Stereochemistry and Mechanism of the Brønsted Acid-Catalyzed Intramolecular Hydrofunctionalization of an Unactivated Cyclic Alkene

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Supporting Information

Experimental procedures, analytical and spectroscopic data, and copies of NMR spectra (25 pages).

General Methods

Acid-catalyzed reactions were performed in glass tubes sealed with a Teflon-coated septum. Room temperature is 23 °C. NMR spectra were obtained on a Varian spectrometer operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR in $CDCl_3$ unless noted otherwise. ^{2}H NMR spectra were recorded in toluene that contained one drop of toluene-d_8 as reference. IR spectra were obtained on a Bomen MB-100 FT IR spectrometer. Gas chromatography was performed on a Hewlett-Packard 5890 gas chromatograph equipped with a 25 m polydimethylsiloxane capillary column. LCMS was performed on an Agilent Technologies 1100 Series LC/MSD-Trap SL equipped with an Agilent Zorbax C-18 with 3.5 μm particle 1 × 150 mm column. Flash column chromatography was performed employing 200-400 mesh silica gel (EM). Thin layer chromatography (TLC) was performed on silica gel 60 F254. Elemental analyses were performed by Complete Analysis Laboratories (Parsippany, NJ). Error limits for rate constants refer to the standard deviation of the slope of the respective kinetic plot or from the standard deviation of multiple experiments.

N-(2-Cyclohex-2'-enyl-2,2-diphenylethyl)-*p*-toluenesulfonamide (**1a**),[S1] 2-(2'-cyclohexenyl)-2,2-diphenylethanol (**1b**),[S2] 1,3-dideuterio-2-cyclohexen-1-ol,[S3] and 2-deuterio-2-cyclohexen-1-ol[S4] were synthesized employing published procedures. Ether, methylene chloride, and toluene were purified by passage through columns of activated alumina under nitrogen. Toluene-d_8 was distilled from sodium/benzophenone ketyl under N_2. Reagents were obtained though major chemical suppliers and were used as received, with the exception of thionylchloride, which was distilled from triphenylphosphite prior to use.

Substrates

1,3-Dideuterio-3-chlorocyclohexene (S1). A solution of 1,3-dideuterio-2-cyclohexen-1-ol (3.0 g, 30 mmol) in ether (80 mL) was added to a solution of thionylchloride (5.2 g, 44 mmol) in ether (30 mL) at room temperature and the resulting solution was stirred for 30 min, quenched with saturated

aqueous $NaHCO_3$, and extracted with ether. The combined ether extracts were washed with brine, dried ($MgSO_4$), and concentrated to give **S1** as a pale yellow oil that used in subsequent steps without further purification.

***N*-(2-1'-3'-Dideuteriocyclohex-2'-enyl-2,2-diphenylethyl)-*p*-toluenesulfonamide (1a-1',3'-d_2).**[S1] A solution of diphenylacetonitrile (3.61 g, 18.7 mmol) in DMF (19 mL) was added slowly via syringe to a stirred suspension of sodium hydride (0.45 g, 19 mmol) in DMF (6 mL) at room temperature. The resultant green mixture was stirred for 1 h and cooled to 0 °C. Crude **S1** (2.22 g, 18.8 mmol) was added dropwise and the mixture was gradually warmed to room temperature and stirred for 8 h. The reaction mixture was poured into an ice/water mixture (100 mL) and extracted with ether (3 x 30 mL). The combined ether extracts were washed with water (2 x 20 mL), dried ($MgSO_4$), filtered, and concentrated to give diphenyl(1,3-dideuteriocyclohex-2-enyl)acetonitrile (**S2**) as a white powder that was used in subsequent steps without further purification. ^{1}H NMR analysis of **S2** revealed ≥95% deuteration at the C1 position and ~85% deuteration at the C3 position.

A solution of crude **S2** (~18.7 mmol) in diethyl ether (62 mL) was added dropwise to a suspension of $LiAlH_4$ (2.13 g, 56.1 mmol) in ether (13 mL) at 0 °C. The mixture was refluxed for 16 h, cooled to 0 °C, and treated sequentially with water (2 mL) and 15% aqueous NaOH (2 mL). The resulting suspension was stirred for 30 min, and treated with an additional portion of water (3 mL). The resulting suspension was filtered through a mixture of Celite and $MgSO_4$, eluting generously with ether. The filtrate was concentrated to give 2-(1',3'-dideuteriocyclohex-2'-enyl)-2,2-diphenylethylamine (**S3**) as a viscous yellow oil which was employed in the subsequent step without further without purification. ^{1}H NMR analysis of **S3** revealed ≥95% deuteration at the C1' position and ~85% deuteration at the C3' position.

A solution of *p*-toluenesulfonyl chloride (3.57 g, 18.7 mmol) and triethylamine (6 mL) in methylene chloride (25 mL) was added via syringe to a solution of crude **S3** (~18.7 mmol). The resultant yellow solution was stirred at room temperature for 6 h and then treated sequentially with water (10 mL) and 1N HCl (10 mL) and extracted with methylene chloride. The combined organic extracts were washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated to give a

yellow solid that was recrystalized from hot EtOAc/hexanes to give **1a**-1',3'-d_2 (4.38 g, 54% over 3 steps) as a colorless crystals. Mass spectral analysis of **1a**-1',3'-d_2 (corrected for ^{13}C isotopomers) revealed an 83:17 mixture of d_2 (m/z = 434.2) and d_1 (m/z = 433.3) isotopomers. ^{1}H NMR analysis of **1a**-1',3'-d_2 revealed ~95% deuteration of the C1' position (δ 3.22) and ~85% deuteration of the C3' (δ ~5.60) position of the cyclohexenyl substituent.

For S2: ^{1}H NMR (400 MHz): δ 7.48 (d, *J* = 8.4 Hz, 2 H), 7.37 (d, *J* = 8.4 Hz, 2 H), 7.32-7.15 (m, 6 H), 5.87-5.82 (m, ~0.15 H), 5.46 (s, 1 H), 2.07 – 1.91 (m, 2 H), 1.81-1.73 (m, 1 H), 1.54-1.38 (m, 3 H).

For S3: ^{1}H NMR (400 MHz): δ 7.31-7.15 (m, 10 H), 5.78 (s, 1 H), 5.63-5.57 (m, ~0.15 H), 4.75 (br s, 2 H), 3.42 (d, *J* = 13.2 Hz, 1 H), 3.25 (d, *J* = 13.2 Hz, 1 H), 1.88 – 1.71 (m, 1 H), 1.70-1.36 (m, 4 H), 0.94 (dt, *J* = 4, 12 Hz, 1 H).

For 1a-1',3'-d_2: ^{1}H NMR: δ 7.52 (d, *J* = 8.0 Hz, 2 H), 7.28-7.20 (m, 8 H), 7.12-7.08 (m, 4 H), 5.69 (s, 1 H), 5.62-5.58 (m, ~0.17 H), 3.85 (dd, *J* = 5.4, 7.6 Hz, 1 H), 3.61 (dd, *J* = 7.6, 11.6 Hz, 1 H), 3.50 (dd, *J* = 5.4, 11.6 Hz, 1 H), 2.41 (s, 3 H), 1.90-1.72 (m, 2 H), 1.69-1.56 (m, 1 H), 1.55-1.37 (m, 2 H), 0.88 (dt, *J* = 2.8, 12.1 Hz, 1 H). ^{13}C{^{1}H} NMR: δ 143.3, 143.1, 141.2, 136.1, 129.6, 129.2, 129.1, 128.3, 128.0, 127.9, 127.4, 127.0, 126.8, 126.5, 54.0, 50.1, 38.7 (t, *J* = 18 Hz), 24.9, 24.7, 24.3, 22.0, 21.5 (C3' carbon not observed). MS (ESI, M^+): 434.2 (83%), 433.3 (17%).

***N*-Deuterio-*N*-(2-cyclohex-2'-enyl-2,2-diphenylethyl)-*p*-toluenesulfonamide (1a-*N*-*d*).** A biphasic mixture of **1a** (220 mg, 0.50 mmol), toluene-d_8 (1.0 mL), and D_2O (1.0 mL) was stirred at room temperature for 30 min. An aliquot (0.50 mL) of the organic layer was removed via syringe and transferred to an oven-dried NMR tube capped with a rubber septum and was analyzed by NMR spectroscopy without further isolation. This same sample was employed in acid-catalyzed deuterioamination without further purification. Owing to the nominal solubility of water in toluene (0.033%), this sample also contained 7.9 μmol (~16 mM) D_2O. ^{1}H NMR analysis of **1a**-*N*-*d* revealed ~90% deuteration of the sulfonamide nitrogen atom. ^{1}H NMR (toluene-d_8): δ 7.63 (d, *J* = 7.5 Hz, 2 H), 7.22-7.07 (m, 10 H), 6.90 (d, *J* = 8.0 Hz, 1 H), 5.85 (d, *J* = 10.5 Hz, 1 H), 5.64-5.58 (m, 1 H), 3.82 (d, *J*

= 11.8 Hz, 1 H), 3.67 (d, *J* = 11.8 Hz, 1 H), 3.38-3.30 (m, 1 H), 2.09 (s, 3 H), 1.97-1.90 (m, 1 H), 1.84-1.75 (m, 1 H), 1.64-1.42 (m, 3 H), 1.10-1.01 (m, 1 H). ^{2}H NMR (toluene): δ 4.24.

2-Deuterio-3-chlorocyclohexene (S4). A solution of 2-deuterio-2-cyclohexen-1-ol (2.6 g, 26 mmol) in ether (70 mL) was added to a solution of thionyl chloride (4.7 g, 40 mmol) in ether (16 mL) at room temperature. The resulting solution was stirred for 90 min, quenched with satd. $NaHCO_3$ (aq), and extracted with ether. The combined ether extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated to give **S4** as a pale yellow oil that was employed in subsequent steps without further purification.

