Enantioconvergent Cross-Couplings of Racemic Alkylmetal Reagents with Unactivated Secondary Alkyl Electrophiles: Catalytic Asymmetric Negishi α-Alkylations of *N*-Boc-pyrrolidine

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Supporting Information

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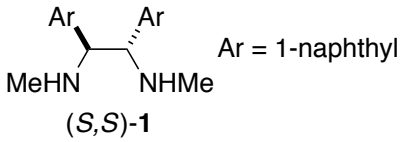
I. General Information

Unless otherwise noted, all anhydrous solvents were purified and dried using a solvent-purification system that contained activated alumina. All reagents were purchased from Sigma-Aldrich, unless otherwise noted. ZnI_2 and $NiCl_2$•glyme were purchased from Strem Chemicals. (*S,S*)- and (*R,R*)-1,2-Bis-(1-naphthyl)-ethylenediamine dihydrochloride (>99% ee) were purchased from Diaminopharm. 1,4-Dibromobutane-2,2,3,3-d_4 was purchased from CDN Isotopes. Iodocycloheptane and 4-bromo-1-tosylpiperidine were prepared from the corresponding alcohols via standard methods.[1] Enantiomerically enriched (*S*)-*N*-(*tert*-butoxycarbonyl)-2-(tributylstannyl)pyrrolidine was prepared according to a literature procedure.[2]

HPLC analyses were carried out on an Agilent 1100 Series system, using Daicel CHIRALCEL® columns (internal diameter 4.6 mm, column length 250 mm, particle size 5 μm). GC analyses were performed on a Hewlett Packard HP 6850 Series apparatus with a Varian GC capillary column (WCOT fused silica 25 m × 0.25 mm; stationary phase: CP CHIRASIL-DEX CB; film thickness 0.25 μm). Flash chromatography was performed on SiO_2 (visualization by thin layer chromatography, staining with a solution of $KMnO_4$).

(1) Dudnik, A. S.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 10693–10697.
(2) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231–3239.

II. Synthesis of Ligand 1



(*S*,*S*)-**1**

(1*S*,2*S*)-*N*,*N*′-Dimethyl-1,2-di(naphthalen-1-yl)ethane-1,2-diamine. This procedure was adapted from a procedure reported by Denmark.[3] A solution of (*S*,*S*)-1,2-bis(1-naphthyl)ethylenediamine (1.63 g, 5.22 mmol) in CH_2Cl_2 (52 mL) was cooled to 0 °C in an ice–water bath. Formic acid (1.18 mL, 31.4 mmol, 6.00 equiv) was added dropwise via a pipette, and then *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (3.01 g, 15.7 mmol, 3.00 equiv) was added portionwise over 5 min. Next, the ice–water bath was removed, and the mixture was allowed to warm to room temperature. The progress of the reaction was monitored using TLC and LC–MS, which showed that it was complete within 30 min. The reaction mixture was poured into a 250-mL separatory funnel, and then it was extracted with CH_2Cl_2 (2 x 50 mL). The organic layers were combined, washed with an aqueous solution of HCl (1.0 M; 25 mL) and then water (50 mL), dried (Na_2SO_4), and concentrated. The residue was dissolved in CH_2Cl_2/EtOAc and passed through a short pad of silica, eluting with EtOAc to give the bis(formamide) (1.89 g, 5.13 mmol).

A 500-mL round-bottomed flask was charged with the bis(formamide) (1.89 g, 5.13 mmol) and a stir bar, and then it was flushed with nitrogen. Dimethoxyethane (200 mL) was added, and then the resulting solution was cooled to 0 °C in an ice–water bath. Next, $LiAlH_4$ (powder; 1.65 g, 43.6 mmol, 8.50 equiv) was cautiously added in ~10 portions over 20-30 min. The ice–water bath was then removed, and the reaction flask was fitted with a reflux condenser. The reaction vessel was placed in a pre-heated oil bath and heated at reflux for 60 min. The progress of the reaction was monitored using LC–MS, which showed that it was complete within 80 min, during which time the suspension turned dark-green. The reaction mixture was allowed to cool to room temperature, and then the flask was placed in an ice–water bath. The condenser was removed and, in air, the excess $LiAlH_4$ was quenched by the very careful addition of water (0.5 mL), aqueous NaOH (1.0 M; 2.0 mL), and water (1.0 mL). These three additions were carried out over 30-45 min, and vigorous stirring was maintained throughout. The reaction flask was then fitted with a reflux condenser, and the suspension was heated at 80 °C for 2 h. The mixture was allowed to cool to room temperature, and then it was filtered through a pad of celite, washing with THF (4 x 50 mL). The filtrate was concentrated to provide a tan–yellow solid, which was washed with a minimal amount of pentane, yielding the title compound (1.69 g, 4.98 mmol, 95%). If necessary, the diamine can be recrystallized from pentane.

A similar procedure was performed using (*R*,*R*)-1,2-bis(1-naphthyl)ethylenediamine (1.91 g, 6.11 mmol), providing the (*R*,*R*) ligand (1.93 g, 5.68 mmol, 93%).

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(3) Denmark, S. E.; Su, X.; Nishigaichi, Y.; Coe, D. M.; Wong, K.-T.; Winter, S. B. D.; Choi, J. Y. *J. Org. Chem.* **1999**, *64*, 1958–1967.

III. Enantioconvergent Negishi Cross-Couplings (Tables 2 and 3)

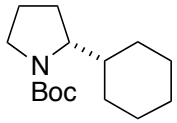
Preparation of the Racemic Organozinc Reagent from *N*-Boc-Pyrrolidine. An oven-dried 40-mL vial was charged with a 1.5 cm stir bar and *N*-Boc-pyrrolidine (1.20 g, 7.00 mmol), capped with a PTFE-lined pierceable cap, wrapped with electrical tape, and placed under vacuum (through a needle attached to a vacuum manifold; <0.5 Torr) for 15 min. The vial was back-filled with nitrogen, and then *N*,*N*,*N*′,*N*′-tetramethylethyldiamine (1.05 mL, 7.00 mmol, 1.0 equiv) was added in two portions using a 1-mL syringe. Next, anhydrous Et_2O (14.0 mL) was added via syringe, the resulting mixture was stirred, and then it was cooled to –78 °C in a dry-ice–acetone bath. *s*-BuLi (1.43 M in cyclohexane; 5.4 mL, 7.70 mmol, 1.1 equiv) was added in two portions over 1-2 min using a 5-mL syringe. The resulting mixture was stirred vigorously at –78 °C for 3.5 h prior to addition of the solution of ZnI_2. Meanwhile, ZnI_2 (1.12 g, 3.50 mmol, 0.50 equiv) was added to an oven-dried 20-mL vial equipped with a 1.0 cm stir bar, and then the vial was capped with a PTFE-lined pierceable cap, wrapped with electrical tape, and placed under vacuum (0.5 Torr) for 30 min. The vial was back-filled with nitrogen, anhydrous THF (7.0 mL) was added, and the mixture was stirred vigorously until it was homogenous (this can take up to 1.5 h). This solution of ZnI_2 was then added via syringe over 2-3 min to the 40-mL vial containing the lithiated *N*-Boc-pyrrolidine (vacuum grease was applied around the inlet of the needle). The resulting mixture was stirred for 30 min at –78 °C, and then it was removed from the dry-ice–acetone bath and stirred at room temperature for 60 min, until it was homogenous (gentle warming in a water bath can aid this process). The resulting organozinc reagent was used directly in the cross-coupling.

General Procedure: Enantioconvergent Negishi Cross-Coupling. An oven-dried 20-mL vial was charged with a 1.0 cm stir bar and $NiCl_2$•glyme (33.0 mg, 0.150 mmol). A separate oven-dried 4-mL vial was charged with (*R*,*R*)-**1** (57.9 mg, 0.170 mmol), which was tipped into the 20-mL vial. The 20-mL vial was closed with a PTFE pierceable cap, wrapped with electrical tape, and placed under N_2 by backfilling and evacuating the vial through a needle (three cycles). Anhydrous THF (4.5 mL) was added via syringe, and the mixture was stirred for 2 h, during which time a blue–green thick suspension formed. The electrophile (1.00 mmol) was added via microsyringe to this mixture (if the electrophile was a solid, it was added as a solution in THF (0.5 mL)), which was stirred for 2 min. The organozinc solution (6.2 mL, 1.55 mmol) was added to the gently stirring catalyst/electrophile mixture, during which time the reaction mixture became homogenous and turned from blue–green to orange–red. The reaction mixture was stirred vigorously for 60 h at room temperature. Next, ethanol (1.0 mL) was added, and Et_2O was added to bring the volume of the reaction mixture to 20 mL. The mixture was passed through a plug of celite (3 cm x 5 cm (l x w)), and the vial and the celite were rinsed with Et_2O (100 mL). The filtrate was concentrated, and the residue was purified by flash chromatography.

A second run was conducted with (*S*,*S*)-**1**.

Unless otherwise noted, the cross-coupling products were converted for ee determination into the corresponding *N*-4-toluenesulfonamides via the following method. After purification of the product, a small aliquot (~20 mg) was placed in a 4-mL vial equipped with a stir bar. CH_2Cl_2 (0.50 mL) and then trifluoroacetic acid (70 μL) were added, and the mixture was stirred for 1 h. Next, aqueous $NaHCO_3$ (2 mL) was added to quench the reaction. The organic layer was removed via pipet, and the aqueous layer was extracted with Et_2O (2 x 2 mL). The combined organic layers were concentrated, dissolved in CH_2Cl_2 (0.50 mL), and then treated

with TsCl (20 mg) and NEt_3 (50 μL). After ~10 h, the reaction mixture was concentrated, dissolved in 2-propanol/hexanes, passed through a short plug of silica, and analyzed by chiral HPLC.



(*R*)-*tert*-Butyl 2-cyclohexylpyrrolidine-1-carboxylate (Table 2, entry 1). The title compound was prepared according to the General Procedure with iodocyclohexane (130 μL, 1.00 mmol) as the electrophile. Purification by flash chromatography (40:1→10:1 hexanes/ethyl acetate) yielded a thick, colorless oil. HPLC analysis of the product: Diacel CHIRALCEL IA column; 1% 2-propanol in hexanes; retention times: 28.3 min (minor), 31.1 min (major). Run 1: 81% yield (205 mg, 0.81 mmol), 92% ee.

