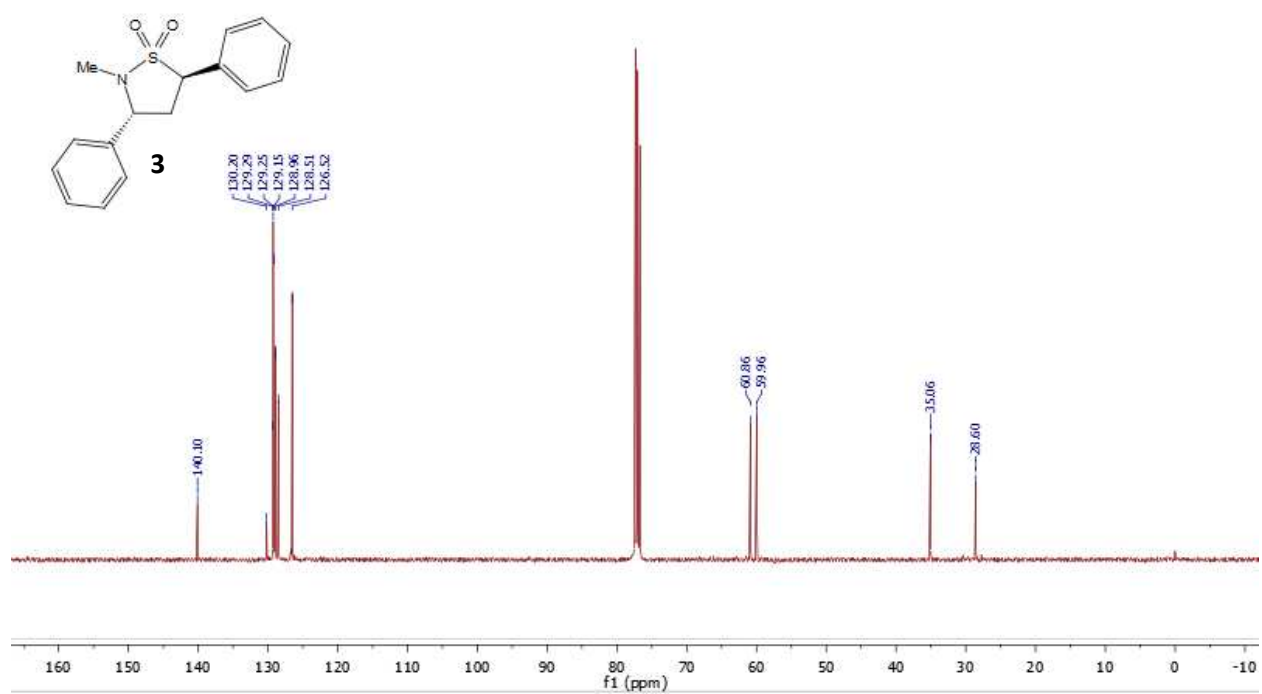
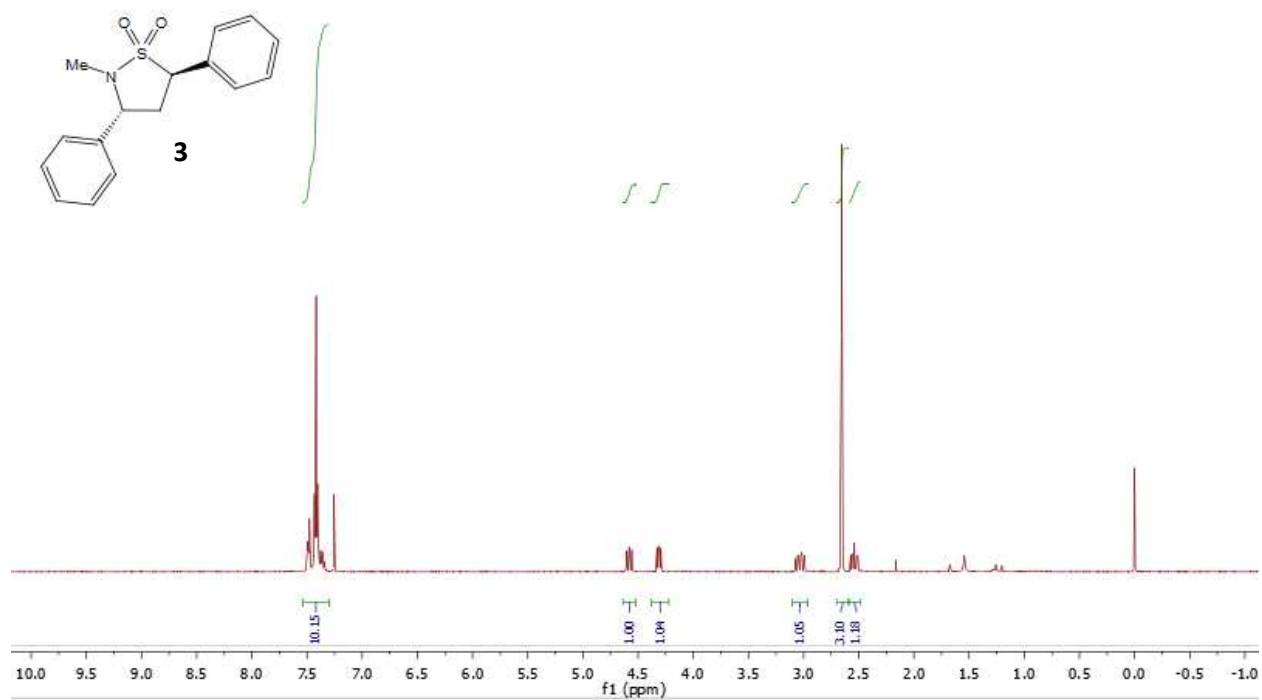