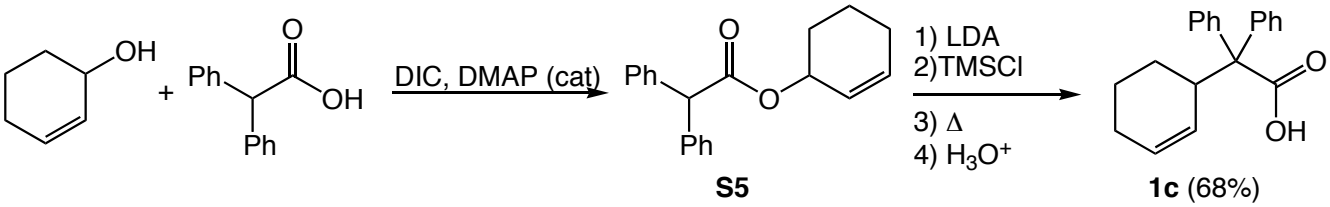
***N*-(2-2'-deuteriocyclohex-2'-enyl-2,2-diphenylethyl)-*p*-toluenesulfonamide (1a-2'-d_1).** Isotopomer **1a**-2'-d_1 was prepared in 64% yield from **S4** and using a procedure analogous to that used for preparation of sulfonamide **1a.** Mass spectral analysis of **1a**-2'-d_1 (corrected for ^{13}C isotopomers) revealed a 75:25 mixture of d_1 (m/z = 433.3) and d_0 (m/z = 432.2) isotopomers. ^{1}H NMR: δ 7.48 (d, *J* = 8 Hz, 2 H), 7.24-7.14 (m, 8 H), 7.07-7.00 (m, 4 H), 5.64 (d, +*10.8 Hz, 0.2 H), 5.60-5.48 (m, 1 H), 3.79 (dd, *J* = 5.6, 7.2 Hz, 1 H), 3.55 (dd, *J* = 7.6, 11.6 Hz, 1 H), 3.40 (dd, *J* = 5.2, 11.6 Hz, 1 H), 3.21-3.12 (m, 1 H), 2.35 (s, 3 H), 1.84-1.65 (m, 2 H), 1.62-1.50 (m, 1 H), 1.48-1.32 (m, 2 H), 0.87-0.76 (m, 1 H). ^{2}H NMR (toluene): δ 3.73. ^{13}C{^{1}H} NMR (d_1 isotopomer only): δ 143.5, 143.2, 141.4, 136.2, 129.8, 129.5, 129.4, 129.2, 128.5, 127.9 (br m), 127.6, 127.2, 126.9, 126.7, 54.2, 50.2, 39.2, 25.0, 24.5, 22.2, 21.6. MS (ESI, M^+): 433.3 (75%), 432.2 (25%).

2-(1',3'-Dideuteriocyclohex-2'-enyl)-2,2-diphenylethanol (1b-1',3'-d_2). Isotopomer **1b**-1',3'-d_2 was synthesized in 80% yield over two steps from **S1** using a procedure similar to that used to prepare protio isotopomer **1b**.[2] Mass spectral analysis of **1b**-1',3'-d_2 (corrected for ^{13}C isotopomers) established a 96:4 mixture of d_2 [m/z = 263.1 ($M^+ - H_2O$)] and d_1 [m/z = 262.1 ($M^+ - H_2O$)] isotopomers. ^{1}H NMR analysis of **1b**-d_2 revealed ≥95% deuteration of the C1' and C3' positions of the cyclohexenyl substituent. ^{1}H NMR: δ 7.37-7.18 (m, 10 H), 5.78 (s, 1 H), 4.20 (dd, *J* = 1.2, 6.8 Hz, 2 H), 1.92-1.47 (m, 5 H), 1.16 (t, *J* = 7.0 Hz, 1 H), 1.04 (dt, *J* = 3.2, 12.4 Hz, 1 H). ^{13}C{^{1}H} NMR: δ 144.2, 124.5, 129.5, 129.4, 128.9, 128.0, 127.5, 126.3, 126.2, 68.1, 56.0, 38.6 (t, *J* = 14.9 Hz), 24.9,

24.8, 22.4, (C3' carbon not observed). MS (ESI, $M^+ - H_2O$): 263.1 (96%), 262.1 (4%).

2-(2-Cyclohexenyl)-2,2-diphenylacetic acid (1c, Scheme S1). Diisopropylcarbodiimide (0.73 g, 5.8 mmol) was added to a solution of 2-cyclohexen-1-ol (0.50 g, 5.1 mmol), diphenylacetic acid (1.38 g, 6.50 mmol), and DMAP (65 mg, 0.53 mmol) in CH_2Cl_2 (16 mL) at 0 °C and the resulting suspension was stirred for 2 h at 0 °C and 1 h at room temperature (Scheme S1). The resulting suspension was filtered and the filtrate was concentrated under vacuum to give an oily residue that was chromatographed (SiO_2; hexanes–EtOAc = 99:1) to give 2-cyclohexenyl-2,2-diphenylacetate (**S5**) (1.41 g, 97%) as a white solid that was used in subsequent steps without further purification.

A solution of *n*-BuLi (3.90 mL, 2.47 M in hexanes, 9.63 mmol) was added dropwise to a stirred solution of diisopropylamine (1.01 g, 9.93 mmol) in THF (20 mL) at –78 °C and stirred for 30 minutes with gradual warming to 0 °C. The resulting solution was then transferred into a solution of **S5** in THF (50 mL) at –78 °C to form a bright yellow solution that was stirred for 1 h at –78 °C. Chlorotrimethylsilane (1.1 g, 10 mol) was added to the reaction mixture via syringe and the resulting solution was stirred 1 h at –78 °C, warmed to 45 °C over 2 h, and stirred for 10 h. The resulting mixture was cooled to 0 °C, treated with 1N HCl, stirred for 45 min at 0 °C, warmed to room temperature, and extracted with ether. The combined ether extracts were washed with 1N HCl and brine, dried ($MgSO_4$), and concentrated. Chromatrography (SiO_2; 15% ether in pentane) of the residue gave **1c** (0.96 g, 68%) as a white solid.



Scheme S1

For S5: TLC (hexanes–EtOAc = 99:1): R_f = 0.30. ^{1}H NMR: δ 7.32-7.21 (m, 10 H), 5.92 (dt, *J* = 1.2, 10 Hz, 1 H), 5.71-5.66 (m, 1 H), 5.32-5.30 (m, 1 H), 5.00 (s, 1 H), 2.09-1.89 (m, 2 H), 1.88-1.79 (m, 1 H), 1.73-1.53 (m, 3 H). ^{13}C{^{1}H} NMR: δ 172.2, 139.0, 133.1, 128.8, 128.7, 128.7, 128.6, 127.3, 125.5, 69.1, 57.4, 28.3, 25.0, 18.9. HRMS calcd (found) for $C_{24}H_{28}O_2$ (M^+): 292.1463 (292.1465).

For 1c: TLC (pentane–ether = 8:1): R_f = 0.30. ^{1}H NMR: δ 10.8 (br s, 1 H), 7.34-7.23 (m, 10 H), 5.67 (br d, *J* = 10.5, 1 H), 5.62-5.57 (m, 1 H), 3.81-3.75 (m, 1 H), 1.94-1.81 (m, 2 H), 1.72-1.63 (m, 1 H), 1.58-1.48 (m, 1 H), 1.42 (br s, 1 H), 1.02 (dq, *J* = 3.0, 12.5 Hz, 1 H). ^{13}C{^{1}H} NMR: δ 179.0, 140.8, 139.7, 130.4, 130.4, 129.8, 128.1, 127.8, 127.4, 127.2, 127.0, 64.6, 40.0, 25.8, 25.2, 22.1. HRMS calcd (found) for $C_{24}H_{28}O_2$ (M^+): 292.1463 (292.1465).

2-(1',3'-Dideuteriocyclohex-2'-enyl)-2,2-diphenylacetic acid (1c-1',3'-d_2). Isotopomer **1c**-1',3'-d_2 was synthesized in 65% yield from 1,3-dideuterio-2-cyclohexen-1-ol and employing a procedure analogous to that used for preparation of **1c**. Mass spectral analysis of **1c**-1',3'-d_2 (corrected for ^{13}C isotopomers) established a >99:<1 mixture of d_2 [m/z = 294.2 (M^+)] and d_1 [m/z = 293.2 (M^+)] isotopomers. ^{1}H NMR analysis of **1c**-d_2 revealed ≥95% deuteration of the C1' and C3' positions of the cyclohexenyl substituent.

For S5-d_2: ^{1}H NMR: δ 7.35-7.23 (m, 10 H), 5.71 (s, 1 H), 5.02 (s, 1 H), 2.10-1.91 (m, 2 H), 1.89-1.81 (m, 1 H), 1.74-1.54 (m, 3 H). ^{13}C{^{1}H} NMR: δ 172.1, 130.9, 132.7 (t, *J* = 18 Hz), 128.61, 128.56, 128.5, 128.4, 127.1, 125.1, 68.3 (br t), 57.2, 28.0, 24.7, 18.7.

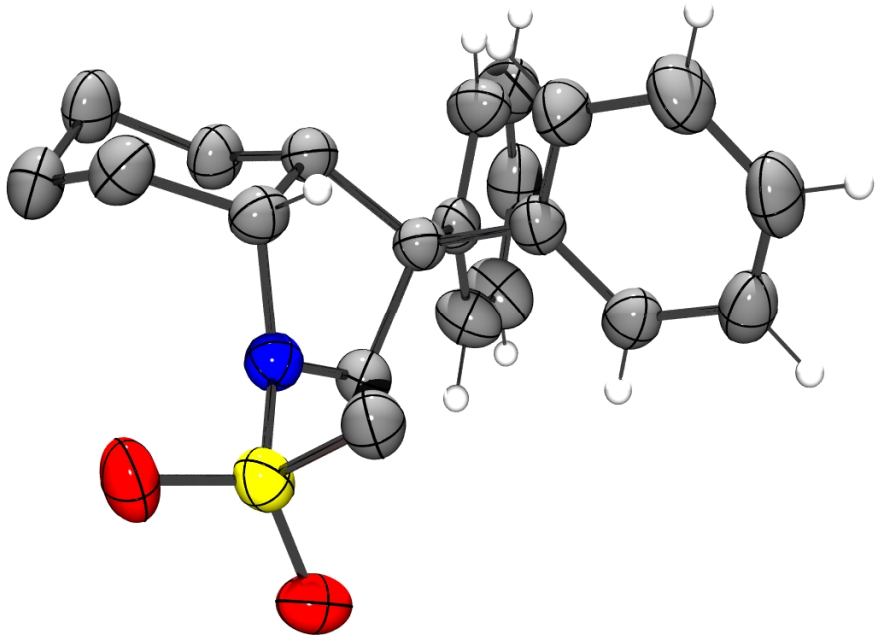
For 1c-1',3'-d_2: TLC (hexanes–EtOAc = 4:1): R_f = 0.25. ^{1}H NMR: δ 10.85 (br s, 1 H), 7.38-7.21 (m, 10 H), 5.68 (s, 1 H), 1.97-1.80 (m, 2 H), 1.74-1.62 (m, 1 H), 1.60-1.49 (m, 1 H), 1.48-1.32 (m, 1 H), 1.03 (dt, *J* = 2.5, 12.2 Hz, 1 H). ^{13}C{^{1}H} NMR: δ 180.4, 140.6, 139.6, 130.5, 130.4, 129.5 (t, *J* = 5.3), 128.0, 127.7, 127.4, 127.1, 127.0, 64.6, 39.5 (t, *J* = 14.5), 25.7, 25.0, 22.0. HRMS calcd (found) for $C_{20}H_{18}D_2O_2$ (M^+): 294.1589 (294.1587). MS (ESI, M^+): 294.2 (99.5%), 293.2 (0.5%).

