Concerning the Potential Reversibility of Carbometalation in Alkoxide-directed Ti(O*i*-Pr)$_4$-mediated Reductive Cross-Coupling of Homoallylic Alcohols with Aromatic Imines

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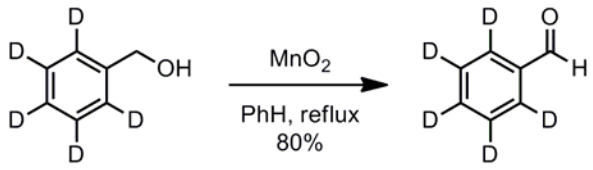
SUPPORTING INFORMATION

Experimental Procedures and Spectral Data

General. All reactions were conducted in flame-dried glassware under a nitrogen or argon atmosphere using dry solvents, unless otherwise noted. Dry diethyl ether was obtained by passing inhibitor-free, HPLC grade solvents through activated alumina columns. Dry tetrahydrofuran was obtained by distillation over sodium metal and benzophenone. Titanium(IV) tetraisopropoxide was purified by vacuum distillation prior to use. Cyclopentylmagnesium chloride and *n*-butyllithium, purchased as solutions in diethyl ether and hexanes, respectively, were titrated by the Watson–Eastham method[1] using 1,10-phenanthroline and *sec*-butanol. Commercially available homoallylic alcohol **18** was distilled under nitrogen atmosphere prior to use. Imine **20**[2] and homoallylic alcohol **19**[3] were prepared according to literature procedures. All other commercially available reagents were used as received. ^{1}H NMR data were recorded at 400 MHz or 500 MHz on a Bruker AM-400 or Bruker AM-500 spectrometer. ^{1}H NMR chemical shifts were reported relative to residual chloroform (7.26 ppm) or tetramethylsilane (0.00 ppm). ^{13}C NMR data were recorded at 101 MHz or 126 MHz on a Bruker AM-400 or Bruker AM-500 spectrometer. ^{13}C NMR chemical shifts were reported relative to the central line of chloroform-*d* (77.23 ppm). Infrared spectra were recorded on a Thermo Electron Nicolet 6700 FT-IR spectrometer. Low resolution mass spectrometry was performed on a Waters Micromass ZQ or Varian 500-MS Quadrupolar Ion Trap mass spectrometer using electrospray ionization. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography on 250 μm E. Merck silica gel plates (60F-254) and visualized with UV light or potassium permanganate stain. Flash column chromatography was performed using silica gel obtained from Silicycle (P60, particle size 40–63 μm).

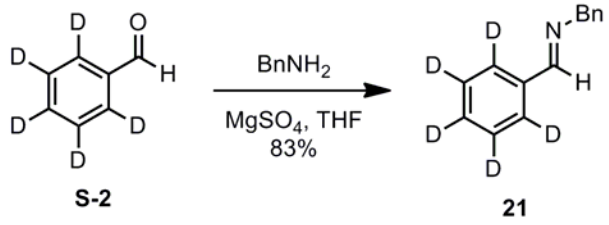


S-1 **S-2**

Synthesis of benzaldehyde-*2,3,4,5,6-d*$_5$ (S-2). A mixture of alcohol **S-1** (98 atom% D; 1.01 g, 8.92 mmol) and activated MnO_2 (2.33 g, 26.8 mmol) in reagent grade benzene (45 mL) was refluxed with azeotropic removal of H_2O for 15 h (Dean-Stark apparatus). The reaction was cooled to room temperature, filtered through celite, and concentrated to afford aldehyde **S-2** as a clear, pale yellow oil (795 mg, 80%). The product was used without further purification.

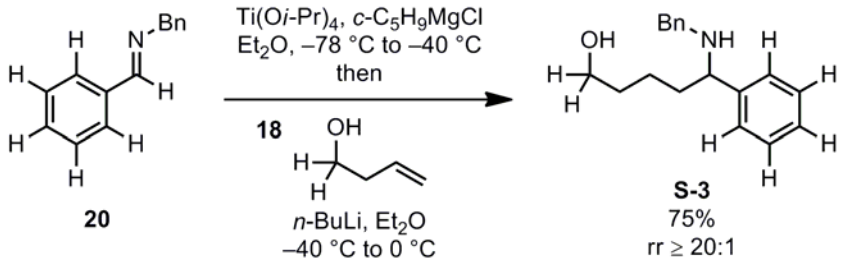
Data for benzaldehyde-*2,3,4,5,6-d*$_5$ (S-2): ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.03 (s, 1H); ^{13}C

NMR (126 MHz, $CDCl_3$) δ 192.56 (s), 136.50 (s), 134.15 (t, J = 24.4 Hz), 129.53 (t, J = 24.5 Hz), 128.70 (t, J = 24.7 Hz); IR (thin film, NaCl) ν_{max} 3064, 2819, 2738, 2696, 1844, 1830, 1772, 1693, 1653, 1597, 1584, 1539, 1490, 1475, 1455, 1391, 1339, 1311, 1289, 1205, 1167, 1072, 1023, 1001, 924, 828, 747 cm^{-1}; LRMS (ESI) m/z calc'd for $[C_7HD_5O+H]^+$ 112.1, found 111.9.



Synthesis of (*E*)-*N*-benzylidene-*2,3,4,5,6-d*$_5$-1-phenylmethanamine (21). To a solution of aldehyde **S-2** (780 mg, 7.02 mmol) in THF (30 mL) were added $MgSO_4$ (490 mg) and benzylamine (770 μL, 755 mg, 7.05 mmol). The mixture was stirred for 16 h, then filtered through celite and concentrated. The crude product was distilled (117–118 °C, 0.35 mm) to afford imine **21** as a clear, pale yellow oil (1.17 g, 83%).

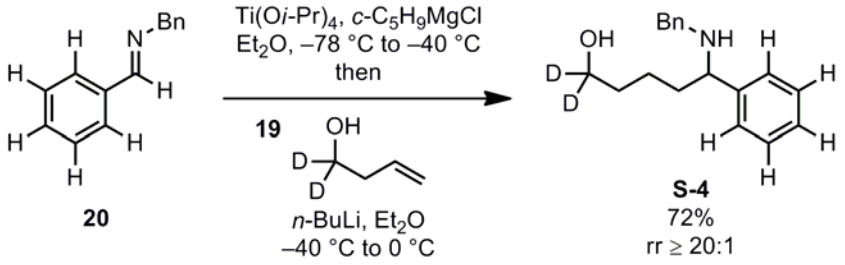
Data for (*E*)-*N*-benzylidene-*2,3,4,5,6-d*$_5$-1-phenylmethanamine (21): ^1H NMR (500 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.38–7.24 (m, 4H), 7.31–7.25 (m, 1H), 4.85 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.14 (s), 139.52 (s), 136.23 (s), 130.44 (t, J = 24.5 Hz), 128.70 (s), 128.29 (t, J = 24.6 Hz), 128.18 (s), 128.06 (t, J = 24.4 Hz), 127.18 (s), 65.27 (s); IR (thin film, NaCl) ν_{max} 3028, 2840, 2280, 1645, 1603, 1544, 1496, 1452, 1393, 1366, 1344, 1322, 1290, 1231, 1164, 1051, 1029, 959, 852, 816, 733 cm^{-1}; LRMS (ESI) m/z calc'd for $[C_{14}H_8D_5N+H]^+$ 201.1, found 201.1.



Synthesis of (±)-5-(benzylamino)-5-phenylpentan-1-ol (S-3). To a solution of imine **20** (84 μL, 88.2 mg, 0.452 mmol) and Ti(O*i*-Pr)$_4$ (200 μL, 192 mg, 0.676 mmol) in Et_2O (1.5 mL) at −78 °C was added *c*-C_5H_9MgCl (1.99 M in Et_2O, 680 μL, 1.35 mmol) in a dropwise manner. The mixture was warmed to −40 °C over 30 min then stirred for 1 h at this temperature. In a

separate flask, a solution of alcohol **18** (58 μL, 48.6 mg, 0.674 mmol) in Et_2O (1.0 mL) at −78 °C was treated with *n*-BuLi (2.49 M in hexanes, 275 μL, 0.685 mmol) and warmed to 0 °C over 15 min. The alkoxide solution was added in a dropwise manner to the brown solution of imine–Ti complex at −40 °C via cannula, then the mixture was warmed to 0 °C over 30 min and stirred at this temperature for additional 6 h. The reaction was quenched by addition of H_2O (1 mL) followed by rapid stirring until the precipitate became white in color. The mixture was diluted with saturated aqueous $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 20 mL). The organic extracts were combined, dried over $MgSO_4$ then concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (10→30% acetone/hexanes) to afford amino alcohol **S-3** as a clear, colorless oil (91 mg, 75%).