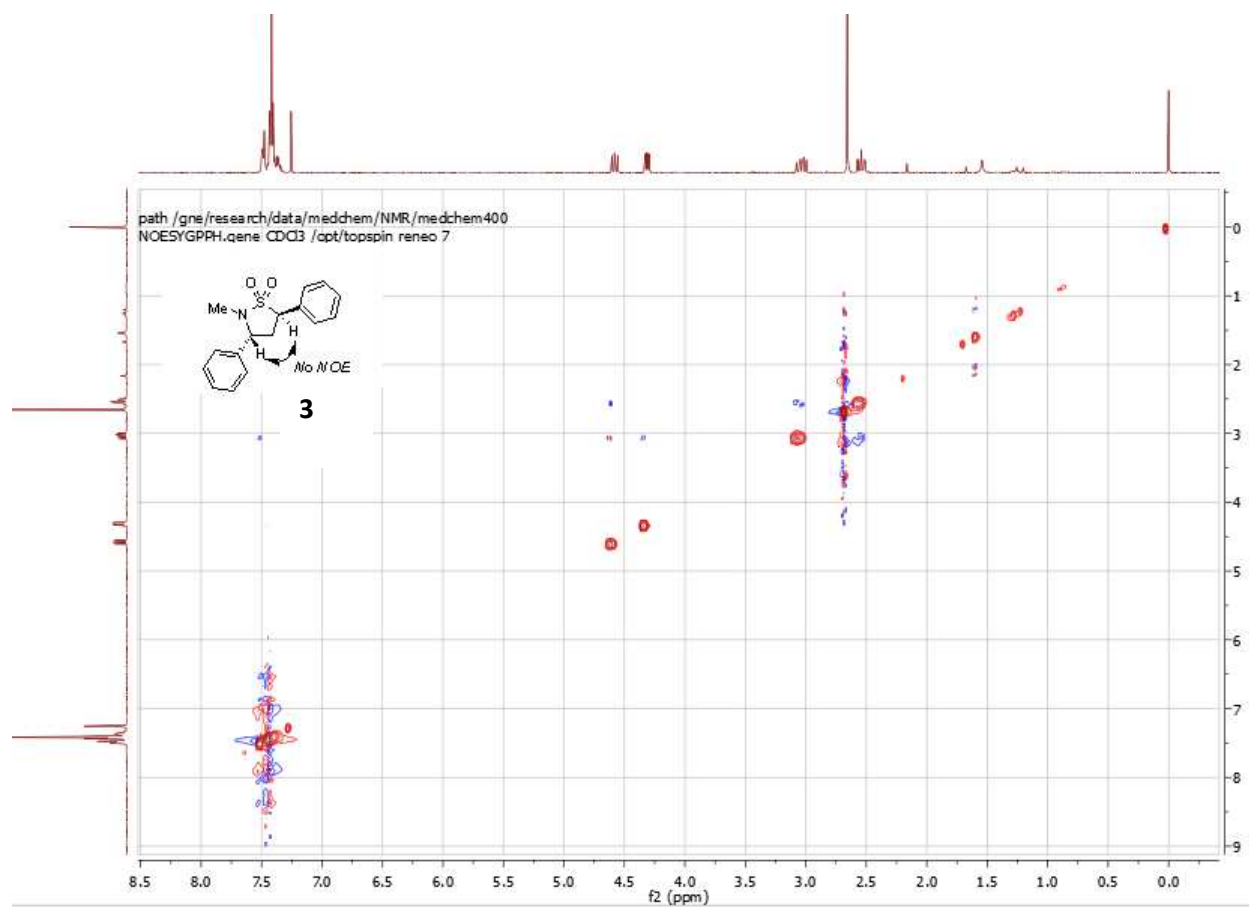


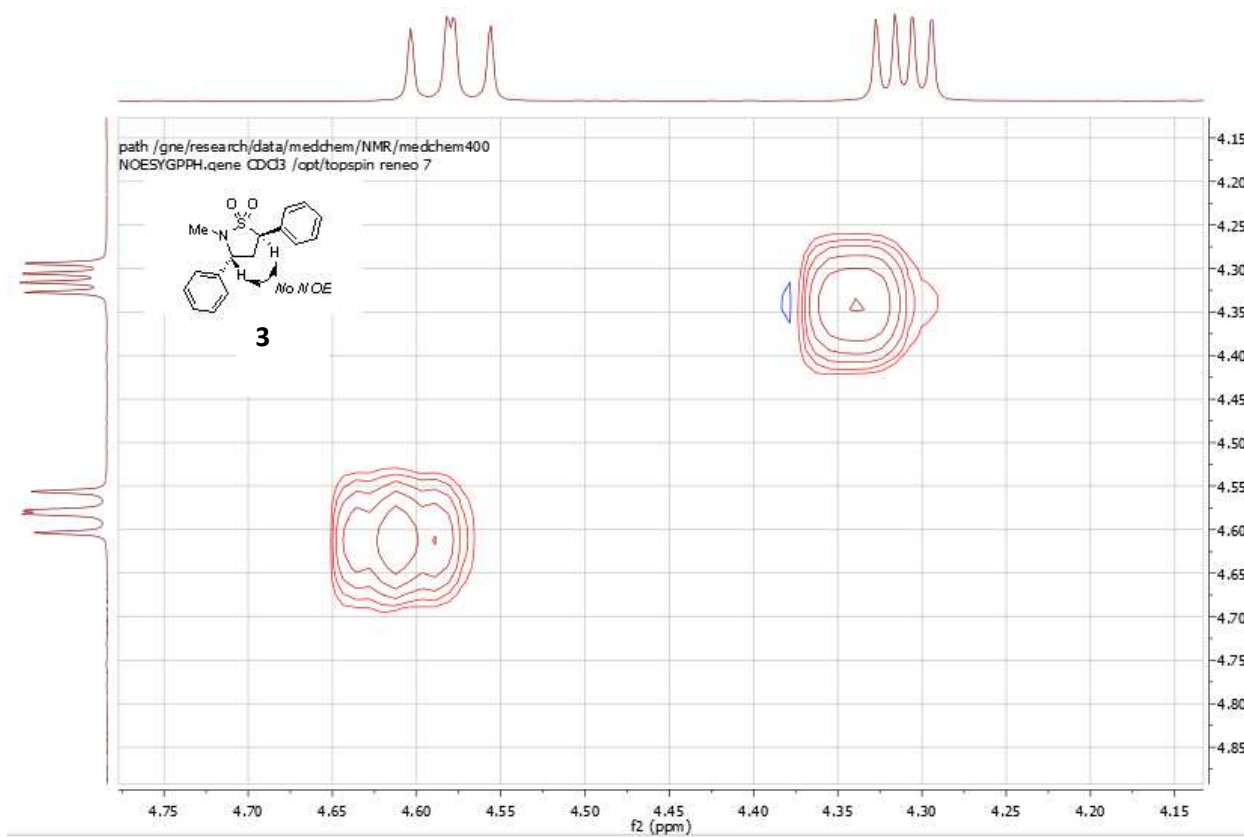