2a and Isotopomers

***rac*-(3aR,7aR)-3,3-Diphenyl-1-(*p*-toluenesulfonyl)-octahydroindole (2a).** Triflic acid (0.7 μL, 7.5×10^{-3} mmol) was added via syringe to a solution of **1a** (64.7 mg, 0.150 mmol) in toluene (0.3 mL). The resulting solution was heated at 60 °C for 3 h, cooled to room temperature, and filtered through a plug of silica gel. Solvent was evaporated under vacuum to give **2a** (64.5 mg, 100 %) as a white solid. Slow evaporation of a toluene solution of **2a** gave crystals of **2a** suitable of X-ray diffraction (Figure S1). ^{1}H NMR (800 MHz, 45 °C): δ 7.43 (d, *J* = 8.0 Hz, 2 H), 7.19 (t, *J* = 8.0 Hz, 2 H), 7.09 (t, *J* = 8.0 Hz, 1 H), 7.07 - 6.98 (m, 9 H), 4.48 (d, *J* = 11.1 Hz, 1 H; *H2*), 4.25 (d, *J* = 11.1 Hz, 1 H, *H2*), 3.78 (m, 1 H, *H7a*), 2.95 (dt, *J* = 10.4, 4.8 Hz, 1 H, *H3a*), 2.49 (br d, *J* = 14.4 Hz, 1 H, $H7_{eq}$), 2.32 (s, 3 H), 1.58 (m, 1 H, $H7_{ax}$), 1.55-1.41 (m, 4 H, *H5* and *H6*), 1.28-1.15 (m, 2 H, *H4*). ^{13}C{^{1}H} NMR: d 145.1, 143.8, 142.8, 134.2, 129.3, 128.5, 128.4, 127.6, 127.1, 126.7, 126.1, 125.7, 59.1, 58.2, 55.5, 44.3, 28.8, 25.5, 24.5, 21.5, 20.1.

X-ray data for 2a: Monoclinic, P2(1)/c, *T* = 296 K, *a* = 8.8385(10) Å, *b* = 26.705(3) Å, *c* = 9.4913(11) Å, β = 94.690(8)° , V = 2232.8(5) Å^3, *Z* = 4, $R[F^2 > 2\sigma(F^2)] = 0.042$, $wR(F^2) = 0.138$. CCDC-798744 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Figure S1. ORTEP diagram of **2a** with thermal ellipsoids shown at 50% probability. Tosyl group is omitted for clarity.



Assignment of Aliphatic Protons of 2a. The aliphatic protons of **2a** were unambiguous assigned on the basis of combined ^{1}H–^{1}H 800 MHz COSY and ^{1}H–^{1}H NOESY analysis at 45 °C in $CDCl_3$ (Figures S2 – S4). Relevant $^{2}J_{HH}$ and $^{3}J_{HH}$ coupling constants (Figure S2) were determined from these spectra and from ^{1}H NMR analysis of deuterated isotopomers **2a**-3a,7$_{eq}$-d_2 and **2a**-7$_{ax}$-d_1. Central to the determination of the relative configuration of the deuterated isotopomers **2a**-3a,7$_{eq}$-d_2 and **2a**-7$_{ax}$-d_1 is the assignment of protons H7$_{ax}$ and H7$_{eq}$. As noted in reference 38 of the main text, neither the through-bond nor through-space interactions of H7$_{ax}$ and H7$_{eq}$ with H7a proved reliable for assigning H7$_{ax}$ and H7$_{eq}$. Rather, these protons were assigned by the presence of a strong NOESY cross peak between the axial tertiary proton H3a [δ 2.95 (td, J = 4.8, 10.4 Hz)] and H7$_{ax}$ [δ 1.58 (m, 1 H)] and the absence of a cross peak between H3a and H7$_{eq}$ [δ 2.49 (br d, J = 14.4 Hz)] (Figure S4).

Figure S2. Numbering scheme (left structure), relevant $^{1}H–^{1}H$ coupling constants (center structure), and key NOESY interactions (right structure) for compound **2a**.

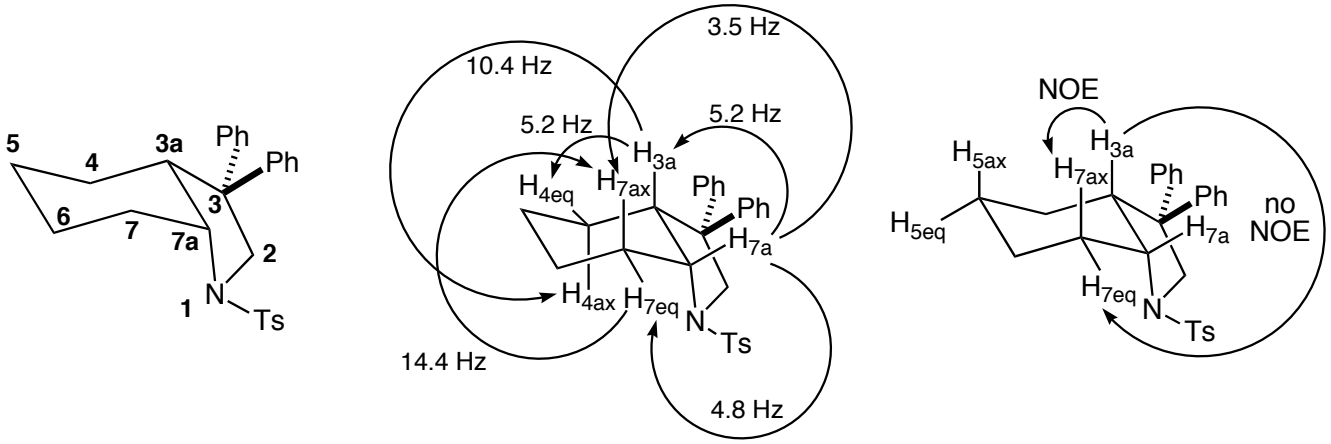


Figure S3. ^{1}H-^{1}H COSY 800 MHz NMR spectrum of **2a** at 45 °C in $CDCl_3$.

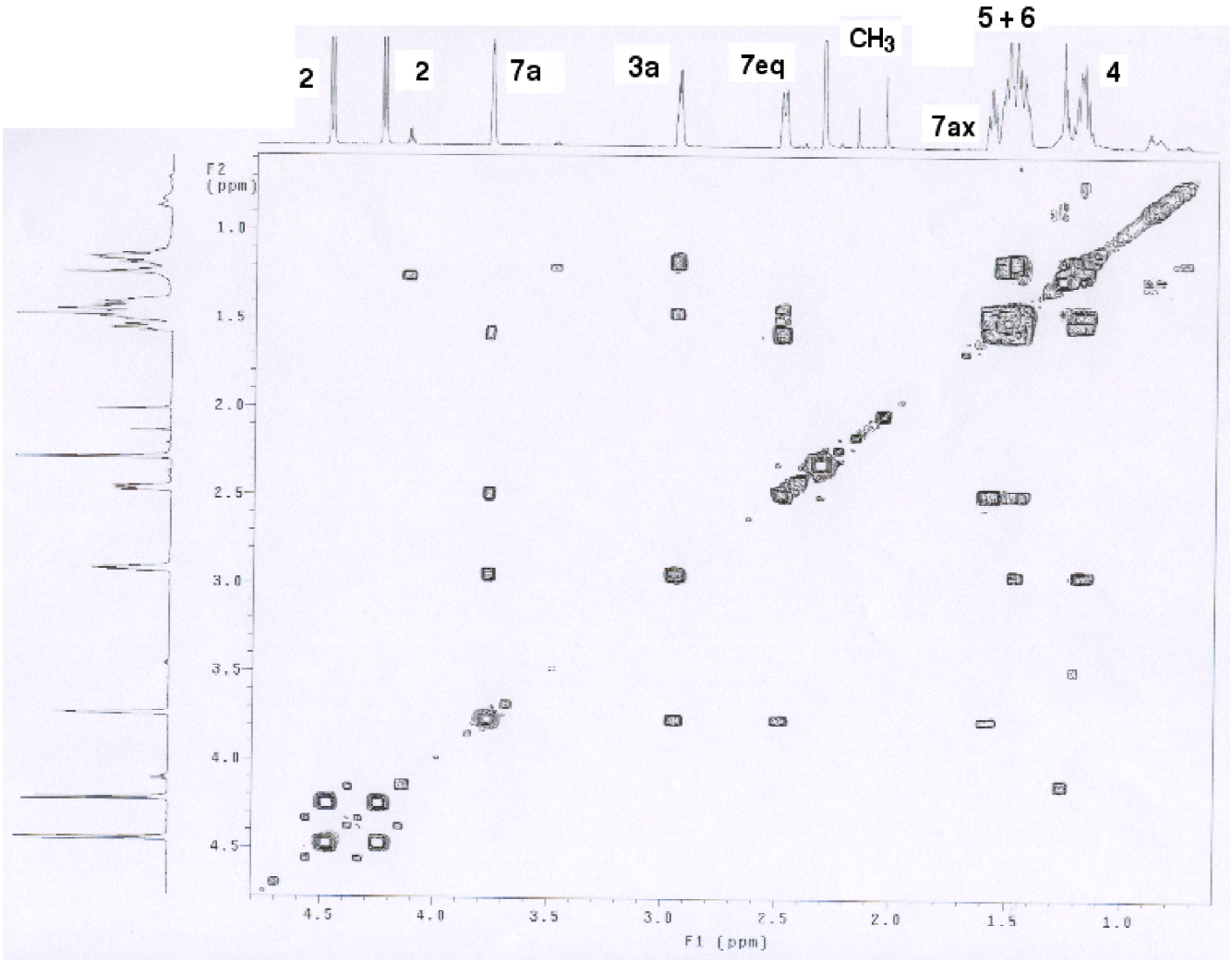
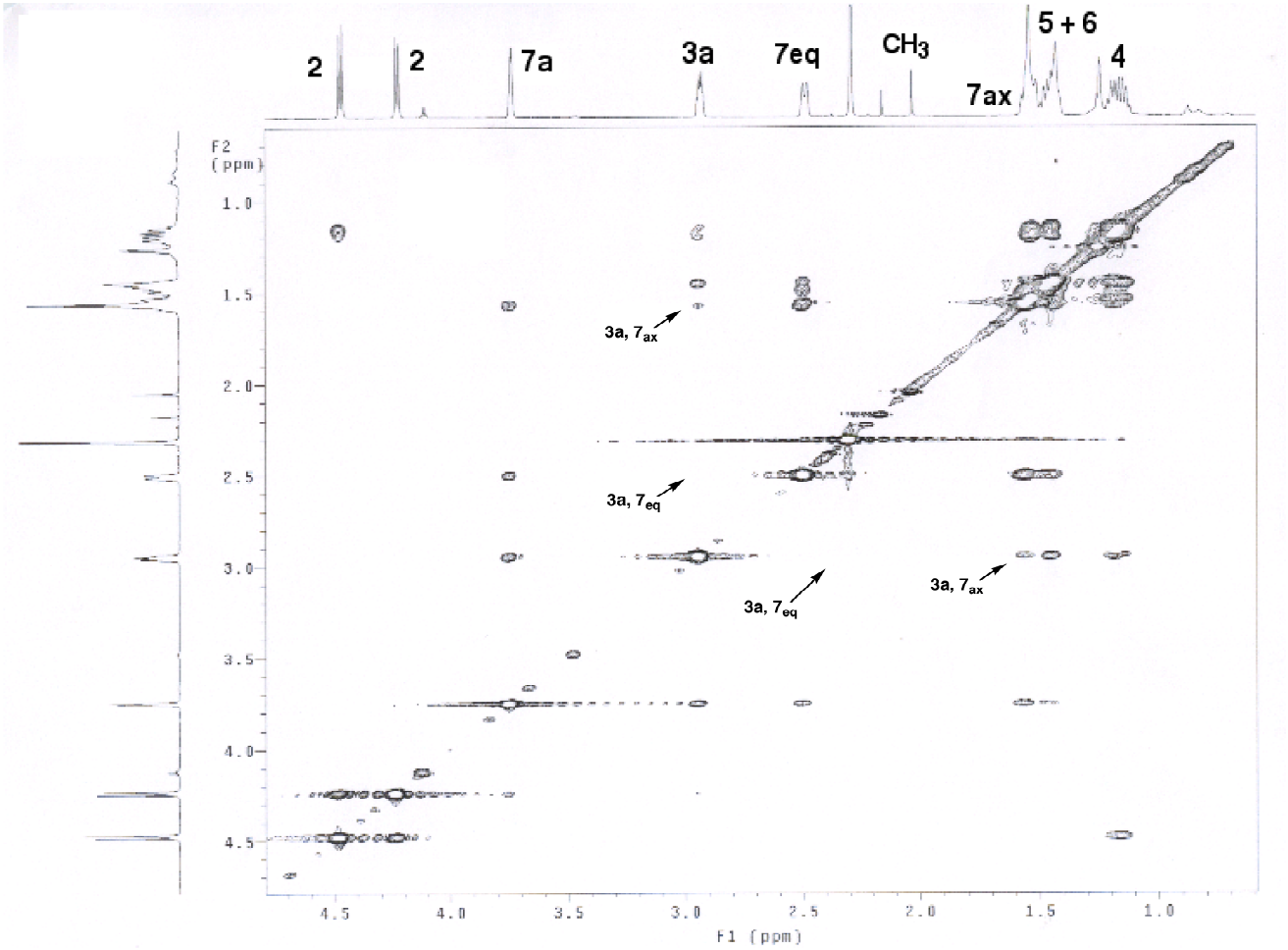