Run 2: 79% yield (201 mg, 0.79 mmol), 94% ee.

Gram-scale reaction. To a round-bottom flask under N_2 was added $NiCl_2$•glyme (200 mg, 0.900 mmol) and (*R,R*)-**1** (350 mg, 0.100 mmol). The flask was evacuated and back-filled with N_2 (through a needle) four times, and then THF (25 mL) and a stir bar were added. The septum-capped flask was fitted with a balloon of N_2, and the mixture was stirred for 2 h. Iodocyclohexane (780 μL, 6.00 mmol) was added via syringe, followed by the solution of the nucleophile (36 mL, 9.0 mmol). The reaction mixture was stirred at room temperature for 60 h, and then it was worked up according to the standard procedure, which furnished the product in 74% yield (1.12 g, 4.42 mmol), 94% ee.

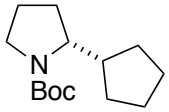
^{1}H NMR (d_4-MeOH, 400 MHz, 328 K) δ 3.65 (q, J = 5.5 Hz, 1H), 3.49 – 3.39 (m, 1H), 3.17 (dt, J = 10.0, 5.2 Hz, 1H), 1.85 – 1.64 (m, 8H), 1.58 (d, J = 12.7 Hz, 2H), 1.44 (s, 9H), 1.27 – 0.94 (m, 5H);

^{13}C NMR (d_4-MeOH, 101 MHz, 328 K) δ 155.4, 79.1, 61.9, 46.4, 41.1, 29.9, 27.7, 27.4, 26.3, 26.0, 23.3;

IR (film) 3392, 2971, 2928, 2852, 1693, 1477, 1449, 1392, 1254, 1170, 1109, 1030, 975, 951, 927, 882, 863, 712 cm^{-1};

LRMS (LCMS EI): calcd for $C_{11}H_{20}NO_2$ [M–(isobutylene)+H] 198.2, found 198.2;

$[\alpha]^{25}_D$ = +68° (c = 0.20, $CHCl_3$) from (*R,R*)-**1**.



(*R*)-*tert*-Butyl 2-cyclopentylpyrrolidine-1-carboxylate (Table 2, entry 2). The title compound was prepared according to the General Procedure with iodocyclopentane (126 μL, 1.00 mmol) as the electrophile. Purification by flash chromatography (40:1→10:1 hexanes/ethyl acetate) yielded a colorless oil. HPLC analysis of the product: Diacel CHIRALCEL IA column; 1% 2-propanol in hexanes; retention times: 27.7 min (minor), 31.9 min (major). Run 1: 90% yield (215 mg, 0.90 mmol), 82% ee.

Run 2: 92% yield (220 mg, 0.92 mmol), 82% ee.

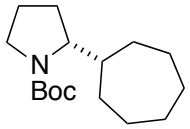
^{1}H NMR (d_4-MeOH, 400 MHz, 328 K) δ 3.84 – 3.80 (m, 1H), 3.49 – 3.41 (m, 1H), 3.25 – 3.19 (m, 1H), 2.16 – 2.06 (m, 1H), 1.93 – 1.46 (m, 10H), 1.45 (s, 9H), 1.30 – 1.15 (m, 2H);

^{13}C NMR (d_4-MeOH, 101 MHz, 328 K) δ 155.5, 79.2, 60.8, 45.9, 44.1, 29.4, 28.4, 27.4, 24.8, 24.7, 22.8;

IR (film) 3372, 2956, 2870, 1694, 1478, 1453, 1393, 1340, 1284, 1254, 1172, 1107, 969, 915, 874, 770 cm^{-1};

LRMS (LCMS EI): calcd for $C_{10}H_{18}NO_2$ [M–(isobutylene)+H] 184.1, found 184.1;

$[\alpha]^{25}_D$ = +84° (c = 0.20, $CHCl_3$) from (*R,R*)-**1**.



(*R*)-*tert*-Butyl 2-cycloheptylpyrrolidine-1-carboxylate (Table 2, entry 3). The title compound was prepared according to the General Procedure with iodocycloheptane (146 μL, 1.00 mmol) as the electrophile. Purification by flash chromatography (20:1→10:1 hexanes/ethyl acetate) yielded a colorless oil. HPLC analysis of the product: Diacel CHIRALCEL AD-H column; 1% 2-propanol in hexanes; retention times: 28.6 min (minor), 30.8 min (major). Run 1: 48% yield (127 mg, 0.48 mmol), 83% ee.

Run 2: 52% yield (138 mg, 0.52 mmol), 85% ee.

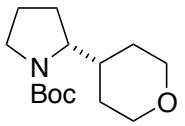
^{1}H NMR (d_4-MeOH, 400 MHz, 328 K) δ 3.69 – 3.64 (m, 1H), 3.53 – 3.48 (m, 1H), 3.20 – 3.14 (m, 1H), 2.08 – 2.05 (m, 1H), 1.84 – 1.46 (m, 14H), 1.45 (s, 9H), 1.26 – 1.16 (2H);

^{13}C NMR (d_4-MeOH, 101 MHz, 328 K) δ 155.3, 79.2, 62.7, 31.5, 28.2, 27.9, 27.5, 27.4, 27.0, 26.9, 23.3;

IR (film) 2971, 2925, 2856, 1693, 1478, 1456, 1398, 1255, 1172, 1108, 918, 860, 772 cm^{-1};

LRMS (LCMS EI): calcd for $C_{12}H_{22}NO_2$ [M–(isobutylene)+H] 212.2, found 212.2;

$[\alpha]^{25}_D$ = +54° (c = 0.20, $CHCl_3$) from (*R,R*)-**1**.



(*R*)-*tert*-Butyl 2-(tetrahydro-2*H*-pyran-4-yl)pyrrolidine-1-carboxylate (Table 2, entry 4). The title compound was prepared according to the General Procedure with 4-iodotetrahydro-2*H*-pyran (212 mg, 1.00 mmol) as the electrophile. Purification by flash chromatography (10:1→2:1 hexanes/ethyl acetate) yielded a thick, colorless oil. HPLC analysis of the product: Diacel CHIRALCEL AD-H column; 3% 2-propanol in hexanes; retention times: 46.4 min (minor), 56.6 min (major). Run 1: 98% yield (250 mg, 0.98 mmol), 91% ee.

Run 2: 94% yield (240 mg, 0.94 mmol), 93% ee.

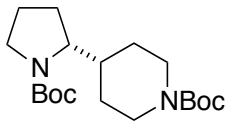
^{1}H NMR (d_4-MeOH, 400 MHz, 328 K) δ 3.95 (d, J = 11.0 Hz, 2H), 3.71 (broad s, 1H), 3.46 (d, J = 9.4 Hz, 1H), 3.39 – 3.27 (m, 2H), 3.28 – 3.20 (m, 1H), 2.00 – 1.75 (m, 7H), 1.45 (s, 9H), 1.43 – 1.29 (m, 2H);

^{13}C NMR (d_4-MeOH, 101 MHz, 328 K) δ 155.5, 79.4, 67.8, 67.6, 61.3, 46.4, 38.6, 29.8, 28.2, 27.4, 26.6, 23.2;

IR (film) 3362, 2970, 2842, 2755, 1695, 1391, 1240, 1169, 1104, 1013, 985, 960, 926, 877, 773 cm^{-1};

LRMS (LCMS EI): calcd for $C_{10}H_{18}NO_3$ [M–(isobutylene)+H] 200.1, found 200.2;

$[\alpha]^{25}_D$ = –66° (c = 0.20, $CHCl_3$) from (*S*,*S*)-**1**.



(*R*)-*tert*-Butyl 4-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)piperidine-1-carboxylate (Table 2, entry 5). The title compound was prepared according to the General Procedure with *tert*-butyl 4-iodopiperidine-1-carboxylate (311 mg, 1.00 mmol) as the electrophile. Purification by flash chromatography (4:1→2:1 hexanes/ethyl acetate) yielded a colorless solid. HPLC analysis of the product (derivatized with benzyl chloroformate): Diacel CHIRALCEL IA column; 7% 2-propanol in hexanes; retention times: 34.3 min (major), 44.9 min (minor). Run 1: 97% yield (342 mg, 0.97 mmol), 94% ee.

Run 2: 96% yield (339 mg, 0.96 mmol), 93% ee.

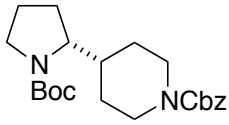
^{1}H NMR (d_4-MeOH, 400 MHz, 328 K) δ 4.18 – 4.06 (m, 2H), 3.71 (s, 1H), 3.46 (q, *J* = 7.1, 6.1 Hz, 1H), 3.27 – 3.17 (m, 1H), 2.66 (t, *J* = 12.5 Hz, 2H), 1.90 – 1.75 (m, 5H), 1.56 (d, *J* = 12.9 Hz, 2H), 1.45 (s, 9H), 1.44 (s, 9H), 1.31 – 1.09 (m, 2H);

^{13}C NMR (d_4-MeOH, 101 MHz, 328 K) δ 155.5, 155.1, 79.5, 61.2, 46.4, 44.0, 43.8, 39.7, 28.9, 27.4, 27.3, 26.8, 23.3;

IR (film) 2973, 2931, 1695, 1365, 1283, 1234, 1169, 1137, 1109, 976, 953, 916, 875, 771 cm^{-1};

LRMS (LCMS EI): calcd for $C_{10}H_{19}N_2O_2$ [M–(isobutylene x 2)–CO_2+H] 199.1, found 199.2;

$[\alpha]^{25}_D$ = +54° (c = 0.20, $CHCl_3$) from (*R*,*R*)-**1**.



(*R*)-Benzyl 4-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)piperidine-1-carboxylate (Table 2, entry 6). The title compound was prepared according to the General Procedure with benzyl 4-iodopiperidine-1-carboxylate (345 mg, 1.00 mmol) as the electrophile. Purification by flash chromatography (4:1→2:1 hexanes/ethyl acetate) yielded a white solid. HPLC analysis of the product (not derivatized): Diacel CHIRALCEL OD-H column; 3% 2-propanol in hexanes; retention times: 29.4 min (minor), 34.3 min (major). Run 1: 95% yield (368 mg, 0.95 mmol), 92% ee.