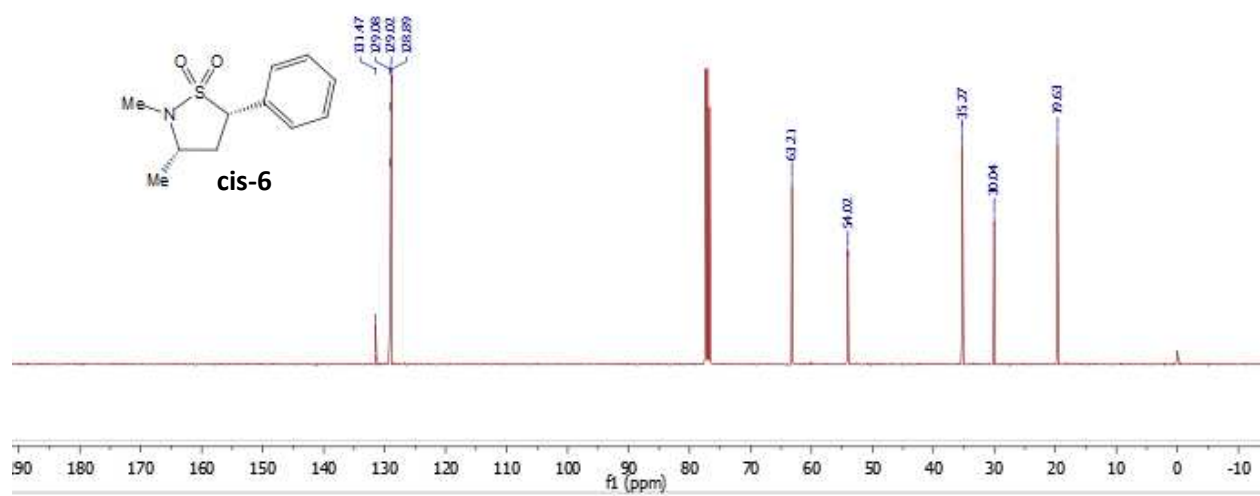
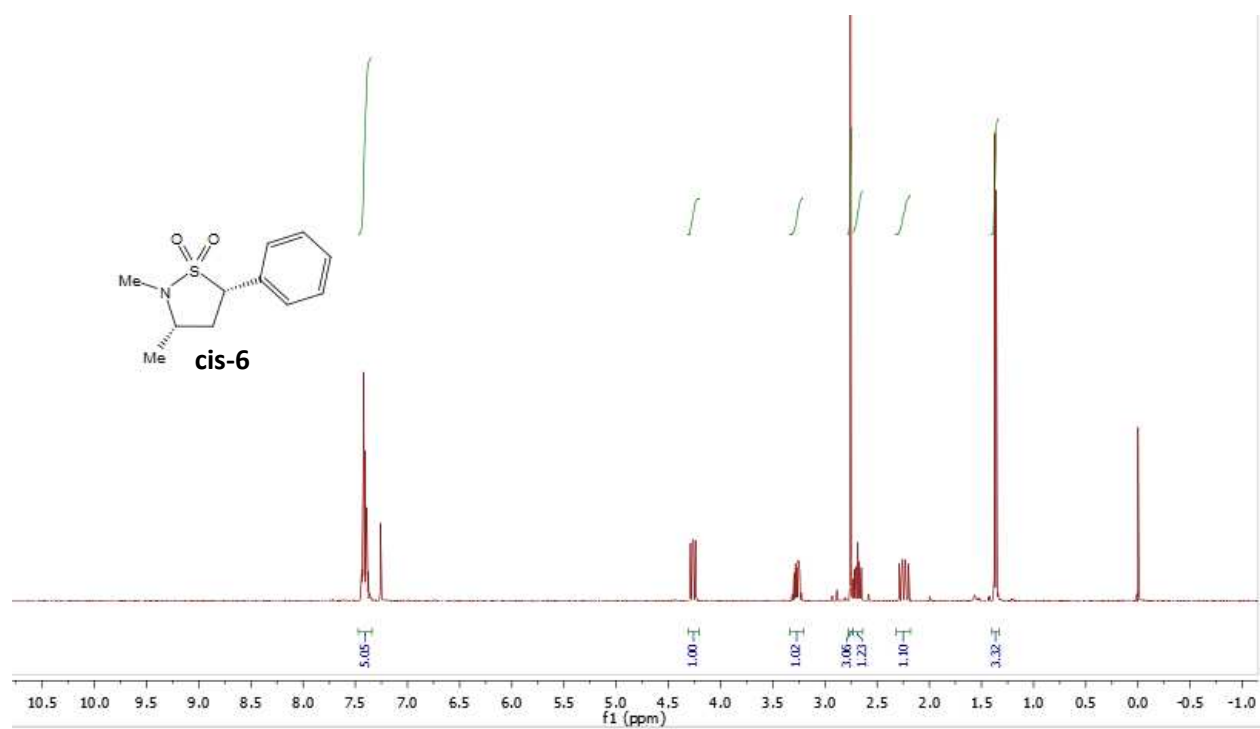