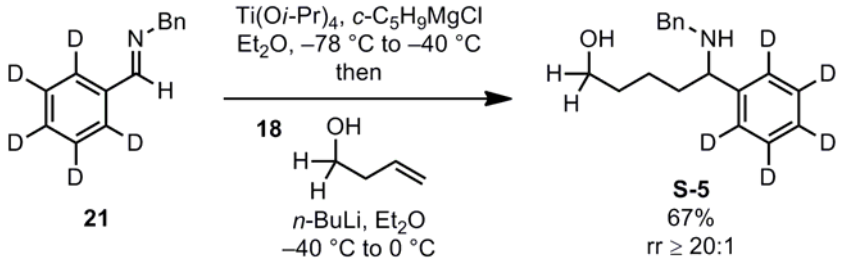
Data for (±)-5-(benzylamino)-5-phenylpentan-1-ol (S-3): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.20 (m, 10H), 3.66–3.49 (m, 5H), 1.79–1.60 (m, 2H), 1.59–1.43 (m, 4H), 1.42–1.30 (m, 1H), 1.29–1.16 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.02, 140.48, 128.54, 128.46, 128.30, 127.43, 127.16, 127.00, 62.64, 62.36, 51.55, 38.00, 32.70, 22.61; IR (thin film, NaCl) ν_{max} 3323 (br), 3105, 3084, 3061, 3027, 3003, 2934, 2859, 1950, 1879, 1810, 1602, 1584, 1547, 1494, 1454, 1361, 1329, 1308, 1199, 1155, 1107, 1066, 1028, 984, 911, 848, 761, 735, 699 cm^{-1}; LRMS (ESI) *m*/*z* calc'd for $[C_{18}H_{23}NO+H]^+$ 270.2, found 270.6; R_f 0.27 (silica gel, 3:7 acetone/hexanes).



Synthesis of (±)-5-(benzylamino)-5-phenylpentan-*1,1-d*$_2$-1-ol (S-4). To a solution of imine **20** (84 μL, 88.2 mg, 0.452 mmol) and Ti(O*i*-Pr)$_4$ (200 μL, 192 mg, 0.676 mmol) in Et_2O (1.5 mL) at −78 °C was added *c*-C_5H_9MgCl (1.99 M in Et_2O, 680 μL, 1.35 mmol) in a dropwise manner. The mixture was warmed to −40 °C over 30 min then stirred for 1 h at this temperature. In a separate flask, a solution of alcohol **19** (57 μL, 50.2 mg, 0.677 mmol) in Et_2O (1.0 mL) at −78 °C was treated with *n*-BuLi (2.49 M in hexanes, 275 μL, 0.685 mmol) and warmed to 0 °C over 15 min. The alkoxide solution was added in a dropwise manner to the brown solution of imine–Ti complex at −40 °C via cannula, then the mixture was warmed to 0 °C over 30 min and stirred at this temperature for additional 6 h. The reaction was quenched by addition of H_2O (1 mL)

followed by rapid stirring until the precipitate became white in color. The mixture was diluted with saturated aqueous $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 20 mL). The organic extracts were combined, dried over $MgSO_4$ then concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (10→30% acetone/hexanes) to afford amino alcohol **S-4** as a clear, colorless oil (88 mg, 72%).

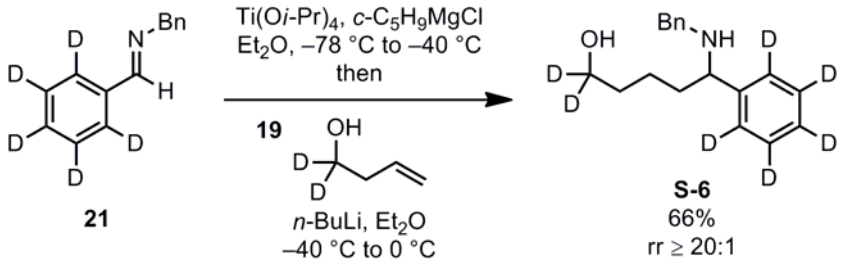
Data for (±)-5-(benzylamino)-5-phenylpentan-*1,1-d*$_2$-1-ol (S-4): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.20 (m, 10H), 3.64 (d, *J* = 13.1 Hz, 1H), 3.61 (app t, *J* = 6.8 Hz, 1H), 3.52 (d, *J* = 13.1 Hz, 1H), 1.80–1.60 (m, 2H), 1.58–1.43 (m, 4H), 1.42–1.29 (m, 1H), 1.28–1.16 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.13 (s), 140.60 (s), 128.58 (s), 128.50 (s), 128.34 (s), 127.47 (s), 127.20 (s), 127.03 (s), 62.68 (s), 61.81 (quintet, *J* = 21.3 Hz), 51.61 (s), 38.10 (s), 32.55 (s), 22.59 (s); IR (thin film, NaCl) ν_{max} 3322 (br), 3084, 3061, 3027, 3003, 2931, 2858, 2190, 2086, 1950, 1879, 1810, 1602, 1584, 1494, 1454, 1361, 1307, 1198, 1180, 1135, 1110, 1072, 1028, 1002, 967, 911, 846, 763, 738, 699 cm^{-1}; LRMS (ESI) *m*/*z* calc'd for $[C_{18}H_{21}D_2NO+H]^+$ 272.2, found 272.6; R_f 0.27 (silica gel, 3:7 acetone/hexanes).



Synthesis of (±)-5-(benzylamino)-5-phenyl-*d*$_5$-pentan-1-ol (S-5). To a solution of imine **21** (83 μL, 90.5 mg, 0.452 mmol) and Ti(O*i*-Pr)$_4$ (200 μL, 192 mg, 0.676 mmol) in Et_2O (1.5 mL) at −78 °C was added *c*-C_5H_9MgCl (1.99 M in Et_2O, 680 μL, 1.35 mmol) in a dropwise manner. The mixture was warmed to −40 °C over 30 min then stirred for 1 h at this temperature. In a separate flask, a solution of alcohol **18** (58 μL, 48.6 mg, 0.674 mmol) in Et_2O (1.0 mL) at −78 °C was treated with *n*-BuLi (2.49 M in hexanes, 275 μL, 0.685 mmol) and warmed to 0 °C over 15 min. The alkoxide solution was added in a dropwise manner to the brown solution of imine–Ti complex at −40 °C via cannula, then the mixture was warmed to 0 °C over 30 min and stirred at this temperature for additional 6 h. The reaction was quenched by addition of H_2O (1 mL) followed by rapid stirring until the precipitate became white in color. The mixture was diluted with saturated aqueous $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 20 mL). The organic extracts were combined, dried over $MgSO_4$ then concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (10→30% acetone/hexanes) to afford amino

alcohol **S-5** as a clear, colorless oil (83 mg, 67%).