Run 2: 92% yield (355 mg, 0.92 mmol), 90% ee.

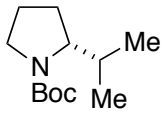
^{1}H NMR (d_4-MeOH, 400 MHz, 328 K) δ 7.36 – 7.26 (m, 5H), 5.10 (s, 2H), 4.19 (d, *J* = 16 Hz, 2H), 3.70 (broad s, 1H), 3.48 – 3.42 (m, 1H), 3.24 – 3.18 (m, 1H), 2.74 (broad s, 2H), 1.95 – 1.75 (m, 5H), 1.60 – 1.50 (m, 2H), 1.45 (s, 9H), 1.30 – 1.10 (m, 2H);

^{13}C NMR (d_4-MeOH, 101 MHz, 328 K) δ 155.6, 155.5, 136.9, 128.1, 127.6, 127.4, 80.8, 79.4. 66.8, 61.1, 46.4, 44.2, 44.0, 39.0, 28.8, 27.4, 27.2, 23.3;

IR (film) 2971, 2842, 1694, 1454, 1393, 1240, 1169, 1104, 1013, 985, 955, 926, 876, 772 cm^{-1};

LRMS (LCMS EI): calcd for $C_{17}H_{25}N_2O_2$ [M–(isobutylene)–CO_2+H] 289.2, found 289.2;

$[\alpha]^{25}_D$ = +42° (c = 0.20, $CHCl_3$) from (*R*,*R*)-**1**.



(*R*)-*tert*-Butyl 2-isopropylpyrrolidine-1-carboxylate (Table 2, entry 7). The title compound was prepared according to the General Procedure with 2-iodopropane (100 μL, 1.00 mmol) as the electrophile. Purification by flash chromatography (40:1→10:1 hexanes/ethyl acetate) yielded a colorless oil. HPLC analysis of the product: Diacel CHIRALCEL IA column; 1% 2-propanol in hexanes; retention times: 31.8 min (minor), 34.8 min (major). Run 1: 83% yield (177 mg, 0.83 mmol), 91% ee.

Run 2: 86% yield (188 mg, 0.86 mmol), 89% ee.

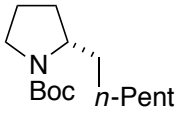
^{1}H NMR (d_4-MeOH, 400 MHz, 328 K) δ 3.70 – 3.62 (m, 1H), 3.52 – 3.42 (m, 1H), 3.21 (broad s, 1H), 2.09 (broad s, 1H), 1.94 – 1.71 (m, 4H), 1.45 (s, 9H), 0.88 (d, *J* = 7.0 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H);

^{13}C NMR (d_4-MeOH, 101 MHz, 328 K) δ 155.4, 155.3, 79.3, 78.9, 62.6, 62.5, 46.4, 30.6, 29.9, 27.4, 26.2, 25.3, 23.8, 23.1, 18.5, 15.9 (rotamers);

IR (film) 2966, 2874, 1698, 1468, 1392, 1366, 1255, 1172, 1105, 916, 876, 772 cm^{-1};

LRMS (LCMS EI): calcd for $C_8H_{16}NO_2$ [M–(isobutylene)+H] 158.1, found 158.2;

$[\alpha]^{25}_D$ = –49° (c = 0.20, $CHCl_3$) from (*S*,*S*)-**1**.



(*S*)-*tert*-Butyl 2-hexylpyrrolidine-1-carboxylate (Table 2, entry 8). The title compound was prepared according to the General Procedure with 1-iodohexane (148 μL, 1.00 mmol) as the electrophile. Purification by flash chromatography (10:1 hexanes/ethyl acetate) yielded a colorless oil. HPLC analysis of the product: Diacel CHIRALCEL IA column; 1% 2-propanol in hexanes; retention times: 39.9 min (minor), 50.4 min (major). Run 1: 89% yield (227 mg, 0.89 mmol), 58% ee.

Run 2: 80% yield (204 mg, 0.80 mmol), 58% ee.

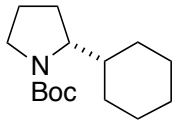
^{1}H NMR (d_4-MeOH, 400 MHz, 328 K) δ 3.75 – 3.68 (m, 1H), 3.55 – 3.25 (m, 2H), 1.95 – 1.60 (m, 6H), 1.45 (s, 9H), 1.31 (broad s, 8H), 0.90 (t, *J* = 6.4 Hz, 3H);

^{13}C NMR (d_4-MeOH, 101 MHz, 328 K) δ 155.0, 79.2, 57.4, 45.8, 34.1, 31.6, 30.1, 29.0, 27.5, 25.9, 22.5, 22.3, 13.0;

IR (film) 2961, 2928, 2872, 1697, 1457, 1393, 1365, 1255, 1173, 1106, 915, 865, 772 cm^{-1};

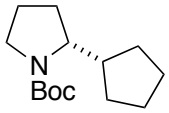
LRMS (LCMS EI): calcd for $C_{11}H_{22}NO_2$ [M–(isobutylene)+H] 200.2, found 200.2;

$[\alpha]^{25}_D$ = –10.5° (c = 0.20, $CHCl_3$) from (*S*,*S*)-**1**.



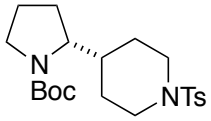
(*R*)-*tert*-Butyl 2-cyclohexylpyrrolidine-1-carboxylate (Table 3, entry 1). The title compound was prepared according to the General Procedure with cyclohexyl bromide (123 μL, 1.00 mmol) as the electrophile at 35 °C. Purification by flash chromatography (40:1→10:1 hexanes/ethyl acetate) yielded a thick, colorless oil. HPLC analysis of the product: Diacel CHIRALCEL IA column; 1% 2-propanol in hexanes; retention times: 28.3 min (minor), 31.1 min (major). Run 1: 38% yield (96 mg, 0.38 mmol), 93% ee.

Run 2: 44% yield (112 mg, 0.44 mmol), 91% ee.



(*R*)-*tert*-Butyl 2-cyclopentylpyrrolidine-1-carboxylate (Table 3, entry 2). The title compound was prepared according to the General Procedure with bromocyclopentane (107 μL, 1.00 mmol) as the electrophile. Purification by flash chromatography (40:1→10:1 hexanes/ethyl acetate) yielded a colorless oil. HPLC analysis of the product: Diacel CHIRALCEL IA column; 1% 2-propanol in hexanes; retention times: 27.7 min (minor), 31.9 min (major). Run 1: 76% yield (182 mg, 0.76 mmol), 87% ee.

Run 2: 84% yield (201 mg, 0.84 mmol), 89% ee.



(*R*)-*tert*-Butyl 2-(1-tosylpiperidin-4-yl)pyrrolidine-1-carboxylate (Table 3, entry 3). The title compound was prepared according to the General Procedure with 4-bromo-1-tosylpiperidine (159 mg, 0.500 mmol) as the electrophile at 35 °C. Purification by flash chromatography (4:1→2:1 hexanes/ethyl acetate) yielded a white solid. HPLC analysis of the product (not derivatized): Diacel CHIRALCEL AS-H column; 5% 2-propanol in hexanes; retention times: 32.2 min (minor), 40.1 min (major). Run 1: 42% yield (86 mg, 0.21 mmol), 88% ee.

Run 2: 46% yield (93 mg, 0.23 mmol), 88% ee.

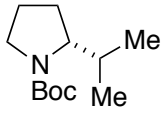
^{1}H NMR (d_4-MeOH, 400 MHz, 328 K) δ 7.63 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 8.2 Hz, 2H), 3.79 (d, J = 11.3 Hz, 2H), 3.67 (s, 1H), 3.49 – 3.35 (m, 1H), 3.25 – 3.10 (m, 1H), 2.42 (s, 3H), 2.23 (t, J = 10.8 Hz, 2H), 1.85 – 1.69 (m, 4H), 1.65 – 1.55 (m, 3H), 1.42 (s, 9H), 1.38 – 1.22 (m, 2H);

^{13}C NMR (d_4-MeOH, 101 MHz, 328 K) δ 155.4, 143.7, 133.7, 129.4, 127.3, 79.4, 60.9, 46.4, 46.2, 38.9, 28.4, 27.4, 26.7, 23.3, 20.0;

IR (film) 2973, 2930, 2879, 1692, 1391, 1364, 1248, 1166, 1108, 932, 875, 816, 772, 727 cm^{-1};

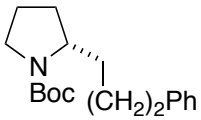
LRMS (LCMS EI): calcd for $C_{17}H_{25}N_2O_4S$ [M–(isobutylene)+H] 353.2, found 353.2;

$[\alpha]^{25}_D$ = +35° (c = 0.20, $CHCl_3$) from (*S*,*S*)-**1**.



(*R*)-*tert*-Butyl 2-isopropylpyrrolidine-1-carboxylate (Table 3, entry 4). The title compound was prepared according to the General Procedure with 2-bromopropane (123 μL, 1.00 mmol) as the electrophile at 35 °C. Purification by flash chromatography (40:1→10:1 hexanes/ethyl acetate) yielded a colorless oil. HPLC analysis of the product: Diacel CHIRALCEL IA column; 1% 2-propanol in hexanes; retention times: 31.8 min (minor), 34.8 min (major). Run 1: 46% yield (182 mg, 0.76 mmol), 87% ee.

Run 2: 55% yield (118 mg, 0.55 mmol), 92% ee.



(*S*)-*tert*-Butyl 2-(3-phenylpropyl)pyrrolidine-1-carboxylate (Table 3, entry 5). The title compound was prepared according to the General Procedure with (3-bromopropyl)benzene (77 μL, 0.500 mmol) as the electrophile. Purification by flash chromatography (20:1→10:1 hexanes/ethyl acetate) yielded a colorless oil. HPLC analysis of the product (not derivatized): Diacel CHIRALCEL OJ-H column; 1% 2-propanol in hexanes; retention times: 10.1 min (major), 11.2 min (minor). Run 1: 57% yield (83 mg, 0.29 mmol), 61% ee.

Run 2: 65% yield (95 mg, 0.33 mmol), 56% ee.