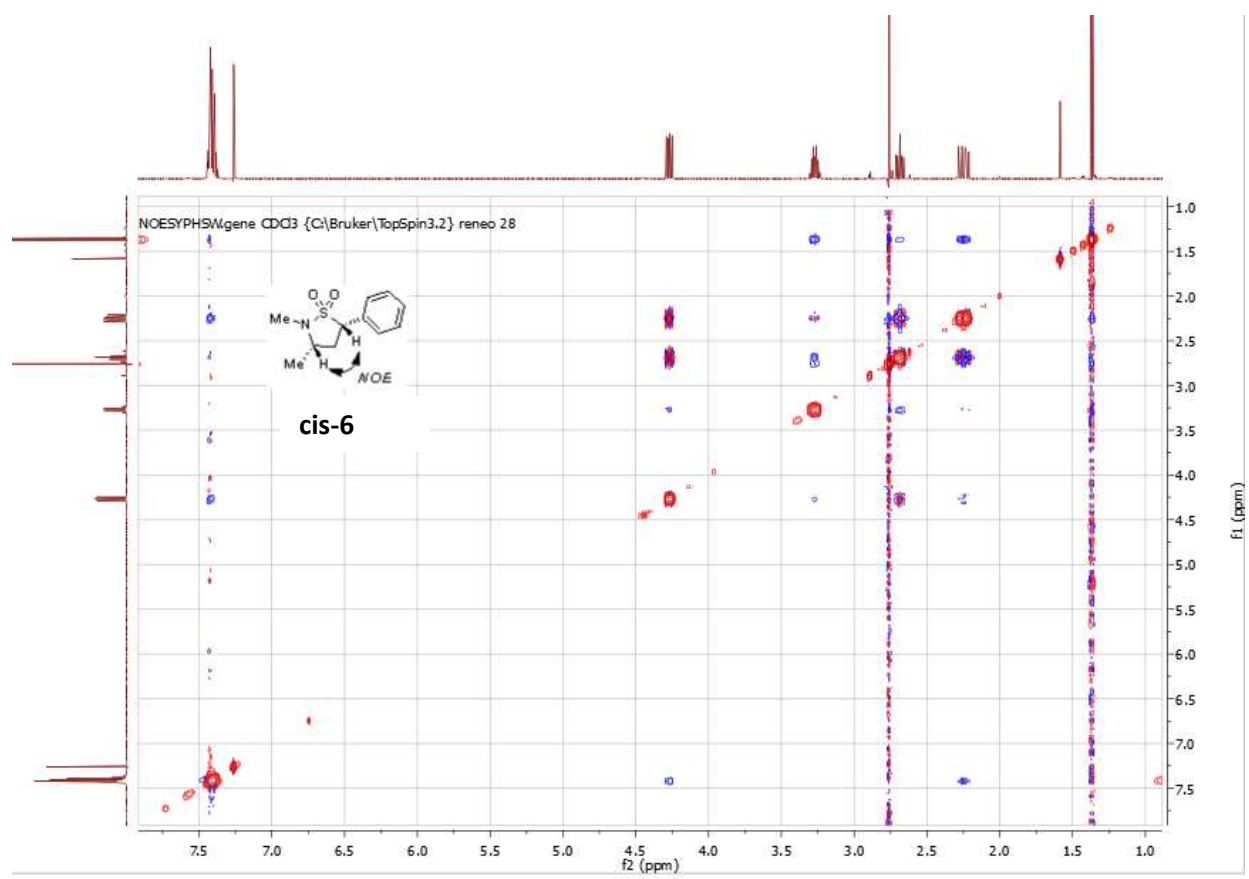


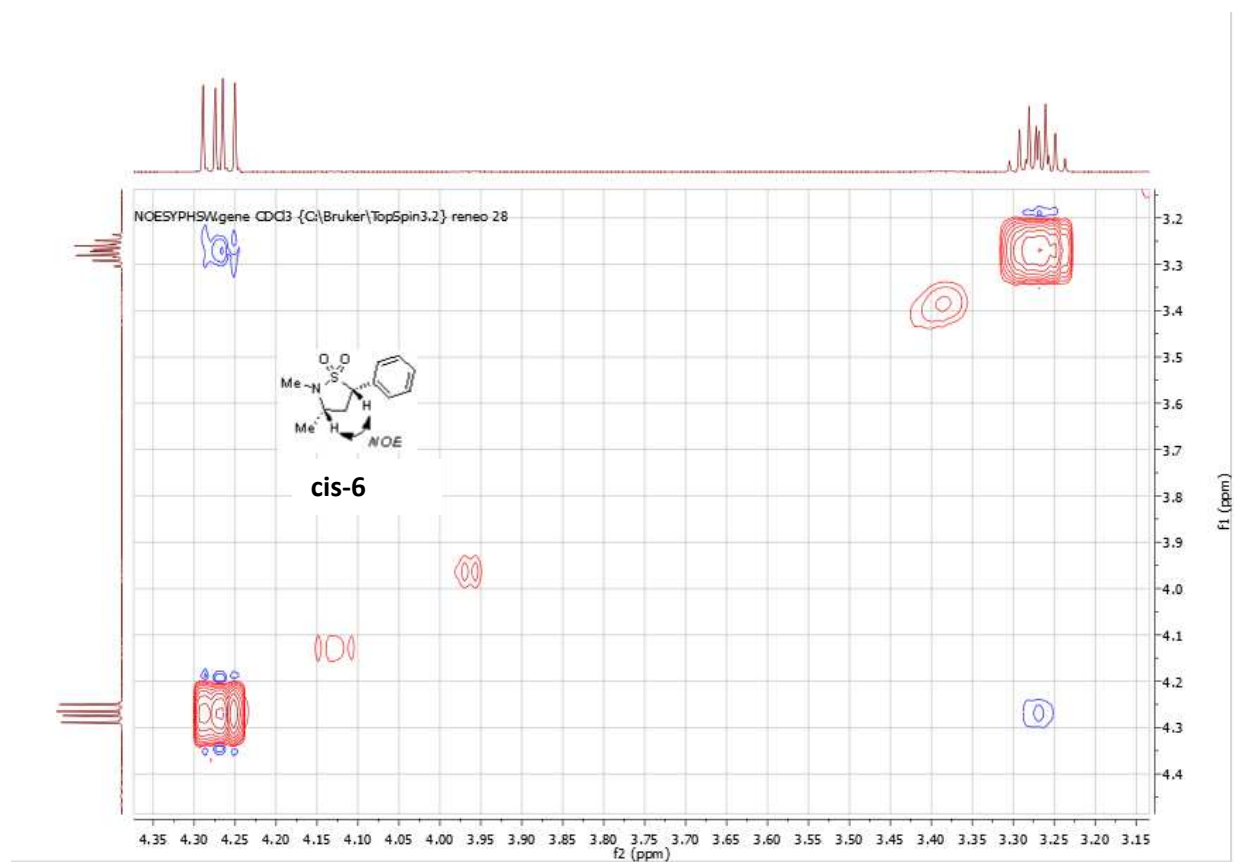