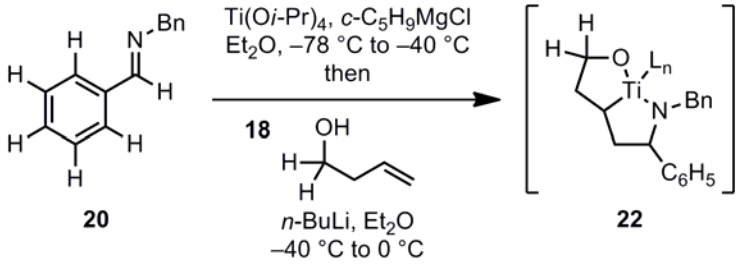
Data for (±)-5-(benzylamino)-5-phenyl-d_5-pentan-1-ol (S-5): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.20 (m, 5H), 3.67–3.49 (m, 5H), 1.81–1.61 (m, 2H), 1.60–1.43 (m, 4H), 1.42–1.30 (m, 1H), 1.29–1.16 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.99 (s), 140.64 (s), 128.52 (s), 128.36 (s), 128.08 (t, J = 23.3 Hz), 127.05 (t, J = 24.3 Hz), 127.05 (s), 126.70 (t, J = 23.5 Hz), 62.65 (s), 62.63 (s), 51.64 (s), 38.12 (s), 32.78 (s), 22.65 (s); IR (thin film, NaCl) ν_{max} 3323 (br), 3085, 3062, 3028, 2932, 2859, 2273, 1950, 1876, 1811, 1603, 1585, 1570, 1495, 1454, 1367, 1314, 1203, 1154, 1072, 1029, 983, 909, 840, 822, 737, 699 cm^{-1}; LRMS (ESI) *m*/*z* calc'd for $[C_{18}H_{18}D_5NO+H]^+$ 275.2, found 275.6; R_f 0.27 (silica gel, 3:7 acetone/hexanes).



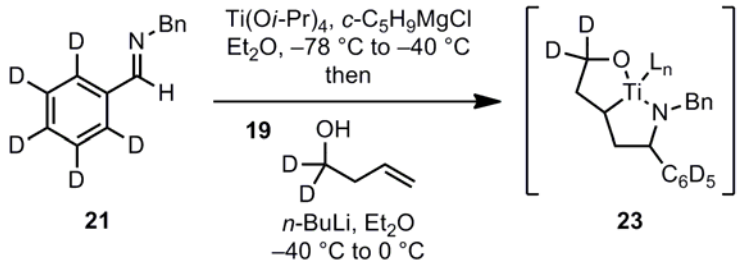
Synthesis of (±)-5-(benzylamino)-5-phenyl-d_5-pentan-*1,1*-d_2-1-ol (S-6). To a solution of imine **21** (83 μL, 90.5 mg, 0.452 mmol) and Ti(O*i*-Pr)$_4$ (200 μL, 192 mg, 0.676 mmol) in Et_2O (1.5 mL) at −78 °C was added *c*-C_5H_9MgCl (1.99 M in Et_2O, 680 μL, 1.35 mmol) in a dropwise manner. The mixture was warmed to −40 °C over 30 min then stirred for 1 h at this temperature. In a separate flask, a solution of alcohol **19** (57 μL, 50.2 mg, 0.677 mmol) in Et_2O (1.0 mL) at −78 °C was treated with *n*-BuLi (2.49 M in hexanes, 275 μL, 0.685 mmol) and warmed to 0 °C over 15 min. The alkoxide solution was added in a dropwise manner to the brown solution of imine–Ti complex at −40 °C via cannula, then the mixture was warmed to 0 °C over 30 min and stirred at this temperature for additional 6 h. The reaction was quenched by addition of H_2O (1 mL) followed by rapid stirring until the precipitate became white in color. The mixture was diluted with saturated aqueous $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 20 mL). The organic extracts were combined, dried over $MgSO_4$ then concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (10→30% acetone/hexanes) to afford amino alcohol **S-6** as a clear, colorless oil (82 mg, 66%).

Data for (±)-5-(benzylamino)-5-phenyl-d_5-pentan-*1,1*-d_2-1-ol (S-6): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.20 (m, 5H), 3.64 (d, J = 13.1 Hz, 1H), 3.61 (dd, J = 7.4, 6.4 Hz, 1H), 3.52 (d, J = 13.1 Hz, 1H), 1.80–1.43 (m, 6H), 1.41–1.29 (m, 1H), 1.28–1.16 (m, 1H); ^{13}C NMR (xx MHz, $CDCl_3$) δ 143.97 (s), 140.62 (s), 128.52 (s), 128.35 (s), 128.08 (t, J = 24.4 Hz), 127.05 (t, J = 23.9

Hz), 127.04 (s), 126.69 (t, J = 24.9 Hz), 62.62 (s), 61.87 (quintet, J = 21.5 Hz), 51.63 (s), 38.11 (s), 32.57 (s), 22.60 (s); IR (thin film, NaCl) ν_{max} 3323 (br), 3085, 3062, 3028, 2932, 2858, 2273, 2191, 2085, 1950, 1876, 1811, 1603, 1585, 1570, 1495, 1454, 1367, 1313, 1203, 1181, 1156, 1133, 1107, 1076, 1028, 967, 908, 839, 822, 738, 699 cm^{-1}; LRMS (ESI) m/z calc'd for $[C_{18}H_{16}D_7NO+H]^+$ 277.2, found 277.6; R_f 0.27 (silica gel, 3:7 acetone/hexanes).

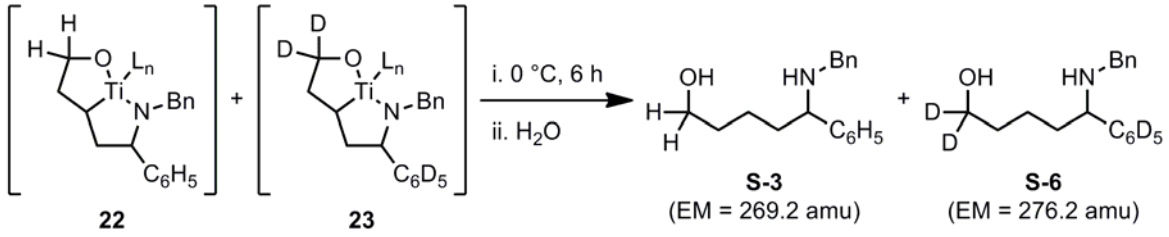


Preparation of titanacycle-d_0 (22). To a solution of imine **20** (84 μL, 88.2 mg, 0.452 mmol) and Ti(O*i*-Pr)$_4$ (200 μL, 192 mg, 0.676 mmol) in Et_2O (1.5 mL) at −78 °C was added *c*-C_5H_9MgCl (1.97 M in Et_2O, 690 μL, 1.36 mmol) in a dropwise manner. The mixture was warmed to −40 °C over 30 min then stirred for 1 h at this temperature. In a separate flask, a solution of alcohol **18** (58 μL, 48.6 mg, 0.674 mmol) in Et_2O (1.0 mL) at −78 °C was treated with *n*-BuLi (2.49 M in hexanes, 280 μL, 0.697 mmol) and warmed to 0 °C over 30 min. The alkoxide solution was added in a dropwise manner to the brown solution of imine–Ti complex at −40 °C via cannula, then the mixture was warmed to 0 °C over 30 min and stirred at this temperature for additional 6 h to provide a solution of **22** that was used immediately in the subsequent crossover experiment.

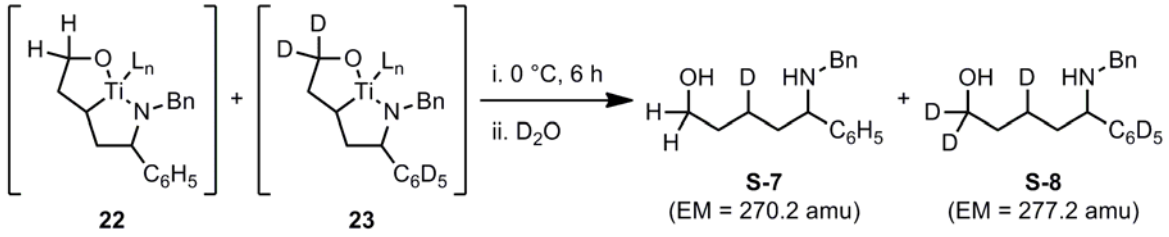


Preparation of titanacycle-d_7 (23). To a solution of imine **21** (83 μL, 90.5 mg, 0.452 mmol) and Ti(O*i*-Pr)$_4$ (200 μL, 192 mg, 0.676 mmol) in Et_2O (1.5 mL) at −78 °C was added *c*-C_5H_9MgCl (1.97 M in Et_2O, 690 μL, 1.36 mmol) in a dropwise manner. The mixture was

warmed to −40 °C over 30 min then stirred for 1 h at this temperature. In a separate flask, a solution of alcohol **19** (57 μL, 50.2 mg, 0.677 mmol) in Et_2O (1.0 mL) at −78 °C was treated with *n*-BuLi (2.49 M in hexanes, 280 μL, 0.697 mmol) and warmed to 0 °C over 30 min. The alkoxide solution was added in a dropwise manner to the brown solution of imine–Ti complex at −40 °C via cannula, then the mixture was warmed to 0 °C over 30 min and stirred at this temperature for additional 6 h to provide a solution of **23** that was used immediately in the subsequent crossover experiment.



