Supporting Information for: Enantiomeric Analysis of Chiral Isotopomers via Microwave Three Wave Mixing

Lincoln Satterthwaite,[*,†] Cristóbal Pérez,[‡] Amanda L. Steber,[‡] Dylan Finestone,[¶] Robert L. Broadrup,[†] and David Patterson[¶]

†*Department of Chemistry, Haverford College, Haverford PA*

‡*Max-Planck Institute for Structure and Dynamics of Matter*

¶*Physics Department, University of California, Santa Barbara*

E-mail: Lincoln.os@gmail.com

Phone: 859 779 2020

Contents

1 Apparatus **S3**

2 Synthesis **S5**

References **S7**

1 Apparatus

The apparatus was briefly described in the text, but will be described in further detail here.

The cell containing the interaction region is thermally anchored to a two stage closed-circuit helium refrigerator (Cryomech PT-415) and additionally shielded by a 40K 6061 aluminum shield, which is anchored to the first stage of the helium refrigerator. The temperatures of the shield and interaction region are monitored by a combination of Lakeshore DT-470 and DT-670 silicon diode thermometers. Cold helium gas is introduced into the cell at a rate of 5 sccm. A good ($< 10^{-6}$ Torr) vacuum) outside the cell is maintained via activated charcoal sorbs which act as strong cryopumps.

The samples of deuterated benzyl alcohol (synthetic methods described in the next section) were injected from a room-temperature syringe, with flow regulated by an AL-4000 syringe pump set to 2.5 μL/min, into a stainless steel 0.007" capillary, which was held at 345K. Fittings were made with standard HPLC parts and PEEK tubing. In traveling down this heated capillary, the sample begins to boil both because of the temperature and the vacuum inside the experiment. The vapor then travels into the cell with the cold buffer gas, and thermalizes rotationally and motionally via collisions with the buffer gas. The buffer gas has a steady-state density of n = 2×10^{14} cm^{-1}: for a mean helium velocity of $v_{\mathrm{He}} = \sqrt{\frac{8k_BT}{\pi m_{\mathrm{He}}}} = 192\,\mathrm{ms}^{-1}$ at $T = 7\,\mathrm{K}$, a flow rate of 4.5sccm, and an aperture area of 2.8cm^2, helium density can be calculated as $n_{He} = \frac{4f}{A * v_{he}}$ where f is the frequency of impact with the walls of the cell.

A 3 μs duration chirped pulse between 0-125 MHz was generated by a Rigol DG4202 arbitrary waveform generator (AWG). It was mixed with a stepped local oscillator provided by a Hittite HMC T2220 signal generator, and both sidebands were up-converted to be between 11.7 - 18.3 GHz. The upconverted signal was amplified by a solid state amplifier (Mercury Systems L1218-32-T325), and broadcast across the cell using horn antenna Pasternack PE9854-15 (drive horn in the apparatus figure). A cryogenic switch (Analog Devices HMC547ALC3) was used to prevent the drive from damaging the detection electronics. The

molecular emission in the form of a free induction decay (FID) was collected via the receiving horn antenna for 20 μs, amplified first by a cryogenically cooled low-noise amplifier (Low Noise Factory LNF-LNC6_20B), then a room-temperature Pasternack PE1524 amplifier, and then down-converted by mixing with the output of the Hittite HMC T2220. The down-converted FID was digitized on an Agilent U1084A high speed PCIe digitizer card. The drive/listen sequence is repeated at 40 KHz, allowing for rapid signal averaging.

For M3WM, the listen horn was rotated such that it was only sensitive to radiation in the $\hat{y}$ polarization. This polarized field was applied every other drive/listen sequence, with a Mini-Circuits ZSDR-230+ RF switch used to modulate the RF field so that the three-wave mixing signal could be monitored in real time.