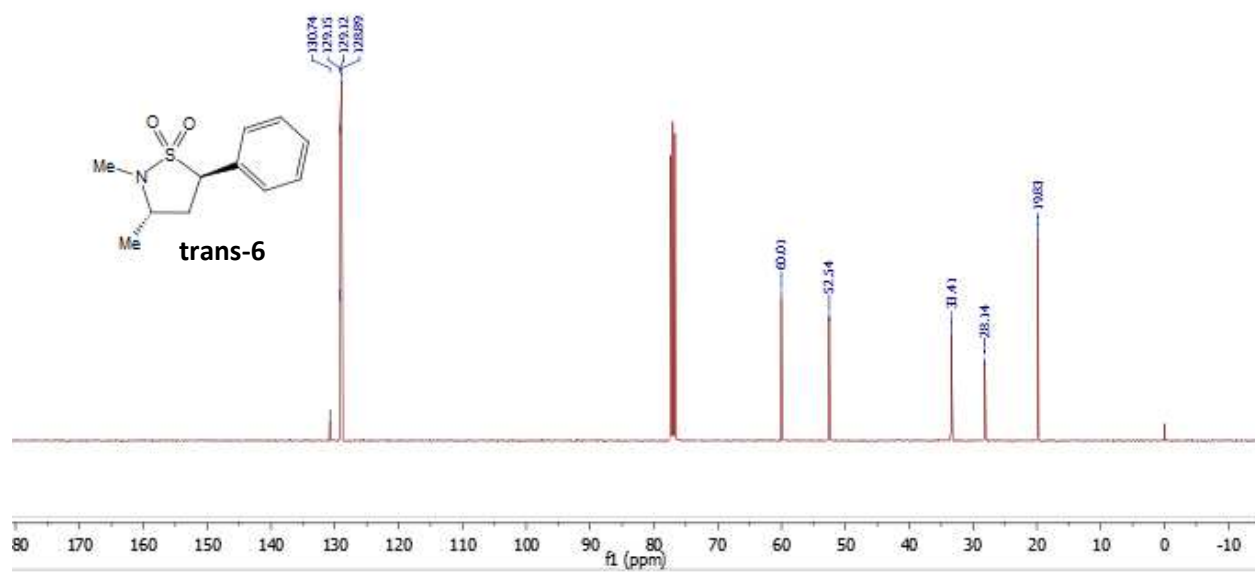
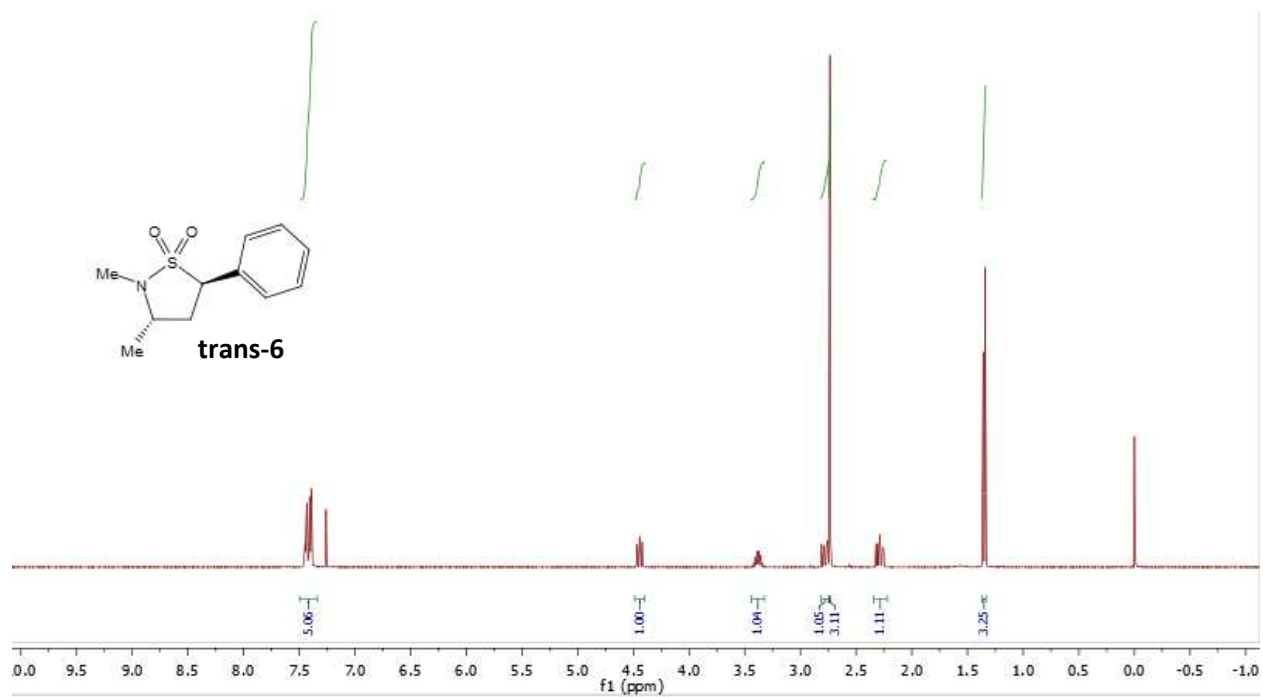