Figure S4. ^{1}H-^{1}H NOESY 800 MHz NMR spectrum of **2a** at 45 °C in $CDCl_3$.



***rac*-(3aR,7R,7aR)-3,3-Diphenyl-1-(*p*-toluenesulfonyl)-(3a,7-$^{2}H_2$)-octahydro-1H-indole (2a-3a,7_{eq}-d_2).** Reaction of **1a**-1',3'-d_2 (65 mg, 0.15 mmol; 83% d_2, 17% d_1 by MS) with triflic acid (0.7 μL, 7.5×10^{-3} mol) in toluene (0.3 mL) at 85 °C for 48 h led to isolation of **2a**-3a,7_{eq}-d_2 (62 mg, 96%) as a white solid. Mass spectral analysis (corrected for ^{13}C isotopomers) established an 83:16 ratio of d_2 [*m/z* = 434.2 (M^+)] and d_1 [*m/z* = 433.3 (M^+)] isotopomers. ^{1}H NMR analysis of **2a**-3a,7_{eq}-d_2 revealed ~95% deuteration of the C3a (δ 2.95) position and ~85% deuteration of the $C7_{eq}$ (δ 2.49) position with no detectable (<5%) accumulation of deuterium at the $C7_{ax}$ or C7a positions (Figure 1, spectrum b). ^{2}H NMR displayed a ~1:1 ratio of resonances at δ 2.96 and δ 2.51 corresponding to the C3a and $C7_{eq}$

positions with no detectable (<5%) accumulation of deuterium at the $C7_{ax}$ or $C7_a$ positions (Figure 1, spectrum c). ^{1}H NMR (500 MHz, 25 °C): δ 7.40 (d, *J* = 8 Hz, 2 H), 7.17 (t, *J* = 8 Hz, 2 H), 7.07 (tt, *J* = 1.0, 6.0 Hz, 1 H), 7.05-6.95 (m, 9 H), 4.47 (d, *J* = 11.0 Hz, 1 H), 4.22 (d, *J* = 11.0 Hz, 1 H), 3.73 (d, *J* = 3.5, 1 H), 2.29 (s, 3 H), 1.60-1.35 (m, 5 H), 1.26-1.08 (m, 2 H). ^{2}H NMR (76 MHz, $CHCl_3$): δ 2.96, 2.51 (~1:1). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 145.2, 143.9, 142.8, 134.3, 129.4, 128.6, 128.5, 127.6, 127.2, 126.7, 126.2, 125.7, 59.0, 58.2, 55.4, 43.8 (t, *J* = 16 Hz), 28.5 (t, *J* = 16 Hz), 25.5, 24.5, 21.5, 20.1. MS (ESI, M^+): 434.2 (83%), 433.3 (16%).

***rac*-(3aR,7S,7aR)-3,3-Diphenyl-1-(*p*-toluenesulfonyl)-(3a,7-2H2)-octahydro-1H-indole (2a-7_{ax}-d_1).** Triflic acid-*O*-*d* (1.3 µL, 0.015 mmol) was added via syringe to an NMR tube that contained a solution of **1a**-*N*-*d* (0.25 mmol; 90% *d* by ^{1}H NMR) in toluene-d_8 (0.50 mL). The resulting solution was heated at 60 °C for 3 h and monitored periodically by ^{1}H NMR spectroscopy. The resulting solution was filtered through a plug of silica gel and solvent was evaporated under vacuum to give pure **2a**-7_{ax}-d_1 (84 mg, 77%) as a white solid. Mass spectral analysis (corrected for ^{13}C isotopomers) established a 90:10 mixture of d_1 [*m/z* = 433.3 (M^+)] and d_0 [*m/z* = 432.2 (M^+)] isotopomers. ^{1}H NMR analysis of **2a**-7_{ax}-d_1 revealed ~90% deuteration of the $C7_{ax}$ position with no detectable (<5%) accumulation of deuterium at the $C7_{eq}$ or C7a positions (Figure 1, spectrum d). Likewise, ^{2}H NMR analysis of **2a**-7_{ax}-d_1 displayed a single resonance at δ 1.50 corresponding to the $C7_{ax}$ position with no detectable (<5%) accumulation of deuterium at the $C7_{eq}$ or C7a positions (Figure 1, spectrum e). ^{1}H NMR: δ 7.41 (d, *J* = 8.4, 2 H), 7.19 (t, *J* = 7.4 Hz, 2 H), 7.12-6.95 (m, 10 H), 4.49 (d, *J* = 11.1 Hz, 1 H), 4.25 (d, *J* = 11.1 Hz, 1 H), 3.75 (t, *J* = 4.8 Hz, 1 H), 2.95 (td, *J* = 5.2, 10.4 Hz, 1 H), 2.51-2.45 (m, 1 H), 2.31 (s, 3 H), 1.57-1.48 (m, 4 H), 1.26-1.08 (m, 2 H). ^{2}H NMR (76 MHz, toluene): δ 1.50. MS (ESI, M^+): 433.3 (90%), 432.2 (10%).

Analysis of Unreacted Starting Material in the DOTf-catalyzed cyclization of 1a-*N*-*d*.

Triflic acid-O-*d* (1.7 µL, 0.019 mmol) was added via syringe to an NMR tube that contained a solution of **1a**-*N*-*d* (0.25 mmol) in toluene that contained a drop of toluene-d_8. The resulting solution

was heated at 60 °C, monitored by ^{2}H NMR to ~50% conversion, and quenched by addition of triethylamine (4 μL). A similar experiment that utilized ^{1}H NMR analysis of a toluene-d_8 solution of **1a**-*N*-*d* and a catalytic amount of DOTf was performed concurrently. ^{2}H NMR analysis of the former solution after quench displayed resonances at δ 4.5, corresponding to the N–D resonance of unreacted **1a**-*N*-*d* and δ 1.58 corresponding to the D7$_{ax}$ resonance of **2a**-7a-d_1 (Figure S5). There was no detectable (< 5%) accumulation of deuterium at the C2' or C3' alkenyl positions of **1a**-*N*-*d* (δ 5.8 and 5.6) or at the C7$_{eq}$ or C7a position of **2a**-7$_{ax}$-d_1. ^{1}H NMR analysis of the latter solution after quench displayed resonances corresponding to the protons of **1a**-*N*-*d* and **2a**-7a-d_1 with no evidence of positional isomerization of **1a**-*N*-*d* (Figure S6).

Figure S5. ^{1}H NMR spectrum of **1a**-*N*-*d* in toluene-d_8 (top spectrum). ^{2}H NMR spectrum of a ~1:1 mixture of **1a**-*N*-*d* and **2a**-7$_{ax}$-d_1 in toluene that contained a drop of toluene-d_8 at 60 °C from partial conversion of the reaction of **1a**-*N*-*d* with DOTf (bottom spectrum).