^{1}H NMR (d_4-MeOH, 400 MHz, 328 K) δ 7.23 (t, J = 7.4 Hz, 2H), 7.18 – 7.09 (m, 2H), 3.73 (broad s, 1H), 3.38 – 3.20 (m, 2H), 2.61 (t, J = 7.3 Hz, 2H), 2.05 – 1.49 (m, 9H), 1.39 (s, 9H);

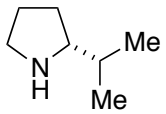
^{13}C NMR (d_4-MeOH, 101 MHz, 328 K) δ 155.0, 142.2, 128.0, 127.9, 125.3, 79.1, 57.3, 45.9, 35.5, 33.6, 29.9, 27.7, 27.4, 22.8;

IR (film) 2971, 2871, 1694, 1603, 1496, 1478, 1453, 1393, 1365, 1255, 1171, 1101, 1030, 915, 878, 772, 749 cm^{-1};

LRMS (LCMS EI): calcd for $C_{14}H_{20}NO_2$ [M–(isobutylene)+H] 234.1, found 234.2;

$[\alpha]^{25}_{D}$ = +21° (c = 0.20, $CHCl_3$) from (*R*,*R*)-**1**.

IV. Determination of Absolute Stereochemistry



(*R*)-2-(Isopropyl)pyrrolidine (Table 2, entry 7). A 20-mL vial was charged with a stir bar and (*R*)-*tert*-butyl 2-isopropylpyrrolidine-1-carboxylate (47.0 mg, 0.222 mmol), prepared as described in the General Procedure using (*R*,*R*)-**1**. CH_2Cl_2 (2.0 mL), triethylsilane (0.5 mL), and then trifluoroacetic acid (100 μL) were added, and the mixture was stirred at room temperature for 3 h. Then, the mixture was transferred to a 100-mL separatory funnel that contained saturated aqueous $NaHCO_3$ (30 mL), rinsing the reaction vessel with CH_2Cl_2 (30 mL total). The

organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The yellow residue was dissolved in Et_2O (50 mL), and this organic layer was extracted with aqueous HCl (1.0 M; 3 x 50 mL). The aqueous phase was basified to pH 14 by the portion-wise addition of solid KOH, and then it was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The title compound was obtained as a colorless oil (14.0 mg, 0.123 mmol, 56%). $[\alpha]^{25}_D = +10.1$ (c = 0.46, EtOH); Lit. $[\alpha]_D = +13.9$ (c = 0.46, EtOH) for the *R* enantiomer.[4]

V. Mechanistic Studies (Figure 1 and eq 6)

Preparation of Enantioenriched Organozinc Reagent (Figure 1). An oven-dried 20-mL vial equipped with a stir bar was charged with (*S*)-*N*-(*tert*-butoxycarbonyl)-2-(tributylstannyl)pyrrolidine (1.84 g, 4.00 mmol), capped with a PTFE-lined pierceable cap, wrapped with electrical tape, and dried under vacuum (through a needle attached to a vacuum manifold; 0.5 Torr) for 15 min. The vial was back-filled with nitrogen, THF (8.0 mL) was added, and then the solution was cooled to –78 °C using a dry-ice–acetone bath. *n*-BuLi (2.50 M in hexanes; 1.76 mL, 4.40 mmol, 1.1 equiv) was added dropwise over 1-2 min, and then the reaction mixture was stirred vigorously at –78 °C for 2.0 h prior to the addition of the solution of ZnI_2. Meanwhile, in a glovebox, ZnI_2 (638 mg, 2.00 mmol, 0.50 equiv), a stir bar, and THF (4.0 mL) were added in turn to an oven-dried 20-mL vial. The vial was capped with a PTFE-lined pierceable cap and wrapped with electrical tape, and then the mixture was stirred vigorously until it was homogenous (this can take up to 1.5 h). The vial was removed from the glovebox, and connected to a Schlenk line. The solution of ZnI_2 was transferred over 3-5 min via syringe to the 20-mL vial that contained the lithiated *N*-Boc-pyrrolidine (grease was applied to the vial cap in the area surrounding the needle inlet). The resulting mixture was stirred at –78 °C for 30 min, and then it was removed from the dry-ice–acetone bath and stirred at r.t. for 10 min, at which time it was homogenous. The nitrogen inlet was then removed, and the vial was transferred to the glovebox. The total volume was measured as 16.0 mL using a 20-mL syringe, equating to a 0.25 M solution of the organozinc reagent. The enantiomeric purity of the organozinc reagent was confirmed by cross-coupling a portion of the material with bromobenzene according to the procedure described by Campos.[5]

Nickel-Catalyzed Cross-Coupling (Figure 1). In a glovebox, an oven-dried 20-mL vial was charged with $NiCl_2$•glyme (16.5 mg, 0.0750 mmol) and a stir bar. A separate oven-dried 4-mL vial was charged with (*R,R*)-**1** (29.0 mg, 0.0195 mmol), which was then tipped into the 20-mL vial. THF (1.0 mL) was added to the 4-mL vial via syringe, and this washing was transferred to the 20-mL vial via pipette. The 4-mL vial was rinsed further with THF (0.50 mL), and this solution was also added to the 20-mL vial. The 20-mL vial was capped with a PTFE pierceable cap, and the reaction mixture was stirred for 2 h, during which time a blue–green thick suspension formed. Iodocyclohexane (105 mg, 0.500 mmol) was weighed into a 4-mL vial, and

(4) Tseng, C. C.; Terashima, S.; Yamada, S.-I. *Chem. Pharm. Bull.* **1977**, *25*, 29–40.

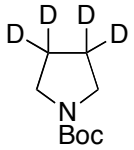
(5) Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C.-y. *J. Am. Chem. Soc.* **2006**, *128*, 3538–3539.

THF (0.50 mL) was added via syringe. The solution was transferred to the 20-mL vial that contained the catalyst. Additional THF (0.25 mL) was added to the 4-mL vial, and this washing was transferred to the 20-mL vial, which was capped and stirred for 2 min. Two 2-mL syringes were charged with the organozinc solution (0.25 M; 3.0 mL, 0.75 mmol). The 20-mL vial was opened, and the organozinc solution was added to the gently stirred mixture, during which time the reaction mixture became homogenous and turned from blue–green to orange–red–brown. The vial was capped, gently shaken to ensure homogeneity, and then wrapped with electrical tape. The vial was removed from the glovebox, and the reaction mixture was stirred vigorously for 60 h at room temperature. Next, ethanol (0.50 mL) was added via syringe, and then the cap was removed, and the vial was filled with Et_2O. The suspension was passed through a plug of silica (3 cm x 5 cm (l x w)), rinsing with Et_2O (100 mL). The filtrate was concentrated, and the residue was purified by flash chromatography to furnish the desired product. The ee was determined by chiral GC analysis (CP CHIRASIL-DEX CB, isotherm: 115 °C, 260 min; retention times: 216.2 min (minor), 220.2 min (major). For ligand (*R,R*)-**1**: Run 1: 81% yield (102 mg, 0.40 mmol), 96% ee.

Run 2: 78% yield (98 mg 0.39 mmol), 95% ee.

For ligand (*S,S*)-**1**: Run 1: 84% yield (106 mg, 0.42 mmol), 87% ee.

Run 2: 83% yield (105 mg, 0.42 mmol), 88% ee.



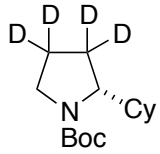
***tert*-Butyl (3,3,4,4-d_4)-pyrrolidine-1-carboxylate.** A solution of *tert*-butyl carbamate (280 mg, 2.40 mmol) and 1,4-dibromobutane-2,2,3,3-d_4 (550 mg, 2.50 mmol) in DMF (5 mL) was added dropwise over 5 min to a round-bottom flask that contained DMF (15 mL) and NaH (60% mineral oil dispersion; 350 mg) at 0 °C. The reaction mixture was stirred at room temperature for 1.0 h, and then the reaction was quenched with water (15 mL), and the mixture was neutralized with aqueous HCl (0.5 M). The product was extracted with EtOAc (25 mL), and the organic layer was dried (Na_2SO_4) and concentrated. The product was purified by flash chromatography (4:1 hexane/ethyl acetate), which furnished the product as a colorless oil in 43% yield (180 mg, 1.03 mmol).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.29 (s, 4H), 1.45 (s, 9H);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 154.7, 78.9, 45.6, 28.5, 24.6 (q, J = 21 Hz);

IR (film) 2976, 2933, 2873, 2235, 2139, 1699, 1478, 1455, 1403, 1365, 1339, 1255, 1184, 1153, 1160, 1116, 1093, 905, 871, 771 cm^{-1};

LRMS (LCMS EI): calcd for $C_5H_6D_4NO_2$ [M–(isobutylene)+H] 120.1, found 120.1;



(*R*)-*tert*-Butyl 2-cyclohexyl-(3,3,4,4-d_4)-pyrrolidine-1-carboxylate (eq 6). The title compound was prepared according to the General Procedure from iodocyclohexane (33 μL, 0.25 mmol) and *tert*-butyl (3,3,4,4-d_4)-pyrrolidine-1-carboxylate (65 mg, 0.38 mmol). Purification by flash chromatography (40:1→10:1 hexanes/ethyl acetate) yielded a thick, colorless oil. Run 1: 70% yield (45 mg, 0.17 mmol), 93% ee.

Run 2: 68% yield (44 mg, 0.16 mmol), 93% ee.

^{1}H NMR (d_4-MeOH, 400 MHz, 328 K) δ 3.64 (d, J = 4.9 Hz, 1H), 3.43 (d, J = 10.9 Hz, 1H), 3.17 (d, J = 10.7 Hz, 1H), 1.83 – 1.63 (m, 4H), 1.59 (d, J = 12.7 Hz, 2H), 1.45 (s, 9H), 1.30 – 0.92 (m, 5H);

^{2}H NMR ($CHCl_3$, 61 MHz, 328 K) δ 1.76 (broad s);

LRMS (LCMS EI): calcd for $C_{11}H_{16}D_4NO_2$ [M–(isobutylene)+H] 202.3, found 202.2.