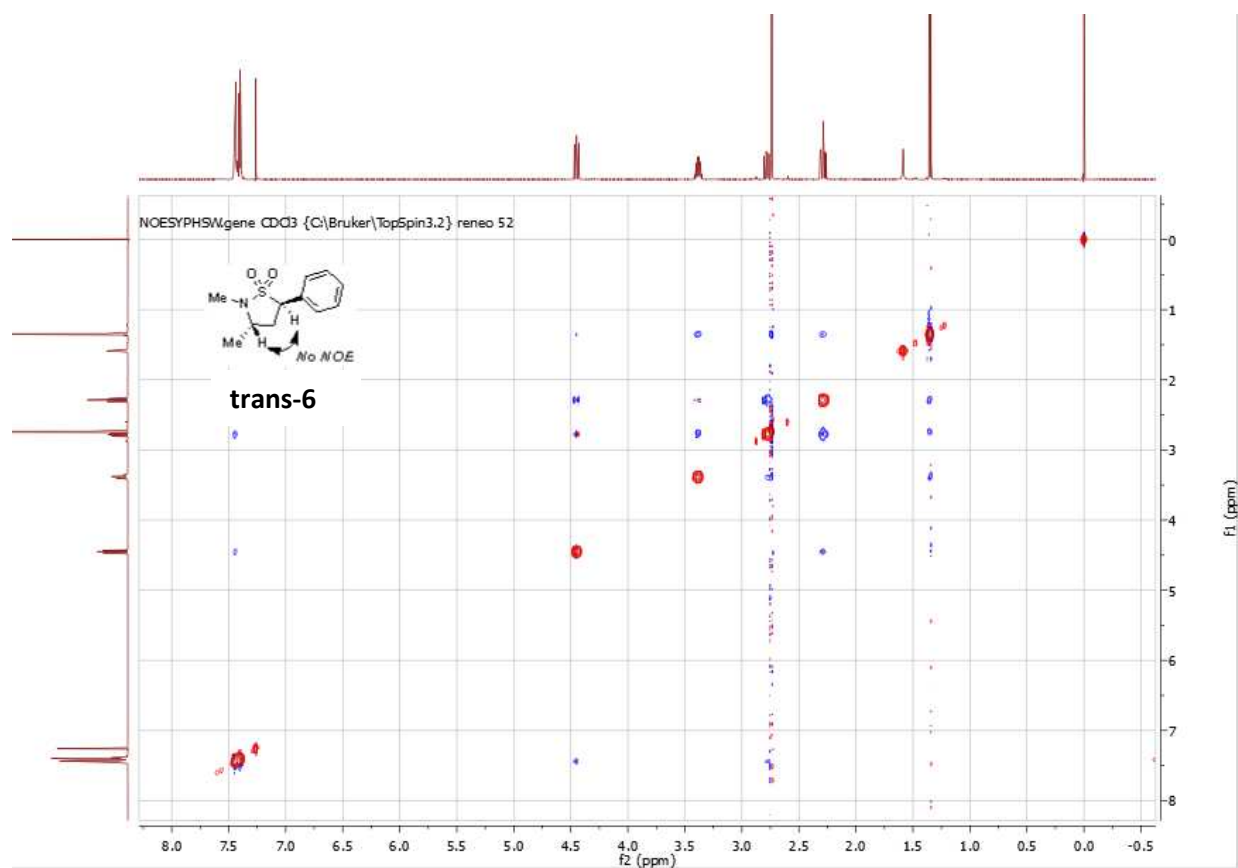




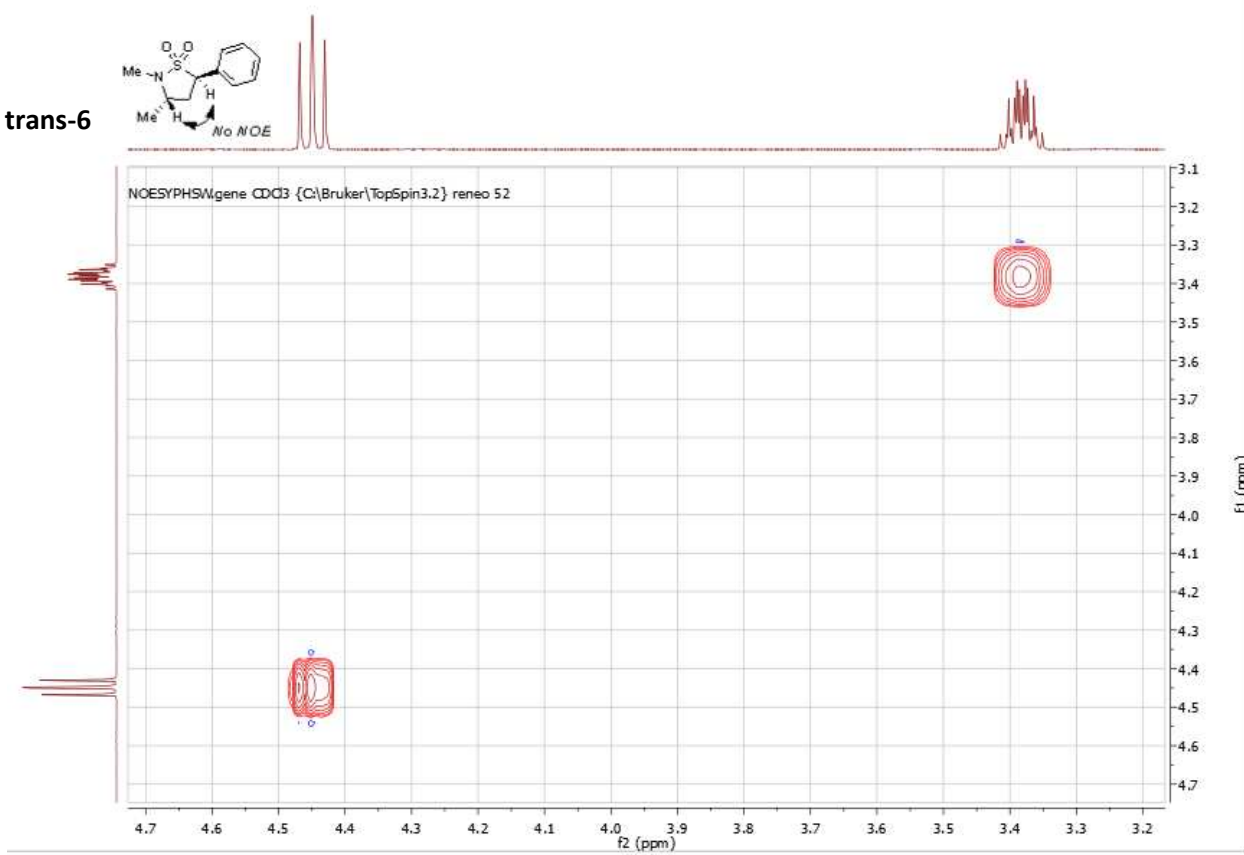