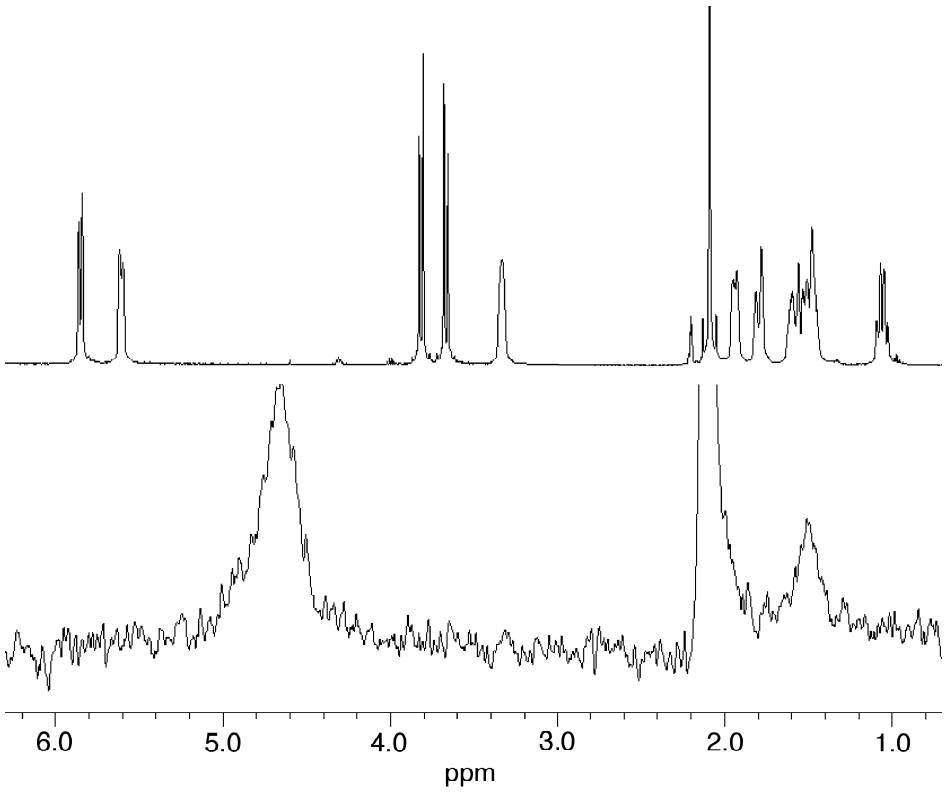
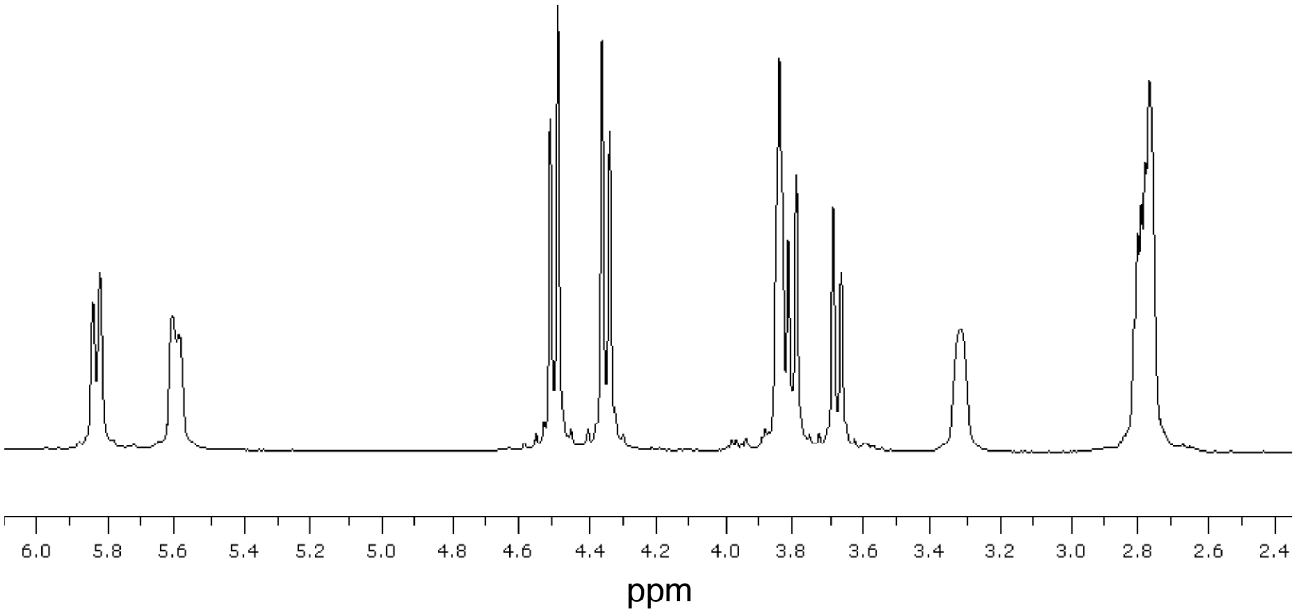


Figure S6. ^{1}H NMR spectrum of a ~1:1 mixture of **1a**-*N*-*d* and **2a**-7$_{ax}$-d_1 in toluene-d_8 at 60 °C from partial conversion of the reaction of **1a**-*N*-*d* with DOTf.



***rac*-(3aR,7aR)-3,3-Diphenyl-1-(*p*-toluenesulfonyl)-(7a-^{2}H)-octahydro-1H-indole (2a-7a-d_1).** Reaction of **1a**-2'-d_1 (65 mg, 0.15 mmol; 25% d_0, 75% d_1 by MS) with triflic acid (0.7 μL, 7.5 × 10^{-3} mol) in toluene (0.3 mL) at 60 °C for 3 h led to isolation of **2a**-7a-d_1 (63 mg, 96%) as a white solid. Mass spectral analysis of **2a**-7a-d_1 (corrected for ^{13}C isotopomers) established a 76:24 mixture of d_1 [*m/z* = 433.3 (M^+)] and d_0 [*m/z* = 432.2 (M^+)] isotopomers. ^{1}H NMR analysis of **2a**-7a-d_1 revealed ~75% deuteration of the C7a position (δ 3.78) with no detectable (<5%) accumulation of deuterium at the C7$_{eq}$ or C7$_{ax}$ positions (Figure 1, spectrum f). ^{2}H NMR analysis of **2a**-7$_{ax}$-d_1 revealed a single resonance corresponding to deuteration of the C7a position at δ 3.78 with no detectable (<5%) accumulation of deuterium at the C7$_{eq}$ or C7$_{ax}$ positions. ^{1}H NMR (500 MHz): δ 7.42 (d, *J* = 8 Hz, 2 H), 7.19 (t, *J* = 7.5 Hz), 7.12-6.94 (m, 10 H), 4.49 (d, *J* = 11 Hz, 1 H), 4.27 (d, *J* = 11 Hz, 1 H), 3.79-3.74 (m, 0.22 H), 2.98-2.93 (m, 1 H), 2.52 (d, *J* = 13.5 Hz, 1 H), 2.31 (s, 3 H), 1.62-1.40 (m, 5 H), 1.29-1.10 (m, 2 H). ^{2}H NMR ($CHCl_3$): δ 3.78. ^{13}C{^{1}H} NMR: δ 145.2, 143.9, 142.8, 134.3, 129.3, 128.6, 128.4, 127.6, 127.1, 126.7, 126.1, 125.7, 59.1, 58.7 (t, *J* = 21 Hz), 58.2, 55.5, 44.3, 44.2, 28.8, 28.6,

25.5, 24.6, 21.5, 20.1. MS (ESI, M^+): 433.3 (76%), 432.2 (24%).

2b and Isotopomers

***rac*-(3aR,7aR)-3,3-Diphenyloctahydrobenzofuran (2b).** A solution of **1b** (42 mg, 0.15 mmol) and triflic acid (0.7 µL, 7.5×10^{-3} mol) in toluene (0.3 mL) was heated at 60 °C for 3 h to give **2b** (39 mg, 93%) as a white solid. ^{1}H NMR: δ 7.36 (br d, *J* = 7.5 Hz, 2 H), 7.21-7.15 (m, 4 H), 7.10-7.04 (m, 4 H), 4.78 (d, *J* = 8.5 Hz, 1 H, *H2*), 4.66 (d, *J* = 8.5 Hz, 1 H, *H2*), 4.14-4.11 (m, 1 H, *H7a*), 2.71 (ddd, *J* = 4.3, 5.7, 10.2 Hz, 1 H, *H3a*), 1.89 (br d, *J* = 13.5 Hz, 1 H, $H7_{eq}$), 1.66 - 1.50 (m, 2 H, $H4_{eq}$ and $H5_{eq}$), 1.46-1.31 (m, 3 H, $H7_{ax}$ and *H6*), 1.11 (tq, *J* = 3.2, 12.6 Hz, 1 H, $H5_{ax}$), 0.91 (dq, *J* = 3.4, 12.9 Hz, 1 H, $H4_{ax}$). ^{13}C{^{1}H} NMR: δ 146.5, 143.7, 128.6, 128.3, 126.9, 126.2, 126.1, 76.4, 74.6, 59.7, 44.6, 29.0, 25.8, 24.6, 20.2, (one carbon resonance obscured).

Assignment of Aliphatic Protons of 2b. The aliphatic protons of **2b** were assigned on the basis of combined ^{1}H, ^{1}H–^{1}H COSY and ^{1}H–^{1}H NOESY analysis (Figures S7 – S9). In contrast to the analyses of **2a** and **2c**, the NOESY spectrum of *cis*-**2b** displayed no distinguishing cross peak between H3a and $H7_{ax}$ (Figure S9). Rather, these protons were assigned by the presence of a NOESY cross peak between the axial tertiary proton $H5_{ax}$ (δ 1.11) and $H7_{ax}$ (δ 1.4) and the absence of a cross peak between $H5_{ax}$ (δ 1.11) and $H7_{eq}$ (δ 1.89) (Figure S9).

Figure S7. Numbering scheme and key NOESY interactions for compounds **2b**.

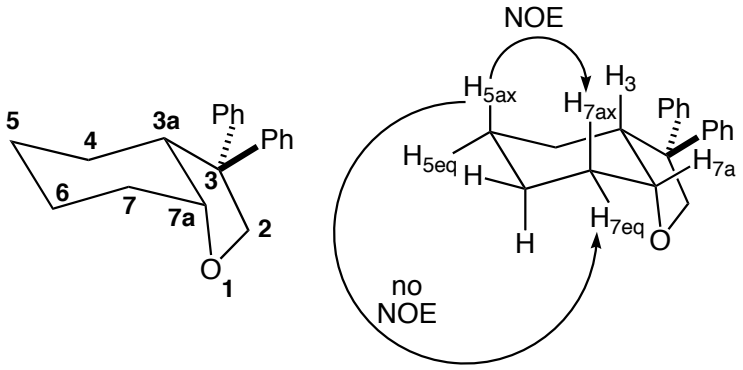


Figure S8. ^{1}H-^{1}H COSY 500 MHz NMR spectrum of **2b** at 25 °C in $CDCl_3$.