Crossover experiment 1. Solutions of titanacycle intermediates **22** and **23** (1.5 mL each), prepared as described above, were transferred to a single flask via gas-tight syringe, and the resulting mixture was stirred at 0 °C for 6 h. The reaction was quenched by addition of H_2O (1 mL) followed by rapid stirring until the precipitate became white in color. The mixture was diluted with saturated aqueous $NaHCO_3$ (20 mL) and extracted with EtOAc (1 × 60 mL). The organic phase was washed successively with H_2O and brine (1 × 20 mL each), then dried over $MgSO_4$ and concentrated *in vacuo*. Analysis of the crude product by LRMS (ESI) indicated two peaks at *m*/*z* 270.7 and 277.7 ($[M+H]^+$ for **S-3** and **S-6**, respectively), confirming the absence of crossover products.



Crossover experiment 2. Solutions of titanacycle intermediates **22** and **23** (1.5 mL each), prepared as described above, were transferred to a single flask via gas-tight syringe, and the

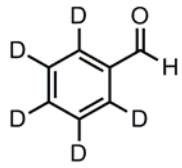
resulting mixture was stirred at 0 °C for 6 h. The reaction was quenched by addition of D_2O (1 mL) followed by rapid stirring until the precipitate became white in color. The mixture was diluted with saturated aqueous $NaHCO_3$ (20 mL) and extracted with EtOAc (1 × 60 mL). The organic phase was washed successively with H_2O and brine (1 × 20 mL each), then dried over $MgSO_4$ and concentrated *in vacuo*. Analysis of the crude product by LRMS (ESI) indicated two peaks at *m*/*z* 271.7 and 278.7 ($[M+H]^+$ for **S-7** and **S-8**, respectively), confirming quantitative deuterium incorporation.

References:

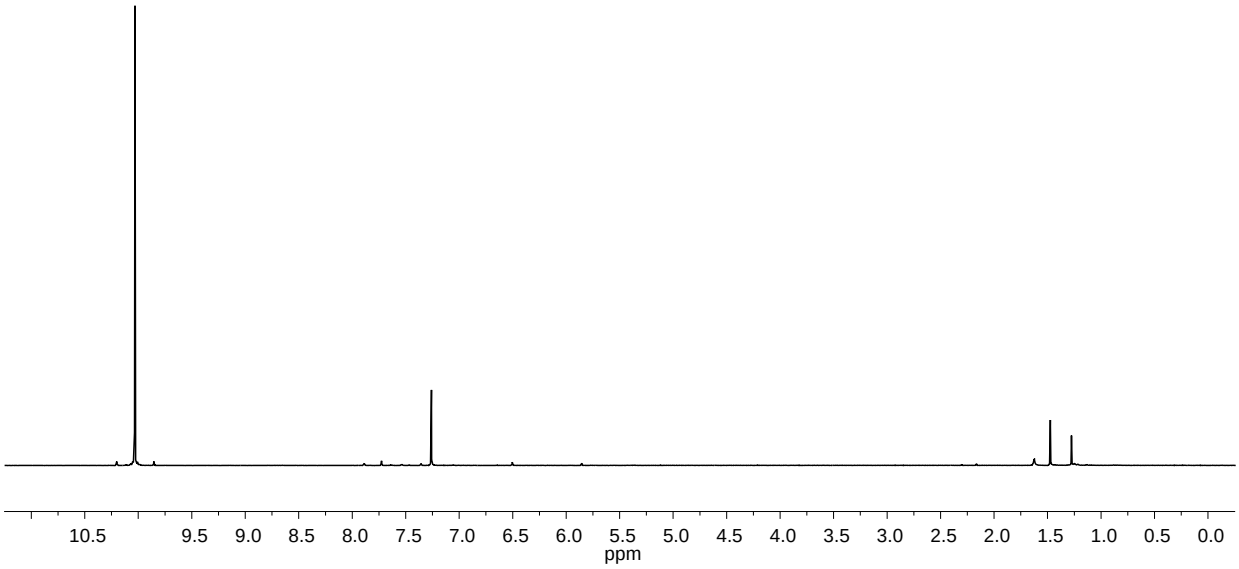
(1) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.

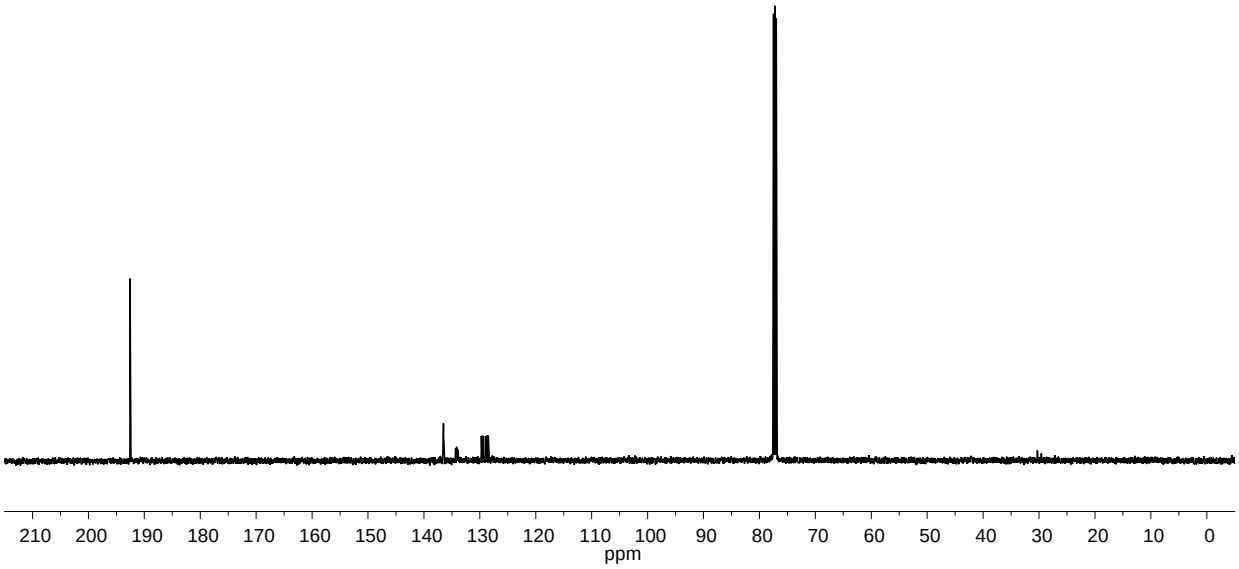
(2) Simion, A.; Simion, C.; Kanda, T.; Nagashima, S.; Mitoma, Y.; Yamada, T.; Mimura, K.; Tashiro, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2071.

(3) Negishi, E.; Boardman, L. D.; Sawada, H.; Bagheri, V.; Stoll, A. T.; Tour, J. M.; Rand, C. L. *J. Am. Chem. Soc.* **1988**, *110*, 5383.