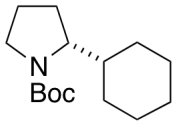


Table 2, entry 1
***d*$_4$-MeOH, 400 MHz, 328 K**

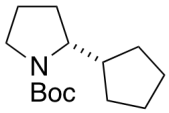
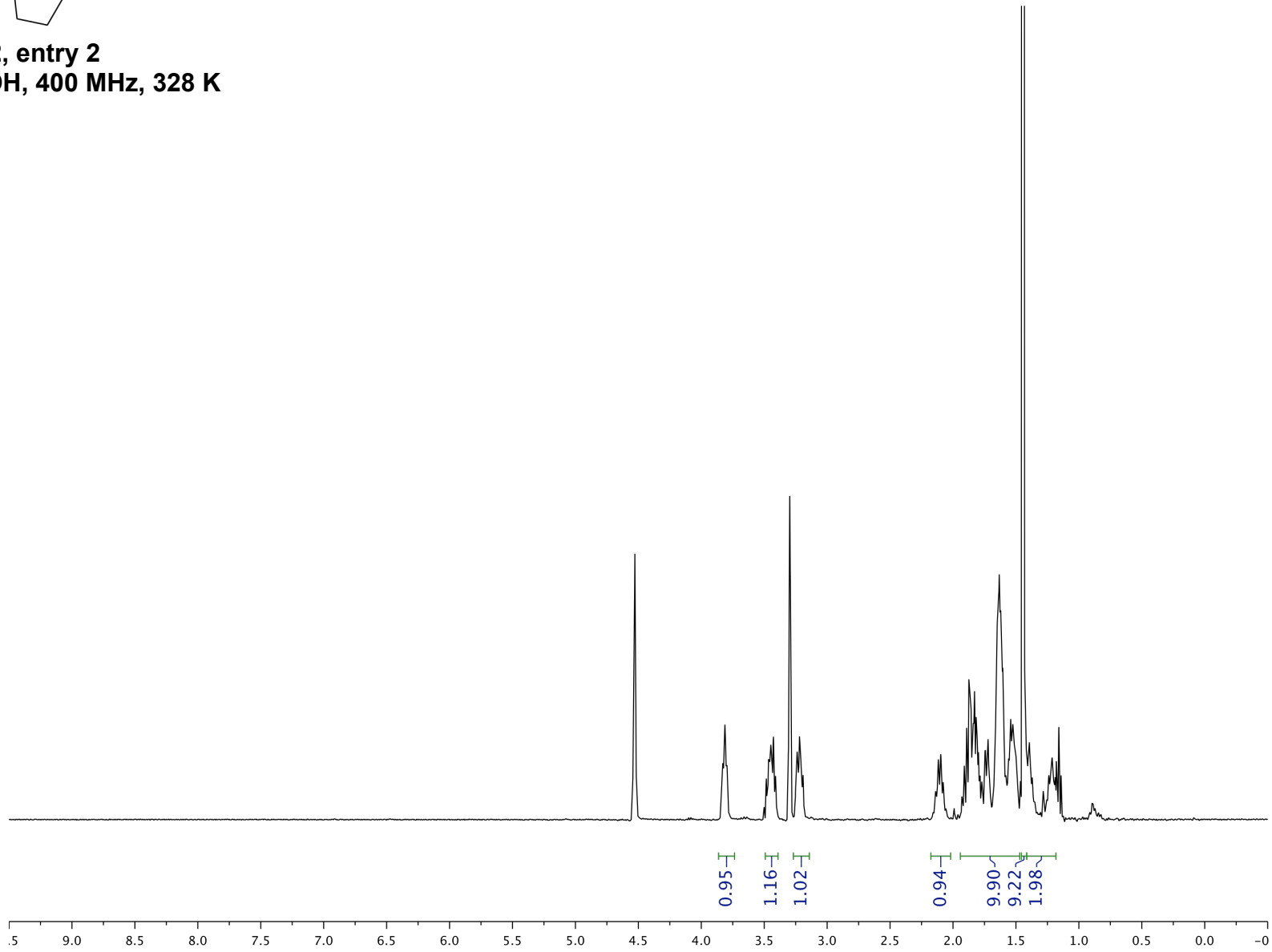


Table 2, entry 2
***d*$_4$-MeOH, 400 MHz, 328 K**



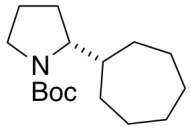
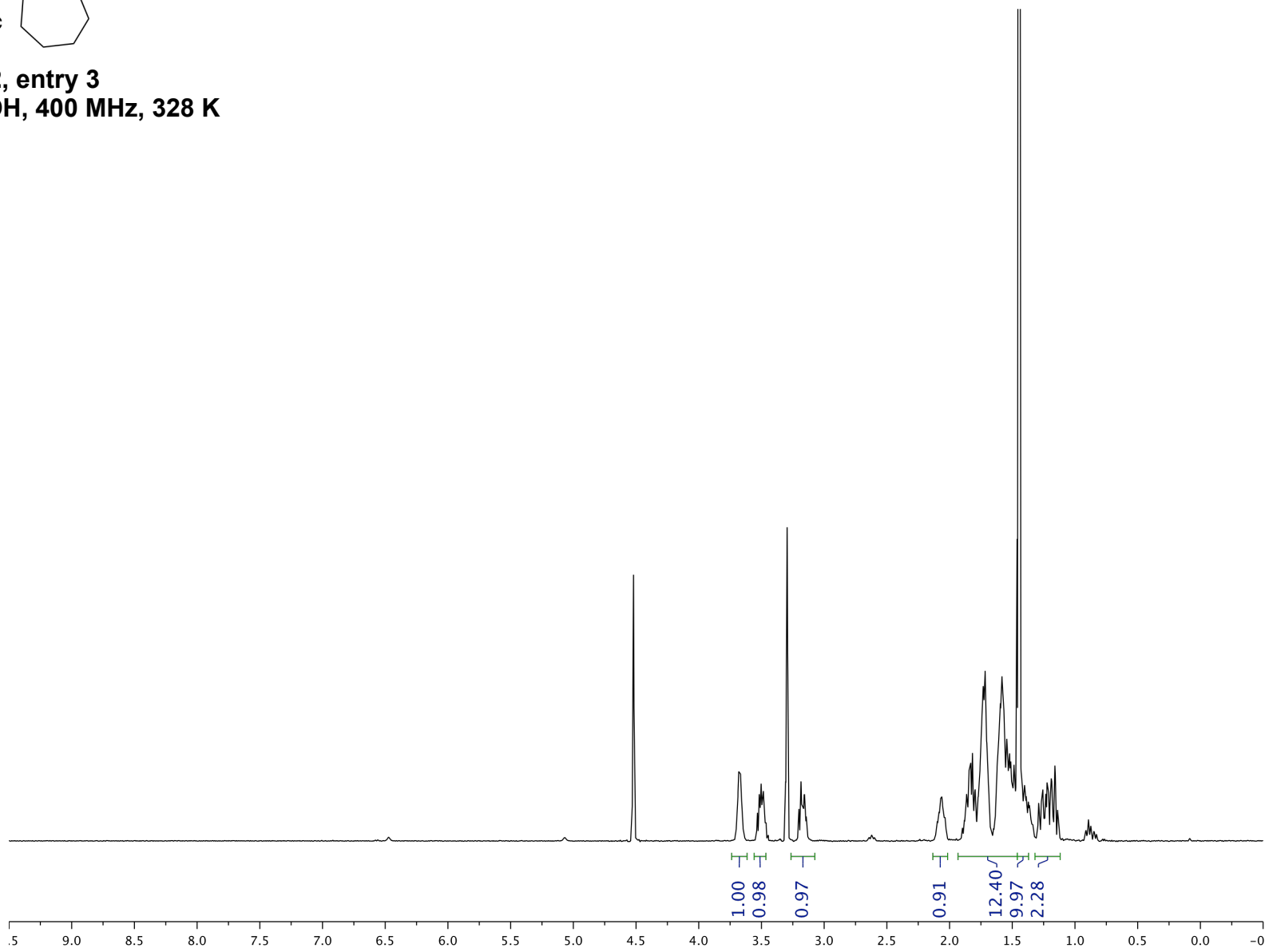


Table 2, entry 3
***d*$_4$-MeOH, 400 MHz, 328 K**



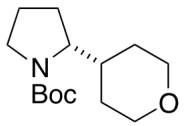
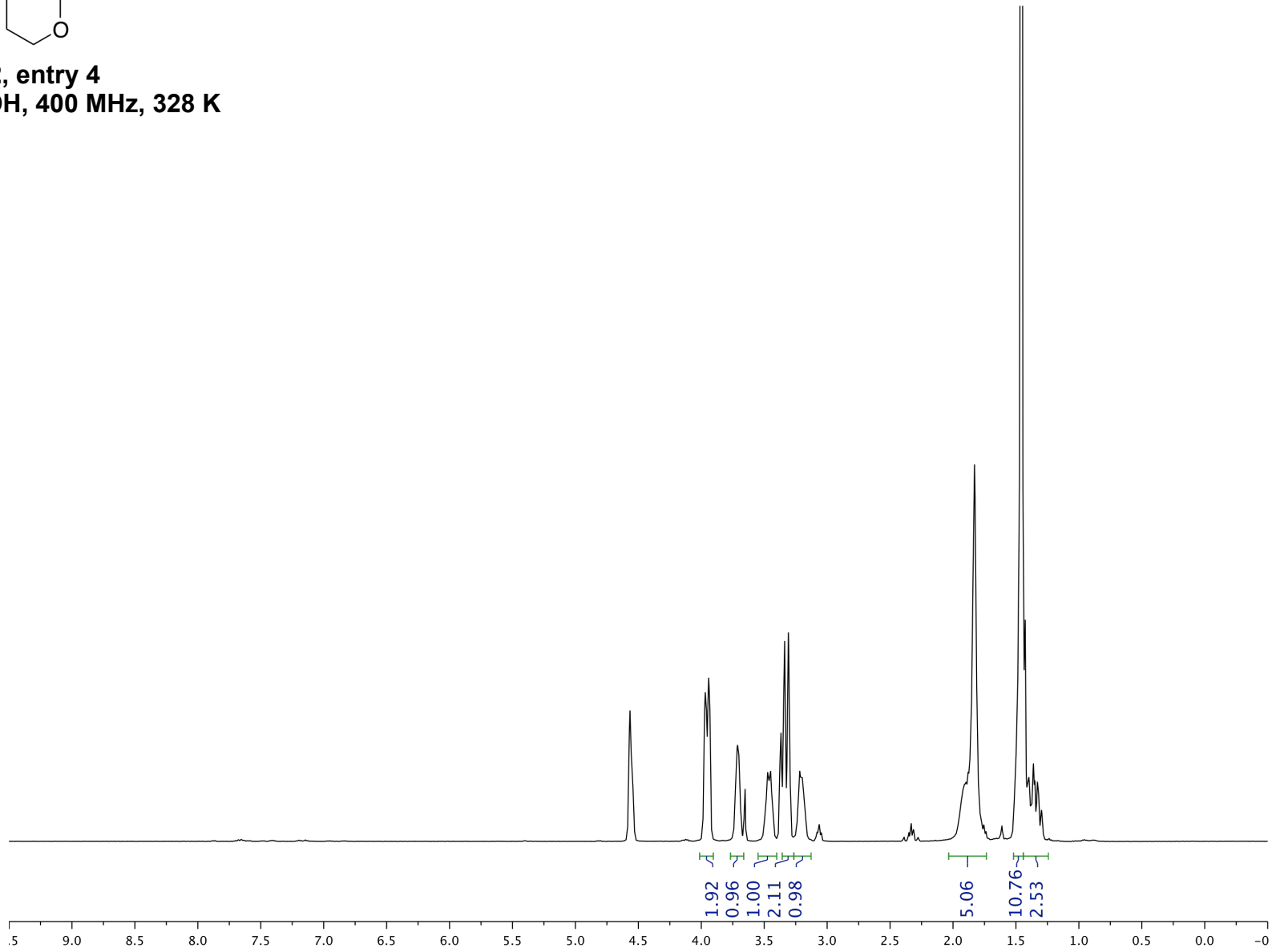