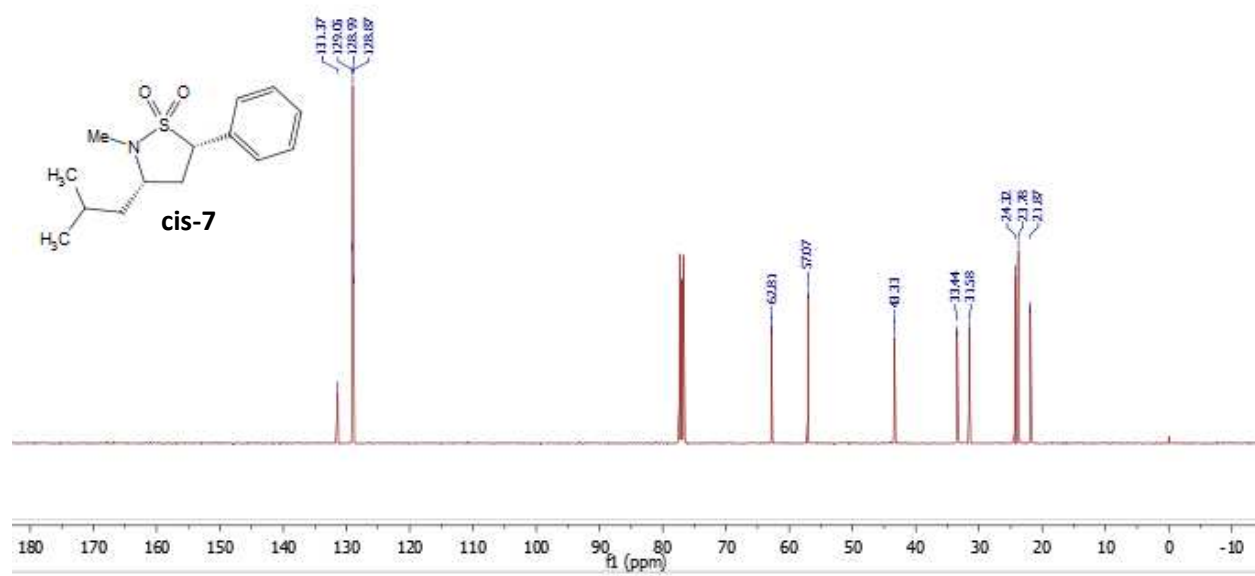
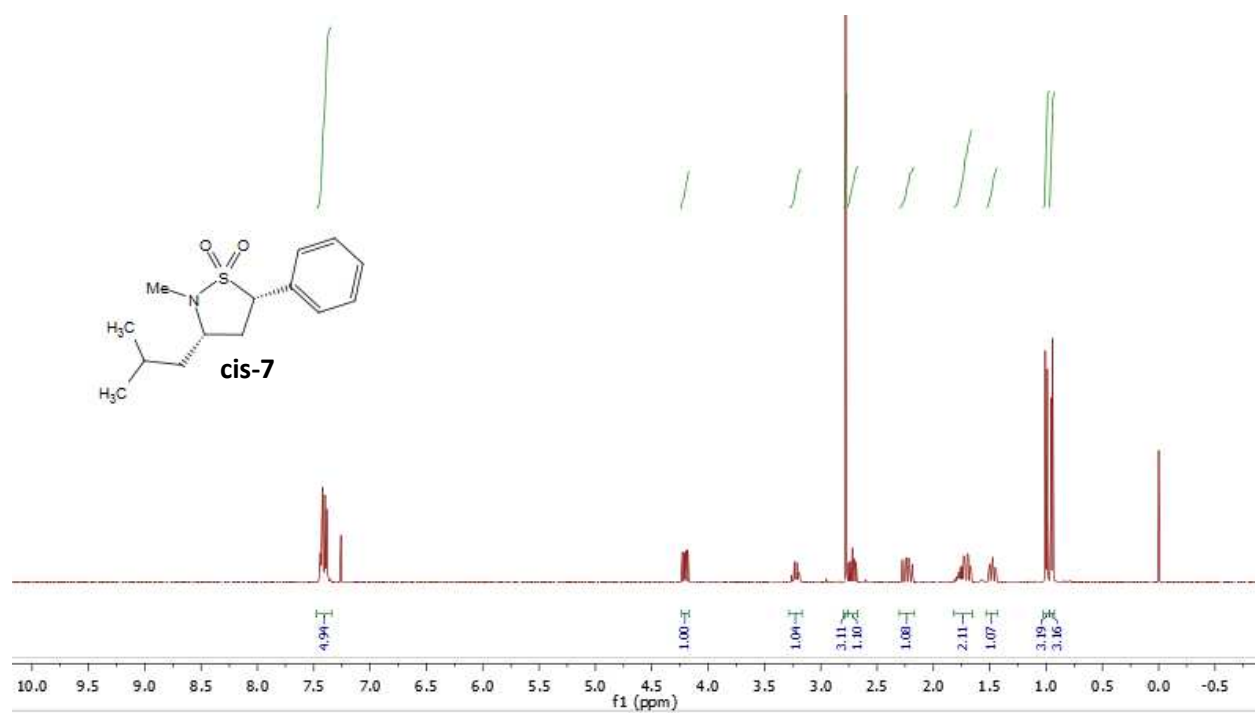