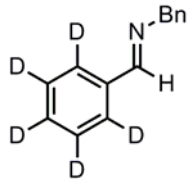


S-2

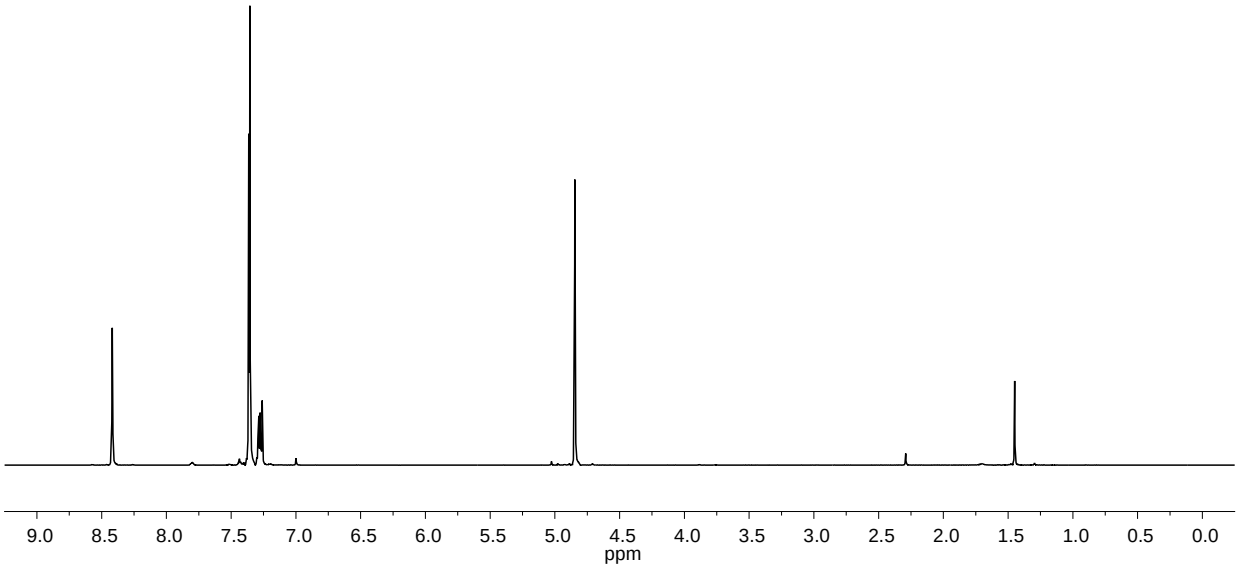


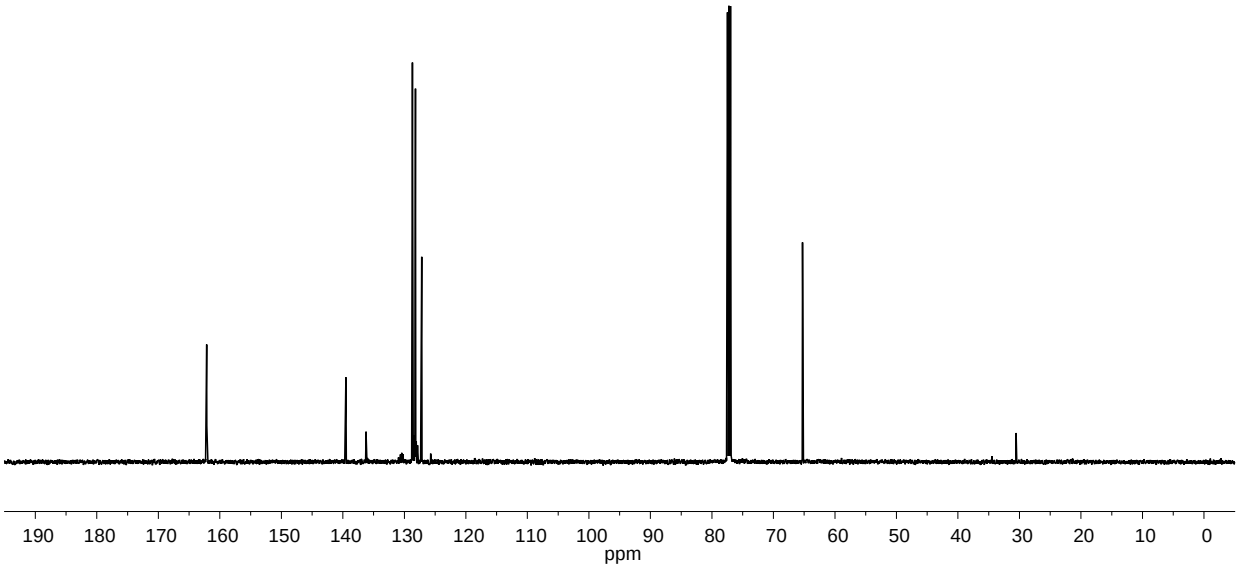


^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) of compound **S-2**

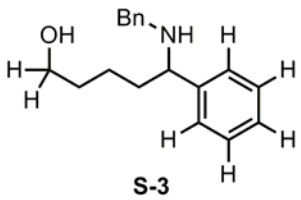


21

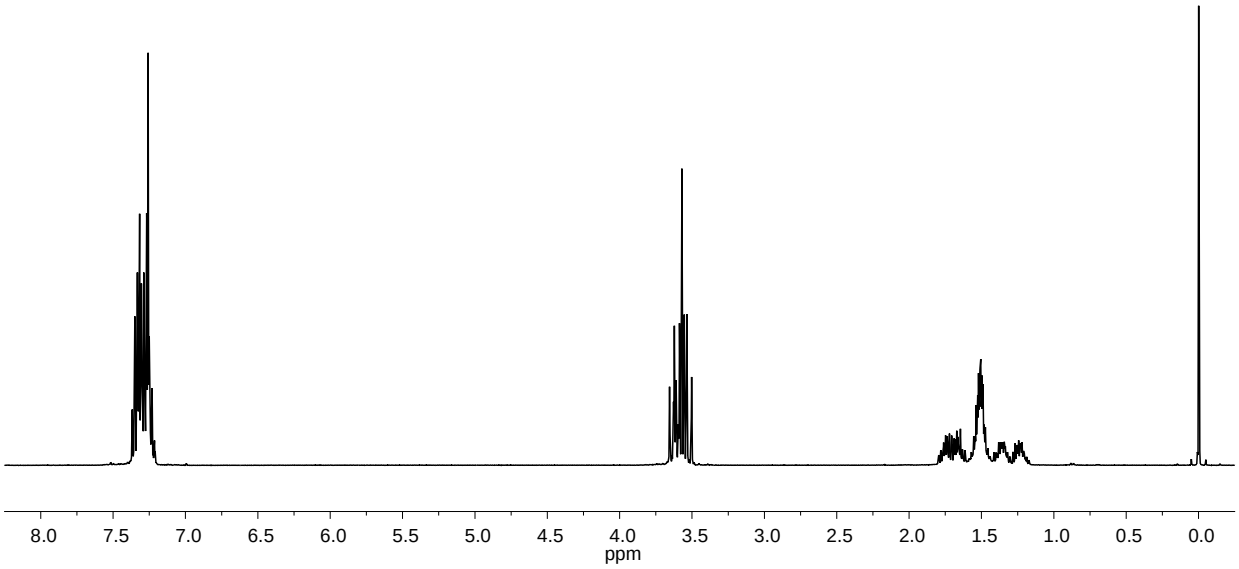


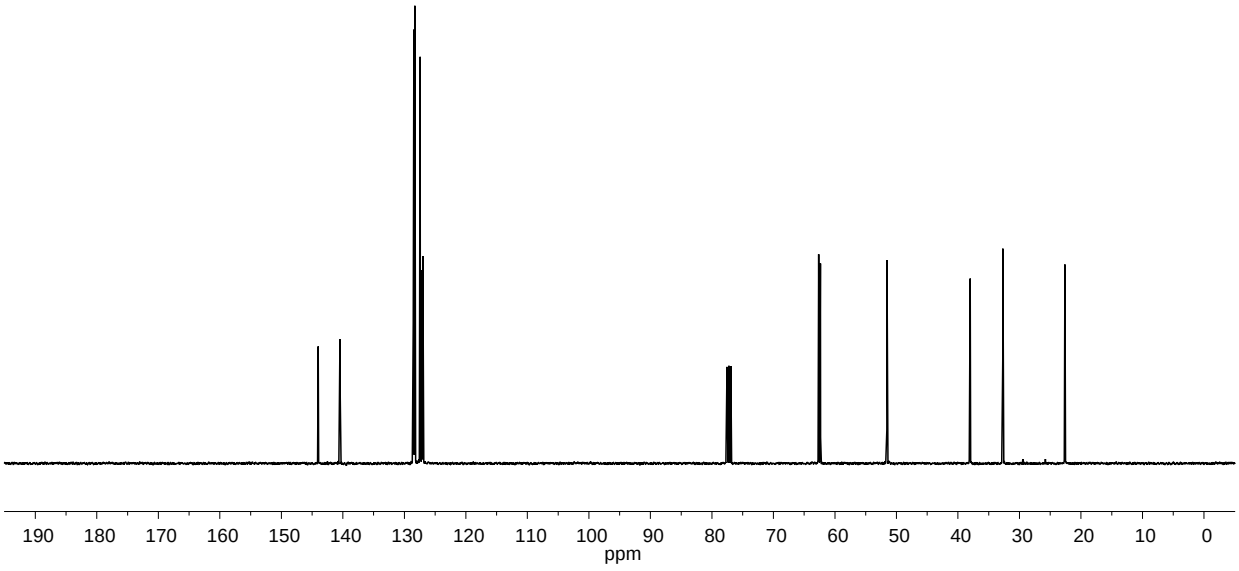


^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) of compound **21**