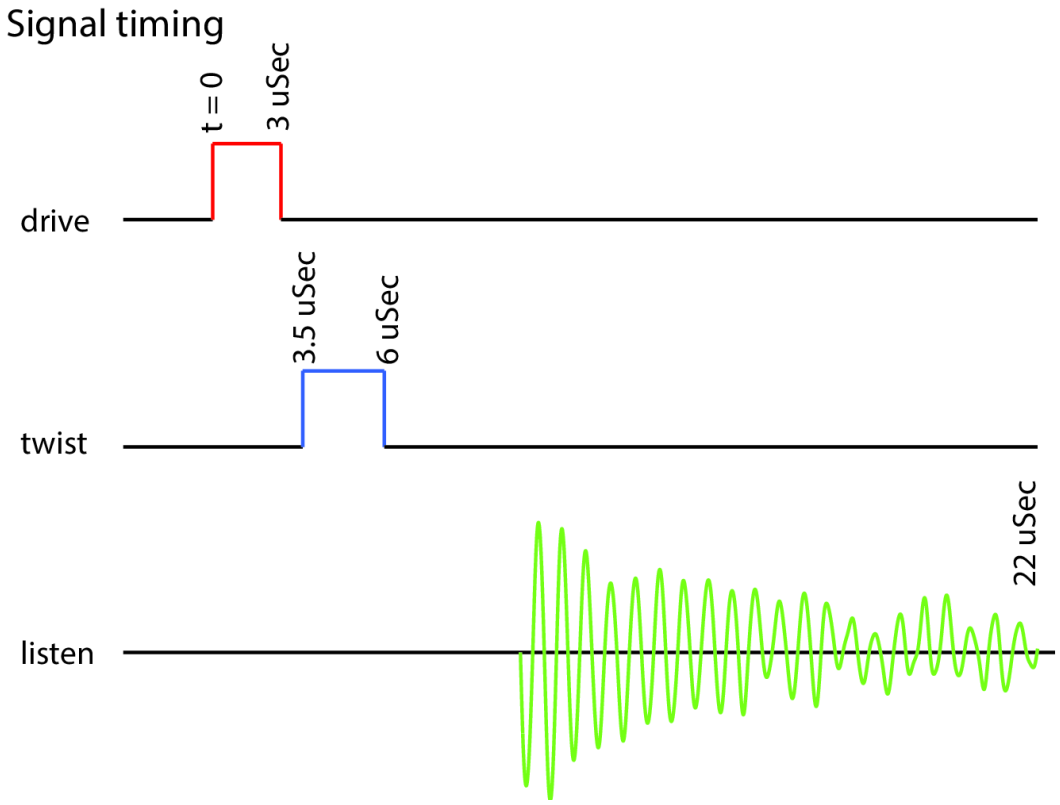

Figure S1: Timing diagram for the drive, twist, and listen pulses.

2 Synthesis

Benzyl alcohol was selected for these experiments because of its conformational simplicity and ease of synthesis. All isotopically enriched reagents were purchased from Cambridge Isotope Laboratories. (+)-α-pinene was purchased from Alfa Aesar and used as received. All other reagents and solvents purchased and used as received from Aldrich except where noted. The chiral synthesis is based on H.C. Brown's hydroboration and the Midland alpin-borane reduction.[1–3] All syntheses were carried out in-house.

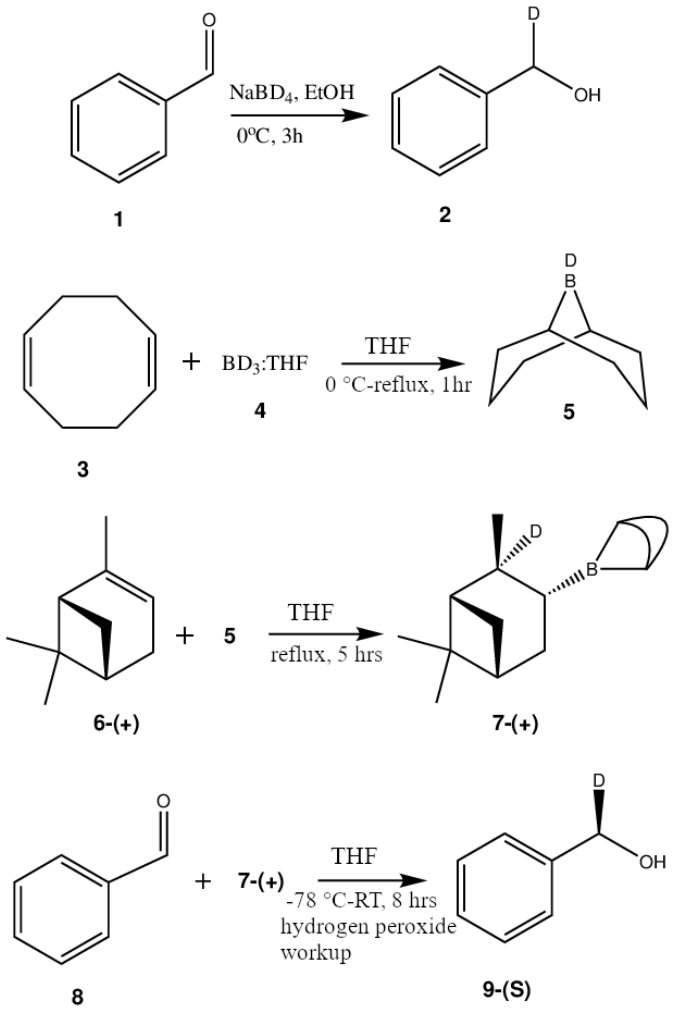

Figure S2: Reaction schemes for benzyl alcohol syntheses via sodium borohydride reduction and Midland Alpine-borane® reduction. (+) alcohols were -α-D_1

Benzyl-α-D_1-alcohol **(2)**

Sodium borodeuteride (0.91g, 22 mmol, 1.02 equiv) was stirred for 10 minutes in 25 mL absolute ethanol over ice. Freshly distilled benzaldehyde (2.18 mL, 21.5 mmol) was added to the flask and stirred for 3h going from 0 ^{o}C to rt. 5 mL saturated ammonium chloride and 20 mL deionized water added to quench. Ethanol was then removed via rotary evaporation, and aqueous layer was extracted with 3x20 mL diethyl ether. Organic layers were combined and washed with brine. Solvent was removed under reduced pressure to yield clear benzyl alcohol.