Table 2, entry 4
***d*$_4$-MeOH, 400 MHz, 328 K**



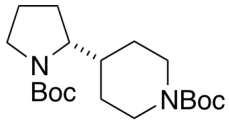
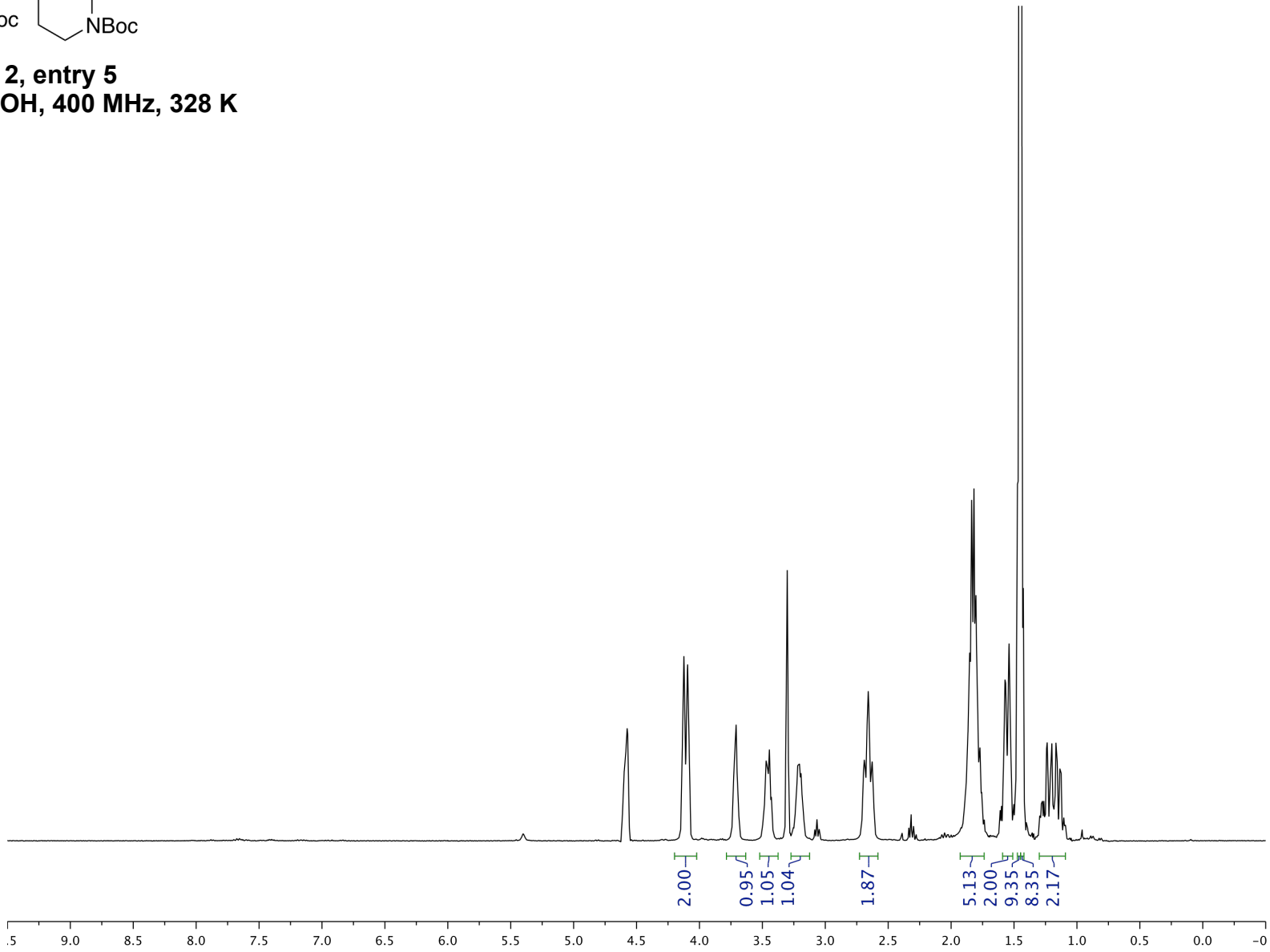


Table 2, entry 5
***d*$_4$-MeOH, 400 MHz, 328 K**



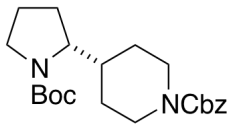


Table 2, entry 6
***d*$_4$-MeOH, 400 MHz, 328 K**

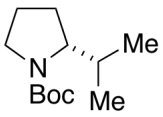
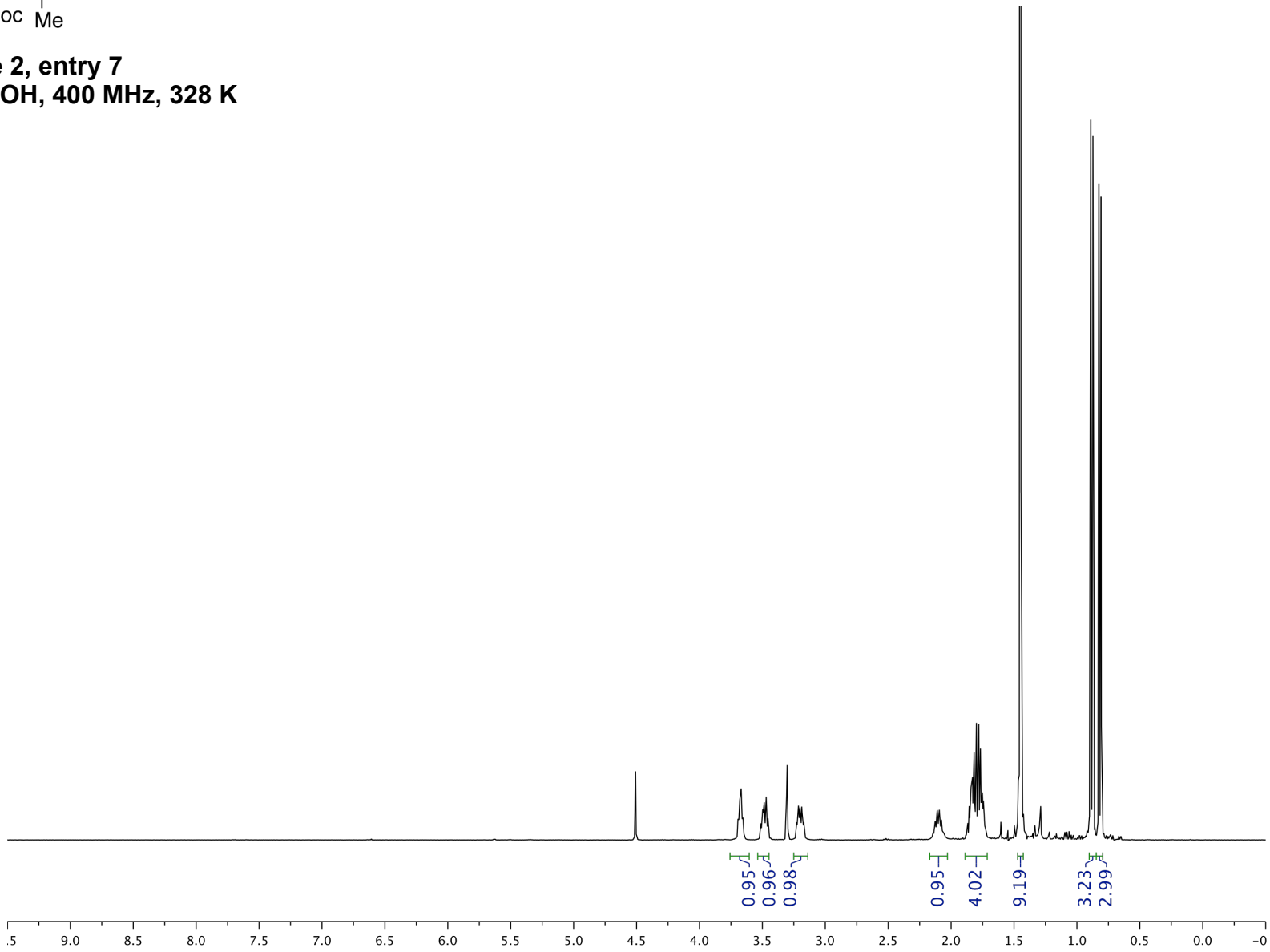