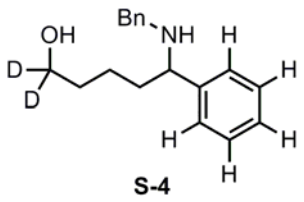


S-3

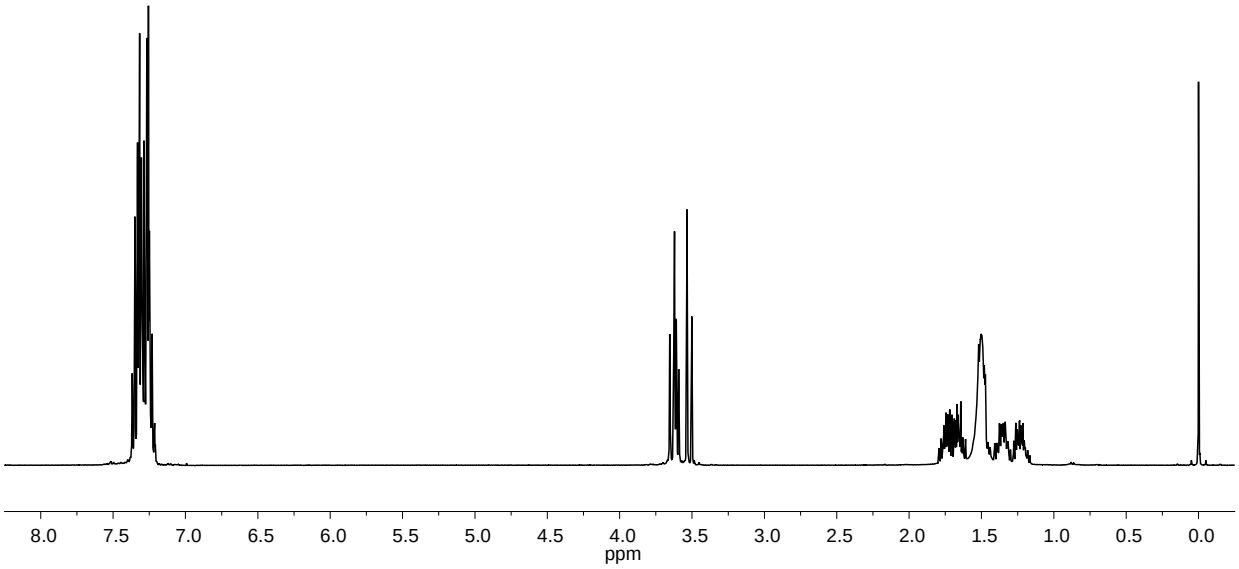


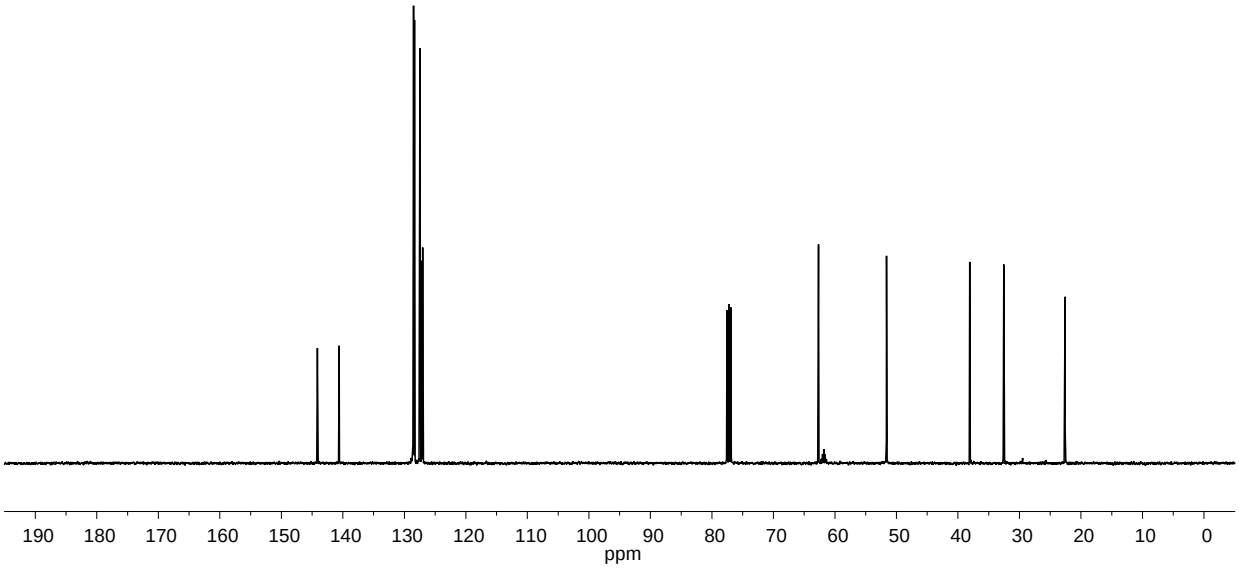


^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) of compound **S-3**

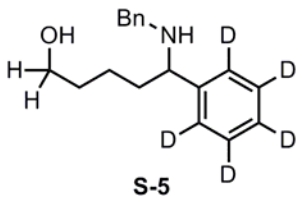


S-4

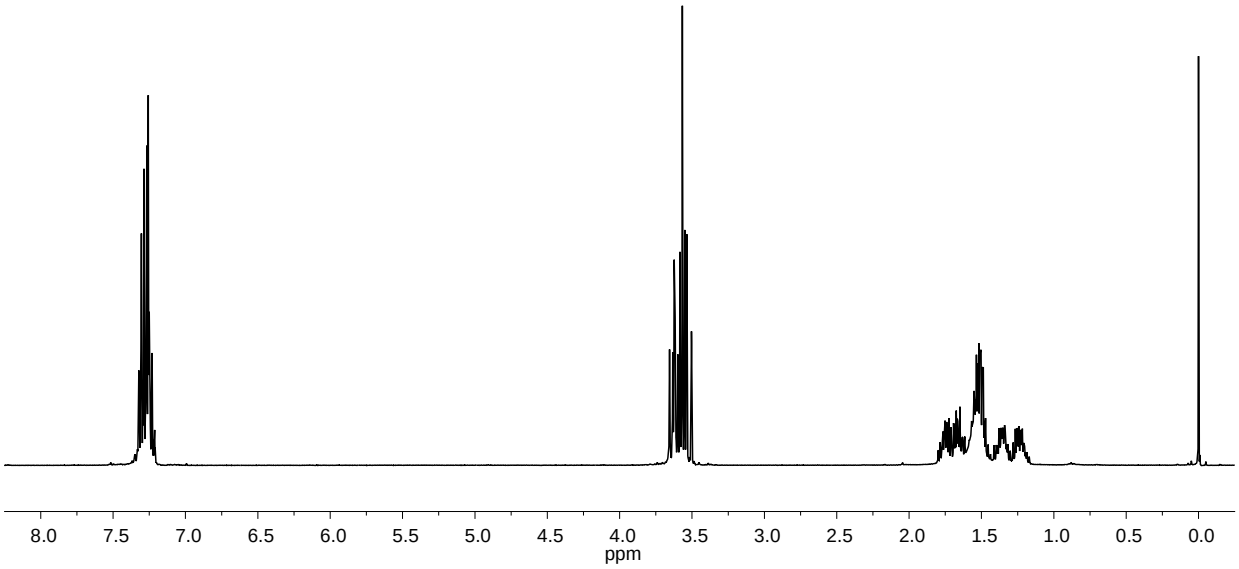


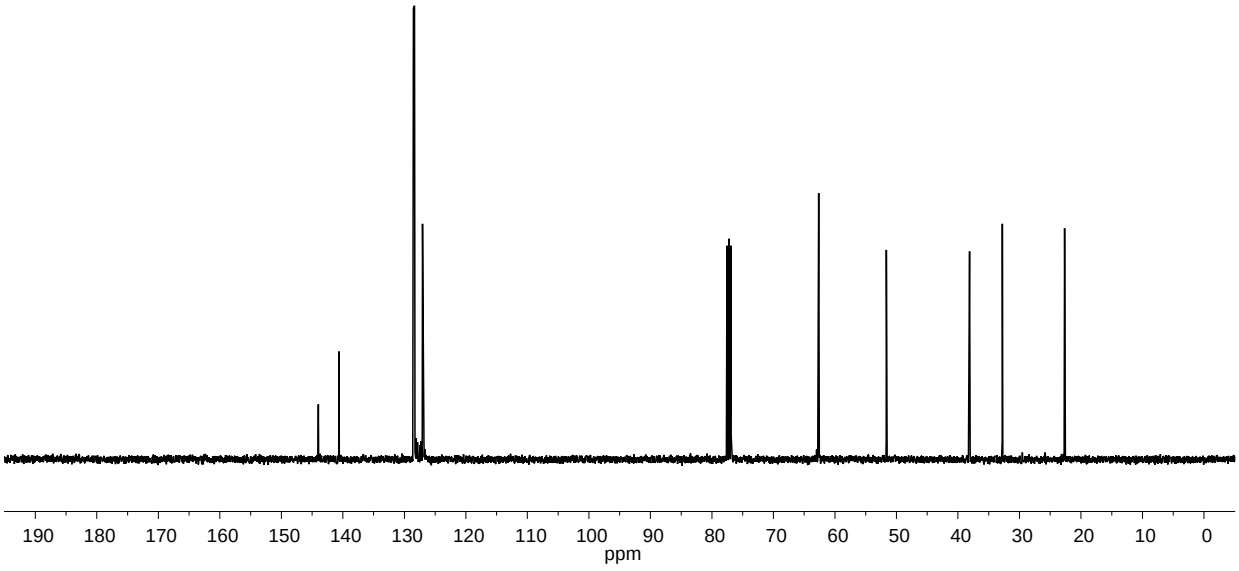


^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) of compound **S-4**