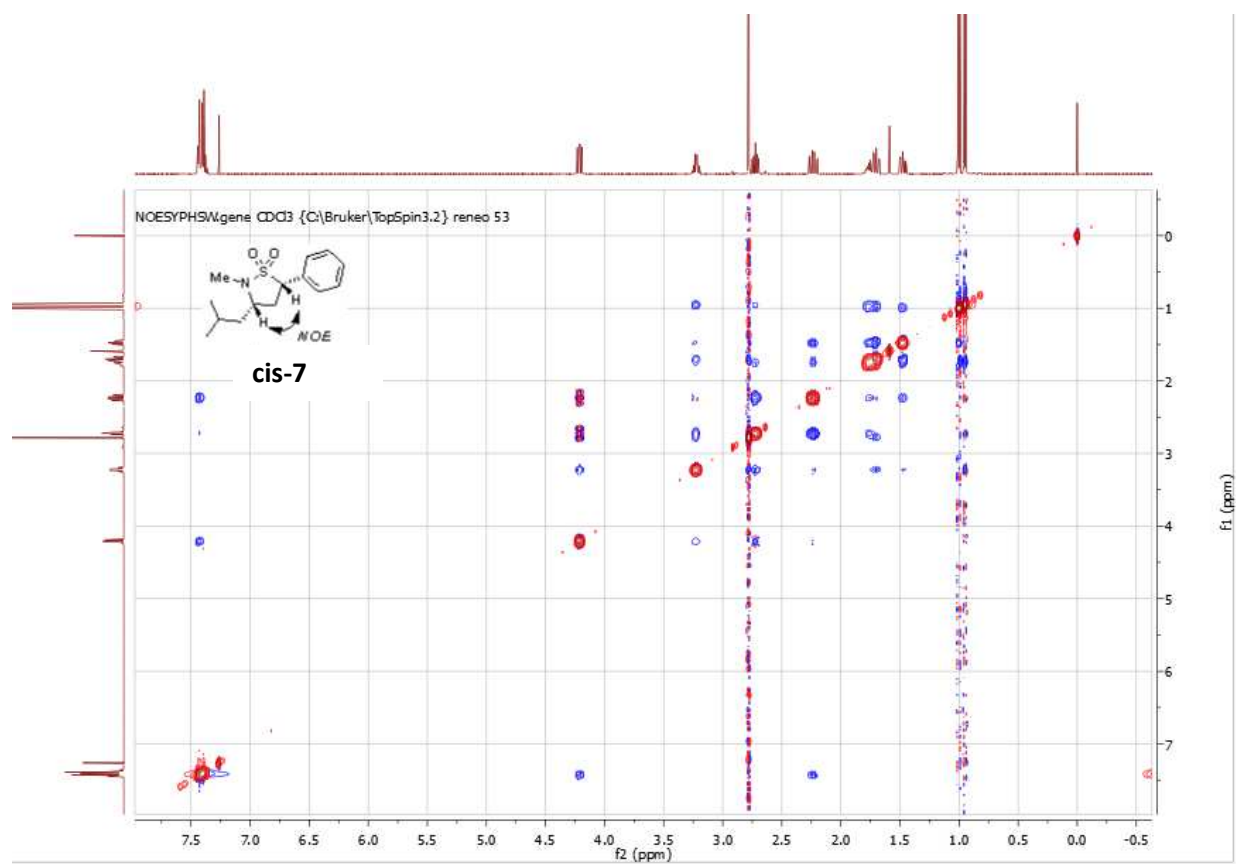




trans-6







cis-7