Table 2, entry 7
***d*$_4$-MeOH, 400 MHz, 328 K**



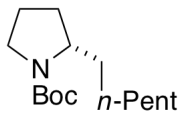
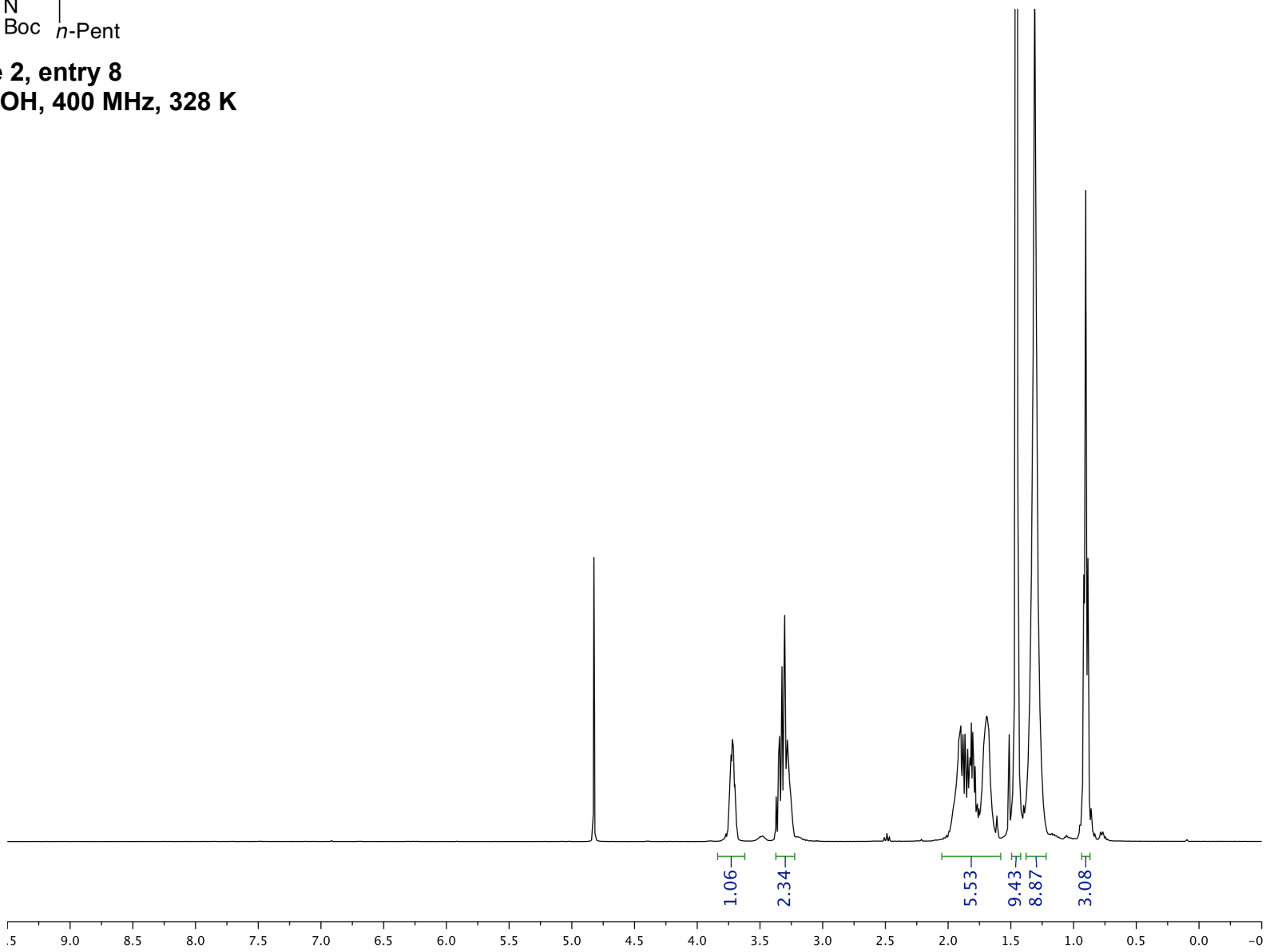


Table 2, entry 8
***d*$_4$-MeOH, 400 MHz, 328 K**



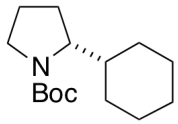


Table 3, entry 1
***d*$_4$-MeOH, 400 MHz, 328 K**

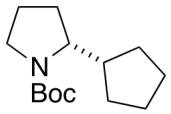
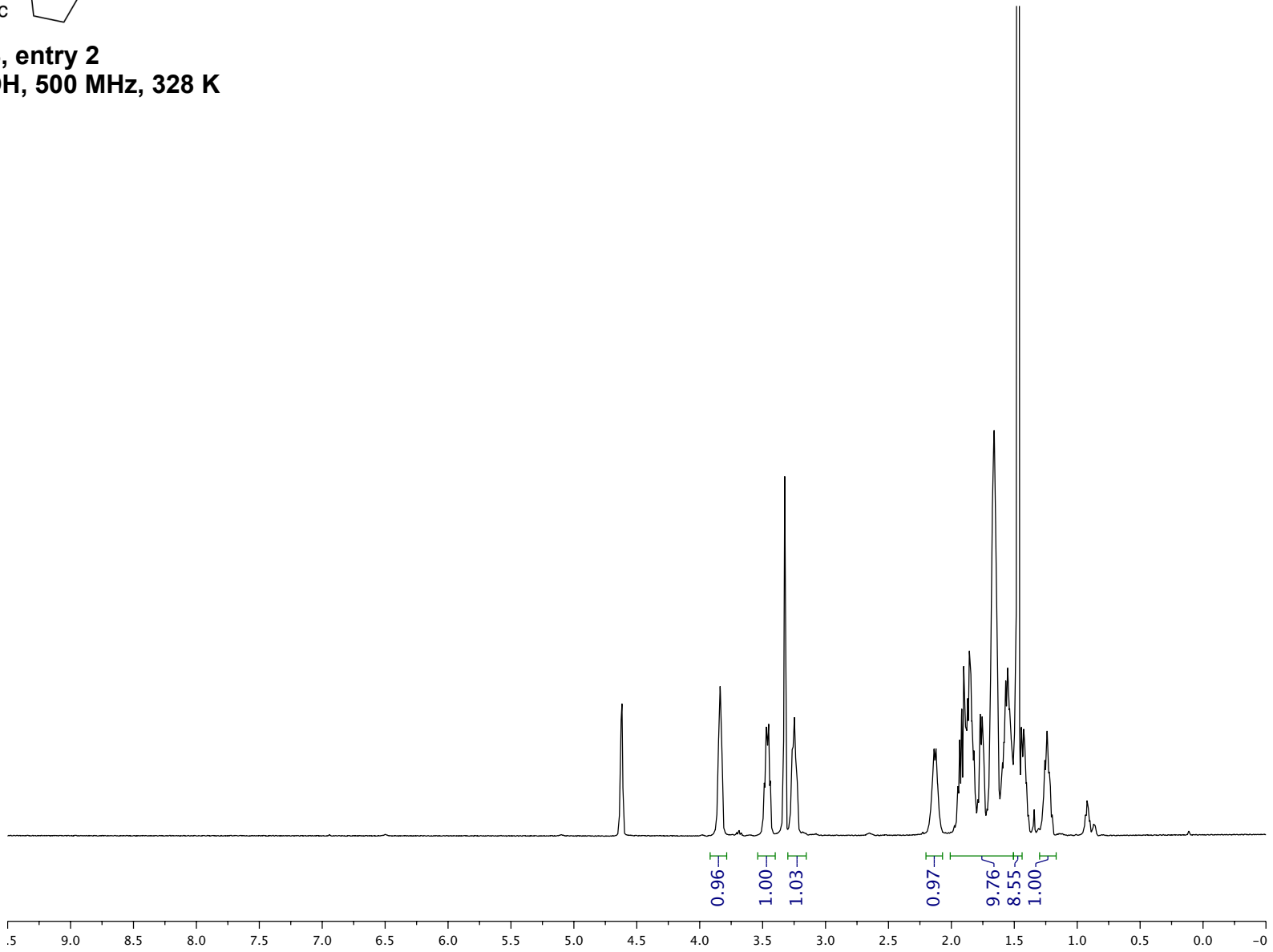


Table 3, entry 2
***d*$_4$-MeOH, 500 MHz, 328 K**



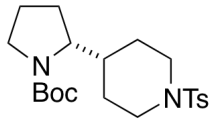
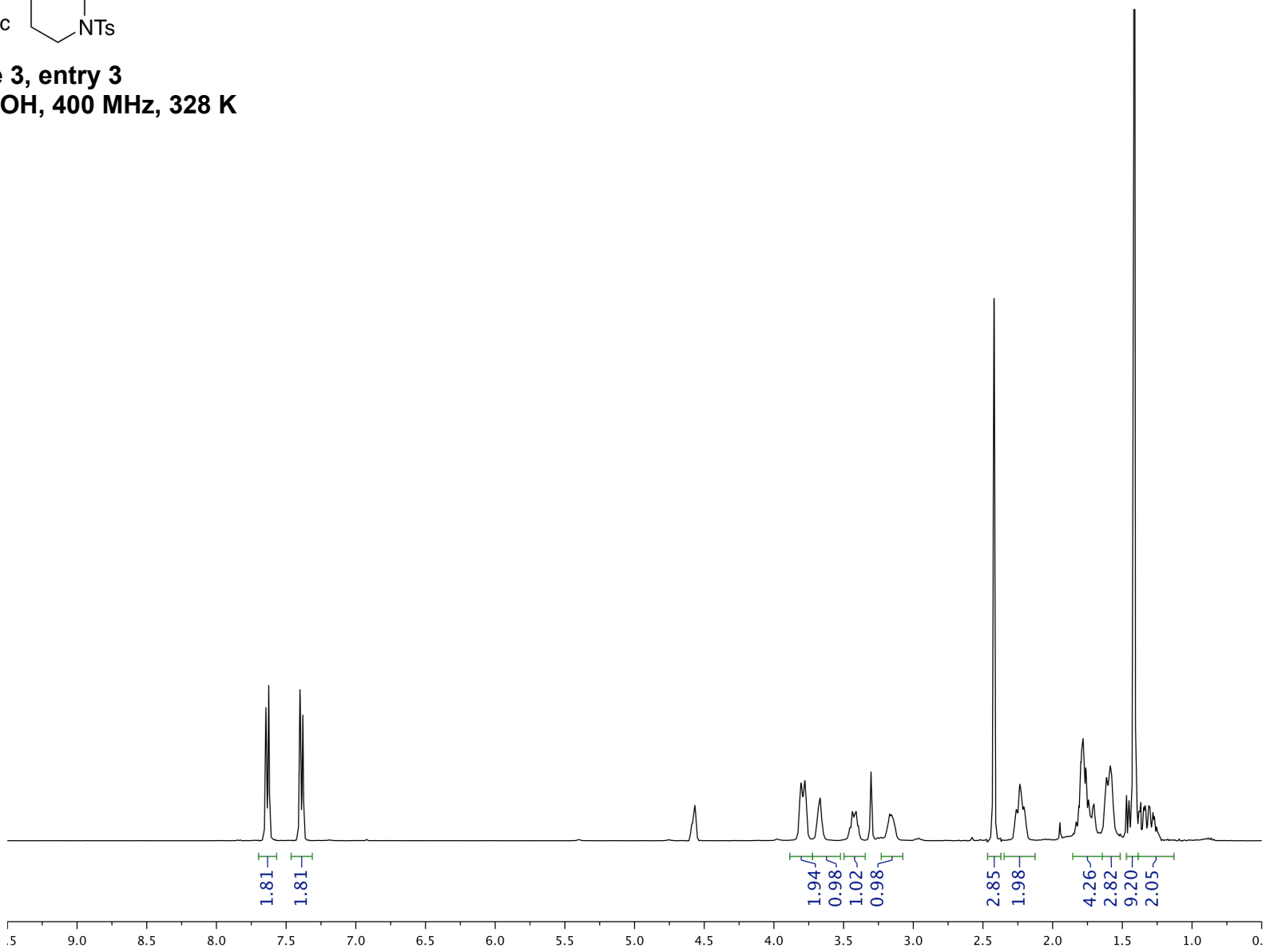