9-D-9-borabicyclo[3.3.1]nonane **(5)**

Glassware was flame dried and assembled under argon flow and allowed to cool. A 1M deuterated borane-THF solution (100 mL, 100 mmol, 1 equiv.) was cannulated into a three-necked flask immersed in an ice-saltwater bath. A THF solution of 1M 1,5-cyclooctadiene (100 mL, 100 mmol, 1 equiv.) was then added dropwise to the rapidly stirring solution over the course of 1 hour. After addition, the ice-saltwater bath was replaced by an oil bath and the reaction mixture was brought to a gentle reflux for 1 hour. The flask was cooled to yield 200 mL solution of 0.5M 9-D-9-BBN in THF **(5)**

Deuterated (±)-Alpine-Borane **7-(±)**

This procedure was carried out four times, thrice with (+)-α-pinene and once with (-)-α-pinene following the exact same procedure. (-)-α-pinene was purchased from Alfa Aesar and used as received. To 200 mL room temperature 0.5M **5** in a 500 mL three-necked flask with a scrupulously dry reflux condenser **(5)** was added $(\pm)-\alpha$-pinene (17.4 mL, 120 mmol, 1.2 equiv, which was slowly brought to reflux. Reaction mixture remained at reflux for 5 hours, after which it was slowly allowed to cool. THF was removed under reduced pressure, and a portion of liberated α-pinene removed under 30 torr vacuum at 40°C for 2 hours. Approximately 30 mL of thick, clear, neat **(±)-7** remained in the flask.

(R/S)-benzyl-α-D_1-alcohol (**R/S-9**)

This procedure was performed twice, once with (-)-Alpine-Borane and once with (+)-

Alpine-Borane. To the neat H_2 solution of **(±)-7** was added freshly re-distilled benzaldehyde (7.2 mL, 71.5 mmol, ∼0.7 equiv) with the use of a dry ice/acetone bath at -78 ^{o}C. This addition was done dropwise, as it is exothermic. The reaction mixture was allowed to come to room temperature and allowed to stir for 8 hours. After this, to the reaction mixture was added 50 mL THF to dilute the reaction mixture. Approximately 30 mL of 30% hydrogen peroxide was added dropwise to oxidize the newly created borane complex. Addition of hydrogen peroxide is exothermic enough to maintain the reaction mixture at 40 °C for 3 hours of dropwise addition. The reaction mixture was worked up with 3x30mL ether. The combined organic layers were washed with brine and dried over anhydrous magnesium sulfate. The resulting clear oil was distilled under vacuum at 80 °C, with the second fraction being **(R/S)-9**

NMR taken at 500 MHz for ^1H, and 125.7 MHz for ^{13}C

R: ^{13}C NMR δ 20.5 (s), 23.6 (s), 27.6 (s), 34.2 (s), 38.4 (s), 41.7 (s), 47.7 (s), 64.5 (q), 77.3 (t), 128.4 (t), 140.8 (s)

^{1}H NMR δ 0.92 (s), 1.02 (d), 1.11 (s), 1.24 (s), 1.79 (m), 2.37 (m), 2.90 (s,b), 4.60 (s), 7.34 (m)

S:^{13}C NMR δ 20.1 (s), 23.2 (s), 34.2 (s), 38.4 (s), 41.7 (s), 47.7 (s), 64.5 (q), 76.9 (t), 127.5 (t)

^{1}H NMR δ 0.92 (s), 1.02 (d), 1.11 (s), 1.24 (s), 1.79 (m), 2.37 (m), 2.90 (s,b), 4.60 (s, b), 7.34 (m)

References

(1) Knights, E. F.; Brown, H. C. Cyclic hydroboration of 1,5-cyclooctadiene. A simple synthesis of 9-borabicyclo[3.3.1]nonane, an unusually stable dialkylborane. *Journal of the American Chemical Society* **1968**, *90*, 5280–5281.

(2) Midland, M. M. Asymmetric reductions with organoborane reagents. *Chemical Reviews*

1989, *89*, 1553–1561.

(3) Midland, M. M.; Graham, R. S.; Hawkins, J. M.; Sharpless, K. B. *Organic Syntheses* **1985**, *63*.