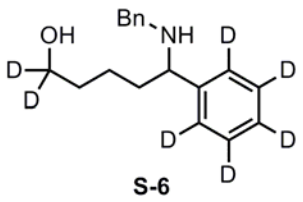


S-5

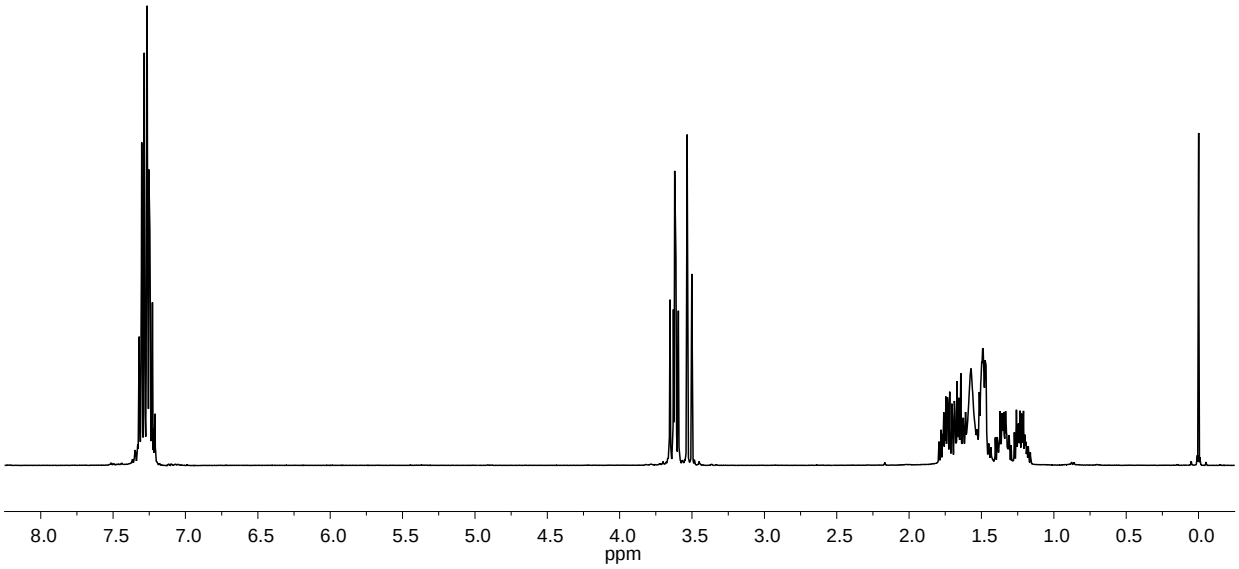


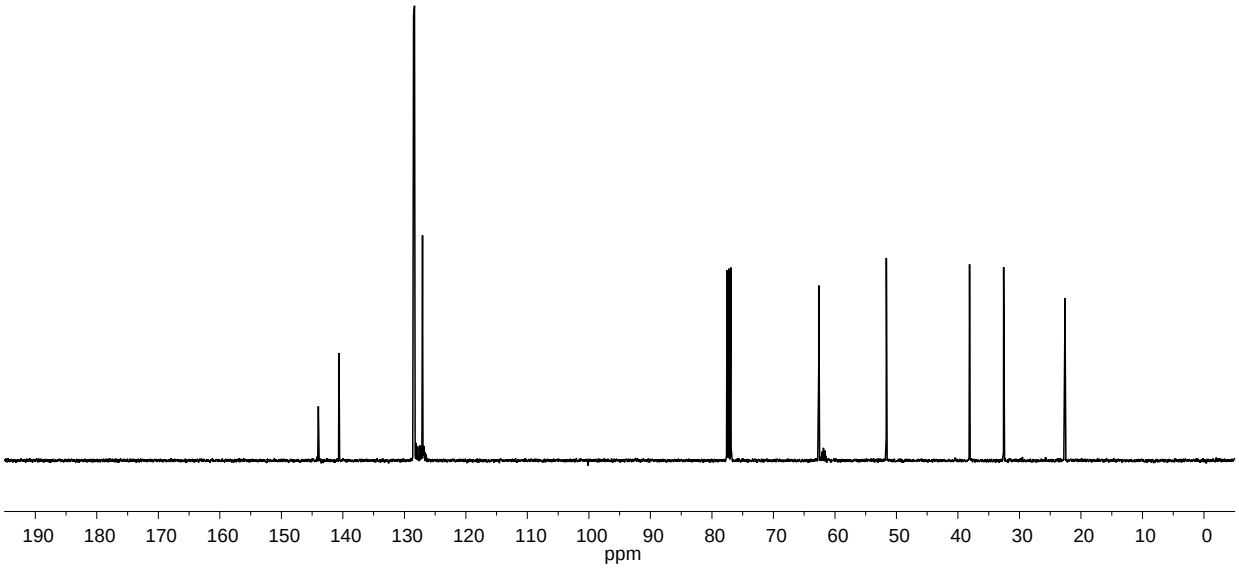


^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) of compound **S-5**



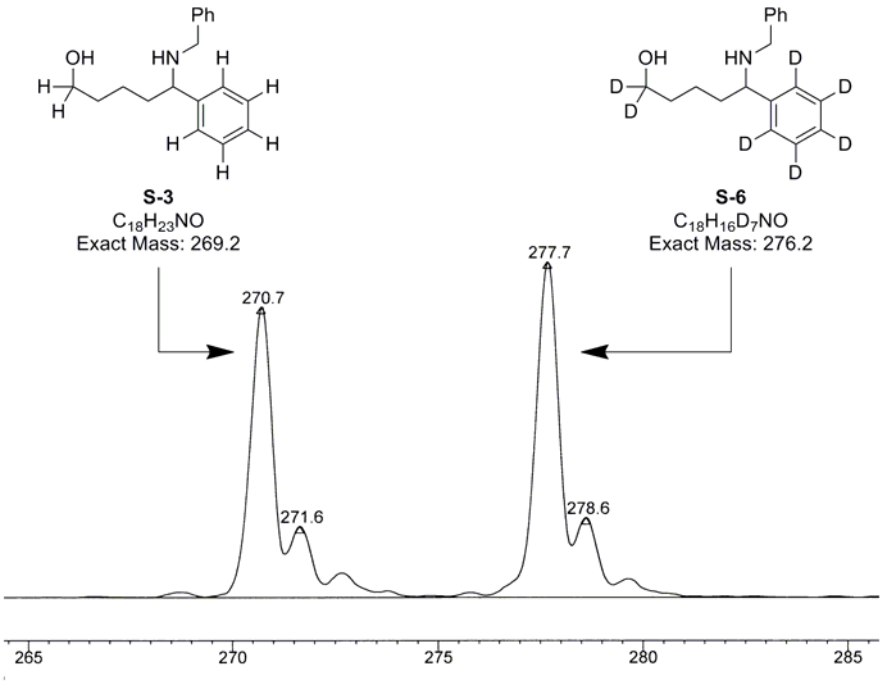
S-6



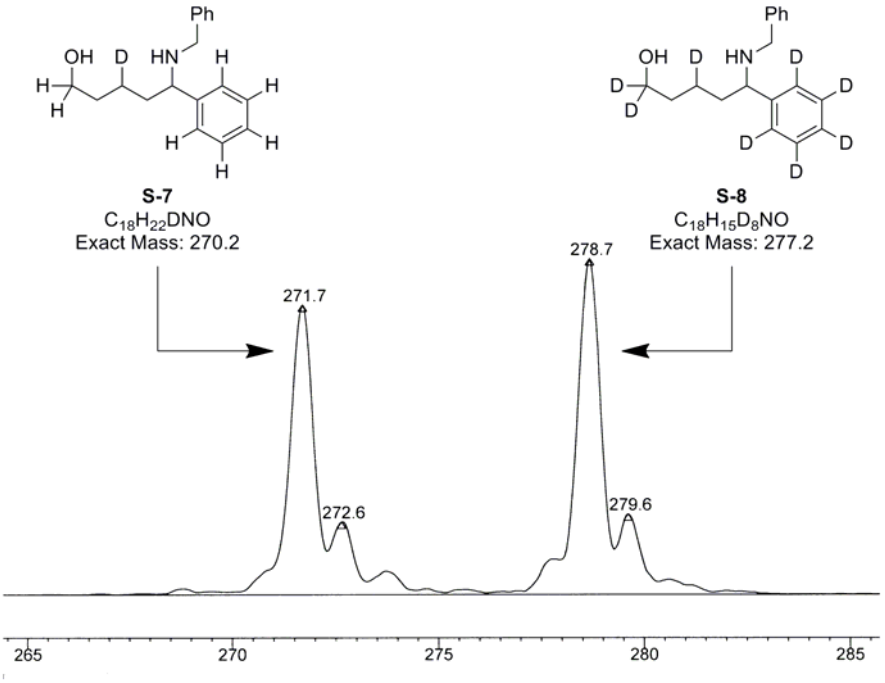


^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) of compound **S-6**