Table 3, entry 3
***d*$_4$-MeOH, 400 MHz, 328 K**



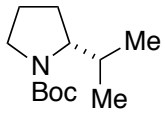
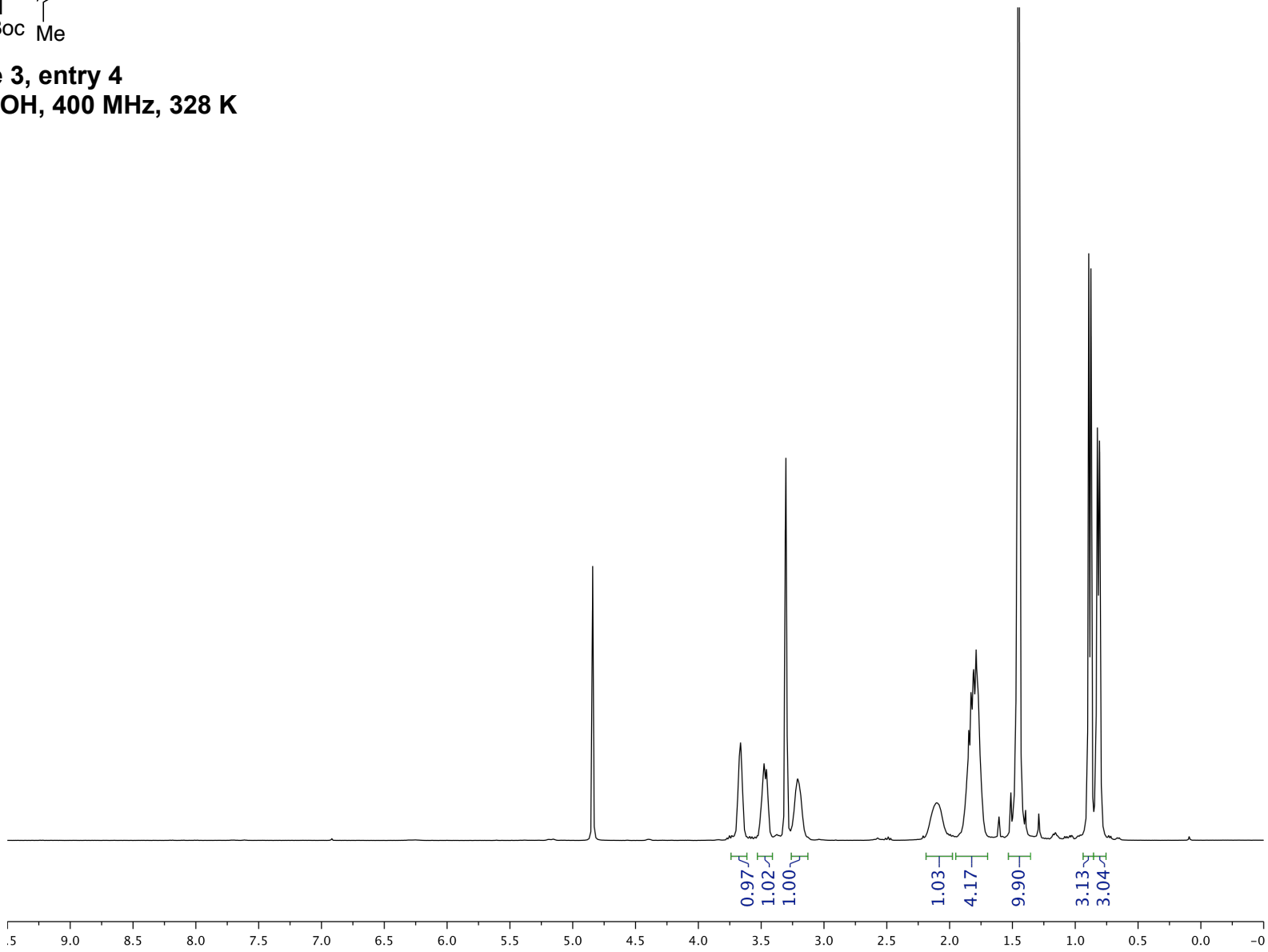


Table 3, entry 4
***d*$_4$-MeOH, 400 MHz, 328 K**



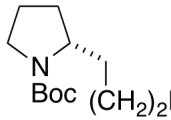
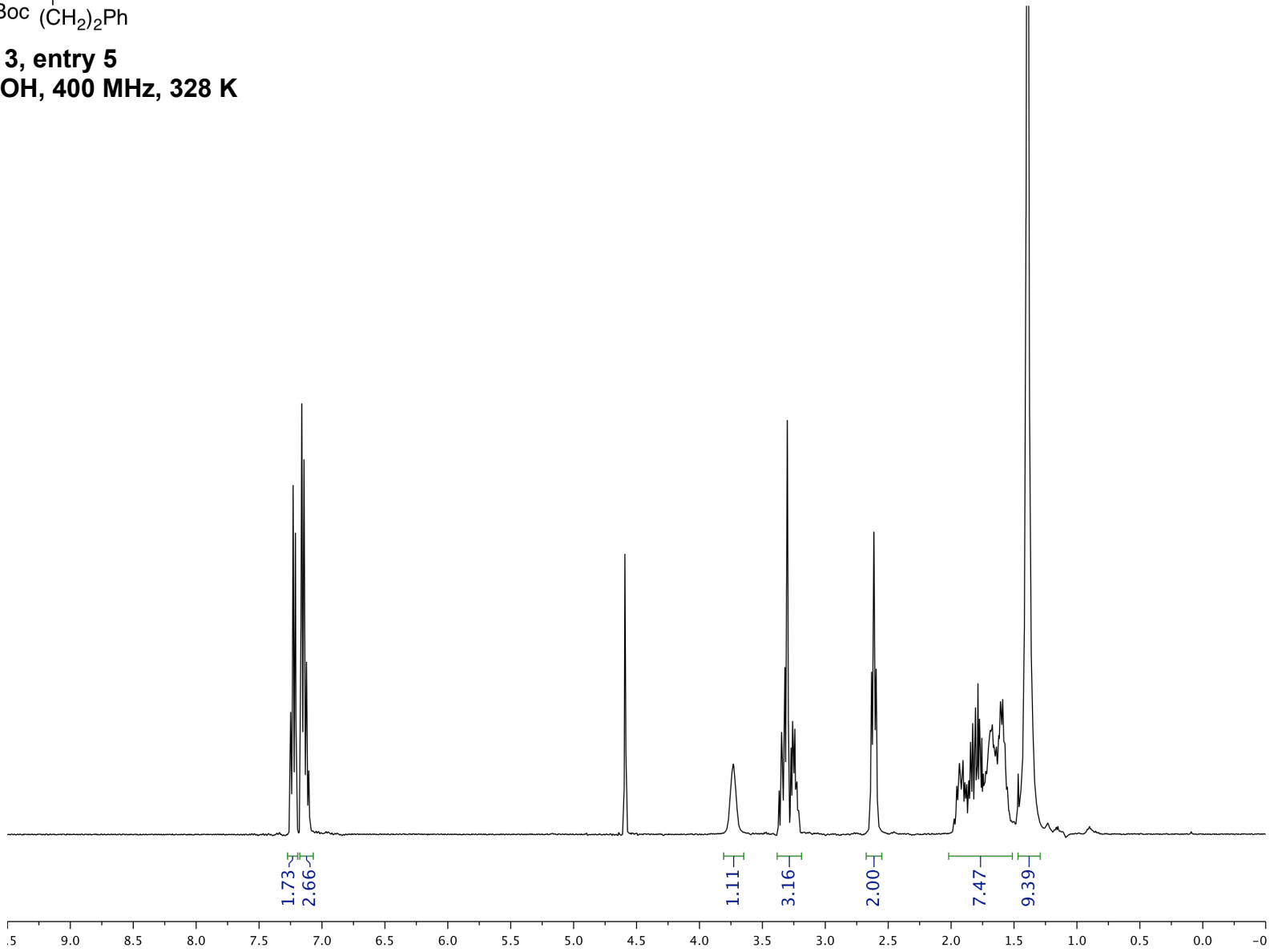
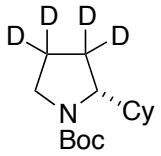


Table 3, entry 5
***d*$_4$-MeOH, 400 MHz, 328 K**





eq 6
***d*$_4$-MeOH, 400 MHz, 328 K**