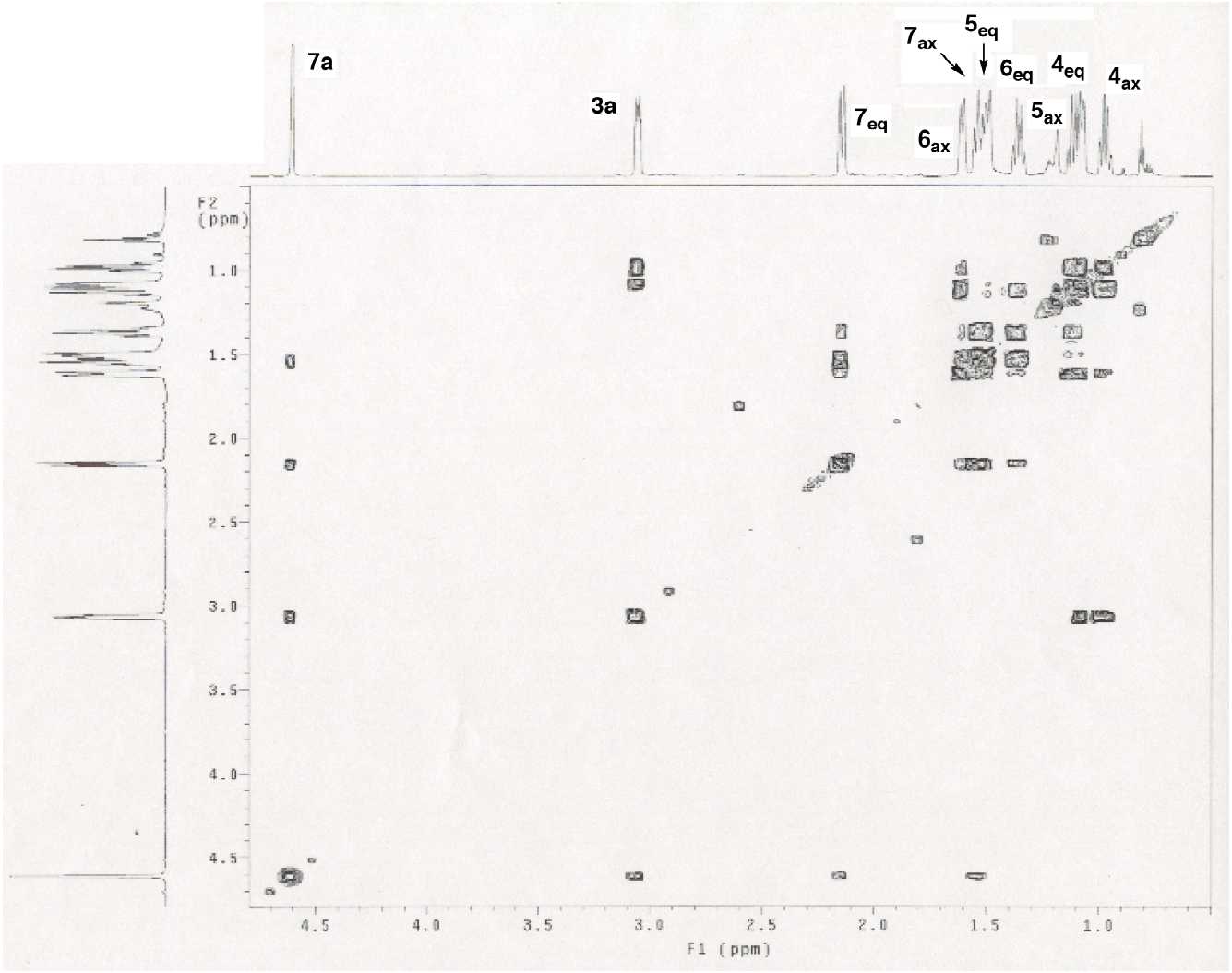
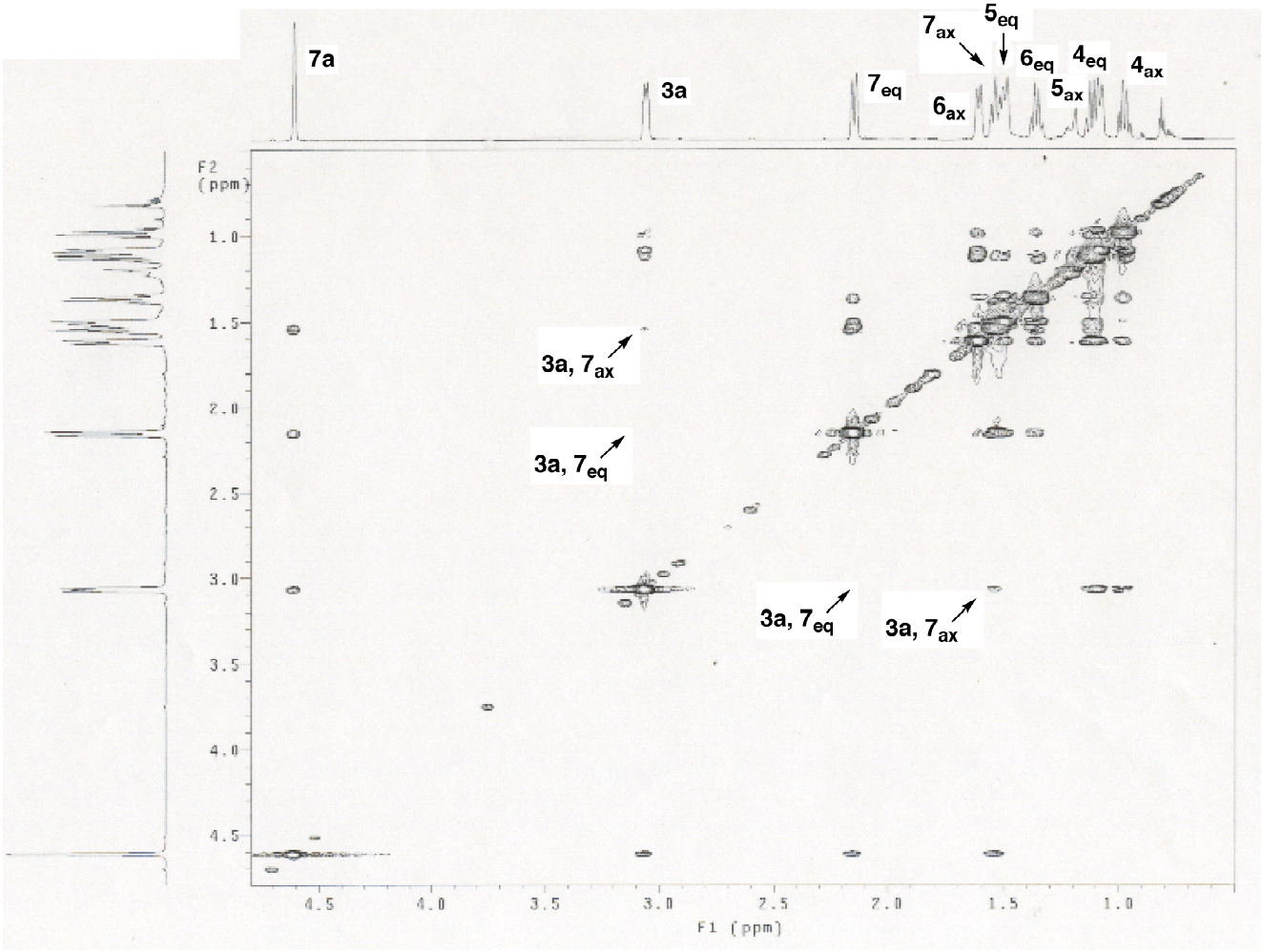


Figure S9. ^{1}H-^{1}H NOESY 500 MHz NMR spectrum of **2b** at 25 °C in $CDCl_3$.



***rac*-(3aR,7R,7aR)-3,3-Diphenyl-(3a,7-$^{2}H_2$)-octahydrobenzofuran (2b-3a,7_{eq}-d_2).** Treatment of **1b**-1',3'-d_2 (42 mg, 0.150 mmol, 96% d_2 by MS) with triflic acid (0.7 μL, 7.5×10^{-3} mol) in toluene (0.3 mL) at 85 °C for 48 h led to isolation of **2b**-3a,7_{eq}-d_2 (40 mg, 96%) as a white solid. Mass spectral analysis of **2b**-3a,7_{eq}-d_2 (corrected for ^{13}C isotopomers) established a 95:3:2 ratio of d_2 [*m/z* = 281.1 (M^+)], d_1 [*m/z* = 280.1 (M^+)], and d_0 [*m/z* = 279.1 (M^+)] isotopomers. ^{1}H and ^{2}H NMR analysis of **2b**-3a,7_{eq}-d_2 revealed >95% deuteration of the $C7_{eq}$ (δ 1.89) and C3a (δ 2.71) positions with no detectable (≤5%) deuteration at the $C7_{ax}$ (δ 1.34) and C7a (δ 4.11) positions (Figure 2, spectra b and c). ^{1}H NMR: δ 7.35 (br d, *J* = 8.4 Hz, 2 H), 7.24-7.02 (m, 8 H), 4.78 (d, *J* = 8.6 Hz, 1 H), 4.66 (d, *J* = 8.6 Hz, 1 H), 4.11 (d, *J* = 2.8 Hz, 1 H), 1.66-1.53 (m, 2 H), 1.44-1.03 (m, 4 H), 0.86 (dt, *J* = 2.4, 13.6, 1 H). ^{2}H NMR

($CHCl_3$): δ 2.81, 1.99. $^{13}C\{^1H\}$ NMR: δ 146.5, 143.7, 128.6, 128.3, 126.9, 126.2, 126.1, 76.3, 74.6, 59.6, 44.1 (t, *J* = 16 Hz), 28.7 (t, *J* = 16 Hz), 25.7, 24.6, 20.1, (one carbon resonance obscured). MS (ESI, M^+): 281.1 (95%), 280.1 (2%), 279.1 (2%).

2c and Isotopomers

***rac*-(3aR,7aR)-3,3-diphenylhexahydrobenzofuran-2(3H)-one (2c).** A solution of **1c** (45 mg, 0.15 mmol) and triflic acid (0.7 μL, 7.5×10^{-3} mol) in toluene (0.3 mL) was stirred at 60 °C for 3 h to give **2c** (43 mg, 96%) as a white solid. ^1H NMR: δ 7.50 (d, *J* = 7.7 Hz, 2 H), 7.35 (d, *J* = 7.7 Hz, 2 H), 7.27 (t, *J* = 7.5 Hz, 2 H), 7.19 (q, *J* = 8.6, 3 H), 7.10 (t, *J* = 7.2, 1 H), 4.61 (br s, 1 H, *H7a*), 3.07 (td, *J* = 5.8, 11.6 Hz, 1 H, *H3a*), 2.16 (br d, *J* = 15.1 Hz, 1 H, $H7_{eq}$), 1.6 (br d, *J* = 13.0 Hz, 1 H, $H6_{ax}$), 1.57-1.47 (m, 2 H, $H7_{ax}$ and $H5_{eq}$), 1.39-1.33 (m, 1 H, $H6_{eq}$), 1.15-1.06 (m, 2 H, $H5_{ax}$ and $H4_{eq}$), 1.01-0.95 (m, 1 H, $H4_{ax}$). $^{13}C\{^1H\}$ NMR: δ 177.1, 140.0, 138.5, 129.1, 128.5, 128.1, 127.9, 127.7, 126.6, 75.1, 62.7, 43.2, 27.7, 25.8, 24.0, 19.7.