(a) H_2O quench

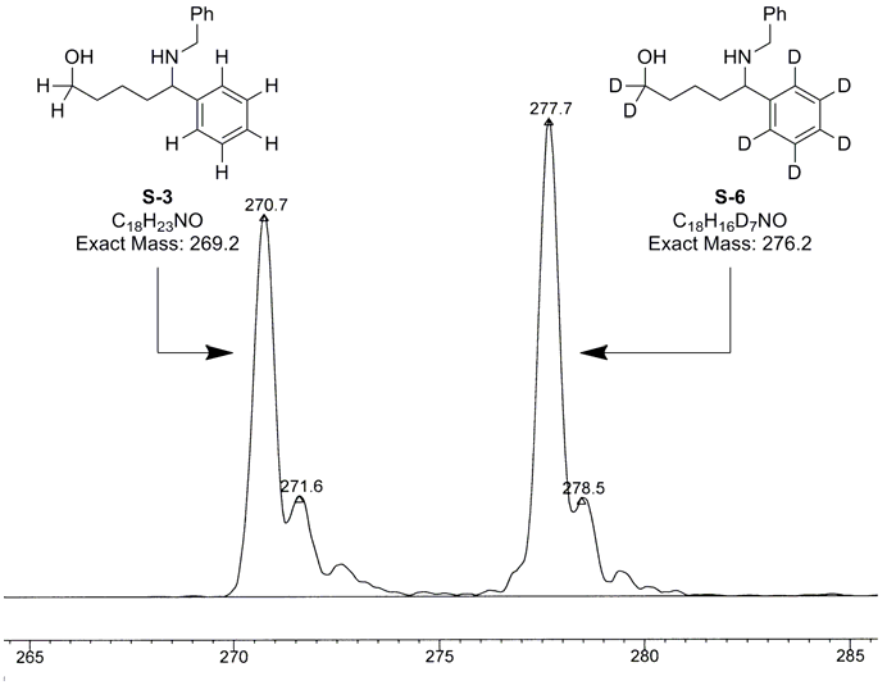


(b) D_2O quench

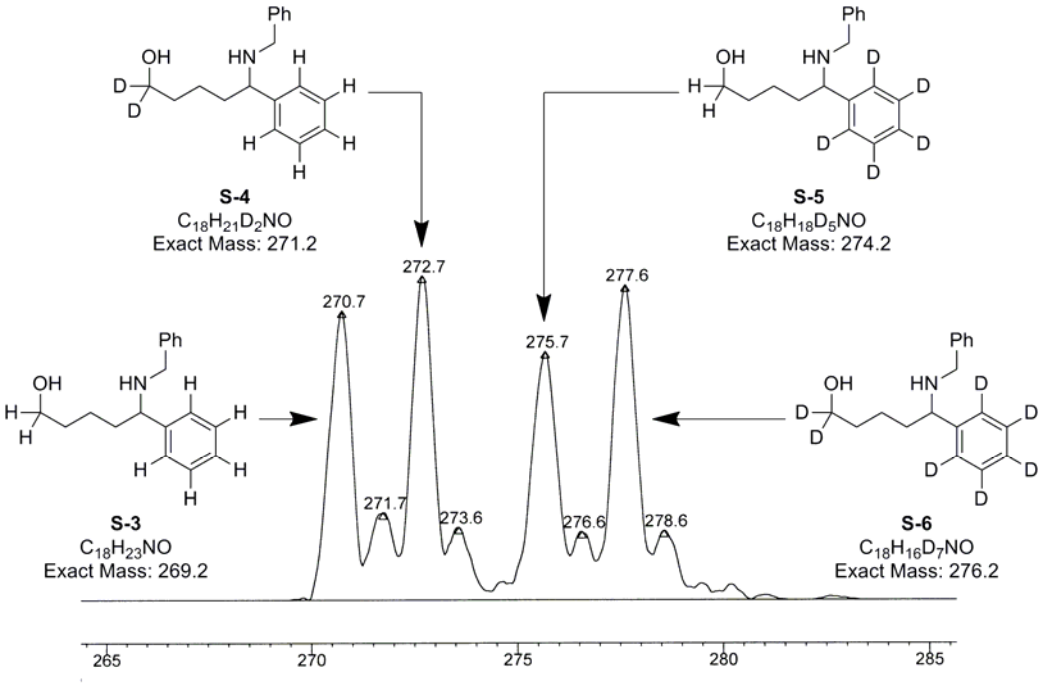


LRMS (ESI) of crude products from crossover experiments

(a) Mixture of **S-3** and **S-6** (1:1 by weight)



(b) Mixture of **S-3**, **S-4**, **S-5**, and **S-6** (1:1:1:1 by weight)



LRMS (ESI) of reference mixtures prepared from isotopically pure amino alcohols