The aliphatic protons of **2c** were unambiguous assigned on the basis of combined ^1H–^1H COSY and ^1H–^1H NOESY analysis (Figures S10 and S11). Key to the assignment of the aliphatic protons of **2c** was the presence of strong NOESY cross peak between the axial tertiary proton $H3_a$ (δ 3.07) and $H7_{ax}$ (δ 1.5) and the absence of a cross peak between $H3_a$ and $H7_{eq}$ (δ 2.16) (Figure S11).

Figure S10. ^{1}H-^{1}H COSY 800 MHz NMR spectrum of **2c** at 25 °C in $CDCl_3$.

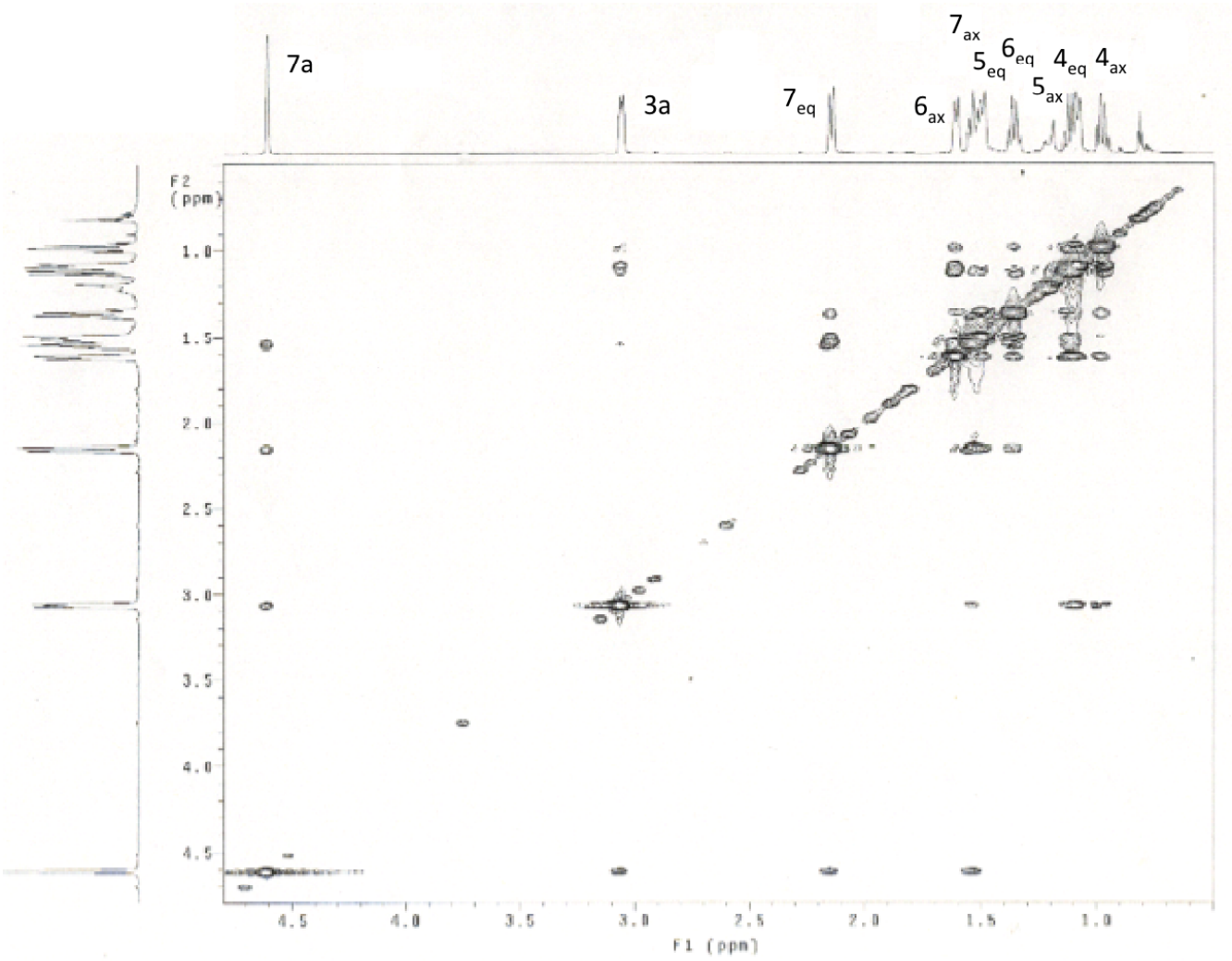
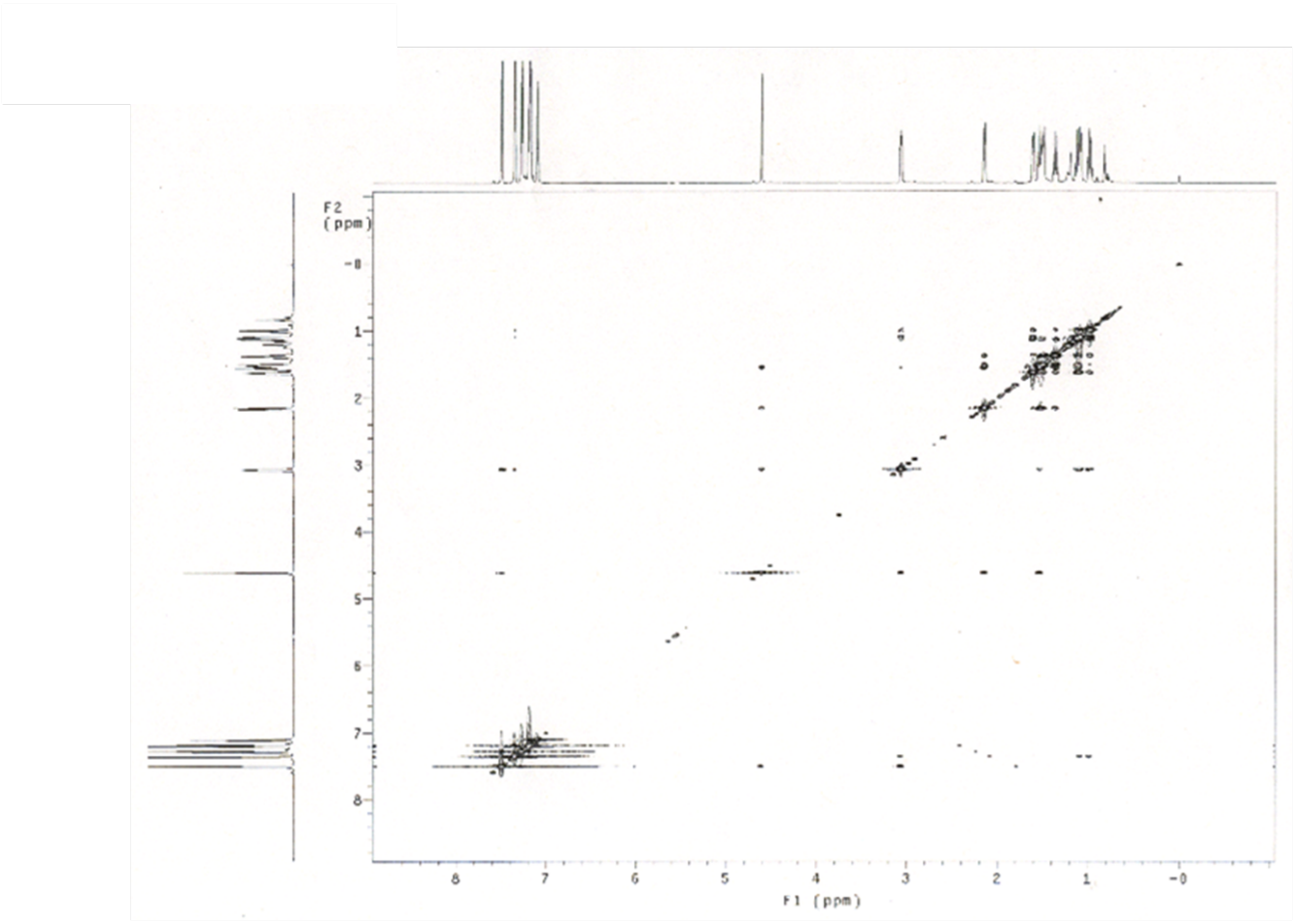


Figure S11. ^{1}H-^{1}H NOESY 800 MHz NMR spectrum of **2c** at 25 °C in $CDCl_3$.



***rac*-(3aR,7R,7aR)-3,3-diphenyl-(3a,7-2H2)-hexahydrobenzofuran-2(3H)-one (2c-3a,7_{eq}-d_2).** A solution of **1c**-1',3'-d_2 (45 mg, 0.15 mmol, >99% d_2 by MS) and triflic acid (0.7 µL, 7.5×10^{-3} mol) in toluene (0.3 mL) was stirred at 80 °C for 48 h to give **2c**-3a,7_{eq}-d_2 (45 mg, 100%) as a white solid. Mass spectral analysis (corrected for ^{13}C isotopomers) established a >98:<2 ratio of d_2 [*m/z* = 317.2 (M^+ + Na)] and d_1 [*m/z* = 316.2 (M^+ + Na)] isotopomers. ^{1}H and ^{2}H NMR analysis of **2c**-3a,7_{eq}-d_2 revealed ≥95% deuteration of the $C7_{eq}$ (δ 2.16) and C3a (δ 3.07) positions and ≤5% deuteration at the $C7_{ax}$ (δ 1.55) position (Figure 3, spectra b and c), ^{1}H NMR: δ 7.51 (d, *J* = 8.8 Hz, 2 H), 7.38 (d, *J* = 8.4 Hz, 2 H), 7.28 (t, *J* = 8.0 Hz, 2 H), 7.22-7.17 (m, 3 H), 7.13-7.08 (m, 1 H), 4.61 (br d, *J* = 2.8 Hz, 1 H), 1.66-1.46 (m, 3 H), 1.43-1.30 (m, 1 H), 1.23-1.05 (m, 2 H), 1.04-0.93 (m, 1 H). ^{2}H NMR ($CHCl_3$):

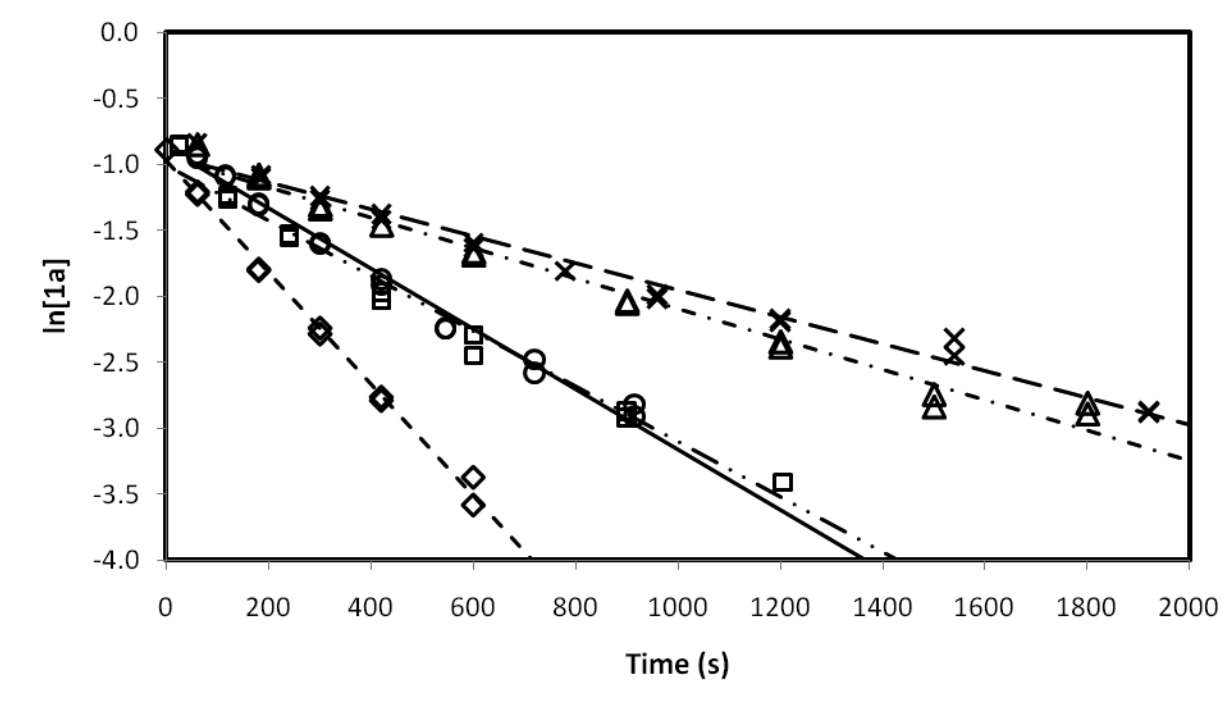
δ 3.14, 2.22. $^{13}C\{^{1}H\}$ NMR: δ 177.1, 139.9, 138.5, 129.0, 128.5, 128.1, 127.8, 127.6, 126.6, 75.0, 62.6, 42.7 (t, *J* = 16 Hz), 27.3 (t, *J* = 16 Hz), 25.7, 23.9, 19.6. LCMS (ESI, M^+ + Na): 317.2 (98.1%), 316 (1.4%).

Kinetic Experiments

Triflic acid (5.00 μL, 5.6×10^{-2} mmol, 25 mM) was added via a gas-tight syringe equipped with a stainless steel needle into a solution of **1a** (488 mg, 1.13 mmol, 0.50 M) in dry toluene (2.25 mL) that had been pre-equilibrated at 62.5 °C. The reaction mixture was stirred and aliquots were periodically removed via syringe. Aliquots were quenched with saturated aqueous $NaHCO_3$, extracted with acetonitrile, and analyzed by liquid chromatography equipped with a UV detector. The conversion of **1a** to **2a** was quantitative and occurred without formation of intermediates or byproducts. Furthermore, analysis of stock solutions of **1a** and **2a** revealed that the UV response factors of **1a** and **2a** were not significantly different (≤ 0.1%) over the concentration range utilized in these experiments. For these reasons, the concentration of **1a** was determined from the integration of the peaks in the LC spectrum corresponding to **1a** and **2a** according to the formula [**1a**] = 0.50 M × {[**1a**]/[**1a**] + [**2a**]}. A plot of ln[**1a**] versus time was linear to ~3 half-lives (Figure 4, Table 2), with an observed rate constant of k_{obs} = 4.2 ± 0.1 × 10^{-3} s^{-1}. Employing a similar procedure, observed rate constants for the reaction of **1a** with triflic acid were determined at [HOTf] = 5.0 mM and 12.6 mM at 62 °C in toluene (Figure 4, Table 2). A plot of k_{obs} versus [HOTf] was linear over this range, which provided the second-order rate constant for hydroamination of **1a** of k_2 = 3.3 ± 0.3 × 10^{-1} s^{-1} (Figure 5). Observed rate constants for the reaction of **1a** (0.5 M) with HOTf (~25 mM) in toluene were determined as a function of temperature from 39-72 °C (Table 2, Figure S12). An Eyring plot of the corresponding second-order rate constants (Figure 6), specifically a plot of ln (k_2/T) versus 1000/T, gave with linear regression y = –4.88x + 6.66 [or y = –4880x + 6.66 for plot of ln(k_2/T) versus 1/T}. Activation parameters for the conversion of **1a** to **2a** were determined according to the permutations of the Eyring Equation: $\Delta H^{\ddagger} = -mR$ and $\Delta S^{\ddagger} = [b - \ln(k_B/h)]R$, where *m* and *b* are the slope and y-intercept, respectively of the linear regression from the Eyring plot, *R* is the universal gas constant (1.987 cal mol^{-1} K^{-1}), k_B is the Boltzmann constant and *h* is

Plank's constant.

Figure S12. First-Order Plots for the Conversion of **1a** ([**1a**]$_0$ = 0.50 M) to **2a** Catalyzed by Triflic Acid in toluene [HOTf] = 12.6 mM at 72 °C (●); [HOTf] = 25.2 mM at 62.5 °C (♦); [HOTf] = 25.2 mM at 53.0 °C (■); [HOTf] = 25.2 mM at 39 °C (▲); and [HOTf] = 25.1 mM at 45.5 °C (×).



α-Secondary Kinetic Isotope Effect: A mixture of **1a** (162 mg, 0.376 mmol) and **1a**-2'-d_1 (74% d_1, 326 mg, 0.754 mmol) was dissolved in toluene (2.25 mL). Mass spectral analysis of the resulting solution revealed a 47.6:52.4 mixture of d_0:d_1 isotopomers. The solution was equilibrated at 59.5 °C and triflic acid (4.0 mg, 0.057 mmol) was added. The resulting solution was stirred and aliquots were removed periodically via syringe, quenched with saturated aqueous $NaHCO_3$, extracted with acetonitrile, and analyzed by LCMS for conversion and isotopic abundance. The concentrations of **1a** and **1a**-2'-d_1 were determined from total conversion, obtained by integration of the peaks in the LC spectrum corresponding to **1a** + **1a**-2'-d_1 and **2a** + **2a**-7a-d_1 and from the isotopic ratios **1a**:**1a**-2'-d_1 and **2a**:**2a**-7a-d_1 determined from MS analysis of the corresponding LC peaks (Table S1). Plots of ln[**1a**] and ln[**1a**-2'-d_1] versus time were linear to ~3 half lives with observed rate constants of k_{obs} = 2.19 ± 0.03 × 10^{-3} s^{-1} and k_{obs} = 2.51 ± 0.05 × 10^{-3} s^{-1}, respectively (Figure 7), which correspond to an inverse KIE of k_D/k_H = 1.15 ± 0.03.

Table S1. Total Conversion and Isotope Ratios as a Function of Time for the Reaction of a 47.6:52.4 mixture of **1a** and **1a**-2'-d_1 catalyzed by HOTf (5 mol %) in Toluene at 59.5 °C as Determined from LC/MS Analysis

time (s)	(**1a** + **1a**-2'-d_1) : (**2a** + **2a**-7a-d_1)	**1a**-d_0 : **1a**-2'-d_1	**2a**-d_0 : **2a**-7a-d_1
0	100 : 0	47.6 : 52.4	—
129	71.3 : 28.7	47.9 : 52.1	45.7 : 54.3
368	46.3 : 53.7	48.3 : 51.7	46.3 : 53.7
424	39.6 : 60.4	47.9 : 52.1	45.4 : 54.6
483	32.4 : 67.6	48.4 : 51.6	46.0 : 54.0
544	28.3 : 71.7	48.6 : 51.4	45.7 : 54.3
604	25.4 : 74.6	48.8 : 51.2	46.6 : 53.4
720	18.5 : 81.5	49.1 : 50.9	45.9 : 54.1
853	13.8 : 86.2	49.6 : 50.4	46.8 : 53.2
958	11.0 : 89.0	50.1 : 49.9	46.8 : 53.2
1083	8.0 : 92.0	50.9 : 49.1	46.9 : 53.1
1202	6.1 : 93.9	51.9 : 48.1	47.0 : 53.0

Calculated maximum a-secondary KIE for the conversion of 1a-2'-d_1 to 2a-7a-d_1: The Streitwieser's[S5] approximation of the Bigeleisen equation estimates the theoretical maximum kinetic isotope effect by:

$$\left(\frac{k_{\mathrm{H}}}{k_{\mathrm{D}}}\right) = e^{\left[\frac{0.187}{T}\Sigma\left(v_{\mathrm{H}} - v_{\mathrm{H}}^{\ddagger}\right)\right]}$$

Substituting known stretching and bending frequencies for the sp^2 carbon of *cis*-2-butene[S6] as a model for those of **1a** and the methine carbon of a secondary alcohol[S6] as a model for **2b** the equation becomes:

$$\left(\frac{k_{\mathrm{H}}}{k_{\mathrm{D}}}\right) = e^{\left[\frac{0.187}{T}(2980-2900+1425-1340+852-1340)\right]} = e^{\frac{-60.4}{T}}$$

At T = 333 K, this equation predicts a maximum KIE for the conversion of **1a** to **2a** of k_H/k_D = 0.834 of k_D/k_H = 1.20.

References

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S6. Values employed for *cis*-2-butene (cm^{-1}): 2980 (stretching), 1425 (in-plane bending), 852 (out-of-plane bending).[S7] Values employed for secondary alcohol (cm^{-1}): 2900 (stretching), 1340 (in-plane binding), 1340 (out-of-plane bending).[7]

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